Chronic diarrhoea

SAPA WEBINAR

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Declaration

- No conflicts of interest

Outline

- Definitions
- The triple burden or recurrent/ persistent enteritis
- Approach to chronic diarrhoea by type of diarrhoea
- Investigation
- Management
- Some brief cases

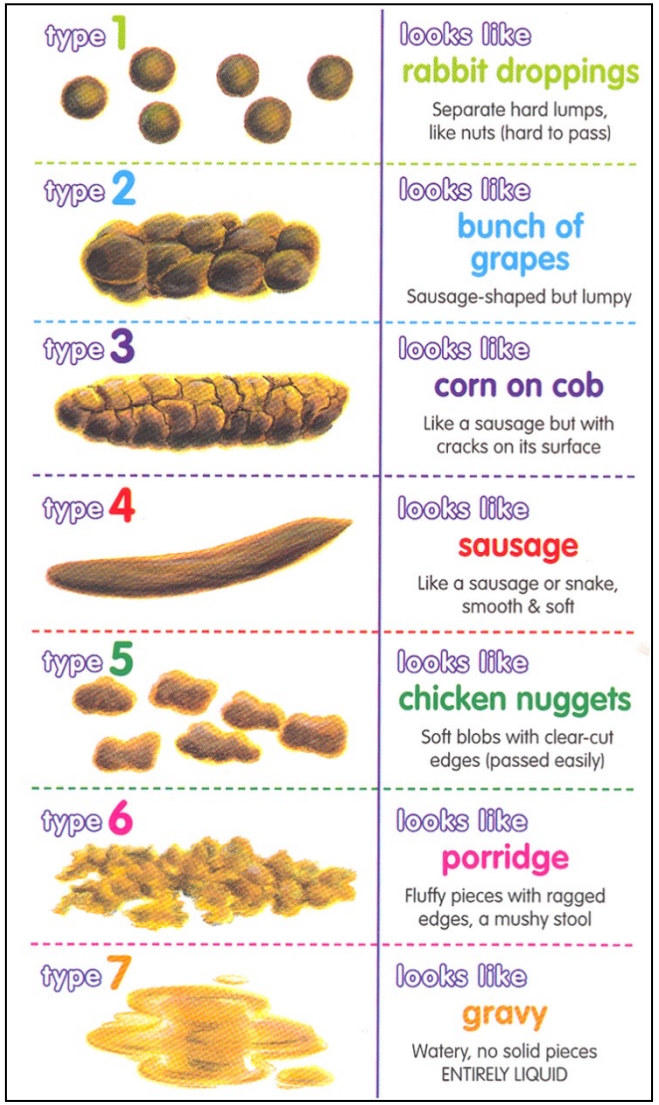
Definitions

Normal stool frequency in young children

Age group	Minimal	Maximal
Infant breast-fed	1 per 10—14 days	10 per day
Infant/toddler (3 years)	1 per 2 days	3—4 per day
Older children	3 per week	3 per day

- WHO definition of diarrhoea:
  - 3 or more loose or watery stools (taking the shape of the container) in a 24-hour period
  - Breastfed infants: “looser / more frequent than normal”
  - Acute: <14 days duration
  - Persistent: ≥14 days duration (but >7 days worrying)
- Dysentery: small volume, bloody, mucoid stools + abdominal pain / toxicity

Anonymous; Bulletin of the World Health Organization 1988; 66:709-17.



The Bristol Stool Form Scale

Definitions

- Increase in frequency, water content compared to previous pattern for the individual
- Stool output > 10ml/kg/day (> 200ml/day for adults)
- Persistent diarrhoea >14 days
  - Risk factors: formula feeding, age < 3/12 at onset, malnutrition, immune suppression/HIV, associated illness, nosocomial infections in hosp
  - Consenquence of multiple/simultaneous enteric infections which lead to mucosal injury – vicious cycle of further diarrhoea, malnutrition, infections
- Chronic diarrhoea> 2 weeks
  - Related acute infective onset: persisting diarrhoea spectrum
  - Causes diverse: longstanding intestinal dysfunction, maldigestion and malabsorption

How big a problem?

- Diarrhoeal disease is the 2nd leading cause of death in kids <5 yrs
  - kills around half a million children <5 yrs
  - leading cause of malnutrition <5 years of age
  - Most deaths occurring in Sub Saharan Africa and South East Asia
  - If current trends continue, 4.4 million children will die before their 5th birthday 1n 2030

- Diarrhoea can contribute to 40% of disability-adjusted life years globally (DALYs)

Liu et al. Lancet 2015;385:430-40, Troeger. Lancet Glob Health 2018; 6:e255-69

The triple burden of recurrent enteritis!

