

New Developments in the management of diarrhea



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Natalie Schellack

Faculty of Health Sciences

Department of Pharmacology

University of Pretoria

Email: natalie.schellack@up.ac.za



Overview

01 Overview of Diarrhoea

02 Pathophysiology

03 Current remedies

04 Future opportunities



Disclaimer

- I have no actual or potential conflict of interest in relation to this program/presentation.
- Thank you for Abbott to provide me with the opportunity to present my talk today, Abbott the views expressed are my own.



BY STAYSKAL FOR THE TAMPA TRIBUNE

Understanding the current landscape

Atlas

ATLAS was the Titan god who bore the sky aloft. He personified the quality of endurance - Atlas was also the god who instructed mankind in the art of astronomy, a tool which was used by sailors in navigation and farmers in measuring the seasons.

These roles were often combined and Atlas becomes the god who turns the heaven on their axis, causing the stars to revolve.



AFTER THE FLOODS: DIARRHEAL DISEASE THREATS LURK BEHIND NATURAL DISASTERS

Sep 22, 2017 | defeatDD



Protecting your wine collection during loadshedding and natural disasters

13 OCT 2023 SAVE | EMAIL | PRINT | PDF



In the latest annual report by master of wine, Tim Atkin, South Africa is currently producing the greatest wines in its history. The 2023 South Africa Special Report rates wines on a 100-point scale, with the top-rated red wine this year achieving a perfect score of 100 points. These exceptional wines are often produced in small quantities and are highly sought after, making them quite expensive.



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9260017/pdf/JNMA-60-246-225.pdf>

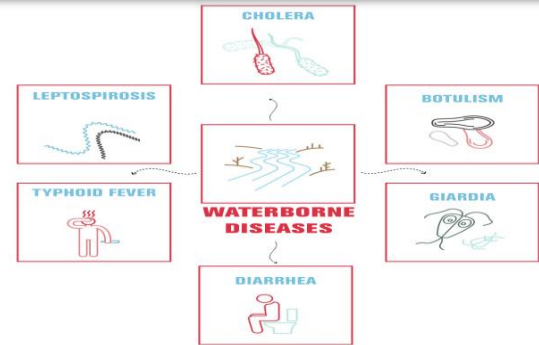
NATIONAL / 30 MAY 2023

South Africa joins countries grappling with cholera on the continent

By Mg Reporter



Diarrhoea



Major Water-Borne Diseases

Case Presentation

- A 35-year-old male patient presented to the outpatient department with **a two-day history of watery diarrhea**, abdominal cramps, and mild dehydration. The patient reported no significant medical history or recent travel. Upon physical examination, the patient appeared moderately dehydrated, with a heart rate of 100 beats per minute and blood pressure of 110/70 mmHg.
- Diagnostic Assessment:
- Stool analysis revealed the presence of **enterotoxigenic *Escherichia coli* (ETEC)** as the causative agent of the acute diarrhea. The patient's laboratory investigations showed no signs of electrolyte imbalances or other systemic complications.

Definition

- Diarrhoea is a common symptom that can range in severity from an **acute, self-limited annoyance** to a severe, life-threatening illness. Patients may use the term "diarrhea" to refer to increased frequency of bowel movements, increased stool liquidity, a sense of **fecal** urgency, or **fecal incontinence**

