Diarrhea

Prof. G. Zuliani

The horror of cholera in Bangladesh in the early 1970's. Can we now control and prevent it? See pages five and six.

Definitions

- Diarrhea: excessive loss of fluids and electrolytes in the stools with increase in liquidity and frequency (>3 times/day)
- Dysentery: diarrhea with ***blood and mucus***, rectal tenesmus, abdominal pain, and fever
- Pseudodiarrhea/hyperdefecation: increased stool frequency (more than 3 times daily) with a normal daily stool weight of less than 2-300 g
- Encopresis: involuntary "fecal soiling" in adults and children who have usually already been toilet trained

Diarrhea

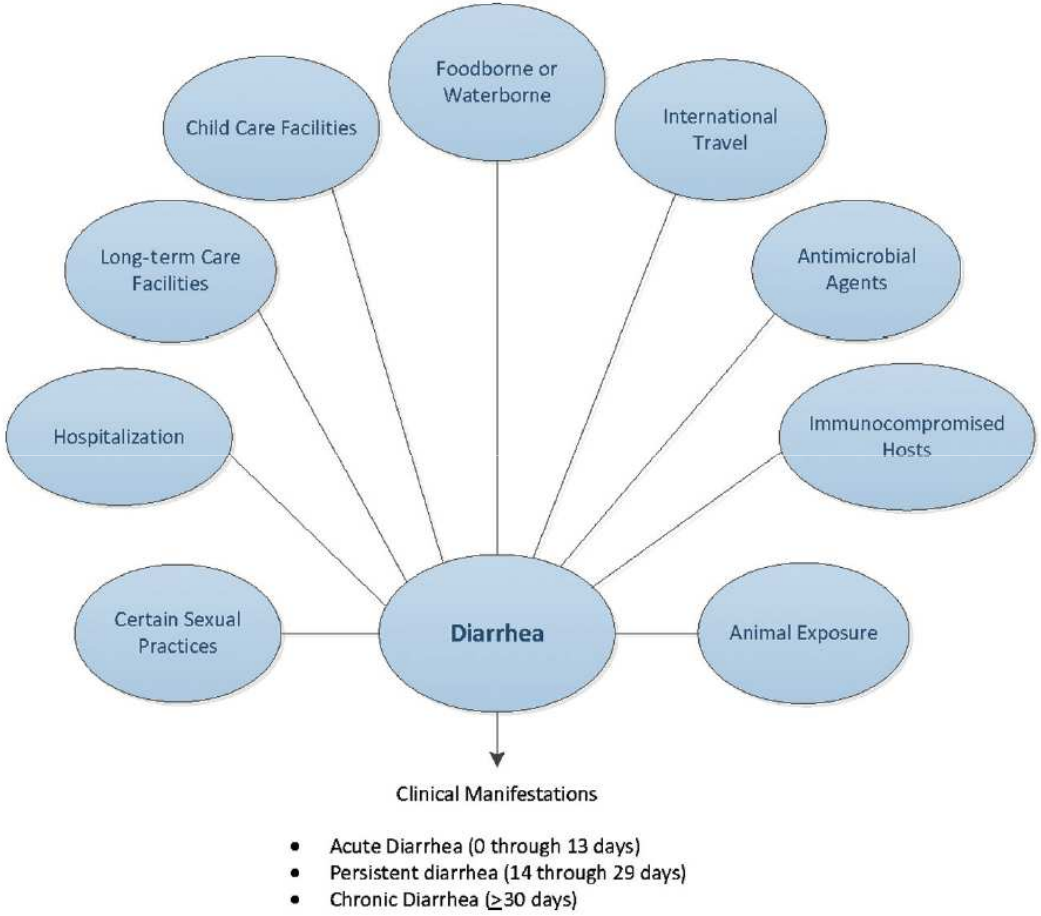


Figure 1. Considerations when evaluating people with infectious diarrhea. Modified from Long SS, Pickering LK, Pober CG, eds. Principles and Practice of Pediatric Infectious Diseases, 4th ed. New York: Elsevier Saunders, 2012.

Definitions

Acute diarrhea	•Presence of three or more loose, watery stools within 24-hours
Dysentery	•Bloody diarrhea, visible blood and mucous present
Persistent diarrhea	•Episodes of diarrhea lasting more than 14 days

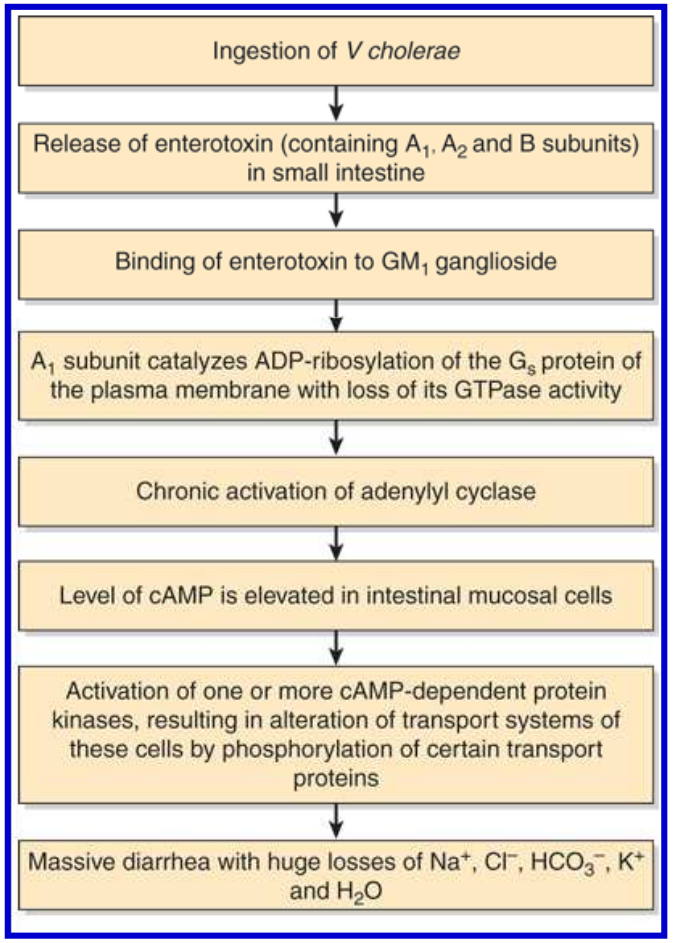
Four mechanisms for diarrhea

- Disturbed intestinal solute transport, water movement across intestinal wall:

1. Secretory
2. Osmotic
3. Dysmotility
4. Inflammatory

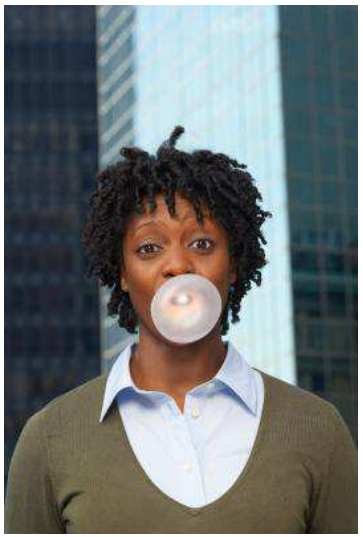
1. Secretory Diarrhea

- Some agents bind to surface receptors increasing ***cAMP*** with increased water secretion
- Watery, large volume, normal osmolality
- Persists during fasting
- No stool leukocytes
- Examples: ***Cholera, toxigenic E.coli, Clostridium difficile,*** cryptosporidium, ***carcinoid, VIPoma***



2. Osmotic Diarrhea

- Occurs after ingesting a poorly absorbed solutes
- Stools are of less volume, acidic, with high osmolality
- Stops with fasting (!)
- No stool leukocytes
- Examples: ***lactase deficiency***, glucose-galactose malabsorption, excess of sugar alcohols, ***lactulose, laxative abuse,***



3. Motility Diarrhea

- Increased motility:
  - **Irritable bowel syndrome (IBS)**
  - **Infections**
  - **Thyrotoxicosis**
  - Excess of Gastro-Colic reflex
  - Post vagotomy
- Decreased motility:
  - Stasis: bacterial overgrowth
  - Pseudo-obstruction, blind loop

4. Inflammatory

- Acute inflammation decreases the mucosal surface area and/or the colonic reabsorption.
- Blood and leukocytes in the stool
- Infectious gastroenteritis
- Dysentery

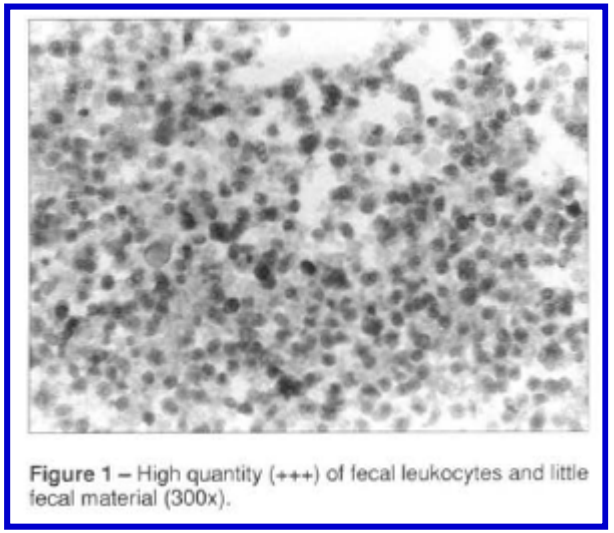


Figure 1 – High quantity (+++) of fecal leukocytes and little fecal material (300x).

1. Acute Diarrhea

Table **1** Epidemiology of acute diarrhea: developed versus developing countries.