- The HAZ drop
  - Enteric infections still kill >1000/day
    - but help stunt over 160m children (30% LDC, 20% all) HAZ drop.
  - Recurrent bouts of Diarrhoea reduce catch-up growth.
- The COGhit
  - Enteric infections also rob cognitive development (COGhit): Up to 10 IQ points (Alzheimer's like deficit) for 1/5 of all children
  - Cognition may be related to how many bouts of Diarrhoea, so the more Diarrhoea episodes, the lower the cognition
- The METsyn
  - Enteric infections may increase adult obesity, metS and CVD (MET-syn)

Guerrant RL, DeBoer et al. Nat Rev Gastroenterol Hepatol 2013;10(4):220

Chronic diarrhoea
>14 days

Nutritional deterioration AND dehydration

Nutritional deterioration WITHOUT dehydration

Normal nutrition and hydration

Age and history of onset

Age and history of onset

Age and history of onset

Neonatal onset

Acute onset prior normality

Appetite maintained

Anorexia

Characteristic findings

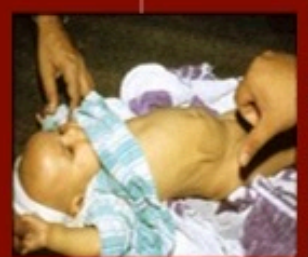
Congenital disorders gut

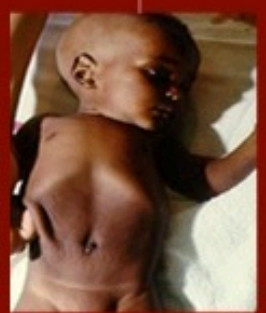
Intestinal mucosal injury

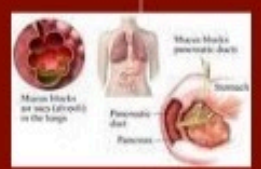
Exocrine pancreatic abnormality

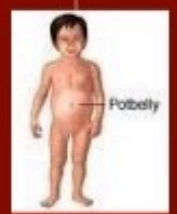
Enteropathy Malabsorption

Toddler's diarrhoea





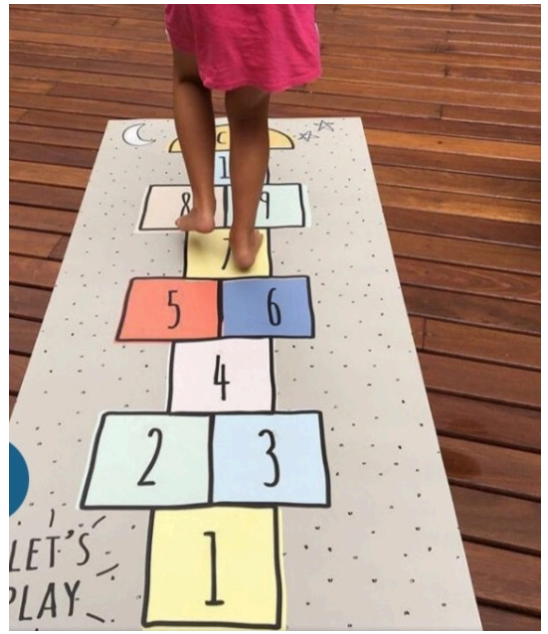




Prof DF Wittenberg

- Identify the type of diarrhoea by pathophysiology

- Secretory
- Osmotic
- Inflammatory
- Dysmotility



Types of diarrhoea

- Osmotic
  - Osmoles in lumen- osmotic gradient with net water secretion and retention
- Secretory
  - Endogenic secretions of substances that induce fluid and elect shifts in absence of osmotic gradient
- Dysmotility
  - Normal epith structures, low transit time, reduced time for absorption
- Inflammatory
  - Enteritis, Infectious colitis, allergic colitis, Primary Immune Def/immune deficiency states, Autoimmune/IBD

Small bowel

Small bowel mucosa- brush-border columnar epith cells, folded into finger like villi

High surface area for absorption

Fluid movement through active transport of ions (Na, Cl, HCO3)