Diarrhea

Problem	Process	Characteristics of Stool	Timing	Associated Symptoms	Setting, Persons at Risk
Acute Diarrhea ¹⁹ (≤14 days) Secretory Infection (non-inflammatory)	Infection by viruses, preformed bacterial toxins (such as <i>S. aureus</i> , <i>B. cereus</i> , <i>C. perfringens</i> , toxigenic <i>E. coli</i> , <i>Vibrio cholerae</i>), cryptosporidium, <i>Giardia lamblia</i> , <i>rotavirus</i>	Watery, without blood, pus, or mucus	Duration of a few days, possibly longer. Lactase deficiency may lead to a longer course.	Nausea, vomiting, periumbilical cramping pain. Temperature normal or slightly elevated	Often travel, a common food source, or an epidemic
Inflammatory Infection	Colonization or invasion of intestinal mucosa (nontyphoid <i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i> , <i>Campylobacter</i> , enteropathic <i>E. coli</i> , <i>Entamoeba histolytica</i> , <i>C. difficile</i>)	Loose to watery, often with blood, pus, or mucus	An acute illness of varying duration	Lower abdominal cramping pain and often rectal urgency, tenesmus; fever	Travel, contaminated food or water. Frequent anal intercourse.
Drug-Induced Diarrhea	Action of many drugs, such as magnesium-containing antacids, antibiotics, antineoplastic agents, and laxatives	Loose to watery	Acute, recurrent, or chronic	Possibly nausea; usually little if any pain	Prescribed or over-the-counter medications
Chronic Diarrhea (≥30 days) Diarrheal Syndrome					
<ul style="list-style-type: none"> Irritable bowel syndrome^{17,18} Cancer of the sigmoid colon 	<p>Change in frequency and form of bowel movements without chemical or structural abnormality</p> <p>Partial obstruction by a malignant neoplasm</p>	<p>Loose; ~50% with mucus; small to moderate volume. Small, hard stools with constipation. May be mixed pattern.</p> <p>May be blood-streaked</p>	<p>Worse in the morning; rarely at night.</p> <p>Variable</p>	<p>Crampy lower abdominal pain, abdominal distention, flatulence, nausea. Urgency, pain relieved with defecation.</p> <p>Change in usual bowel habits, crampy lower abdominal pain, constipation</p>	<p>Young and middle-aged adults, especially women</p> <p>Middle-aged and older adults, especially older than 55 years</p>
Inflammatory Bowel Disease					
<ul style="list-style-type: none"> Ulcerative colitis Crohn's disease of the small bowel (regional enteritis) or colon (granulomatous colitis) 	<p>Inflammation of the mucosa and submucosa of the rectum and colon with ulceration; typically extends proximally from the rectum</p> <p>Chronic transmural inflammation of the bowel wall, in a skip pattern typically involving the terminal ileum and/or proximal colon</p>	<p>Soft to watery, often containing blood</p> <p>Small, soft to loose or watery, usually free of gross blood (enteritis) or with less bleeding than ulcerative colitis (colitis)</p>	<p>Onset ranges from insidious to acute. Typically recurrent; may be persistent. May awaken at night.</p> <p>Insidious onset; chronic or recurrent. Diarrhea may wake the patient at night.</p>	<p>Milder cramping, lower or generalized abdominal pain, anorexia, weakness; fever if severe. May include episcleritis, uveitis, arthritis, erythema nodosum.</p> <p>Crampy periumbilical or right lower quadrant (enteritis) or diffuse (colitis) pain, with anorexia, low fever, and/or weight loss. Perianal or perirectal abscesses and fistulas. May cause small or large bowel obstruction</p>	<p>Often young people. Increases risk of colon cancer.</p> <p>Often young people, especially in late teens, but also in middle age. More common in people of Jewish descent. Increases risk of colon cancer</p>
Voluminous Diarrhea					
<ul style="list-style-type: none"> Malabsorption syndrome Osmotic diarrhea Lactose intolerance Abuse of osmotic purgatives Secretory diarrhea 	<p>Defective membrane transport or absorption of intestinal epithelium (Crohn's, celiac disease, surgical resection); impaired luminal digestion (pancreatic insufficiency); epithelial defects at brush border (lactose intolerance)</p> <p>Deficiency in intestinal lactase</p> <p>Laxative habit, often surreptitious</p> <p>Variable: bacterial infection, secreting villous adenoma, fat or bile salt malabsorption, hormone-mediated conditions (gastrin in Zollinger–Ellison syndrome, vasoactive intestinal peptide)</p>	<p>Typically bulky, soft, light yellow to gray, mushy, greasy or oily, and sometimes frothy; particularly foul-smelling; usually floats in toilet</p> <p>Watery diarrhea of large volume</p> <p>Watery diarrhea of large volume</p> <p>Watery diarrhea of large volume</p>	<p>Onset of illness typically insidious</p> <p>Follows the ingestion of milk and milk products; relieved by fasting</p> <p>Variable</p> <p>Variable</p>	<p>Anorexia, weight loss, fatigue, abdominal distention, often crampy lower abdominal pain. Symptoms of nutritional deficiencies such as bleeding (vitamin K), bone pain and fractures (vitamin D), glossitis (vitamin B), and edema (protein)</p> <p>Crampy abdominal pain, abdominal distention, flatulence</p> <p>Often none</p> <p>Weight loss, dehydration, nausea, vomiting, and cramping abdominal pain</p>	<p>Variable, depending on cause</p> <p>In >50% of African Americans, Asians, Native Americans, Hispanics; in 5%–20% of Caucasians</p> <p>Persons with anorexia nervosa or bulimia nervosa</p> <p>Variable depending on cause</p>