Per year	Estimated episodes of acute diarrhea	Hospitalizations	Deaths
United States	375 million — 1.4 episodes per person per year	900 000 total	6000 total
	> 1.5 million child outpatient visits	200 000 children	300 children
Worldwide	1.5 billion episodes		1.5–2 million children < 5 y
	In developing countries, children < 3 y have 3 episodes per year		

Acute Diarrhea

- **Traveler's diarrhea**
- Infections: - Non-inflammatory
  - Inflammatory: GI + Systemic
- Other medical disease: Acute diverticulitis, superior mesenteric arterial/venous thrombosis, Ischemic bowel disease (IBD)
- Drugs: Virtually all medications:
  - **magnesium or phosphate-containing antacids or supplements, antiarrhythmics, digitalis, broad-spectrum antibiotics, antineoplastics, antihypertensives, bile acids, cholinergic agents (Ache-I), laxatives, NSAIDs, potassium supplements, omega 3 fatty acids, and prostaglandins.**
  - **Medicinal elixirs contain high amounts of sorbitol, which can have a cathartic effect on the bowel (eg. acetaminophen, theophylline, and cimetidine - not listed)**
- Immunocompromised and food allergy

Medications and toxins associated with diarrhea

- **Antibiotics**
- Antiretroviral agents
- Antineoplastic agents
- Anti-inflammatory agents (**NSAIDs**, 5-ASA)
- Antiarrhythmics (including **digitalis**)
- Antihypertensives (β blockers)
- Oral hypoglycemics (metformin, **acarbose**)
- **Antacids (magnesium-containing)**
- **Acid-reducing agents (H2 blockers, PPIs)**
- **Colchicine**
- **Cholinergic agents** (for dementia: donepezil, rivastigmine)
- Prostaglandin analogs (misoprostol)
- **Theophylline**
- Vitamin and mineral supplements
- **Herbal products (OTC)**

Medically Important Diarrhea

- Inflammatory, bloody diarrhea
- With severe volume depletion
- With high fever
- With sever abdominal pain
- Duration > 3 days
- In an impaired host
- Community outbreak

Gastroenteritis

- The most common cause of acute diarrhea in all age groups.
- Clinical manifestations depend on the *organism* and the *host response* to infection.
- A presumptive diagnosis can be made from *epidemiological clues*, good history and physical examination, *laboratory investigations* (not required always)

Etiology of Gastroenteritis

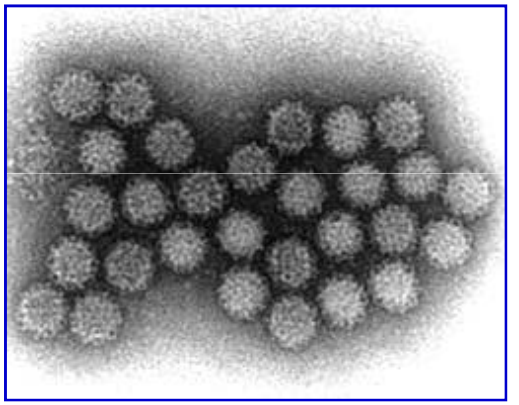
- Non-inflammatory:
  - *Enterotoxin production*
  - *Villus destruction*
  - *Direct adherence to surface*
- Inflammatory:
  - *Direct invasion*
  - *Cytotoxins*

Bacterial enteropathogens

- Non-inflammatory:
  - Enteropathogenic E.coli
  - Vibrio cholerae
- Inflammatory:
  - Salmonella, shigella, yersinia enterocolitica aeromonas, campylobacter jejuni, clostridium difficile, entero-invasive E. coli, shiga toxin producing E. coli.

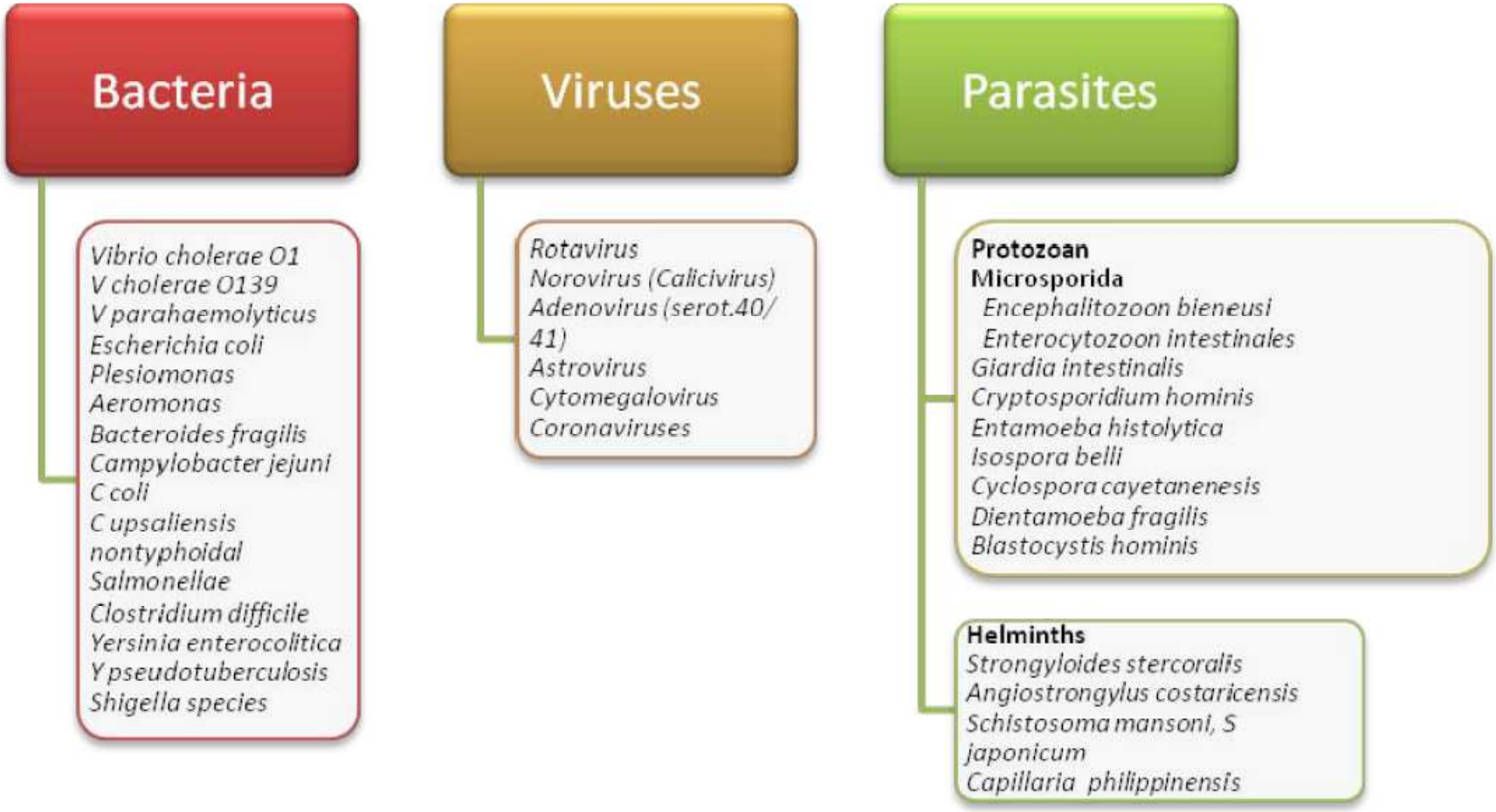
Viral enteropathogens

- Norovirus (hospital, nursing home)
- Rotavirus (children)
- Enteric adenoviruses
- Astrovirus
- Norwalk agent-like virus



Parasitic enteropathogens

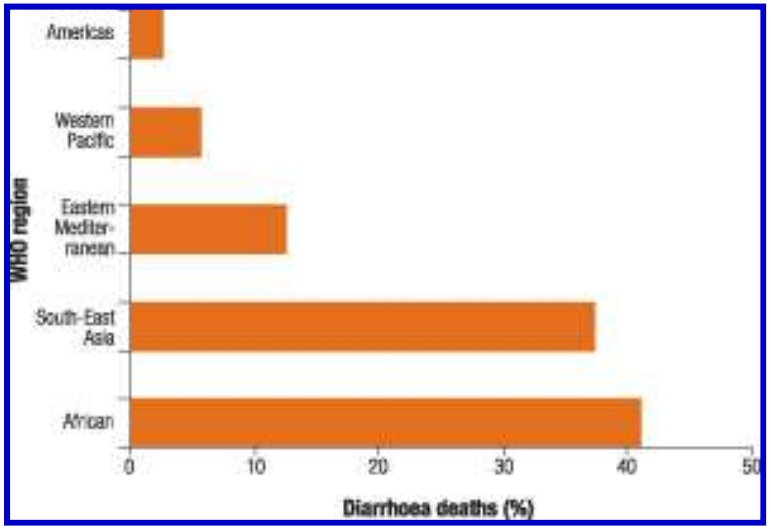
- G. lamblia
- Entamoeba histolytica
- Strongyloides stercoralis
- Cryptosporedium
- Cyclospora and isospora


Bacteria
Vibrio cholerae O1
V cholerae O139
V parahaemolyticus
Escherichia coli
Plesiomonas
Aeromonas
Bacteroides fragilis
Campylobacter jejuni
C coli
C upsaliensis
nontyphoidal
Salmonellae
Clostridium difficile
Yersinia enterocolitica
Y pseudotuberculosis
Shigella species
Viruses
Rotavirus
Norovirus (Calicivirus)
Adenovirus (serot.40/
41)
Astrovirus
Cytomegalovirus
Coronaviruses
Parasites
Protozoan
Microsporida
Encephalitozoon bieneusi
Enterocytozoon intestinales
Giardia intestinalis
Cryptosporidium hominis
Entamoeba histolytica
Isospora belli
Cyclospora cayetanenesis
Dientamoeba fragilis
Blastocystis hominis
Helminths
Strongyloides stercoralis
Angiostrongylus costaricensis
Schistosoma mansoni, S
japonicum
Capillaria philippinensis

Epidemiology of Gastroenteritis

- Major cause of mortality and morbidity in children world wide

- Transmission:
  - person-to-person
  - fecal-oral route
  - water and food borne