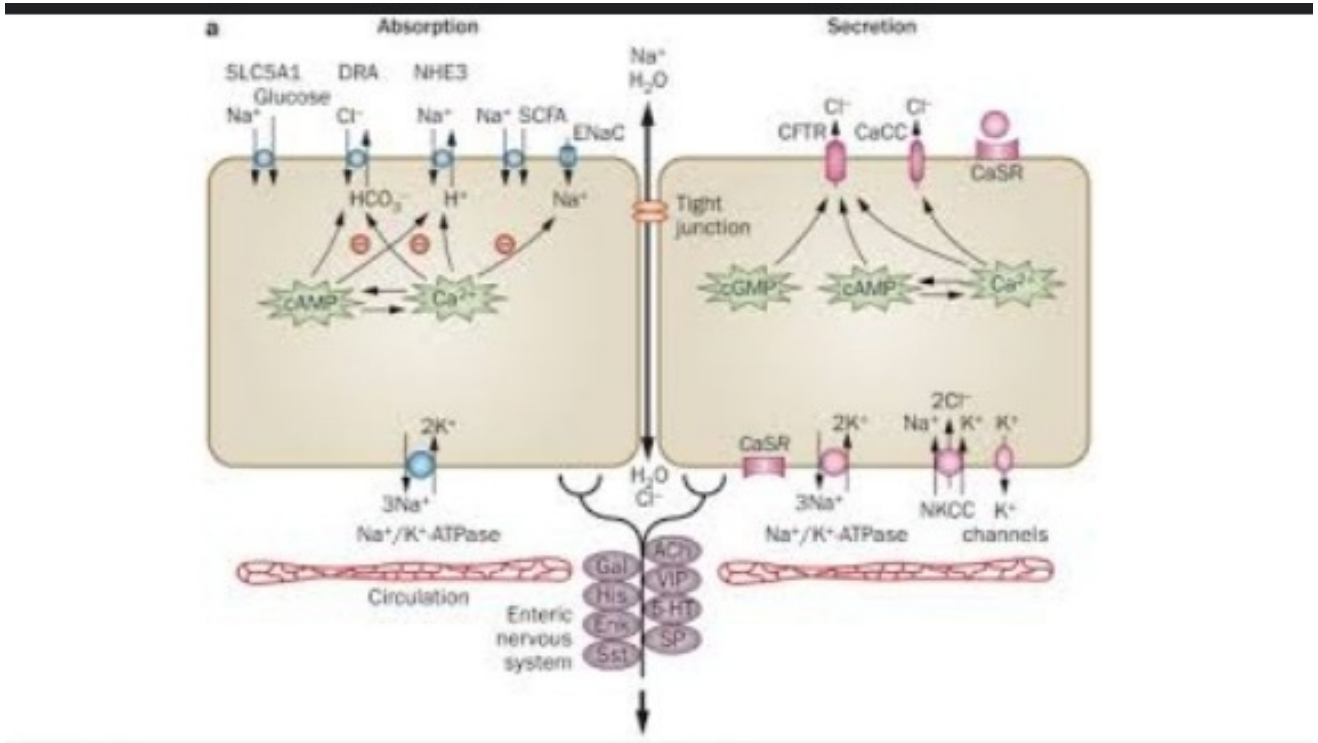
Broadly Na from mucosa to serosa drives absorption

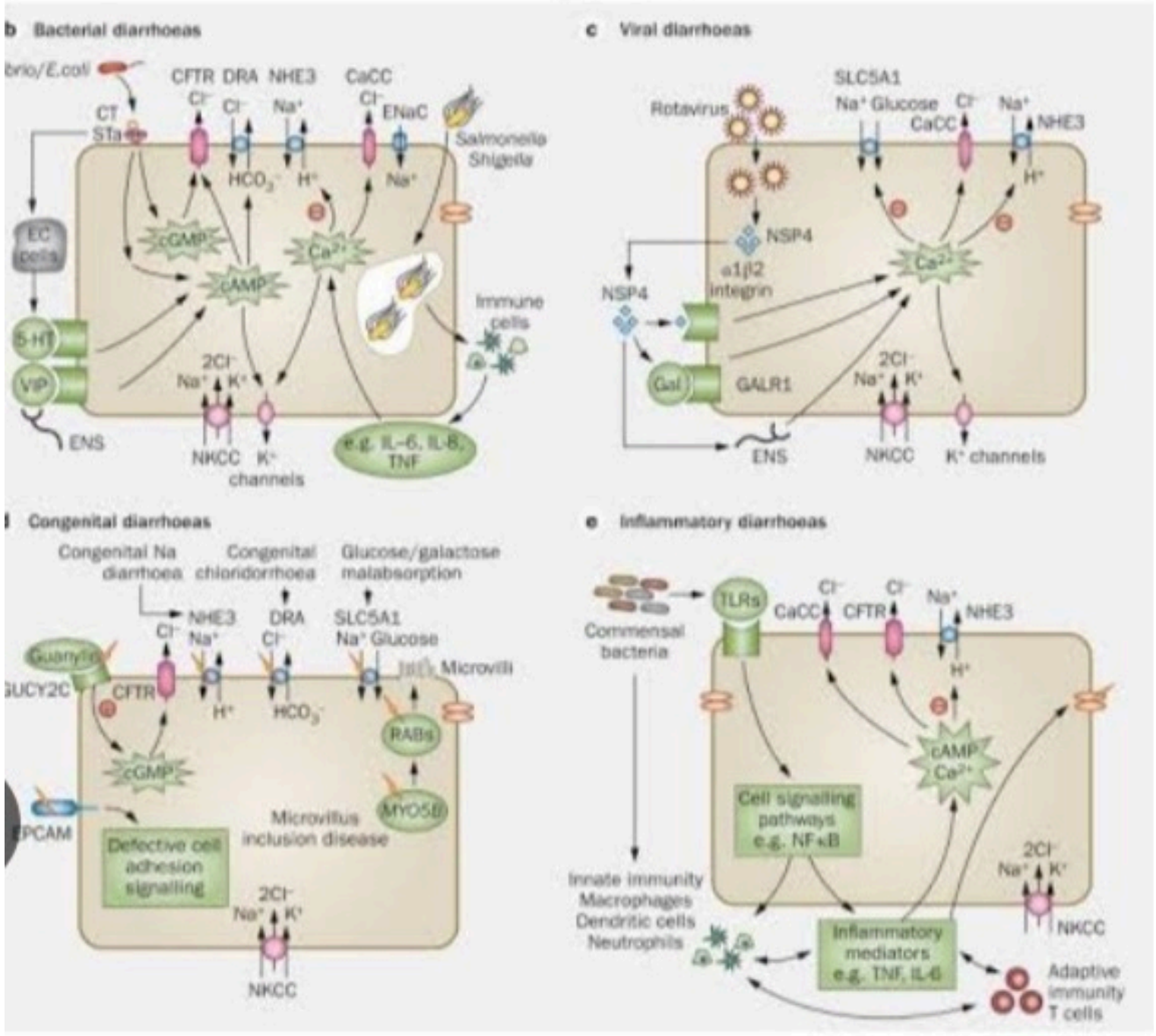
Cl movement in reverse direction drives net secretion

