Vol 42, Pedgihep e-journal:

BASICS OF CHILDHOOD DIFFICULT DIARRHEA.

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Clinical pearls in dealing with childhood DIFFICULT diarrhea.

- Diarrhea needs to be differentiated as small bowel or large bowel diarrhea in the given clinical situation.
- Luminal and non-luminal causes of diarrhea should be guided by history and clinical examination with support of appropriate investigations.
- Long standing Small bowel diarrhea has associated nutrient deficiencies with failure to thrive which is generally not the case with acute to subacute large bowel diarrhea.
- Long standing large bowel diarrhea are more clinically toxic than mal-nutritious small bowel diarrhea.
- functional diarrhea (or toddler's diarrhea) < four years of age and irritable bowel syndrome in those aged 5–18 years are one of the major spectrum in chronic diarrhea in children.1
- Toddler's diarrhea by definition : Rome 111

1. Daily painless, recurrent passage of three or more large, Unformed stools;
2. Symptoms those last more than four weeks;
3. Onset of symptoms that begins between 6 and 36 months Of age;
4. Passage of a stool that occurs during waking hours;
5. There is no failure-to-thrive if caloric intake is adequate

- IBS- DIARHOEA : 5- 18 YRS :Abdominal discomfort (an uncomfortable sensation not Described as pain) or pain associated with two or more of the following at least 25% of the time:

a) Improved with defecation
b) Onset associated with a change in frequency of stool
c) Onset associated with a change in form (appearance)
of stool. No evidence of an inflammatory, anatomic, metabolic,
or neoplastic process that explains the subject's symptoms

- Indicators of a functional etiology are a long duration of symptoms, the lack of significant weight loss, and absence of nocturnal diarrhea.
- Small intestinal bacterial over growth is one of the most common cause of chronic diarrhea.
- Bacterial overgrowth is difficult to detect with hydrogen breath test due to poor standardization2

- Post enteritis syndrome is one of the important cause of persistent diarrhea in children in developing countries needs to be taken in consideration. Stopping lactose should be balanced with obvious advantages of breast milk.Most of the times in authors scenario stopping breast milk is not necessary.
- Food allergies may present with chronic diarrhoea through a non-IgE-mediated mechanism, especially during infancy.3 Food allergies may manifest as small bowel or large bowel diarrhea. In author's view past h/o atopy should be considered in clinical picture.
- Infections causing chronic diarrhea are entero-adherant e-coli,c-parvum,cl. difficle, cmv,noroawalk.
- Inflammatory bowel diseases (IBD), including Crohn's disease, ulcerative colitis and indeterminate colitis, are major causes of chronic diarrhea in older children. In authors view IBD is still one of the rare cause of chronic diarrhea in children.
- Chronic diarrhea may be the manifestation of maldigestion due to exocrine pancreatic disorders.Probable etiology should be suspected depending on age and clinical manifestation.
- Liver disorders may lead to a reduction in the bile salts resulting in fat malabsorption. Bile acid loss may be associated with terminal ileal diseases may be responsible for chronic diarrhea. Most of the situations investigation do-not lead us to diagnosis but history taking and redoing clinical exam is must.
- Congenital diarrheal disorders (CDD) present in newborns. recently proposed a classification of CDDs that includes four groups: digestion, absorption and transport defects, enterocyte differentiation and polarization defects, enteroendocrine cell differentiation defects, intestinal immune response defects.
- Onset of diarrhoea soon after fruit and juice are started is typical of sucrase-isomaltase deficiency. Sucrose-free formula is indicated in sucrase-isomaltase deficiency
- If the stools do not contain occult or gross blood, white blood cells or eosinophils, an inflammatory or food allergy could be reasonably excluded. 4
- Coeliac disease is the single most frequent cause of chronic malabsorptive diarrhea. Early diagnosis by early appropriate referral to pediatric gastroenterology centers is valid opinion.
- Fecal calprotectin concentration <100 ug/g for children aged >12 m suggests no Intestinal inflammation.
- Fecal leukocytes <5/microscopic field indicates no Colonic inflammation
- Measurement of nitric oxide in the fluid obtained from a small bag placed in the rectum (rectal dialysis bag), it quite reliably reflects distal intestinal inflammation. Nitric oxide in rectal dialysate <5 uM of NO2_/NO3_ rules out rectum inflammation5