DIARRHOEA + NORMAL COLONOSCOPY



Colonic

- Bile acid malabsorption
- Microscopic colitis
- Overflow diarrhoea
- Missed pathology



Small Bowel

- Enteritis (e.g. Crohn's)
- Enteropathy (e.g. coeliac)
- Short bowel syndrome
- Ischaemia / Vasculitis



Endocrine

- Diabetes
- Hyperthyroidism
- Addison's
- Hyperparathyroidism



Pancreatic

- Pancreatic insufficiency
- Pancreatic carcinoma
- Cystic fibrosis



Infection

- SIBO
- Giardiasis
- Campylobacter
- C. diff.
- Viral (HIV, COVID-19)



Others

- IBS-D
- MCAS
- Drugs
- Alcohol
- Lymphoma
- Surgery
- NET
- Osmotic
- Autonomic neuropathy

Diarrhoea remains a leading killer of young children, despite the availability of a simple treatment solution

Diarrhoea is a leading killer of children, accounting for approximately 9 per cent of all deaths among children under age 5 worldwide in 2019. This translates to over 1,300 young children dying each day, or about 484,000 children a year, despite the availability of a simple treatment solution.

Deaths caused by diarrhoea among children under 5 are highest in South Asia and sub-Saharan Africa



Pathophysiology

- In the normal state, approximately **9 L of fluid** enters the ***proximal small intestine*** each day.
- Of this fluid **2 L** are ingested through diet the remainder is from ***intestinal secretions*** of which all but **1 L** are absorbed by the small intestine.

Pathophysiology

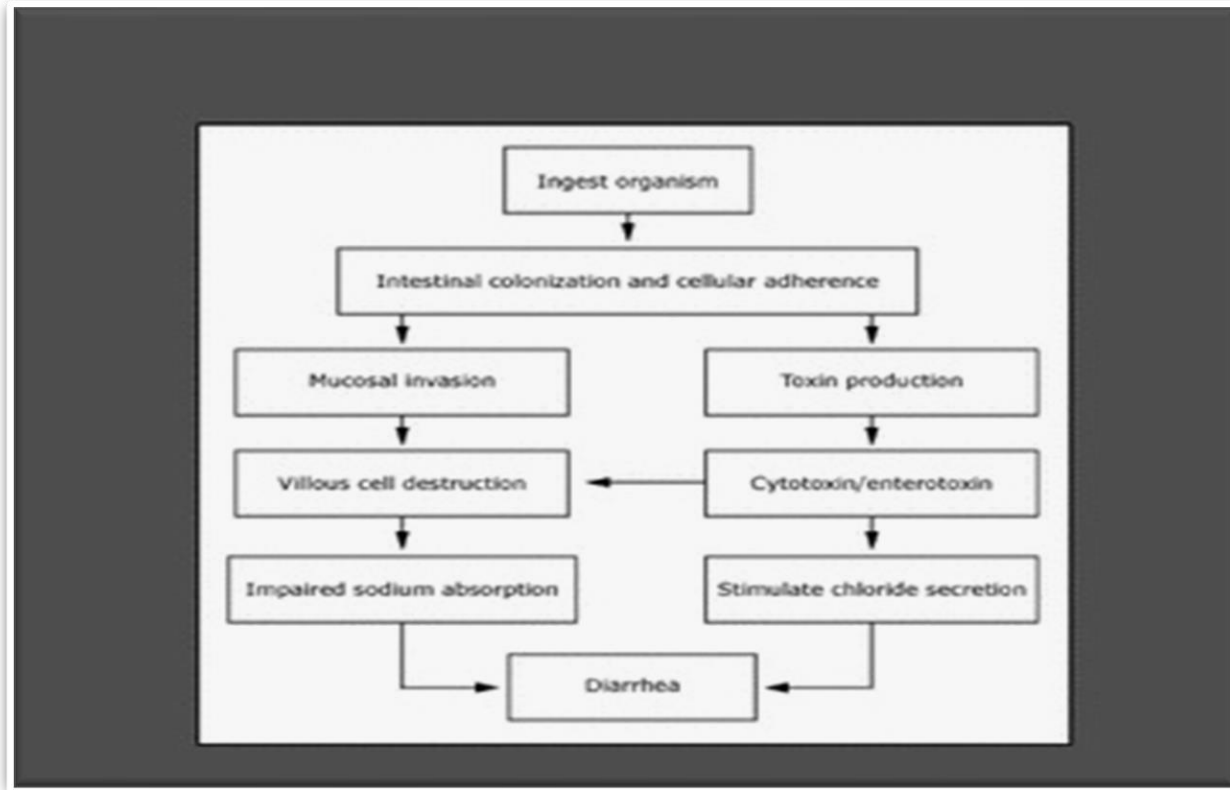
- The colon absorbs most of the remaining fluid, with only 100 mL lost in the stool.
- If the *small intestine* water absorption capacity is exceeded *chyme overloads* the colon leading to diarrhoea.
- The absorptive capacity of the *colon is 5 L*.
- From a medical standpoint, diarrhea is defined as a *stool weight of more than 250 g/24 h*