Intact epithelial barrier function is essential

Tight junctions restrict passive flow of solutes

Normal motility also determines net fluid movement




b Bacterial diarrhoeas
Vibrio/E.coli
CT
STa
CFTR
DRA
NHE3
CaCC
ENaC
Salmonella
Shigella
EC cells
cGMP
cAMP
Ca2+
5-HT
VIP
ENS
2Cl- Na+ K+
NKCC
K+ channels
Immune cells
e.g. IL-6, IL-8, TNF
c Viral diarrhoeas
Rotavirus
SLC5A1
Na+ Glucose
CaCC
NHE3
NSP4
α1β2 integrin
Gal
GALR1
ENS
NKCC
K+ channels
Congenital diarrhoeas
Congenital Na diarrhoea
Congenital chloridorrhoea
Glucose/galactose malabsorption
NHE3
DRA
SLC5A1
Na+ Glucose
Guanylin
GUCY2C
CFTR
Microvilli
RABs
MYO5B
cGMP
EPCAM
Microvillus inclusion disease
Defective cell adhesion signalling
2Cl- Na+ K+
NKCC
e Inflammatory diarrhoeas
Commensal bacteria
TLRs
CaCC
CFTR
NHE3
cAMP Ca2+
Cell signalling pathways e.g. NFκB
Innate immunity Macrophages Dendritic cells Neutrophils
Inflammatory mediators e.g. TNF, IL-6
Adaptive immunity T cells
NKCC

Secretory D, with malabsorption

normal

- Tufting enteropathy

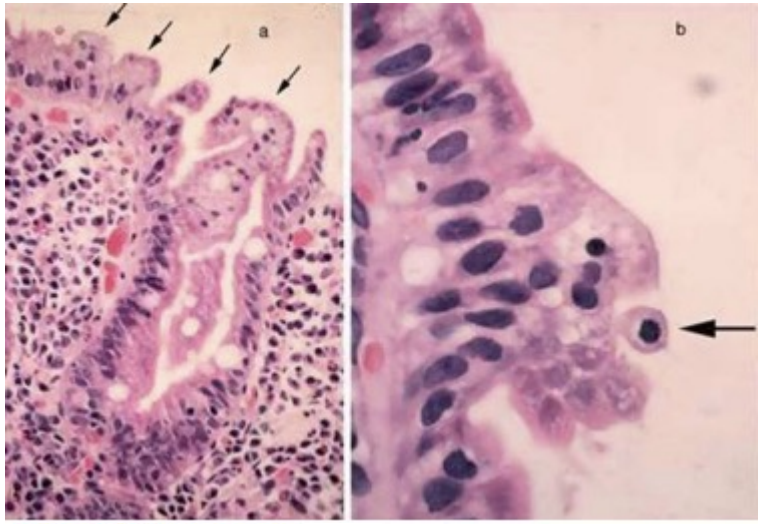


Fig. 1.6 **a** Numerous tufts of enterocytes on the mucosal surface of the duodenum. **b** A characteristic tear-drop-shaped structure *(arrow)* in an epithelial tuft (H&E stain; original magnification: a–x 80; b–x 400). (Reprinted from Ref. [59, Fig. 1], with kind permission from Springer Science and Business Media)

- MVID

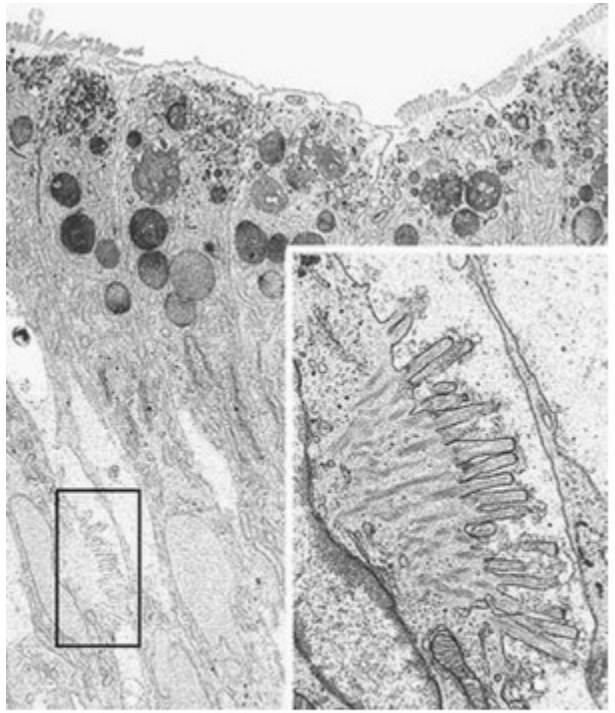
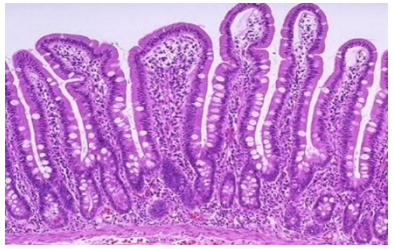