High risk groups

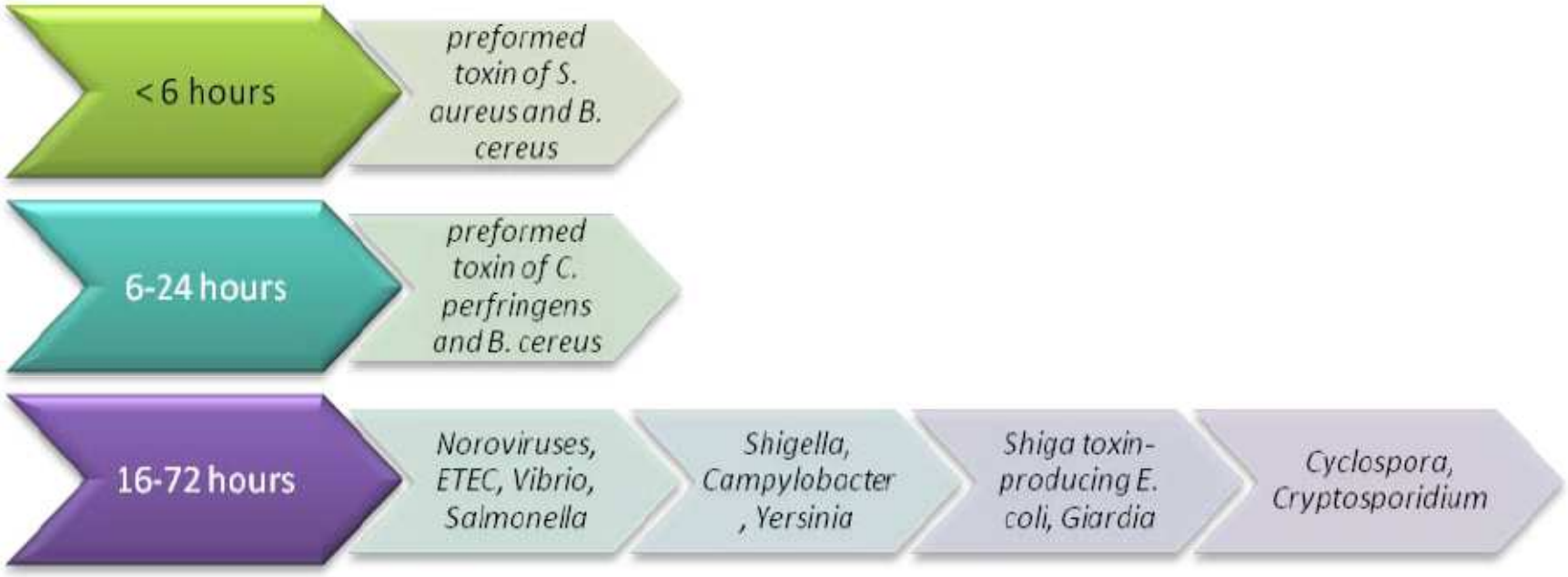
- ***Young age groups***
- Lack of breast feeding
- Exposure to unsanitary conditions
- Attendance to child care centers
- Poor maternal education
- ***Immune deficient individuals***
- Measles
- ***Malnutrition***
- Travel to endemic areas

General approach

- Clinical assessment: Historical points:
  - Diarrhea:
    - duration & severity
    - stool consistency
    - mucous & blood
  - Associated symptoms:
    - GI
    - Fever
    - Neurological Symptoms
    - Others
  - Risk factors
  - Social and family history

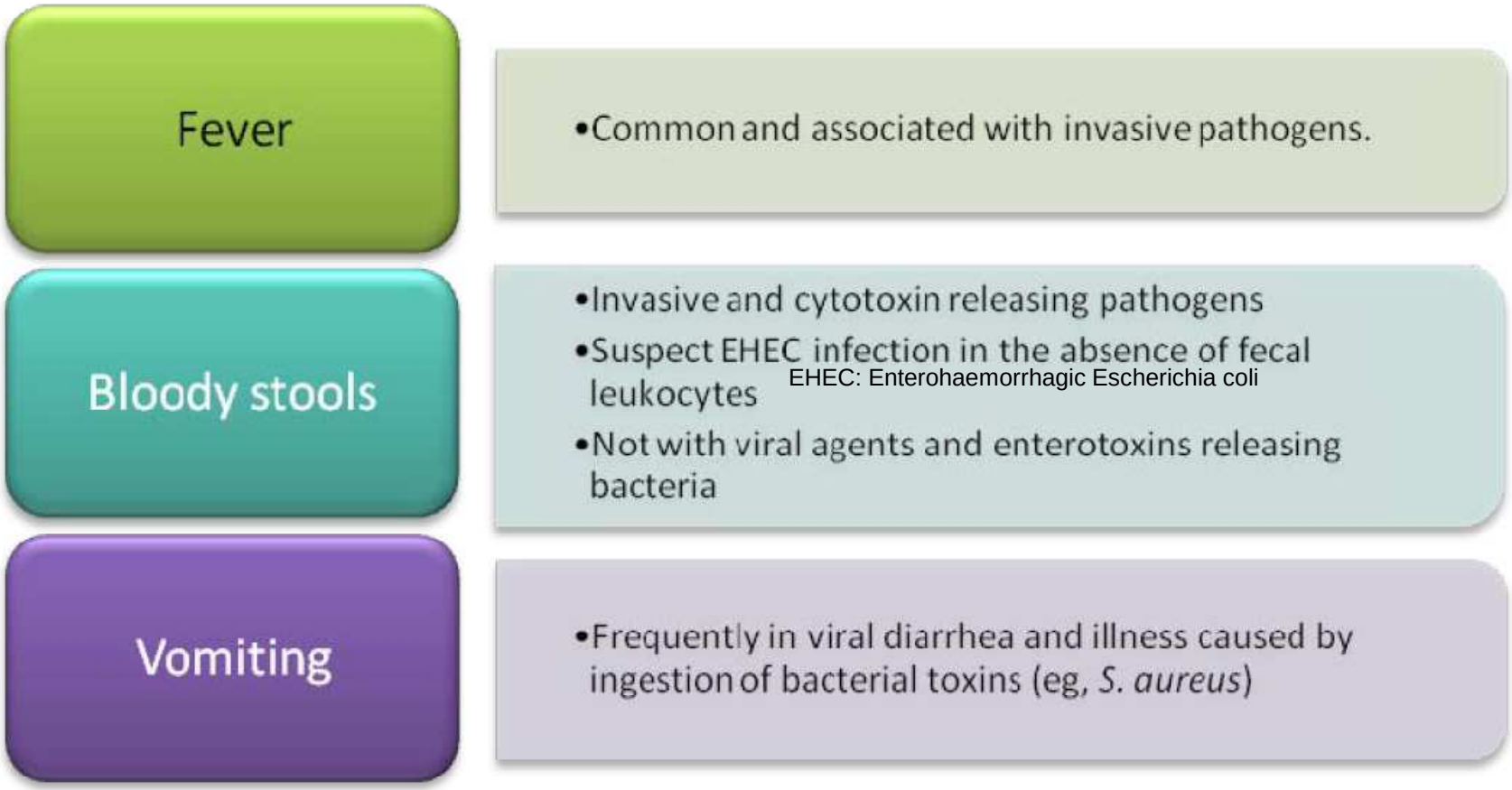
Risk factors and history

Incubation periods



The incubation period and likely causes of diarrhea.

Clinics



EHEC: Enterohaemorrhagic Escherichia coli

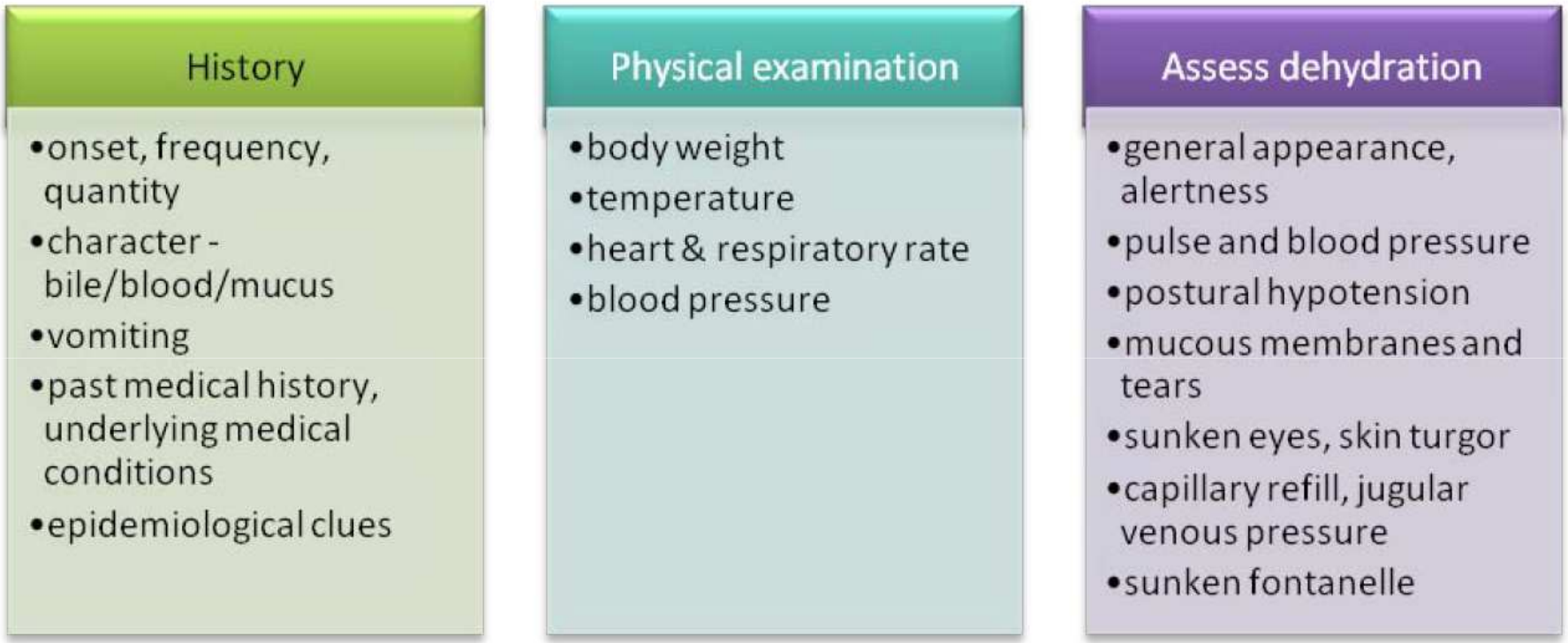
Clinical features of infection with selected diarrheal pathogens.

Clinical features	Pathogens											
	Shigella	*Salmonella*	*Campylobacter*	*Yersinia*	*Norovirus*	*Vibrio*	*Cyclospora*	*Cryptosporidium*	*Giardia*	*Entamoeba histolytica*	*Clostridium difficile*	Shiga toxin–producing *E. coli* (including O157:H7)
Abdominal pain						V	V	V		O	O	
Fever					V	V	V	V		O	O	A
Fecal evidence of inflammation				O		V		O		V		N
Vomiting and/or nausea		O	O	O		V	O	O	O	V		O
Heme-positive stool	V	V	V	O		V					O	
Bloody stool	O	O	O	O		V				V	O	

Key: common: O = occurs, V= variable; not common: A= atypical, N= often not.

