Role of Infection in Chronic Diarrhea

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Special Interests: Peds GI, Liver & Nutrition; Child survival, Immunization; Awareness about Prevention of Childhood diseases.
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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
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.
Microsporidiosis

- 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 coco-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
Enteroaggregative 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 (>10⁵ 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 actinomycobacteria, 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 whippelii

- **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-1

• **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 Cryptosporidium 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