Fig. 1.2 Microvillous in the original label inclusion disease. Villous enterocytes: the *boxed area* shows microvilli on the lateral membrane. *Inset*: Enlargement of the *boxed* area × 6200, *inset* × 22,500. (Reprinted from [20, Fig. 5], with kind permission from Springer Science and Business Media)



Investigation

- Detailed History
- Age of onset of D, ?abrupt, duration
- Type of stool : watery mucous/bloody fatty

- Associated symptoms: bloating, relation to meals and fasting, weight loss, abdominal pain, unexplained fever, vomiting, night awakening
- Dietary history, family history, travel history
- Chronic medication, past medical and surgical history

Investigation- thorough exam

- Thorough systematic exam
- Identify extraintesinal manifestations of gut pathology and extent of severity of the complications
- Hydration status, evidence of micronutrient def, rash, oedema,finger clubbing, jaundice, pallor, arthritis, eye involvement, abdominal distension with organomegaly, or palpable feces, perianal lesions

- Labs: HIV status, FBC diff, U&E, CMP, Blood gas, LFT, ESR, stool mc&s, coeliac serology, Immunoglobulins (IgA,IgG,IgM) CMV VL

Investigation notes: blood tests

- FBC:
  - ↑PLT: chronic inflammation: CMPA, IBD, fe def, Tb
  - ↓WCC: PLE, intestinal lymphangiectasia
  - ↓Hb: Fe def, chronic ds eg Coeliac ds, IBD, CMPA, AutoIEnterop
  - ↑eosinophils : CMPA, eosinophilic gastroenteritis, parasites
- U&E, blood gas
  - AbN electrolytes in congenital D, metabolic alkalosis & ↓ NaCl in CF
- CRP and ESR infectious or inflammatory D
- LFT
  - ↓Alb inflammation, PLE, cholestasis with fatty D, cryptosporidium ass Cholangiopathy in Primary immune def
  - ↑transaminases: extraintestinal manifestations of IBD, Coeliac ds, THEs, CF
- Infection screen include CMV, Coeliac Screen with IgA level (false –ve AB test in selective IgA def

Notes: stool tests

- Stool MC&S
  - +leuks, +RBC suggest inflammatory D
  - Fat globules/fatty acid crystals: impairment in fat digestion/malabspn
  - +ova/parasites/cysts/culture: infectious cause
- C diff toxin: for >1 yr, at-risk groups (eg recurrent antibiotic exposure, hospitalisations)
- Stool electrolytes
  - differentiate between osmotic and secretory diarrhoea
  - Faecal osmolar gap (FOG) :290 – 2x(stool Na + K) mOsm
  - FOG<50 secretory, FOG>100 osmotic

Notes: stool tests

- Fecal reducing substances and pH
  - + in CHO malabsorption, pH<5.3
- Stool elastase
  - ↓ in pancreatic insufficiency (N> 200mg/g stool) false ↓ in high vol diarrhoea
- Fecal calprotectin
  - Marker of gut inflammation
- Stool alpha 1 antitrypsin
  - PLE (N,0.9mg/g stool)

Notes: urine tests

- Urine MC&S
  - exclude UTI’s
- Urine reducing substances
  - + in galactosemia and glucose-galactose malabsorption

	Secretory	Osmotic	Dysmotility	Inflammatory
Defect	↓absorption ↑secretion Electrolyte tport	Maldigestion Malabsorption Transport defects Ingestion of anabsorbable solutes	↓transit time Defect in neuromuscular units	Mucosal damage ↓ absorptive surface ↓colonic reabsorptn ↑motility
Stool	Watery N stool osmolality FOG < 50 No leukocytes	Watery ↑stool osmole pH<5.5 FOG>100 + RED substances No leukocytes	Loose/ N appearing N osmolality N pH Stimulated by gastrocolic reflex No leukocytes	Loose/bloody/mucoid Green + leukocytes ↑ calprotectin
Eg's	Congential CL D Cong Na D Cholera Tufting enteropthy MVID, VIP	Lactase deficiency, PLE, Glu-Gala Tport , Sucrase-isomalt def, Galactosemia Laxative over use	Thyrotoxicosis Functional Diarrh, IBS	Infectious Immune related Allergic, PID, AI : CD, IBD, IPEX
Comments	No Improvement with fasting Might be syndromic, polyhydramnios antenatally	Improves with fasting ↑breath H due to CHO malabsorption, Rx SIBO Newborn onest, exclude anatomical ABN	Functional D (aka CNSD /toddlers):N wt gain, undigested matter may be seen	perianal lesions may suggest PID/VEOIBD