Diarrhoea Mechanisms

- A change in active transport by either *decreased Na⁺ absorption* or *increased chloride secretion*
- A change in the *intestinal motility*
- Increases in the *luminal osmolarity*
- Increases in *tissue hydrostatic pressure*

This leads to:

Pathophysiology



Drugs that can cause Diarrhea

TABLE 17-2 Drugs Causing Diarrhea

Laxatives

- Antacids containing magnesium

Antineoplastics

Auranofin (gold salt)

Antibiotics

- Clindamycin
- Tetracyclines
- Sulfonamides
- Any broad-spectrum antibiotic

Antihypertensives

- Reserpine
- Guanethidine
- Methyldopa
- Guanabenz
- Guanadrel
- Angiotensin-converting enzyme inhibitors

Cholinergics

- Bethanechol
- Neostigmine

Cardiac agents

- Quinidine
- Digitalis
- Digoxin

Nonsteroidal anti-inflammatory drugs

Misoprostol

Colchicine

Proton pump inhibitors

H₂-receptor blockers



Goals in management of Diarrohea

Potential goals in the management of diarrhea are

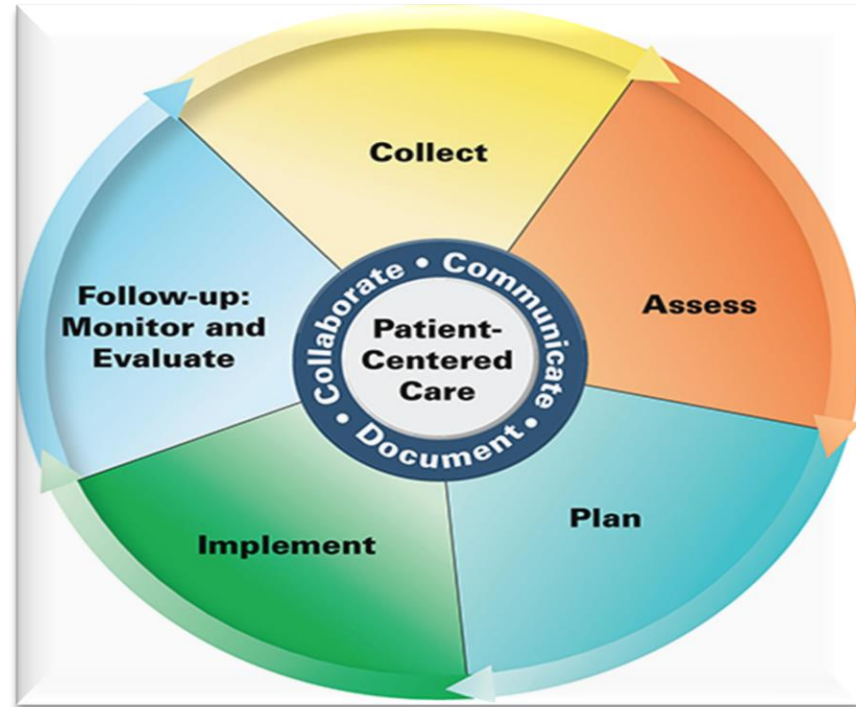
- Correction of **dehydration and electrolyte imbalance**,
- Reduction of **stool output, prevention of recurrence**,
- Prevention of **malnutrition related complications**,
- Improvement of **mucosal barrier**
- Maximization of **nutrient availability**