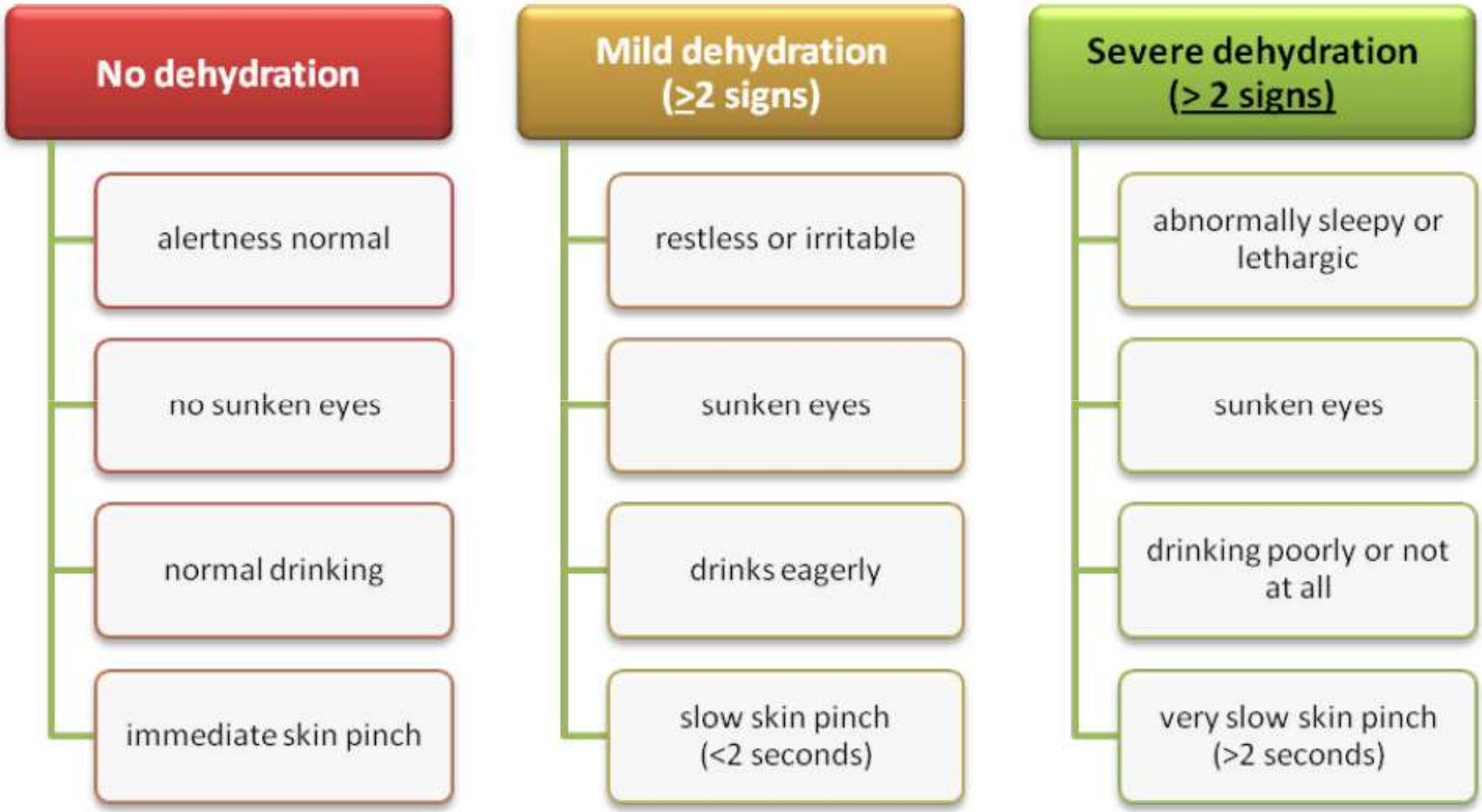
Clinical assessment

- Physical examination:
  - General appearance
  - Dehydration status
    - ***Mild***
    - ***Moderate***
    - ***Severe***
  - Systemic Examination
  - Extra-intestinal manifestations



Evaluation of the acute diarrhea patient.

Dehydration



Extraintestinal manifestations

- ***Reactive arthritis:*** salmonella, shigella, yersinia, campylobacter, c. difficile
- ***Glomerulonephritis***: shigella, campylobacter, yersinia
- ***Hemolytic anemia:*** yersinia, campylobacter
- ***Hemolytic Uremic Syndrome:*** shigella, e. coli
- IgA nephropathy: campylobacter
- Guillain-Barre Syndrome: campylobacter
- Erythema nodosum: yersinia, campylobacter, salmonella

Diagnostic Methods

- **Stool cultures :**
  - **Routine**: salmonella, shigella, yersinia, campylobacter

- **Toxin assays: C. difficile, E. coli**
- Special stains: aeromonas, cryptosporidium
- Duodenal aspirate and Biopsy: giardia, isospora, cryptosporidium.

- **ELISA**
- Colonoscopy and Sigmoidoscopy

1

Perform initial assessment

- Dehydration
- Duration (>1 day)
- Inflammation (indicated by fever, bloody stool, tenesmus)

2

Stratify subsequent management

- Epidemiological clues: food, antibiotics, sexual activity, travel, day-care attendance, other ilness, outbreaks, season
- Clinical clues: bloody diarrhea, abdominal pain, dysentery, wasting, fecal inflammation

3

Consider antimicrobial therapy for specific pathogens

4

Provide symptomatic treatment

- Rehydration
- Treatment of symptoms (if necessary consider bismuth subsalicylate or loperamide if diarrhea is not inflammatory or bloody)

5

Obtain fecal specimen for analysis

- If severe, bloody, inflammatory, or persistent diarrhea or if outbreak suspected

6

Report to public health authorities

- In outbreaks save culture plates and isolates; freeze fecal and food or water specimens at -70°C
- Notifiable in the USA: cholera, cryptosporidiosis, giardiasis, salmonellosis, shigellosis, and inf. with shiga toxin prod. *E.coli*

The approach in adults with acute diarrhea.

World Gastroenterology Organisation practice guideline:
Acute diarrhea

Even with the application of all available laboratory studies, 20-40% of all acute infectious diarrhea remain undiagnosed

Management

- Fluids & electrolytes & refeeding:
  - ***Treating dehydration is the corner-stone in managing diarrhea.***
  - Infants and olders are more susceptible to dehydration
  - Oral rehydration therapy
  - Home remedies
  - Feeding

Oral rehydration solution (ORS) constituents

	mmol/L
Sodium	75
Chloride	65
Glucose, anhydrous	75
Potassium	20
Citrate	10
Total osmolarity	245

Home made ORS recipe

Preparing a 1 (one) litre oral rehydration solution [ORS] using Salt, Sugar and Water at Home'

Ingredients:

- one level teaspoon of salt
- eight level teaspoons of sugar
- one litre of clean drinking or boiled water and then cooled
- 5 cupfuls (each cup about 200 ml.)

5.3 Diet

The practice of withholding food for > 4 hours is inappropriate. Food should be started 4 hours after starting ORT or intravenous fluid. The notes below apply to adults and children unless age is specified.

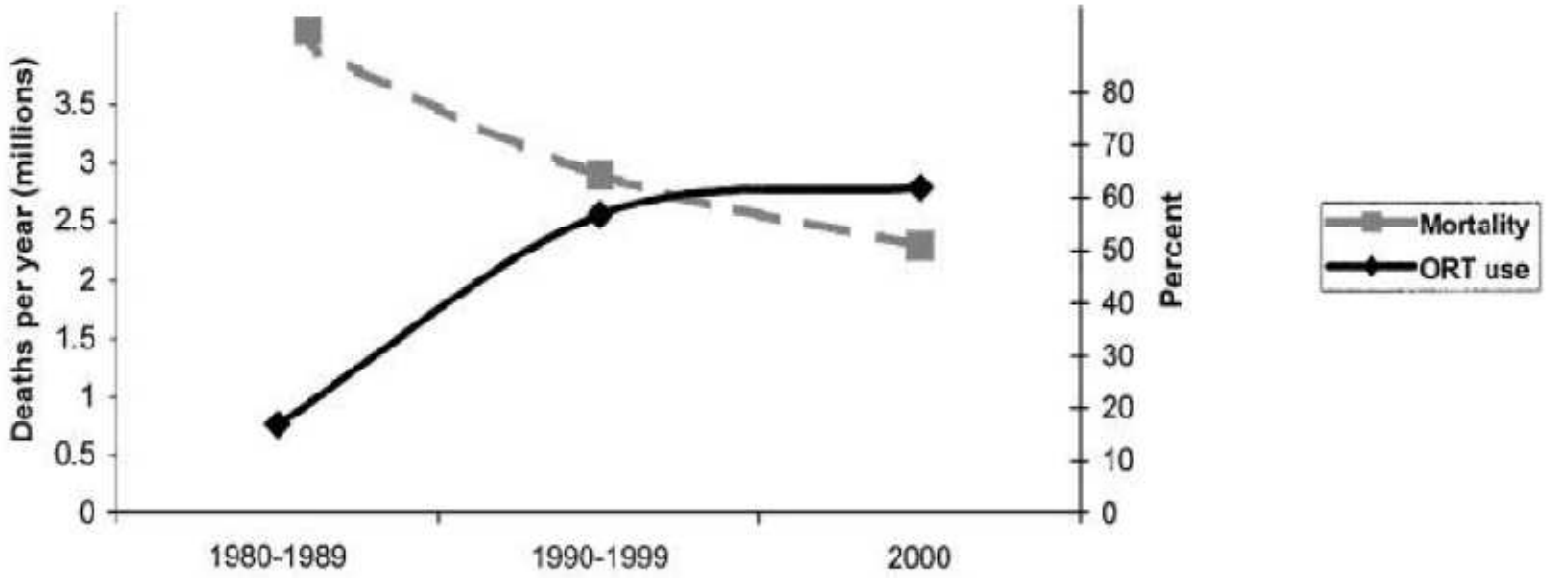
Give:

- An age-appropriate diet — regardless of the fluid used for ORT/maintenance
- Infants require more frequent breastfeedings or bottle feedings — special formulas or dilutions unnecessary
- Older children should be given appropriately more fluids
- Frequent, small meals throughout the day (six meals/day)
- Energy and micronutrient-rich foods (grains, meats, fruits, and vegetables)
- Increasing energy intake as tolerated following the diarrheal episode

Avoid:

- Canned fruit juices — these are hyperosmolar and can aggravate diarrhea.

Rapporto idratazione - mortalità



Inverse association between coverage rates of oral rehydration solution (ORS) use and rates of mortality from diarrhea in various countries.

VIEWPOINT

Oral Rehydration Therapy for Diarrheal Diseases
A 50-Year Perspective

Roger I. Glass, MD, PhD
Fogarty International Center, National Institutes of Health, Bethesda, Maryland.