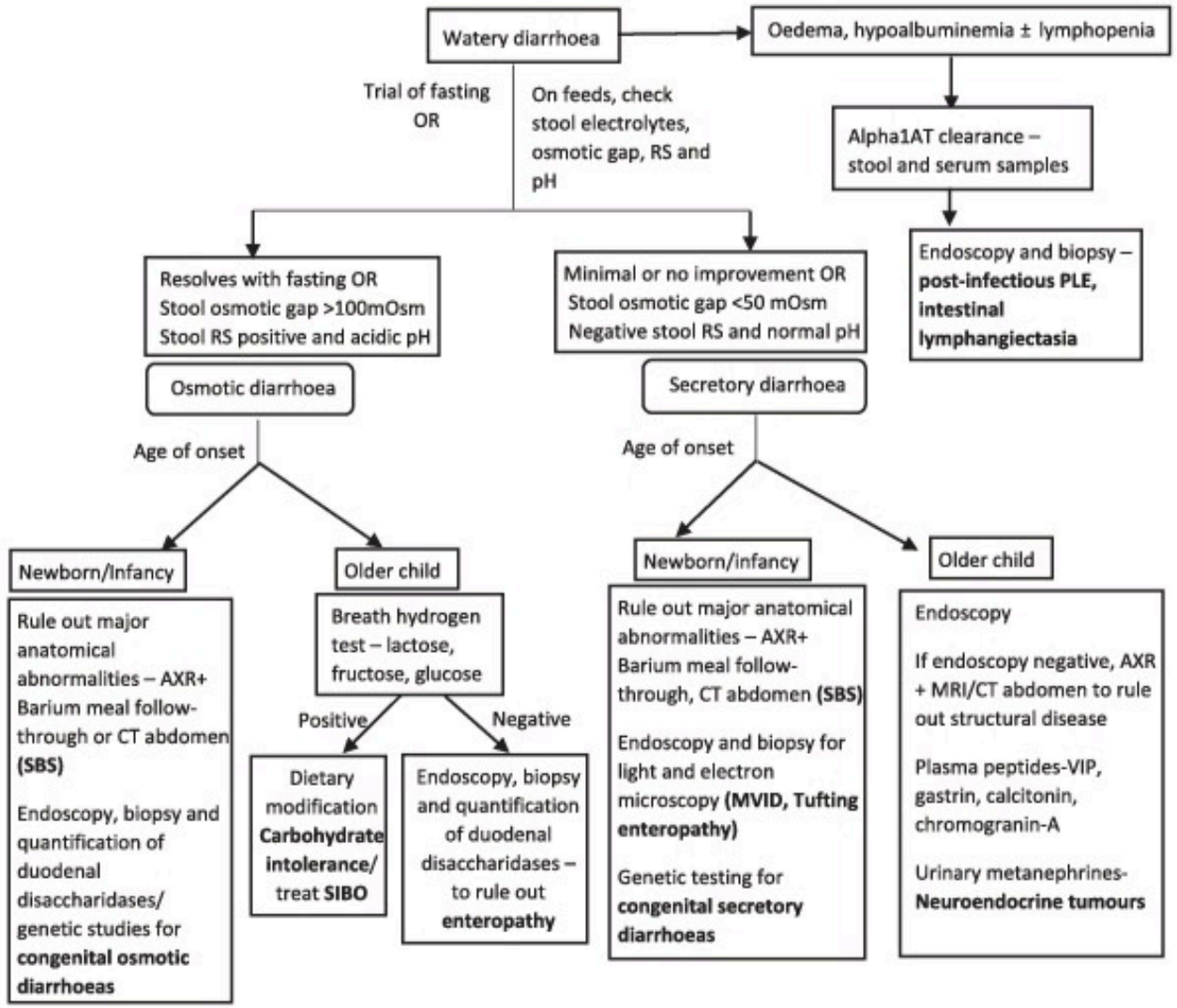


Fig 2 Approach to watery diarrhoea. SBS, short bowel syndrome; RS, reducing substances; AT, antitrypsin; PLE, protein losing enteropathy; SIBO, small intestinal bacterial overgrowth; MVID, microvillous inclusion disease; VIP, vasoactive intestinal peptide.