Treatment: 3 Ds

- **D**ehydration correction– replace the loss of fluid and electrolytes
- **D**iet: Start food as soon as possible
- **D**rug:
 - Anti-infective if infectious origin

Management of Diarrhea

- **Dehydration correction**– replace the loss of fluid and electrolytes
- **Diet:** Start food as soon as possible
- **Drug:**
 - Anti-infective if infectious origin

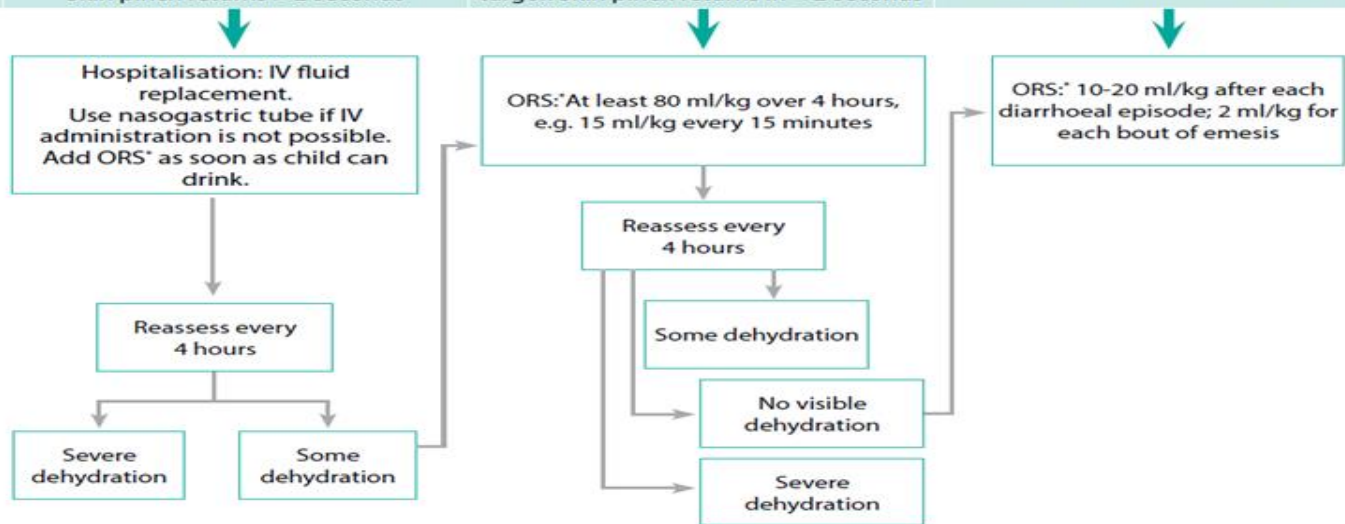





Transmission

- Most of the diarrheal agents are transmitted by the **faecal-oral route**
- Cholera: water-borne disease; transmitted through **water contaminated with faeces**
- Some viruses (such as rotavirus) can be **transmitted through air**
- **Nosocomial transmission** is possible
- **Shigellosis (blood dysentery)** is mainly transmitted person-to-person
- **Shigellosis is a water-washed disease**; transmitted more when there is scarcity of water

