Approach to a neonate with congenital diarrhea

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Introduction:

- Congenital diarrheas and enteropathies (CODEs) are rare cause of devastating persistent and life-threatening intractable diarrhea in infants.
- Evaluation of CODEs is a lengthy process and infrequently leads to a clear diagnosis. Genomic analyses and the development of model systems have increased our understanding of CODE pathogenesis.
- Most CODEs display similar clinical presentation despite different outcomes. Endoscopic biopsies can reveal abnormalities in crypt -villous structure, enterocyte distribution and morphology or inflammatory activities.
- A genetic analysis has become a key component in the diagnostic approach, esp. whole genome sequencing helps in diagnosis.

Classification:

A. Clinically:

I. Diet induced diarrhea "***Osmotic diarrhea***"

II. Enterocyte-transport-related diarrhea "***Secretroy diarrhea***"

B. According to pathophysiology

I. Disorder of Epithelial Nutrient/ Electrolyte transport

II. Disorder of Epithelial Enzymes and Metabolism

III. Disorder of Epithelial Trafficking and Polarity

IV. Disorder of Enteroendocrine Cell Function

V. Immune dysregulation – associated Enteropathies

VI. Others like milk allergy, post infectious enteropathy etc

Evaluation:

History

- Antenatal history (Polyhydramnios, Dilated Bowel loops)
- Age of onset
- Nature of symptoms
- Extraintestinal manifestation
- Recurrent infection
- Nutrition & Diet history
- Family history
- Consanguinity +/-
- Ethnicity

Examination

- Full physical examination
- Growth parameters
- Dysmorphic features
- Skin rash/ Hyperpigmentation

Type of stool

- Watery
- Fatty
- Bloody

Steps in evaluation

A) First Evaluation

1. After history and examination, quantification of stool output other than urine output should be calculated.
2. Frequency and weight of stool to be noted.
3. 24 hours fasting to be done
4. To calculate and note the stool output
5. If diarrhea ceases or reduced more than 50% and Ion Gap is > 50 then it is Osmotic diarrhea.
6. If diarrhea persists and/ or Ion Gap < 50 then it is Secretory diarrhea
7. As per cause, further evaluation can be planned
8. In case of osmotic diarrhea, reduction of osmotic load (Lactose) will help

9. In case of secretory diarrhea, child should be started on TPN and further evaluation should be planned

B) Second Step in Evaluation – Laboratory tests

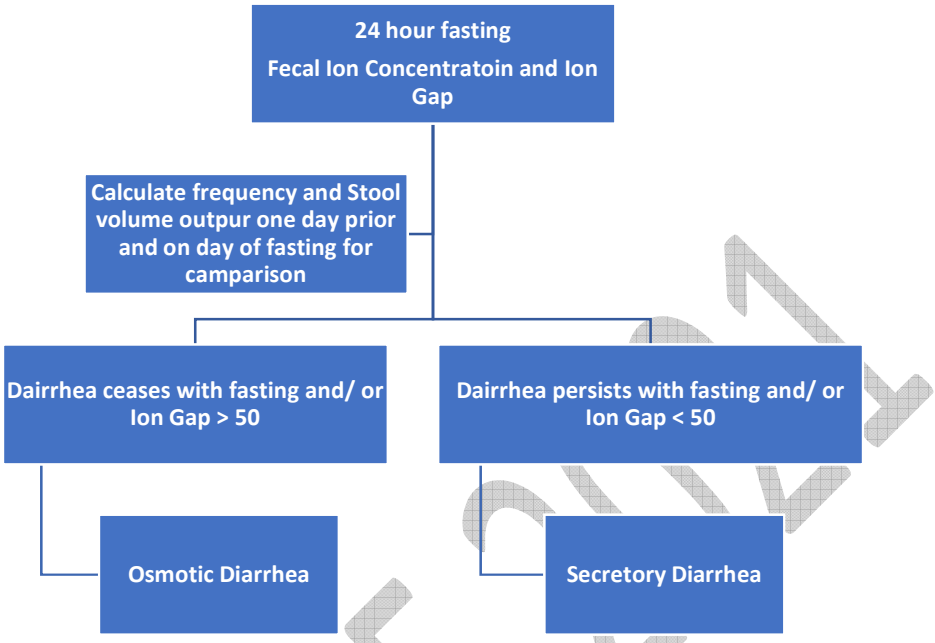

Fig. 1 Approach to broadly categorize the type of diarrhoea

Table. 1 Laboratory tests

Sr. No.	Lab test result	Diagnosis	Further test	Treatment
1	**Fecal pH< 5 and Reducing substance positive**	Lactose Intolerance/ Glcuose Galactose Malabsorption		Reduction in lactose load and lastly lactose free diet
2	**Hypoalbumine mia**	Intestinal biopsy showed dilated lymphatic		MCT based diet
		MVID/ Tufting Enteropathy		TPN +/- Small bowel transplant
		Autoimmmune inflammatory changes		Autoimmune enteropathy
3.	**Fecal Na > 145 mM/L**	Congenital sodium Diarrhea		ORS +/- TPN

4.	**Fecal Cl > 90 mM/L**	Congenital Chloride Diarrhea		ORS +/- TPN
5.	**TG < 10 mg/dl and Cholesterol < 40 mg/dl**	Abetalipoproteinemia/ Hypobetalipoproteinemia / Chylomicron Retentin Disease		MCT based diet + Vitamin ADEK
6	**Hyponatremia with Metabolic alkalosis**	Cystic Fibrosis		Pancreatic Enzyme Replacement
7	**Bloody stool**	Monogenic IBD/ PID		Immunosuppression +/- Bone Marrow Transplant
8	**CT scan showed fibrosed pancreas**	Scwachman Diamond Syndrome		