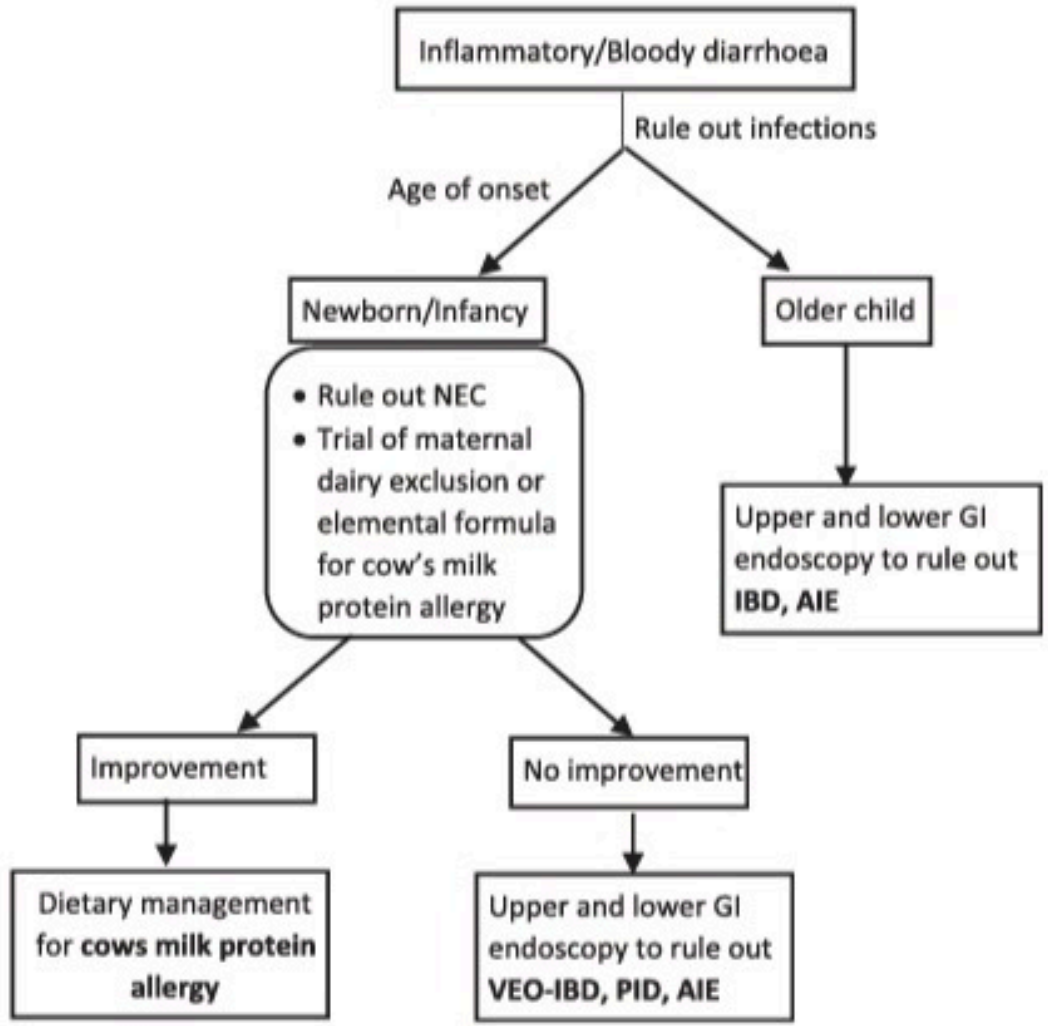


Fig 4 Approach to inflammatory/bloody diarrhoea. AIE, autoimmune enteropathy; IBD, inflammatory bowel disease; NEC, necrotising enterocolitis; PID, primary immunodeficiency; VEO-IBD, very early onset IBD.