	Classification C: severe dehydration	Classification B: some dehydration	Classification A: no visible dehydration
Signs of classification	Two of the signs	Two of the signs, but not severe dehydration	None of the signs
Level of consciousness	Lethargic or unconscious	Restless or irritable	Well alert
Sunken eyes	Sunken eyes	Sunken eyes	Eyes are not sunken
Ability to drink	Drinks poorly, or is not able to drink	Thirsty, drinks eagerly	Drinks normally. There is not excessive thirst
Skin pinch (turgor)	There is a severe decrease in skin turgor. Skin pinch returns > 2 seconds	There is a moderate decrease in skin turgor. Skin pinch returns in < 2 seconds	Skin pinch returns immediately

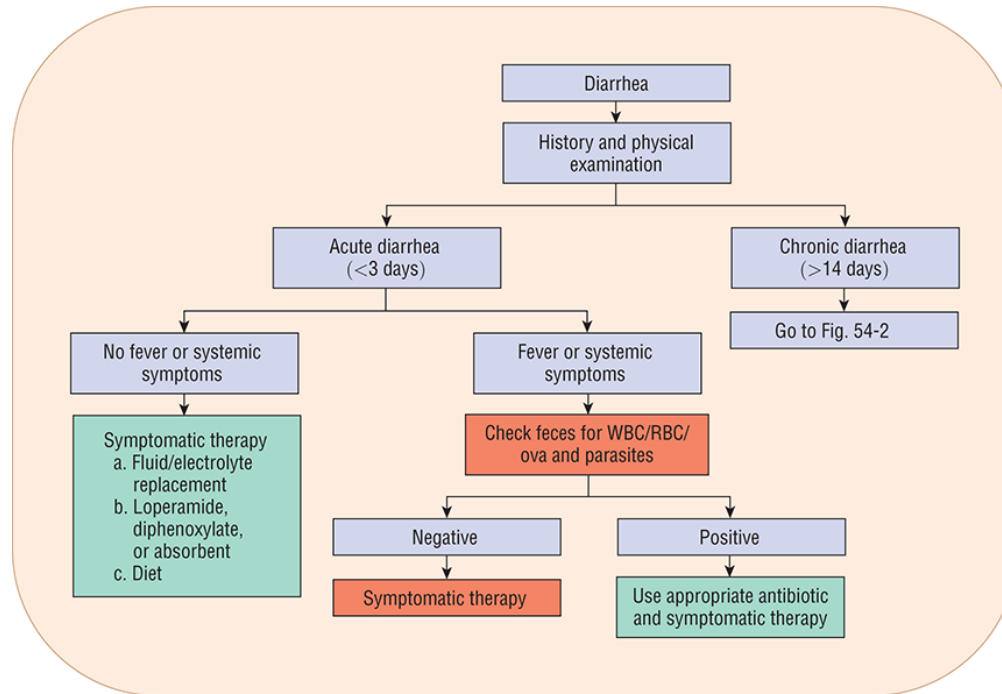


*A homemade sugar and salt solution may be used if an oral rehydration formula is not available:¹⁴



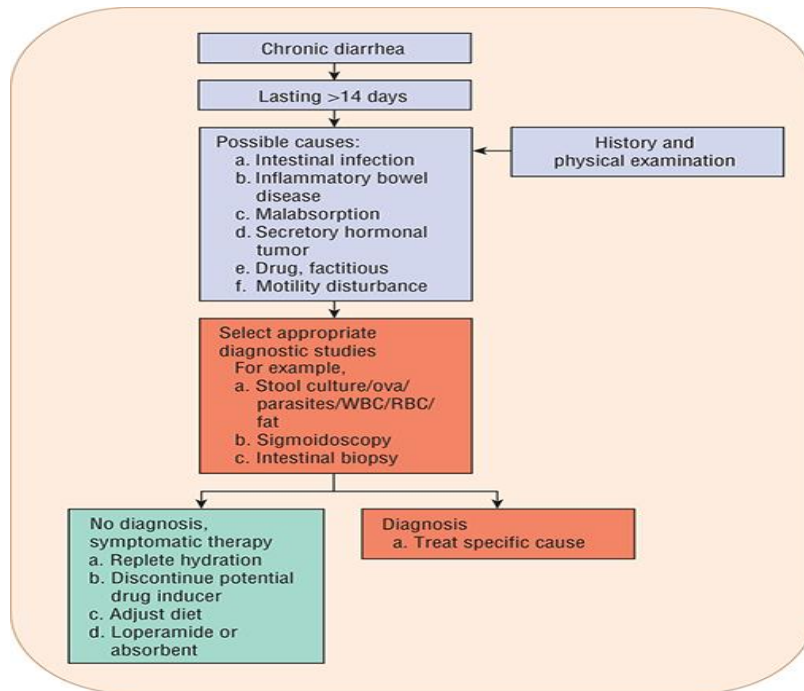
Homemade sugar and salt solution
 ½ level teaspoon of table salt
 plus
 8 level teaspoons of sugar dissolved in 1 litre boiled and then cooled water (1 level teaspoon = 5 ml)