- Continuous enteral nutrition is effective in children with a reduced absorptive function, such as short bowel syndrome, since it extends the time of nutrient absorption through the still functioning surface area.
- Zinc supplementation is an important factor in both prevention and therapy of chronic diarrhea.4
- diarrhoea due to neuroendocrine tumours, microvillus inclusion disease and enterotoxin-induced severe diarrhoea, a trial with somatostatin analogue octreotide may be considered4
- Butyrate has been proposed for the treatment of congenital chloride diarrhea.6
- A meta-analysis compared the effectiveness and complications of reduced-osmolarity ORS versus those of the standard WHO-ORS in 2397 paediatric patients and reported a reduction in stool output, episodes of vomiting and the need for intravenous hydration in the reduced-osmolarityORS group.7
- In a Cochrane review published in 2009, patients who were treated with the Polymer-based ORS were found to have fewer unscheduled IVT and shortened diarrhoea duration compare to the group who was treated with glucose based ORS, although the analysis was under powered.8
- Bismuth subsalicylate is not recommended in treatment of children younger than 3 years old and those with viral illnesses because of risk of reyes syndrome.9
- The potential role of probiotrics in treatment of persistent diarrhea is not known.10
- Octreotide is mainly being used to treat diarrhoea and other hormone-mediated symptoms

caused by carcinoid tumour, VIPomas, glucagonomas 11

- Octreotide has also been used to treat severe refractory diabetic diarrhea. 12
- Octreotide has been tried in dumping syndrome. 13
- Octreotide is tried with severe diarrhea induced by chemotherapy and radiotherapy.
- Octreotide should be discontinued after 2 weeks in patients who have not demonstrated a response to treatment as late response is rare and the drug is expensive.
- Common side effects of Octreotide include abdominal pain, nausea and flatulence and loose stools. Mild steatorrhoea may occur at the beginning of treatment and usually subsides spontaneously in few weeks. After long term treatment, asymptomatic gallbladder stone/sludge may develop
- Proton pump inhibitors and histamine 2 antagonists can be used in the treatment of gastrinoma induced diarrhea.
- Histamine 1 antagonists should be considered in systemic mastocytosis.
- Treatment of small intestine bacterial overgrowth starts with treating the underlying condition if there is the motility disorder, if feasible. Suppression with antibiotics with anaerobic coverage is often used with either a nonabsorbable antibiotic such as rifaximin or other broad-spectrum antibiotic (e.g., tetracycline, penicillin, and cephalosporin)14

- Tropical sprue is one of the most common disorders in certain parts of the developing world. The cause has never been identified.15
- In tropical sprue Folate deficiency is frequent. Histopathology may be indistinguishable from celiac disease with varying degrees of villous atrophy and intraepithelial lymphocytosis Antigliadin antibodies can be positive in a third of patients with tropical sprue.16
- One important histologic feature is the absence or paucity of plasma cells in the biopsy that occurs in common variable immunodeficiency. 17
- When Giardia is identified on biopsies, the careful scrutiny of the lamina propria for the absence of plasma cells should be undertaken by the pathologist. If plasma cells are absent, this may represent combined variable immunoglobulin deficiency and testing quantitative measures of the different immunoglobulin isotypes should be undertaken.18
- Secretory diarrhea exclude aeromonas , micosporidia, Giardia, plesiomonas.
- Trial of bile acid binding drugs may be warranted in persistent secretory diarrhea.
- Autoimmune enteropathy and microvillous inclusion disease present as secretory diarrhea.
- Cystic fibrosis , Abetalipoproteinemia, bile acid malabsorption are important causes of fatty osmotic diarrhea.
- **Protracted diarrhea of infancy (PDI), which resolves despite its initial severity.**
- Intractable diarrhea of infancy (IDI): diarrhea occurring in an infant younger than 3 months of age, lasting more than 2 weeks, with three or more negative stool cultures for bacterial pathogens
- In autoimmune enteritis Diarrhea starting within the first 2 years and is generally SECERTORY associated with or without hypo-parathyroidism , hypothyroidism , DM TYPE 1, eczema.
- severe to total villous atrophy isassociated with crypt hyperplasia. MORE T CELL IN LAMINA PROPRIA LESS T CELL IN ENTEROCYTE. LESS GOBLET CELLS.
- Serologic diagnosis of AIE is not necessary .
- initially, steroid pulses (25 mg/kg) were applied on 3 consecutive days, followed by 2 mg/kg/d, concomitant with tacrolimus. The doses of tacrolimus are adjusted to achieve and maintain blood levels between 8 and 12 ng/mL is earlier treatment of AIE.
- first steroid pulse is insufficient, a second pulse can be given .
- MAINTAIN triple therapy approach, combining tacrolimus, prednisolone, and azathioprine IN AIE.
- LONG TERM trimethoprim-sulfonamide prophylaxis is indicated.
- Diarrhoea in 1st 7 days: glucose galactose mas or congenital lactase deficiency should be suspected.
- In 3 r-6 month diarrhea: fructose mas, glucoamylase, sucrose-isomaltase def should be suspected.
- The diagnosis of FBS(fanconi bickel syndrome) should be considered in patients with hepatomegaly and evidence of a renal tubulopathy. DIAGNOSIS:

Urine analysis will demonstrate evidence of glycosuria, a generalized aminoaciduria, and excessive urinary losses of phosphate and calcium. Uncooked cornstarch has been used to prevent hypoglycemia and to minimize postprandial hyperglycemia

- Cystinuria type I/2/3: NEPHROLITHIASIS. LOOK FOR IN CHRONIC DIARHOEA.
- Lysinuric protein intolerance : AGE AND NEUROLOGICAL DELAY. Marked hepatosplenomegaly and frequent bone fractures are also characteristic of LPI, Citrulline supplements (200 mg/kg/d) and dietary protein restriction (1.5 g/kg/d) are currently used to manage patients with LPI. Oral carnitine supplementation has been shown to be important in a subset of patients described with LPI and hypocarnitinemia.
- Iminoglycinuria: NEUROLOGIC DELAY
- Hartnup disorder: DERMATITIS & NEUROLOGICAL DELAY
- TANGIERS DISEASE: HEPATOMEGALY, SPLEENOMEGALY, LYMPHADENOPATHY
- DIARRHOEA AND DERMATITIS: ACRODERMATITIS ENTEROPATHICA.
- Specifically, plasma triglyceride levels are generally < 10 mg/dL, whereas cholesterol levels range from 25 to 40 mg/dL.Acanthocytosis Endoscopic evaluation of the small bowel can show yellow discoloration, and biopsies have characteristic fat-laden enterocytes located in the upper portion of the villus: ABETALIPOPROTEINEMIA

Drugs inducing steatorrhoea.

Aminoglycosides
Auranofin
Biguanides
Cholestyramine
Colchicine
Highly active antiretroviral therapy
Laxatives
Methyldopa
Octreotide
Orlistat (lipase inhibitor)
Polymixin, bacitracin
Tetracyclines
Thyroid replacement

Drugs that cause diarrhoea in ≥20% of patients
- Alpha-glucosidase inhibitors
- Biguanides
- Auronafin (gold salt)
- Colchicine
- Diacerein
- Highly active antiretroviral therapy
- Prostaglandins
- Tyrosine kinase inhibitors

Drugs that cause diarrhoea in ≥10% of patients
- Antibiotics
- Chemotherapeutic agents
- Cholinergic drugs
- Cisapride (off the market)
- Digoxin
- Immunosuppressives agents
- Metoclopramide
- Orlistat (lipase inhibitor)
- Osmotic laxatives
- Poorly or non-absorbable carbohydrates
- Selective serotonin reuptake inhibitors
- Ticlopidine

Drugs that induce inflammatory diarrhoea.

Etanercept
Ipilimumab
Isotretinoin
Mycophenolate mofetil
NSAIDs
Oral contraceptives
Sodium phosphate
Auranofin
Penicillamine
Oral cyclosporin
Chemotherapeutic agents
Mercaptopurine
Rituximab
HMG-CoA reductase inhibitors
Simvastatin
Lovastatin
Pravastatin
Olmesartan
Antibiotics
NSAIDS
Carbamazepine
Ticlopidine
Flutamide
Selective serotonin receptor inhibitors
Paroxetine
Sertraline

Drugs that induce watery diarrhoea.