Barbara J. Stoll, MD
McGovern School of Medicine, UTHealth, Houston, Texas.

On August 17, 1968, 50 years ago, a report from Bangladesh described the successful use of an oral rehydration solution (ORS) to treat patients hospitalized in shock from cholera gravis.[1] Untreated, severe cholera resulted in high mortality (approaching 40%) from dehydration and shock, but research in the 1940s demonstrated that mortality could be reduced with intravenous (IV) fluids used for both rehydration and maintenance therapy.[2] In settings in which IVs were unavailable, ORS was a "miracle" solution for treatment and survival. The trial was based on years of basic research on the physiology of glucose-mediated sodium transport in the gut to enhance the absorption of fluids and electrolytes and demonstrated that oral rehydration therapy (ORT) promoted positive water and electrolyte balance even during severe diarrhea.

Treatment

- Most cases of acute diarrhea are *self-limited*, and specific therapy is not necessary
- ***Preventing dehydration and restoring fluid losses IV*** with glucose-containing electrolyte solutions
- Oral intake should be encouraged to minimize the risk of dehydration
- ***The misconception that the bowel needs to be at rest or that oral intake will worsen the diarrheal illness should be abandoned.***
- Avoid ***milk*** and ***other lactose-containing products, caffeine***-containing products

Specific therapy

World Gastroenterology Organisation practice guideline:
Acute diarrhea

Antimicrobial agents for the treatment of specific causes of diarrhea.

Specific therapy

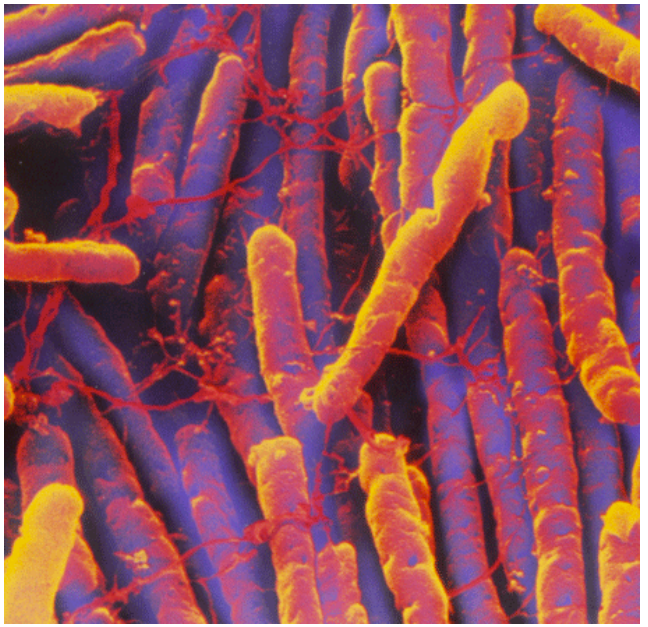
Antimotility:

- Loperamide is the agent of choice for adults (4–6 mg/day; 2–4 mg /day for children > 8 y).
  — Should be used mostly for mild to moderate traveler's diarrhea (without clinical signs of invasive diarrhea).
  — Inhibits intestinal peristalsis and has mild antisecretory properties.
  — Should be avoided in bloody or suspected inflammatory diarrhea (febrile patients).
  — Significant abdominal pain also suggests inflammatory diarrhea (this is a contraindication for loperamide use).
  — Loperamide is not recommended for use in children < 2 y.

Antisecretory agents:

- Bismuth subsalicylate can alleviate stool output in children or symptoms of diarrhea, nausea, and abdominal pain in traveler's diarrhea.
- Racecadotril is an enkephalinase inhibitor (nonopiate) with antisecretory activity, and is now licensed in many countries in the world for use in children. It has been found useful in children with diarrhea, but not in adults with cholera.

Clostridium Difficile Diarrhea

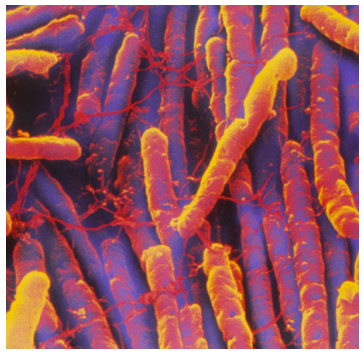


Clostridium Difficile Diarrhea

- Transmission:
  - Carried in GIT of 3% of general population
  - Up to 30% of hospitalized patients become colonized
  - Fecal-Oral Route (?)
  - *Hands of hospital personnel may be important intermediary …*

Clostridium Difficile Diarrhea

- Pathogenesis:
  - Antibiotics suppress drug sensitive normal intestinal flora
  - *C. difficile* multiplies in the GIT
  - Produces: Exotoxin A and Exotoxin B



Clostridium Difficile Diarrhea

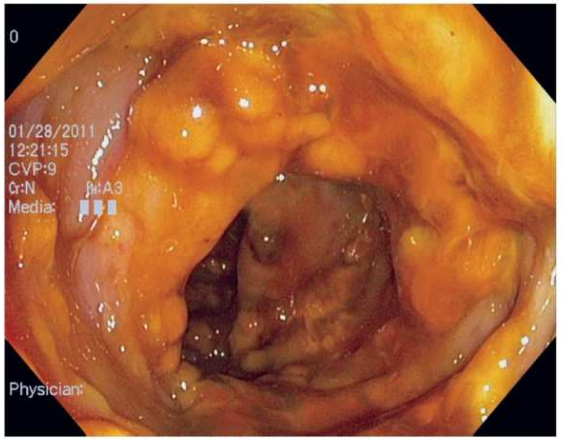
- Exotoxin A (enterotoxin):
  - mechanism of action unknown
  - causes outpouring of fluid and thus a watery diarrhea
- Exotoxin B (cytotoxin):
  - damages colonic mucosa leading to pseudo-membrane formation
  - mechanism via ADP-ribosylation of Rho
  - this causes depolymerization of actin in the cytoskeleton

Severe disease

- Usually, profuse diarrhea; however, in some cases there is little or no diarrhea because of involvement of the cecum and right colon or because of ileus
- Usually severe abdominal pain
- High fever and appearance of toxic effects
- Volume depletion
- Marked leukocytosis
- Peritoneal signs
- Fecal leukocytes
- Radiographic findings can include paralytic ileus, dilated colon (and even toxic megacolon), "thumbprinting" on abdominal plain films, and diffusely thickened or edematous colonic mucosa
- Endoscopy may demonstrate adherent yellow plaques that vary in diameter and in some cases, may coalesce to cover large areas of the mucosa*

Clostridium Difficile Diarrhea

- Clinical S/Sx:
  - **History of antibiotic use (especially PCN or Cephalosporin or Chinolones)**
  - Acute onset of diarrhea
  - Pseudo-membranes *(yellow-white plaques)* on colonic mucosa
  - Non blood
  - **Toxic Megacolon may occur**
  - **Death may occur**



Clostridium Difficile Diarrhea

- Diagnosis:
  - Pseudo-membranes on sigmoidoscopy
  - Presence of exotoxin B in cell cultures → cell death and Inhibition of cytotoxicity by specific antibody (routinely used)
  - ***ELISA for exotoxins A & B***
  - ***Stool Culture***

Clostridium Difficile Diarrhea

- **Treatment:**

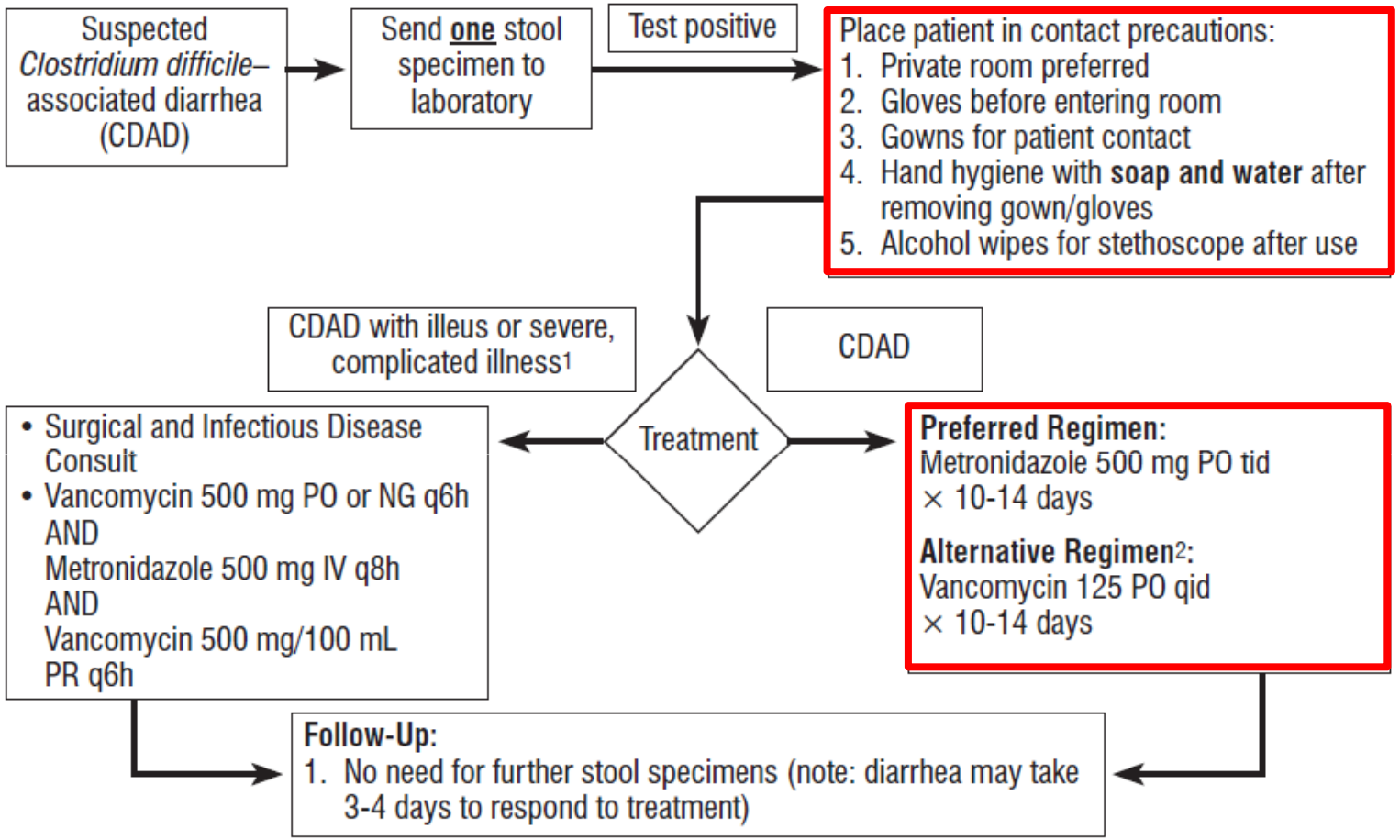
  Metronidazole (if mild)