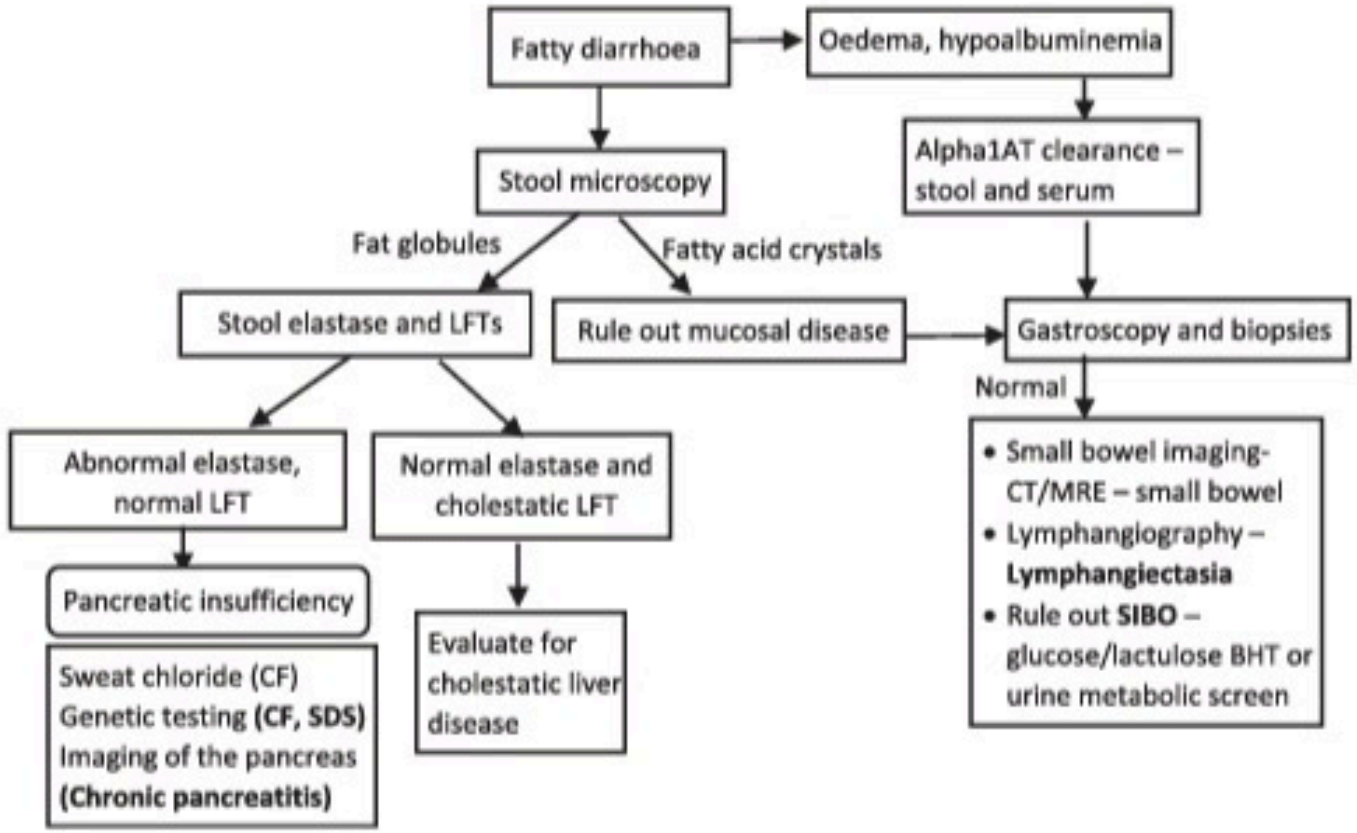


Fig 5 Approach to fatty diarrhoea. AT, antitrypsin; BHT, breath hydrogen test; CF, cystic fibrosis; SDS, Shwachman Diamond syndrome; SIBO, small intestinal bacterial overgrowth.

Management

- Early recognition, assess type of D, determine severity
- Fluid resuscitation and electrolyte correction
- Treat underlying infections or disease process
- Nutritional rehabilitation very important of management
  - Enteral supplementation always preferred to parenteral
  - TPN necessary gut failure, severe dehydrating diarrhoea with significant failure to thrive
- Probiotics? Still insufficient evidence for chronic D, but watch the space!!
- Empiric antibiotics in selective cases

Management

Secretory	Osmotic	Functional Diarrhoea	motility
IV fluids **TPN** **Rx underlying ds** **Loperamide in patients with SBS**	IV fluids/po Lactose-free 1 yr infasoy >1 yr paediasure Keep on for 2-4 weeks Extensively hydrolysed feeds Stop soft feeds <1 yr pepticate, alimentum, alfare >1 yr peptimen junior/nutrini peptisorb In hospital challenge to lactose free feed, standard feed. Stop meds increasing solute load KCL, ORS, Mg, PO4, Bactrim, MVT Lactose/galactose exclusion diet in galactosemia, stop BF Stop laxatives	Reassurance ↓fruit, juice Stop any laxatives IBS- Cognitive behavioural therapy TCAs	Treat ↑T4 Treat any infection Stop any motility agents

Management

Food allergy CMPA	IBD	Coeliac ds	Immune	Infection other
CMP elimintion **Breast milk with maternal exclusion of dairy** **Extensively hydrolysed feed in Formula fed** **Omit offending food for other causes of food allerrgy** **Diet reviews as children may outgrow allergy**	Crohns UC IBD unclassified Diet Immunomodulators Surgery if indicated Stoolcalprotectin Endoscopy with biopsies/capsule endoscopy MRE to monitpr disease progression	Gluten exclusion from diet	PID (Primary immune deficiency) Autoimmune enteropathy eg IPEX syndrome Intestinal lymphangiectasia, Immunosuppression Bactrim prophylaxis Disease specific Mx	Parasites-giardia, viral-CMV, HIV Bact- c diff Treat infection

2 cases of galactosemia

- 6 week old, sex, HIV neg, T
- D 3wks, watery stools, exclusively breastfed
- Dehydration, metabolic acidosis
- 2cm hepatomegaly, abN ALT, hypoglycemia
- No stool leuk, + URED, G-ve UTIs
- GALT deficient
- Diarrhoea resolved on infasoy

- 4 month old, M , HIV neg FF
- FTT, D 3weeks, watery- loose Vom 3/7, swollen legs
- SAM with oedema, severe dehydration, metabolic acidosis,
- Firm 5cm hepatomegaly
- +URED, D stopped on infasoy feeds
- GALT deficient

Case 3 : 2m old f, No HIV exposure,

PC: Diarrhoea, + blood in stools,

no fever, breast fed first 2 weeks of life, then changed to exclusive formula feed with lactogen, maternal sores on breast

- normal birth wt, non remarkable perinatal history
- Diarrhoea started a few days post commencing lactogen feeds
- asymptomatic anaemia, fe deficiency
- No family history of beef allergy

- Generalised skin rash with areas of hypopigmentation, rest of systemic examination N
- Abd USS N, high platelets and ESR
- ?CMPA. Improved on infasoy. Discharged, but came back with diarrhoea after a day when mum found the shops closed to buy infasoy, and gave standard formula.

Case 4 Cystic fibrosis

- 2m old referred, Bfed since birth
- Already been at base for 1/12 with pneumonia
- FTT, chronic diarrhoea.
- No hydramnios, - fam hx,
- Stool loose, foul, no leuk. Stool better on pepticate, elastase<15
- Labs: low Na, low Cl
- CF genetics

Conclusion

- Chronic diarrhoea consequences include significant morbidity and mortality in children
- Causes may be diverse, practical algorithms may help in evaluation, starting with detailed history and examination, blood and stool tests
- Refer early for specialised care

Thank you