

Role of Infection in Chronic Diarrhea

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Well-being of Children**



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Chronic Diarrhea

- **Defined as stool volume of more than 10 g/kg/day in toddlers/infants and**
- **Greater than 200 g/day in older children that lasts for 14 days or more. (nelson 20th ed:)**

Epidemiology

- Exact incidence of chronic diarrhea is not known in Pakistan
- Large-scale studies reported that the **Global prevalence ranges** from 3% - 20%, and the **Reported incidence** is around 3.2 episodes/child year
- In one study **regarding chronic diarrhea from India**, (n=137) children, reported **celiac disease in (26%)**, **parasitic infections in 9%** and **tuberculosis in 5%**.

Introduction

- **Chronic diarrhea in childhood is usually a product/ outcome of acute onset.**
- **Role of infections in chronic diarrhea is well-known: either be direct or indirect**
- **Organisms cause chronic diarrhea, mostly parasites, but certain bacteria and viruses can also be responsible for chronic diarrhea**

CHRONIC DIARRHEA

- **Immunosuppressive conditions**, either **congenital or acquired**, or
- **immuno-suppressive drugs** due to chronic autoimmune disease
- **Prolonged infection caused by usual organism of acute diarrhea** or
- By **unusual** organisms

CHRONIC DIARRHEA

- **Post infectious diarrhea** **despite clearance of organisms**, there is **delayed regeneration of intestinal villi** and consequently chronic diarrhea
- Sometime episode of **acute infectious diarrhea** **aggravate chronic autoimmune disease** [ulcerative colitis] and **causes prolong diarrhea**
- **Small intestinal bacterial overgrowth, tropical sprue** and **Whipple disease** are other examples of chronic diarrhea of infectious etiology

Infective agents

- **Parasites**

(e.g., *Giardia lamblia*, *Cryptosporidium*, *Cyclospora* and *microsporidia* [Small Intestine] and *Entamoeba histolytica* [colon])

- **Bacteria**

- (e.g., *Salmonella*, *Shigella*, *Campylobacter*, *Clostridium difficile*, *Aeromonas*, *Plesiomonas* ; *Mycobacterium Tuberculosis* and *E. coli*)

- **Viruses**

(e.g., norovirus, rotavirus)

or

- Unknown causes **thought to be infectious** (e.g., Brainerd diarrhea)

Parasites

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Giardia lamblia

- **Giardia is a world-wide distribution**
- **It can be found in 15–30% of stools in an endemic areas**
- **It causes chronic diarrhea and malabsorption**
- **Found in areas of low sanitation**
- **Transmission is via ingestion of contaminated water sources**

Giardia lamblia

- **Symptoms** include diarrhea, malaise, flatulence, foul smelling greasy stools, bloating/distention and, less commonly, nausea, anorexia and vomiting
- **Diagnosis** is via **fresh stool** microscopy of **wet** preparation or using **concentration** method
- Sensitivity and specificity of **detection Giardia antigen enzyme immunoassays** have a high specificity and sensitivity (>90%)
- **Treatment** : Metronidazole, Nitazoxanide

Cryptosporidium parvum

- It is distributed **globally with sporadic outbreaks** occurring in developed countries as well as endemic infections occurring in developing countries
- It is **a water and food borne** pathogen
- The illness causes prolonged diarrhea (4 to 6 weeks), there is usually no fever, **if diarrhea last for several months** then fatigue, flatulence, and abdominal pain can be associated
- Diagnosis is made by **stool examination.**

Cryptosporidium parvum

- It causes persistent and intractable diarrhea in patients **with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)** or other immuno-compromising diseases.
- Diagnosis is made by using a **modified acid-fast stain of preserved stool**
- **Immunoassay tests** have increased sensitivity over microscopy
- Cryptosporidium is associated with **a post-infection irritable bowel syndrome** that may occur in up to 40% of patients
- **Treatment** is Nitazoxanide