Clinical Presentation with Brief details as per classification discussed above

A) Disorder of Epitheliac Nutrient/ Electrolyte Transport

Sr. No.	Diagnosis	Clinical Feature	Mutation	Management
1.	**Congenital Chloride Diarrhea**	Polyhydramnios, Severe diarrhea at birth, Born with dilated fluid-filled bowel loops, pseudo-obstruction-like, volvulus,	SLC26A3	Hydration, Electrolyte supplementation, TPN,? Butyrate

		hypochloremic hypokalemic metabolic alkalosis, high fecal chloride level (>90mM/L)		
2	**Congenital Sodium Diarrhea**	Born with dilated fluid-filled bowel loops, pseudo-obstruction-like, volvulus, high fecal Na+, Metabolic acidosis GUCY2C risk of IBD	SLC9A3	Hydration, Nutrient, Electrolyte support, TPN
3	**Glucose-Galactose Malabsorption**	Diarrhea, Severe dehydration, Hypernatremia, Metabolic acidosis, Renal failure, Nephro-calcinosis	SLC5A1	Glucose/Galactose-free diet
4	**Primary Bile Acid Malabsorption**	Watery diarrhea and fat malabsorption	SLC10A2/ SLC51B	Bile acid sequestrants e.g., cholestyramine

B) <u>Disorder of Epithelial Enzymes and Metabolism</u>

a. Alteration in several important enzymes involved in both nutrient absorption as well as epithelial cell metabolism result in severe diarrhea
b. Defects in brush-border enzymes involved in carbohydrate digestion, such as lactase and sucrose-isomaltase, result in a diet-induced diarrhea
c. Onset after intake of carbohydrate-containing formula or food
d. Exhibit grossly normal intestinal biopsy
e. Loss of function mutation in DGAT1 – diarrhea, emesis, PLE, exudative enteropathy, growth failure, induced by enteral intake of lipids.
f. Management: Fat free diet, Cholestyramine, Pancreatic enzymes
g. Mutation in:
    i. Microsomal triglyceride transfer protein (MTTP) resulting in abetalipoproteinemia
    ii. Apolipoprotein B – hypobetalipoproteinemia, or chylomicron retention disease (SAR1B)

C) <u>Disorder of Epithelial Trafficking and Polarity</u>

1. Microvillous Inclusion Disease (MVID)

a. MVID present with severe watery diarrhea and dehydration
b. Microvillous inclusion on electron microscopy in 10% of duodenal enterocytes & villous atrophy
c. Require PN support for life
d. May benefit from liver/ intestinal transplantation if they develop PN-associated complications
e. More recently a non-PN-related phenotype with normal GGT cholestasis was described in patients MYO5B mutations

2. Congenital Tufting Enteropathy (CTE)

a. CTE present with watery, sodium-losing diarrhea in the first weeks of life
b. Mutations in then Epithelial cell adhesion molecule (EpCAM) cause typical form of CTE
c. Syndromic form SPINT2: anal and choanal atresia as well as ophthalmological signs (corneal erosions, optic nerve coloboma, and intermittent exotropia)
d. Intestinal biopsy showed villous atrophy, focal epithelial “Tufts”
e. Management by TPN and Small bowel transplant

3. **Tricho-hepatic-enteric Syndrome (Syndromic Diarrhea)**
    a. Mutations in the TTC37 gene in 60% of cases
    b. Remainder associated with SKIV2L mutation
    c. Multisystemic disease:
        i. Intrauterine growth restriction
        ii. Intractable diarrhea, FTT
        iii. Facial dysmorphism (prominent forehead and cheeks, broad nasal root and hypertelorism)
        iv. Hair abnormalities like wooly and easily removable, hyperkeratosis
        v. Immune disorder: abnormal T-cell function and antibody production
        vi. Liver abnormalities, Skin abnormalities like hyperpigmentation, congenital heart defect, Mental Retardation, Goiteretc
    d. Management by TPN and Immunoglobulin

D) <u>Disorder of Enteroendocrine Cell Function</u>

a. Mutation in NEUROG3, RFX6/ARX, PCSK1
b. Result in generalized mal-absorptive diarrhea
c. Associated with multiple endocrinopathies (IDDM, Hypothyroidism, DI, Adrenal Insufficiency)
d. Diet-induced diarrhea that is not specific to any single nutrient
e. Intestinal biopsies: normal crypt to villous ratio
f. Management: TPN for first several years of life
g. Diarrhea symptoms persist

E) <u>Immune Dysregulation-Associated Enteropathies</u>

a. Monogenic disorders cause dysregulation of the immune system and subsequently inflammation and enteropathy
b. Mutation in FOXP3, ICOS, IL10R, TRIM22, ARPC1B
c. Many of these disorders have been classifies as infantile-onset inflammatory bowel disease
d. Most of these diseases are curable with bone marrow transplantation

Summary:

- Congenital diarrheas cause life threatening intractable diarrhea in infants
- Lack of awareness of these disorders can result in complications and unnecessary surgical procedures
- Management of these patients requires a multidisciplinary team approach
- Genetic testing has become a key component in the diagnostic approach
- Understanding the pathophysiology will aid in future targeted therapeutics.
- Small bowel transplant is treatment and will be possible in India too.

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