  - **500 mg x 3 /die PO, else IV (1-2 weeks)**

  Vancomycin (if severe)

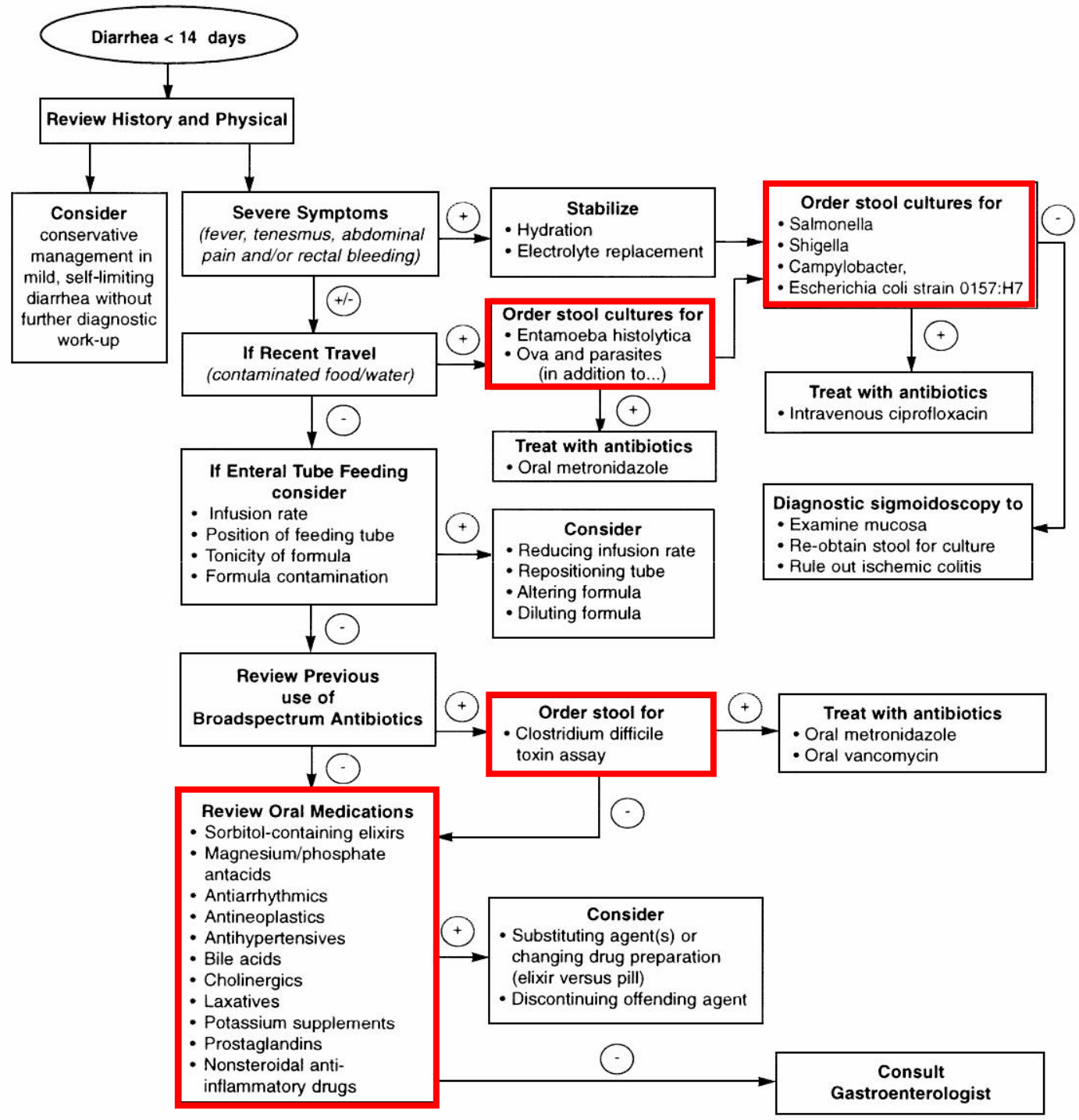
  - **125 mg PO / 6 hrs**
  - **Restrict its use due to antibiotic resistance**

Guidelines for Management of *Clostridium difficile* Toxin-Positive Diarrhea



1 Severe, complicated illness defined as hypotension, shock, or illeus.

2 Consider vancomycin if metronidazole intolerant, failing to respond to metronidazole (ie, failure to improve after 3 to 4 days of therapy), or severe disease defined as WBC ≥15,000 or serum creatinine >1.5 × baseline.


Diarrhea < 14 days
Review History and Physical
Consider conservative management in mild, self-limiting diarrhea without further diagnostic work-up
Severe Symptoms (fever, tenesmus, abdominal pain and/or rectal bleeding)
+
Stabilize
• Hydration
• Electrolyte replacement
Order stool cultures for
• Salmonella
• Shigella
• Campylobacter,
• Escherichia coli strain 0157:H7
-
+/-
If Recent Travel (contaminated food/water)
+
Order stool cultures for
• Entamoeba histolytica
• Ova and parasites (in addition to...)
+
Treat with antibiotics
• Intravenous ciprofloxacin
+
Treat with antibiotics
• Oral metronidazole
-
If Enteral Tube Feeding consider
• Infusion rate
• Position of feeding tube
• Tonicity of formula
• Formula contamination
+
Consider
• Reducing infusion rate
• Repositioning tube
• Altering formula
• Diluting formula
Diagnostic sigmoidoscopy to
• Examine mucosa
• Re-obtain stool for culture
• Rule out ischemic colitis
-
Review Previous use of Broadspectrum Antibiotics
+
Order stool for
• Clostridium difficile toxin assay
+
Treat with antibiotics
• Oral metronidazole
• Oral vancomycin
-
-
Review Oral Medications
• Sorbitol-containing elixirs
• Magnesium/phosphate antacids
• Antiarrhythmics
• Antineoplastics
• Antihypertensives
• Bile acids
• Cholinergics
• Laxatives
• Potassium supplements
• Prostaglandins
• Nonsteroidal anti-inflammatory drugs
+
Consider
• Substituting agent(s) or changing drug preparation (elixir versus pill)
• Discontinuing offending agent
-
Consult Gastroenterologist

2. Chronic Diarrhea

1: Is it "Chronic"? 2: Is it "Diarrhea"?

- ***Four week cut-off:*** Most acute (infectious) diarrheas would have resolved before 4 weeks
- ***Increased frequency of stool (>3/day) is hallmark***
- Most patients consider increased liquidity as essential feature
- Stool weight >200 g/day (not absolute criterion)

- ***Fecal incontinence needs to be excluded and managed as incontinence …***

Chronic Diarrhea

Summary

- Chronic diarrhoea may be defined as the abnormal passage of three or more loose or liquid stools per day for more than four weeks and/or a daily stool weight greater than 200 g/day.
- A clinical definition of chronic diarrhoea based on symptom reporting alone will lead to an overlap with functional bowel disorders such as irritable bowel syndrome.

GUIDELINES

Guidelines for the investigation of chronic diarrhoea, 2nd edition

P D Thomas, A Forbes, J Green, P Howdle, R Long, R Playford, M Sheridan, R Stevens, R Valori, J Walters, G M Addison, P Hill, G Brydon

Table 1 Causes of chronic diarrhoea by mechanism

Colonic
Colonic neoplasia
Ulcerative and Crohn's colitis
Microscopic colitis
Small bowel
Coeliac disease
Crohn's disease
Other small bowel enteropathies (for example, Whipple's disease, tropical sprue, amyloid, intestinal lymphangiectasia)
Bile acid malabsorption
Disaccharidase deficiency
Small bowel bacterial overgrowth
Mesenteric ischaemia
Radiation enteritis
Lymphoma
Giardiasis (and other chronic infection)
Pancreatic
Chronic pancreatitis
Pancreatic carcinoma
Cystic fibrosis
Endocrine
Hyperthyroidism
Diabetes
Hypoparathyroidism
Addison's disease
Hormone secreting tumours (VIPoma, gastrinoma, carcinoid)
Other
Factitious diarrhoea
"Surgical" causes (e.g. small bowel resections, internal fistulae)
Drugs
Alcohol
Autonomic neuropathy

Guidelines for the investigation of chronic diarrhoea, 2nd edition

P D Thomas, A Forbes, J Green, P Howdle, R Long, R Playford, M Sheridan, R Stevens, R Valori, J Walters, G M Addison, P Hill, G Brydon

Supplementary Table 3. Differential Diagnosis of Chronic Diarrhea by Stool Characteristics[6]

- Watery diarrhea
  - Osmotic diarrhea
    - Carbohydrate malabsorption
    - Osmotic laxatives (eg, Mg^{++}, PO_4^{-3}, SO_4^{-2})
  - Secretory diarrhea
    - Bacterial toxins
    - Bile acid malabsorption
    - IBD (some cases)
      - Crohn's disease
      - Microscopic colitis
        - Collagenous colitis
    - Lymphocytic colitis
    - Medications and toxins
    - Disordered motility
      - Diabetic autonomic neuropathy
      - IBS
      - Postsympathectomy diarrhea
      - Postvagotomy diarrhea
    - Endocrinopathies
      - Addison's disease
      - Neuroendocrine tumors
      - Hyperthyroidism
      - Mastocytosis
      - Medullary carcinoma of the thyroid
    - Idiopathic secretory diarrhea (epidemic and sporadic)
    - Stimulant laxative abuse
    - Neoplasia
      - Colon carcinoma
      - Lymphoma
      - Villous adenoma
    - Vasculitis
- Inflammatory diarrhea
  - Diverticulitis
  - Infectious diseases
  - Invasive bacterial infections (eg, tuberculosis, yersinosis)
  - Invasive parasitic infections (eg, amebiasis, strongyloidiasis)
  - Pseudomembranous colitis
  - Ulcerating viral infections (eg, cytomegalovirus, herpes simplex virus)
  - IBD (most cases)
    - Crohn's disease
    - Ulcerative colitis
    - Ulcerative jejunoileitis
    - Microscopic colitis (some cases)
  - Ischemic colitis
  - Neoplasia
    - Colon cancer
    - Lymphoma
  - Radiation colitis
- Fatty diarrhea
  - Malabsorption syndromes
    - Mesenteric ischemia
    - Mucosal diseases (eg, CD, Whipple's disease)
    - SBS
    - SIBO
- Maldigestion
  - Inadequate luminal bile acid concentration
  - Pancreatic exocrine insufficiency