Secretory diarrhoea
Antiarrhythmics (Quinidine, Digoxin)
Amoxicillan-Clavulanate (Augmentin)
Chemotherapeutic agents
Metformin (Glucophage)
Calcitonin
Colchicine
NSAIDs
Misoprostol
Ticlopidine
Increased motility
Macrolides (e.g. Erythromycin)
Metoclopramide (Reglan)
Stimulant laxatives (e.g. Bisacodyl, senna)
Anthraquinones
Diphenylmethane derivatives (bisacodyl)
Oxyphenisatin – withdrawn for hepatotoxicity
Phenolphthalein – withdrawn for carcinogenicity
Ricinoleic acid (castor oil)
Sodium picosulfate – available outside U.S.
Sodium dioctyl sulfosuccinate (docusate)
Osmotic diarrhoea
Magnesium containing preparations (antacids, Laxatives)
Citrates
Phosphates
Sulfates
Sugar
Alcohols (Mannitol, Sorbitol, Xylitol)

Ref:

1. Baber KF, Anderson J, Puzanovova M, Walker LS. Rome II versus Rome III classification of functional gastrointestinal disorders in pediatric chronic abdominal pain. J Pediatr Gastroenterol Nutr 2008;47:299–302.
2. Gasbarrini A, Corazza GR, Gasbarrini G, Montalto M, Di Stefano M, Basilisco G, et al. Methodology and indications ofH2-breath testing in gastrointestinal diseases: the Rome consensus conference. Aliment Pharmacol Ther 2009;(29 Suppl 1):1–49.
3. Berni Canani R, Di Costanzo M, Troncone R. The optimal diagnostic workup for children with suspected food allergy. Nutrition 2011;27:983–7.
4. Best Practice & Research Clinical Gastroenterology 26 (2012) 649–661
5. Berni Canani R, Cirillo P, Bruzzese E, Graf M, Terrin G, Gaudiello G, et al. Nitric oxide production in rectal dialysate is a marker of disease activity and location in children with inflammatory bowel disease. Am J Gastroenterol 2002;97:1574–6.
6. Berni Canani R, Terrin G, Cirillo P, Castaldo G, Salvatore F, Cardillo G, et al. Butyrate as an effective treatment of congenital chloride diarrhea. Gastroenterology 2004;127:630–4.
7. Hahn S, Kim Y, Garner P. Reduced osmolarity oral rehydration solution for treating dehydration due to diarrhoea in children: systematic review. BMJ 2001;323(7304):81–5.
8. Gregorio GV, Gonzales ML, Dans LF, Martinez EG. Polymer-based oral rehydration solution for treating acute watery diarrhoea. Cochrane Database Syst Rev 2009;(2). CD006519
9. Labeling for oral and rectal over-the-counter drug products containing aspirin and nonaspirin salicylates; Reye's Syndrome warning. Final rule. Fed Regist 2003;68(74):18861–9.
10. Bernaola Aponte G, Bada Mancilla CA, Carreazo Pariasca NY, Rojas Galarza RA. Probiotics for treating persistent diarrhea in children. Cochrane Database Syst Rev 2010;(11). CD007401.
11. Gregersen T, Gronbaek H, Worsoe J, Schlageter V, Laurberg S, Krogh K. Effects of Sandostatin LAR on gastrointestinal motility in patients with neuroendocrine tumors. Scand J Gastroenterol 2011;46(7–8):895–902
12. Corbould A, Campbell J. Efficacy of octreotide but not long-acting somatostatin analogue for severe refractory diabetic diarrhoea. Diabet Med 2009;26(8):828–9.
13. Long RG, Adrian TE, Bloom SR. Somatostatin and the dumping syndrome. Br Med J (Clin Res Ed) 1985;290(6472):886–8.
14. Singh VV, Toskes PP. Small bowel bacterial overgrowth: presentation, diagnosis, and treatment. Curr Treat Options Gastroenterol 2004 Feb;7(1):19–28.
15. Farthing MJ. Tropical malabsorption. Semin Gastrointest Dis 2002 Oct;13(4):221–31
16. Morales M, Galvan E, Mery CM, Castro G, Uscanga LF, Robles-Diaz G. Exocrine pancreatic insufficiency in tropical sprue. Digestion 2001;63(1):30–4.
17. Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol 2007 Dec;31(12):1800–12.

18. Malamut G, Verkarre V, Suarez F, Viallard JF, Lascaux AS, Cosnes J, et al. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. Am J Gastroenterol Oct 2011;105(10):2262–75.