Entamoeba histolytica

- It causes both **diarrheal disease and invasive disease** such as liver abscesses
- It is supposed to **cause millions of infections and up to 100 000 deaths** in endemic areas
- Most of the time infection is **asymptomatic or low level disease** with a gradual onset of diarrhea with generalized abdominal tenderness

Entamoeba histolytica

- Fever is usually absent in amoebic disease
- Mucus and/or blood in stool may be present if it penetrates the wall of intestine and causes mucosal damage
- The **diagnosis** is usually made by **stool examination**, but **serology** can also be helpful
- **Colonoscopy** with **biopsy of the ulcers** may directly show the organisms
- **PCR** is an emerging tool
- **Treatment:** Metronidazole, tinidazole ± paromomycin

Cyclospora

- Cyclospora cayatenensis (also called “**blue-green algae**”) is distributed **worldwide**
- It also has been reported as **a cause of traveller’s diarrhea in Nepal**
- In the United States, Cyclospora **epidemics** have been associated **with imported raspberries (Guatemala) and basil (Thailand)**

Cyclospora

- Clinical presentation is watery diarrhea, abdominal cramps, fever, malaise, weight loss, as well as heartburn however can be asymptomatic
- Diarrhea can last up to 3 weeks and patients typically have 5–15 bowel motions per day,
- Human immunodeficiency virus patients typically have more severe disease, with increased weight loss and longer duration of diarrhea
- Diagnosis is by modified acid fast staining of fixed stool samples

Cystoisosporia

- Formerly known as *Isospora belli*, a cause of chronic, but **self-limited watery diarrhea** in individuals
- The **chronic diarrhea** is more common in patients with **immunosuppressed states**
- Although it is **more common in tropical and subtropical** areas, **it has been reported worldwide**
- Transmission is via the fecal-oral route
- The **oocysts passed** in the stool are immature, and will **become infective after being outside the host for several days**
- It is often associated with **eosinophilia**
- Oocysts can be detected in **acid-fast stained stools**.

Microsporidia

- **Both immune competent and immune suppressed individuals can be affected**
- The disease is **more severe in patients with immuno-suppression**
- It is more common **in tropical areas**
- Diagnosis is made by microscopic **stool examination**, or molecular tests such as **PCR**

Bacteria

IN

CHRONIC DIARRHEA

Yersinia Enterocolitica

- A gram negative cocco-bacillus which can cause **both acute and chronic infection**
- Affects the **terminal ileum and proximal colon**
- Transmission to humans is usually **through undercooked pork or contaminated water**
- Acute infection causes fever, diarrhea, occasionally bloody diarrhea, with right lower quadrant pain due to **terminal ileitis and mesenteric adenitis**;
- This presentation **can mimic Crohn's disease or appendicitis**
- **Terminal ileal findings during endoscopy** are edema, ulcers, and round or oval elevations of the mucosa

Yersinia enterocolitica

- Symptoms can last for several weeks, and the **organism can be shed in the stool for up to 3 months**
- Patients with **haemochromatosis** and those being treated with desferoxamine are **more susceptible to systemic infection and sepsis**
- **Post-infectious arthropathy** has also been described
- Organism is cultured with **cold enrichment media techniques**
- **Treatment** with a fluoroquinolone, doxycycline, or trimethoprim–sulfamethoxazole is effective

Aeromonas hydrophila

- It is a **heterotrophic gram negative rod** which is mostly associated with acute diarrhea, although **can cause chronic diarrhea on rare occasions**
- But can sometimes be **'bloody' diarrhea**;
- In developing countries, Aeromonas is commonly found in **drinking water and foods (seafood)**
- **Different strains appear to produce different toxins** including haemolytic, cytotoxic, and enterotoxic