Clinical Gastroenterology and Hepatology 2017;15:182–193

PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Chronic Diarrhea: Diagnosis and Management

Lawrence R. Schiller,* Darrell S. Pardi,‡ and Joseph H. Sellin§

Practical approach

- History
- Physical examination
- Routine laboratory tests (CBC, albumin, ESR/CRP)
- Stool analysis
- Categorize:
  - Watery diarrhea → Secretory / Osmotic
  - Inflammatory diarrhea
  - Fatty diarrhea

Epidemiological and historical features	Implication
Onset: **Congenital** **Abrupt** **Gradual**	 Chloridorrhea Infections, idiopathic secretory diarrhea All other etiologies
Travel history **(exposure to contaminated water)**	Infectious diarrhea *Aeromonas, Plesiomonas* Giardiasis, Cryptosporidiosis
Weight loss	Malabsorption, pancreatic exocrine insufficiency, neoplasm
Dietary history	“Sugar-free” foods with sorbitol, mannitol, lactase deficiency, fructose intolerance
Previous treatments	Medications, radiation enteropathy, surgery (bowel, gallbladder), pseudomembranous colitis
Systemic illness	Hyperthyroidism, IBD, diabetes
Abdominal pain	Mesenteric vascular insufficiency, IBD, IBS
Excessive flatus/bloating	Carbohydrate malabsorption, small bowel bacterial overgrowth
Secondary gain - Fixation on body image	Laxative abuse
Institutionalized patients	Medication, *C. difficile* colitis, tube feeding, ischemia, fecal impaction with overflow diarrhea

Physical examination

Supplementary Table 1. Physical Findings of Interest in Chronic Diarrhea[88]

Findings	Potential implications
Orthostasis, hypotension	Dehydration, neuropathy
Muscle wasting, edema	Malnutrition
Urticaria pigmentosa, dermatographism	Mast cell disease (mastocytosis)
Pinch purpura, macroglossia	Amyloidosis
Hyperpigmentation	Addison's disease ←
Migratory necrotizing erythema	Glucagonoma
Flushing, heart murmur, wheezing	Carcinoid syndrome ←
Dermatitis herpetiformis	Celiac disease
Thyroid nodule, lymphadenopathy	Medullary carcinoma of the thyroid
Tremor, lid lag	Hyperthyroidism ←
Hepatomegaly	Endocrine tumor, amyloidosis
Arthritis	Inflammatory bowel disease, yersiniosis ←
Lymphadenopathy	HIV, lymphoma, cancer ←
Abdominal bruit	Chronic mesenteric ischemia
Anal sphincter weakness	Fecal incontinence

Clinical Gastroenterology and Hepatology 2017;15:182–193

PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Chronic Diarrhea: Diagnosis and Management

Lawrence R. Schiller,* Darrell S. Pardi,‡ and Joseph H. Sellin§

Supplementary Table 2. Epidemiologic Associations and Patient Characteristics[6]

- Travelers
  - Bacterial infection (mostly acute)
  - Protozoal infections (eg, amebiasis, giardiasis)
  - Tropical sprue
- Epidemics and outbreaks
  - Bacterial infection
  - Epidemic idiopathic secretory diarrhea (eg, Brainerd diarrhea)
  - Protozoal infection (eg, cryptosporidiosis)
  - Viral infection (eg, rotavirus)
- Diabetic patients
  - Altered motility (increased or decreased)
  - Associated diseases
    - CD
    - Pancreatic exocrine insufficiency
    - SIBO
  - Drugs (especially acarbose, metformin)
- Patients with acquired immunodeficiency syndrome
  - Drug side effects
  - Lymphoma
  - Opportunistic infections (eg, cryptosporidiosis, cytomegalovirus, herpesvirus, *Mycobacterium avium* complex)
- Institutionalized and hospitalized patients
  - *Clostridium difficile* infection
  - Drug side effects
  - Fecal impaction with overflow diarrhea
  - Ischemic colitis
  - Tube feeding

Clinical Gastroenterology and Hepatology 2017;15:182–193

Chronic Diarrhea: Diagnosis and Management

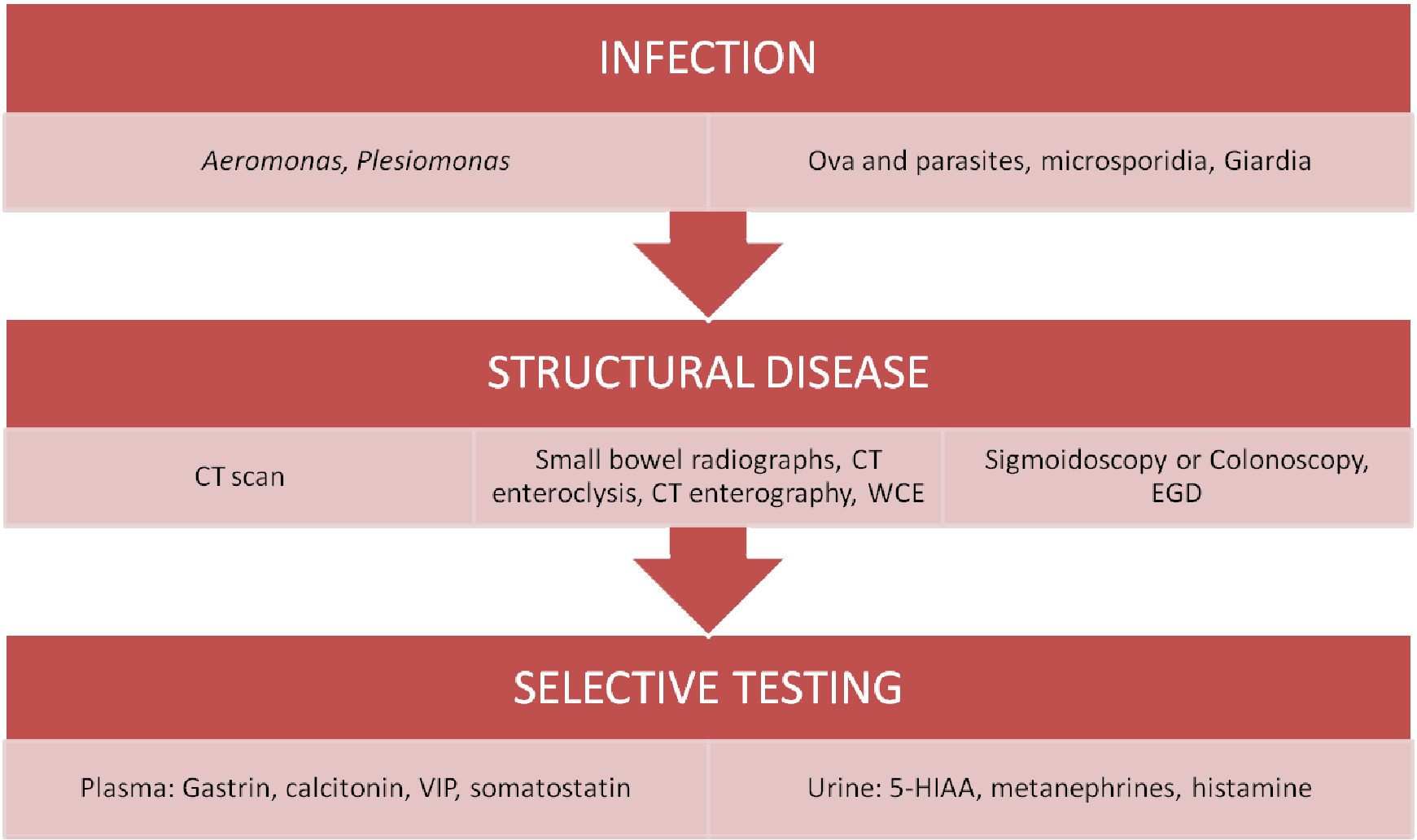
Lawrence R. Schiller,* Darrell S. Pardi,‡ and Joseph H. Sellin§

Stool Analysis

- Directed testing for confirmation based on clinical suspicion, or “broad net” cast in difficult cases
- Categorize diarrhea into 3 possible categories:
- ***Watery***
- ***Inflammatory***
- ***Fatty***
- Timed collection is best, spot tests on random stool sample more practical

- Occult blood
- White blood cells
- pH
- Sudan stain for fat
- Cultures
- Laxative screen
- Electrolytes, osmolality

Chronic Watery Secretory Diarrhea



Chronic Watery Osmotic Diarrhea

- **Magnesium ingestion:**

  - Stool concentration > 90 meq/L

  - **Intentional (*laxative abuse*)** or accidental (***antacids***, ***mineral supplements***)

- **Carbohydrate malabsorption:**

  - ***Lactase deficiency***

  - Fructose intolerance (high fructose corn syrup)

  - Sugar alcohols used as artificial sweeteners (sorbitol, mannitol)

Chronic Inflammatory Diarrhea

Possible diagnosis:

- **Infection (C. difficile, Amebiasis, CMV, TBC)**
- **Bowel Ischemia (not infarction)**
- **Radiation enteritis**
- **Neoplasia**
- **Irritable BD**

- Conditions may produce watery secretory diarrhea
- Diagnosis: Radiographic and endoscopic techniques

Chronic Fatty Diarrhea

- **Steatorrhea usually defined as loss of fat of > 7 g per 24 hours; however 7-14 g range has poor specificity**
- **Three major causes:**

  1. Pancreatic exocrine insufficiency (chronic pancreatitis)

  2. Mucosal diseases (celiac sprue, small bowel bacterial overgrowth)

  3. Lack of bile (advanced primary biliary cirrhosis)
- **Fecal fat concentration:** concentration > 9 g per 100 g suggestive of pancreatic or biliary cause
- Exclude mucosal disease first, then evaluate pancreas (CT, MRCP, EUS)

- In elderly, B12 deficiency, low albumin, previous partial gastrectomy, small bowel diverticula: *suspect small bowel bacterial overgrowth*
- Empiric trial of pancreatic enzyme supplementation

Empiric Therapy of Chronic Diarrhea

Supplementary Table 4. Therapies for Chronic Diarrhea

Drug class	Agent	Dose
Opiates (μ-opiate receptor selective)		
	Diphenoxylate	2.5–5 mg 4 times a day
	Loperamide	2–4 mg 4 times a day
	Codeine	15–60 mg 4 times a day
	Opium tincture	2–20 drops 4 times a day
	Morphine	2–20 mg 4 times a day
Adrenergic agonist		
	Clonidine	0.1–0.3 mg 3 times a day
Somatostatin analogue		
	Octreotide	50–250 μg 3 times a day (subcutaneously)
Bile acid–binding resin		
	Cholestyramine	4 g up to 4 times a day
	Colestipol	4 g up to 4 times a day
	Colesevelam	1875 mg up to twice a day
Fiber supplements		
	Calcium polycarbophil	5–10 g daily
	Psyllium	10–20 g daily

Clinical Gastroenterology and Hepatology 2017;15:182–193

PERSPECTIVES IN CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Chronic Diarrhea: Diagnosis and Management

Lawrence R. Schiller,* Darrell S. Pardi,‡ and Joseph H. Sellin§

Irritable Bowel Syndrome

- **Rome Criteria:**

  Recurrent abdominal pain or discomfort at least 3 days per month for the past 3 months, associated with 2 or more of:

  - Improvement with defecation

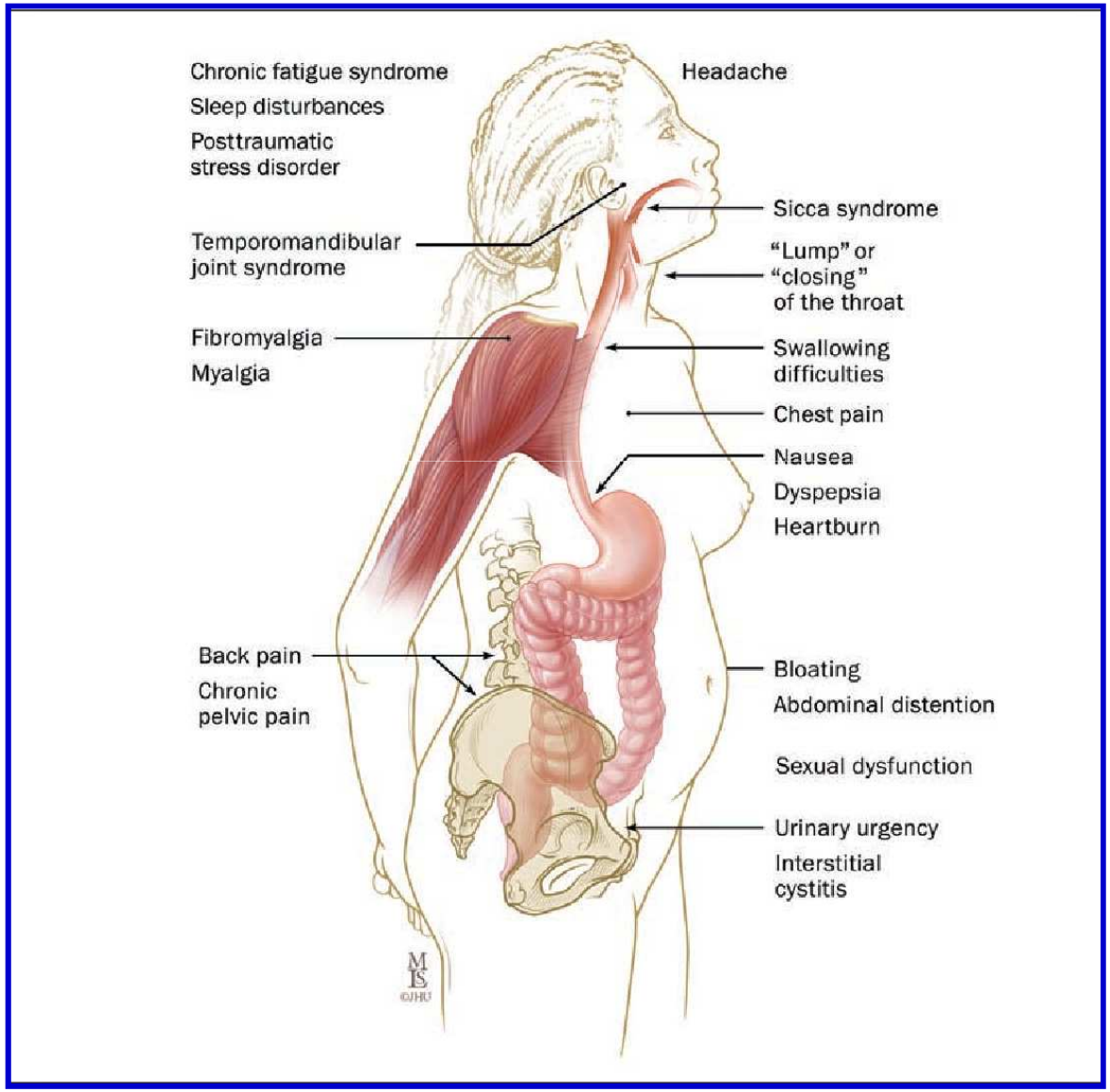
  - Onset associated with a change in frequency of stool

  - Onset associated with a change in form (appearance) of stool

- Periods of constipation are common
- Long history, passage of mucus, exacerbation by stress
- Diarrhea during waking hours, urgency
- Coexistence with other functional disorders

- **Against IBS:** Recent onset, nocturnal diarrhea, bleeding, weight loss, voluminous or greasy stool, abnormal blood tests
- Rule out celiac disease!

Irritable Bowel Syndrome



Summary and recommendations

- Screening blood tests should include full blood count, erythrocyte sedimentation rate, C reactive protein, urea and electrolytes, liver function tests, calcium, vitamin B12, folate, iron studies, and thyroid function. These have a high specificity but low sensitivity for the presence of organic disease (B).
- Although infectious diarrhoea is uncommon in immunocompetent patients from the developed world with chronic symptoms, stool cultures and stool microscopy should be performed (C).
- Coeliac disease is the most common small bowel enteropathy in Western populations. Patients with diarrhoea should be screened for this using serological tests (currently antiendomysium antibodies), which have a high sensitivity and specificity for the disease (A).
- Factitious diarrhoea becomes increasingly common in specialist referral practice, and screening for laxative abuse should be performed early in the course of investigation (B).

GUIDELINES

Guidelines for the investigation of chronic diarrhoea, 2nd edition

P D Thomas, A Forbes, J Green, P Howdle, R Long, R Playford, M Sheridan, R Stevens, R Valori, J Walters, G M Addison, P Hill, G Brydon

Table 3. Summary of Recommendations

1. Patients define diarrhea as loose stools, increased stool frequency, or urgency; physicians should note precisely what the patient means. (1b)
2. Chronic diarrhea is defined by duration of >4 weeks. (2b)
3. Consider comorbid symptoms and epidemiologic clues when constructing a differential diagnosis. (2c)
4. The Rome criteria provide a framework for the diagnosis of IBS and emphasize pain. Other etiologies should be sought when these criteria are not met. (1a)
5. Patients without alarm features who meet criteria for IBS should be treated without further testing. Those who do not respond should be evaluated further. (2b)
6. Specific dietary components may cause or aggravate chronic diarrhea. A careful dietary history is essential. (1a)
7. True food allergies are rare causes of chronic diarrhea in adults. (2b)
8. Many drugs cause diarrhea. Careful review of current medications is essential. (1a)
9. Radiation can cause chronic diarrhea, sometimes starting years after exposure. Clinicians should ask about a history of radiation therapy in these patients. (1a)
10. Patients with chronic diarrhea who have had abdominal surgery may require empiric therapy or diagnostic evaluation. (1a)
11. Testing should be done in the presence of alarm features, when the differential diagnosis can be effectively distinguished on the basis of test results, or when the differential diagnosis remains broad and initial testing will limit the number of additional tests needed. (2c)
12. For disorders without definitive diagnostic tests, therapeutic trials may be reasonable. (2c)
13. When the differential diagnosis is broad, stool testing to characterize the diarrhea can direct further evaluation more precisely. (2c)
14. Stool tests can be used to categorize diarrhea and should be considered when the diagnosis remains obscure after initial assessment. (2c)
15. Fecal lactoferrin or calprotectin can be used as surrogate measures for fecal leukocytes. (1b) Stool chymotrypsin and elastase may have some utility as screening tests for pancreatic insufficiency. (2b)
16. Routine blood tests may provide clues to etiology and fluid and electrolyte status. Other blood tests should be obtained only when demanded by the clinical presentation. (2c)
17. Because of the rarity of peptide-secreting tumors, measurement of circulating peptide levels should be reserved for very select patients. (1b)
18. Imaging studies are useful in some patients with steatorrhea and secretory or inflammatory diarrhea. (1b)
19. Lower gastrointestinal endoscopy with mucosal biopsy is valuable in inflammatory and secretory diarrheas. Colonoscopy has a greater yield than sigmoidoscopy, but multiple biopsies must be obtained from the right and left colon. Biopsy of normal-appearing terminal ileum is not recommended. (1a)
20. Upper endoscopy or enteroscopy with biopsies of the duodenum or jejunum should be done in patients with unexplained steatorrhea. The role of aspiration of enteric contents for quantitative bacterial culture is unclear. (2c)
21. Breath tests can assist with the diagnosis of carbohydrate malabsorption and SIBO. Sensitivity and specificity are variable; therefore, breath tests are not recommended without local validation. (2b)
22. Idiopathic BAM may be more frequent than previously appreciated. Until more specific tests for BAM become widely available, empiric therapy may be the only option available in many clinical settings. (2b)
23. Direct pancreatic function testing is not widely available. Indirect testing (eg, serum trypsin, fecal chymotrypsin, and fecal elastase assays) has limited sensitivity. Imaging and empiric trials of pancreatic enzyme replacement therapy may be the best available methods for assessing the role of pancreatic insufficiency in patients with steatorrhea. (2c)
24. Failure to make a diagnosis is more likely due to overlooking a common cause than missing a rare cause of chronic diarrhea. Physicians should repeat the history and physical examination and review studies already done before ordering additional tests. Repeating tests only should be done with cause. (2c)
25. Opiate antidiarrheals are a mainstay of symptomatic management when specific treatment is not possible. Dosing should be scheduled rather than as needed. (1b)

Clinical Gastroenterology and Hepatology 2017;15:182–193

Lawrence R. Schiller,* Darrell S. Pardi,‡ and Joseph H. Sellin§