Aeromonas hydrophila

- **Small bowel is affected** in approximately two thirds of cases, **but the right colon** can also be involved
- **Case reports:** as a cause of **chronic colitis** that mimicked **ulcerative colitis clinically and endoscopically**
- **Other case reports** suggest that it has **triggered the development of ulcerative colitis**, even after the infection had been cleared
- It is also associated with a number of **other infections**, including **cellulitis and aspiration pneumonia**

Plesiomonas shigelloides

- A gram-negative rod, found **in fresh water** and in **several animal hosts**
- It is associated with an **acute diarrheal syndrome**, which can **sometimes be bloody**, as well as abdominal pain and vomiting
- **Occasionally**, this can persist **as a chronic diarrhea**;
- A retrospective **study in Hong Kong** found **197** isolates of Plesiomonas on stool cultures between 1995 and 1998
- **5.4%** had diarrhea which lasted for over 2 weeks

Plesiomonas shigelloides

- Cases of **chronic colitis** *have been reported*
- **Diagnosis** is made by **stool culture**
- **Antibiotics can shorten the duration** of symptoms
- It is **uniformly resistant** to ampicillin, gentamicin, erythromycin, kanamycin, & streptomycin
- **Sensitive to** chloramphenicol, aminoglycosides, trimethoprim-sulfamethoxazole, fluoroquinolones, tetracycline, third-generation cephalosporins, and imipenem

Enterotoaggregative E. coli

- It has been recognized as a **common cause of travelers' diarrhea**
- Also a cause of **chronic diarrhea in malnourished hosts** in developing countries

Salmonella

- Found in sewage, river water and seawater, and certain foods
- The **attack rate** varies with age
- **Children younger than 1 year old** have the highest attack rate, **especially in the 3- to 5-month range**
- The commonest syndrome is gastroenteritis
- The usual **incubation period** is 6 to 48 hours, but it has been reported to be 12 days

Salmonella

- Initially the predominant symptoms are nausea and vomiting, followed by abdominal cramps and diarrhea
- **Mild watery diarrhea to severe dysentery.**
- Fever is present in 50%
- **Typically, symptoms last 3 to 4 days**
- Diagnosis is made by **stool culture** and **blood cultures** can be positive **because bactremia occurs in 5% to 10% of cases**
- After acute infection, **a chronic carrier state of non-typhoidal *Salmonella* occurs at a rate of about 4 per 1000**

Recurrent Clostridium difficile Infection

- An anaerobic, spore-forming gram positive rod
- **Most common nosocomial infection of the gastrointestinal tract**
- **It is commonly a result of Antibiotic associated diarrhea [AAD]**
- The **toxins** cause diarrhea and **pseudo-membranes** can form in severe cases;
- Frequent outbreaks occur in hospitals and long term care facilities
- **Mortality ranges from 1.2% to 6.9%**
- **ELISA** testing for toxin A and B; sensitivity of 60–80% and specificity of 91–99%
- **PCR-based** testing increases the sensitivity

Recurrent *Clostridium difficile* Infection

- **Treatment** : Most commonly, Metronidazole or vancomycin for 10 days
- **Recurrences** can be as high as 40–60% after one recurrence [more difficult to treat]
- **Other treatments** includes Rifaximin, Fidaxomicin, Probiotics, and immune globulin [all with limited success]
- **Fecal microbiota transplant**: in some cases of refractory or recurrent disease, with a success rate of 92%

Mycobacterium tuberculosis

- **Tuberculosis enterocolitis** generally presents with nonspecific symptoms, including weight loss, fever, diarrhea, blood in the stool, and abdominal pain
- **Cecum and ileocaecal valve** are most commonly affected
- **The pathogenesis of TB enterocolitis:**
 - Ingestion of contaminated food,
 - Haematogenous, [active pulmonary TB]
 - Swallowing of infected sputum, and
 - Contiguous spread from adjacent organs

Mycobacterium tuberculosis

- Endoscopically and histologically, **tuberculosis can mimic Crohn's disease**, so a high index of suspicion is necessary
- **PCR testing** of colonic tissue can confirm the diagnosis
- Tuberculosis generally presents with **transversely oriented ulcerations** with sharp margins and inflamed adjacent tissue
- **A patulous or destroyed ileocaecal valve** is highly suggestive of tuberculosis
- **Treatment:** Anti-tuberculous therapy

Viruses

- **Viral infections of the GI tract are usually self-limited.**
- **Rota virus causes acute diarrhea and may lead to post-enteritis syndrome.**
- **Cytomegalovirus can cause chronic colitis or enteritis in immune suppressed individuals.**

Fungi

- **Uncommon in immuno-competent.**
- **Reports of Candida overgrowth causing chronic diarrhea that responded to anti-fungal therapy**

Immunodeficiency disorders & Chronic diarrhea caused by infections

1- Congenital immunodeficiency disorders

- Selective immunoglobulin A deficiency
- Severe combined immunodeficiency
- Agammaglobulinemia
- X-linked hypogammaglobulinemia
- Wiskott-Aldrich syndrome
- Common variable immunodeficiency disease
- Chronic granulomatous disease

2- Acquired immune deficiency

- HIV infection
- Immunosuppressive therapy and post–bone marrow transplantation

Post-Enteritis Syndrome

- Some proportion of diarrheal illnesses fail to resolve and persist for longer
- **There is a history of an acute attack of diarrhea +**
- **Evidence of ill-health and/or dehydration+**
- **Effort at identification of a specific pathogen**
- **History of poorly formed and frequent stools persisting after a period of two weeks**

POST ENTERITIS SYNDROME

- **Attention to rehydration,**
- **Appropriate screening and treatment of systemic infections and**
- **Enteral / Age appropriate Nutrition,**
- **Rehabilitation with easily digestible diets**
- **Reduction of “Lactose” load**
- **Reduction of drinks with high osmolar load**
- **Administration of Zinc and Vitamin A**
- **Avoidance of over use/ abuse of ANTIBIOTICS.**

Small bowel bacterial overgrowth

- Clinical conditions that alter the gastric pH or small bowel motility;
- **Partial bowel obstruction,**
- Diverticula,
- **Intestinal failure,**
- Intestinal duplications,
- **Diabetes mellitus,**
- Idiopathic intestinal pseudo-obstruction syndrome, and
- **Scleroderma**
- Prematurity,
- **Immuno-deficiency,** and
- Malnutrition

Small bowel bacterial overgrowth

- **Diagnosis:**
- **Culturing small bowel aspirate ($>10^5$ CFU/mL) or**
- **Lactulose hydrogen breath test**
- **Steatorrhea [bacterial de-conjugation of bile salts]**
- **Vitamin B12 malabsorption, and increased Folate level**
- **Microvillus brush border damage with resultant Malabsorption**
- **Stupor, Neurologic dysfunction, and Shock [d-lactic acidosis]**

Small bowel bacterial overgrowth

- **Treatment of underlying causes:** Partial obstruction.
- **The oral administration of antibiotics is the mainstay of therapy**
- **Initial treatment** - 2-4 wk of Metronidazole can provide relief for many months
- **Cycling of antibiotics:** Azithromycin, Trimethoprim-sulfamethoxazole, Ciprofloxacin, and Metronidazole may be required

Tropheryma whipplei

- A gram positive, period acid-Schiff-positive actinobacteria, a **causative organism of Whipple's disease**
- **Difficult to culture;**
- Detected with **PAS staining of biopsy** specimens and **PCR**
- **The clinical manifestations:**
- Migratory Arthralgias, cognitive dysfunction, abdominal pain, **and chronic diarrhea** , weight loss, massive Adenopathy, Ascites , and cognitive dysfunction
- **Endoscopically:** includes oedema, brown discolouration of the mucosa, erythematous spots, and flattened villi

Tropheryma whipplei

- **Treatment: prolonged course of antibiotic therapy**
- **The only randomized prospective treatment trial suggests a 14 day intravenous induction therapy with meropenem or ceftriaxone in combination with an oral continuation therapy with TMP-SMX for 12 months as a treatment modality for this disease**
- **Relapsing disease** is often treated with alternative antibiotics

Presumed Infectious Diarrhea: **Brainerd diarrhea**

- Several outbreaks of acute diarrhea, felt to be infectious, and some develop chronic diarrhea
- **The most well-known outbreak occurred in Brainerd, Minnesota between December 1983 and July 1984**
- One hundred twenty two people were affected, many of whom **had consumed raw milk from a single dairy**
- The diarrhea was characterized as acute in onset **without major systemic symptoms**, as well as a **failure to respond to antimicrobial medications**

TROPICAL SPRUE

- Natives and expatriates of **certain tropical regions** can present with a diffuse lesion of the small intestinal mucosa—tropical sprue
- **Endemic** regions include **South India, the Philippines, and** some islands in the **Caribbean**
- **The etiology is unclear:** it follows outbreaks of acute diarrheal disease **and improves with antibiotic therapy,** an infectious etiology is suspected
- **The incidence is decreasing worldwide: possibly due to common use of antibiotics**

TROPICAL SPRUE

- **Diagnosis** is made by **small bowel biopsy**, which shows villous flattening, crypt hyperplasia, and a chronic inflammatory cell infiltrate of the lamina propria with adjacent lipid accumulation in the surface epithelium
- **Treatment** Nutritional supplementation, including **supplementation of folate and vitamin B12**
- **To prevent recurrence**, 6 mo of therapy with oral folic acid (5 mg) **and** tetracycline or sulfonamides is recommended
- Relapses occur in 10-20% of patients

Post-infectious irritable bowel syndrome

- Acute gastroenteritis followed by typical symptoms of irritable bowel syndrome (IBS);
- **The incidence can vary from 2 to 10%**
- Risk factors: Female gender, and severer acute illness
- **Over a two year period over 50% resolve**
- Post-infectious IBS can occur after bacterial, parasitic or viral gastroenteritis
- **Diarrhea is more common than constipation or alternating diarrhea and constipation**

Conclusion-I

- **Infections** are **an uncommon** cause of chronic diarrhea
- They should be **suspected in high risk individuals** (patients who are **immune-compromised** or individuals with **history of travel to the endemic areas**)
- **Clinical evaluation**, including appropriate stool and blood tests should be able to identify the etiology in most cases
- Bacterial **stool culture** for persistent diarrhea to **exclude pathogens** such as Yersinia, Aeromonas & Plesiomonas.

CONCLUSION- II

- **Parasites should be excluded** as a cause of chronic diarrhea; this should include **3 stool exams for ova and parasites**, as well as **Stool Giardia and Cryptosporidia antigen testing**
- **GI infections** (both bacterial, Parasitic and viral) can result **in post-infectious IBS (PI-IBS)**.
- **Brainerd diarrhea, tropical sprue, and possibly other chronic diarrheas: Infection as Etiology.... Implicated?! ... uncommon entities**

CONCLUSION- III

- **PREVENTION IS BETTER THEN CURE:**
- **HAND WASHING**
- **SAFE WATER**
- **SANITATION**
- **FOOD SAFETY**
- **COOK IT, PEEL IT OR LEAVE IT.**

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PREVENTION IS BETTER THEN CURE

BREAST FEEDING

GOOD NUTRITION

WASH strategy

MICRONUTRIENTS

**[VITAMIN A &
ZINC SULFATE]**

VACCINATION

**[DPT/ MEASLES/
PNEUMOCOCCAL/ Hib
Rota virus]**



Thank You

GREETINGS
WITH
COMMITMENT
FROM ALL THE
FRIENDS OF
CHILDREN:

IQBAL MEMON
KARACHI
PAKISTAN