Supplemental zinc
 The WHO¹⁶ recommends an oral zinc intake for 10-14 days for all episodes of diarrhoea:
 ≤ 6 months: 10 mg/day
 > 6 months: 20 mg/day



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e* Copyright © McGraw Hill. All rights reserved.

Recommendations for treating acute diarrhea. Follow the following steps: (a) Perform a complete history and physical examination. (b) Is the diarrhea acute or chronic? If chronic diarrhea, go to Fig. 54-2. (c) If acute diarrhea, check for fever and/or systemic signs and symptoms (ie, toxic patient). If systemic illness (fever, anorexia, or volume depletion), check for an infectious source. If positive for infectious diarrhea, use appropriate antibiotic/anthelmintic drug and symptomatic therapy. If negative for infectious cause, use only symptomatic treatment. (d) If no systemic findings, then use symptomatic therapy based on severity of volume depletion, oral or parenteral fluid/electrolytes, antidiarrheal agents (see Table 54-4), and diet. (RBC, red blood cells; WBC, white blood cells.)

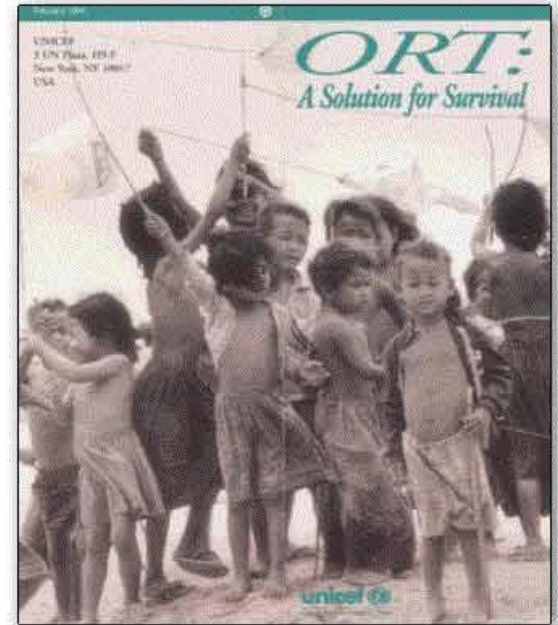


Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e* Copyright © McGraw Hill. All rights reserved.

Recommendations for treating chronic diarrhea. Follow the following steps: (a) Perform a careful history and physical examination. (b) The possible causes of chronic diarrhea are many. These can be classified into intestinal infections (bacterial or protozoal), inflammatory disease (Crohn's disease or ulcerative colitis), malabsorption (lactose intolerance), secretory hormonal tumor (intestinal carcinoid tumor or vasoactive intestinal peptide-secreting tumor [VIPoma]), drug (antacid), factitious (laxative abuse), or motility disturbance (diabetes mellitus, irritable bowel syndrome, or hyperthyroidism). (c) If the diagnosis is uncertain, selected appropriate diagnostic studies should be ordered. (d) Once diagnosed, treatment is planned for the underlying cause with symptomatic antidiarrheal therapy. (e) If no specific cause can be identified, symptomatic therapy is prescribed. (RBC, red blood cells; WBC, white blood cells.)

Oral Rehydration Therapy

The leading British Medical Journal (Lancet) called ORT "potentially the most important medical advance of the century"



	Dose Form	Adult Dose
Antimotility		
Diphenoxylate	2.5 mg/tablet 2.5 mg/5 mL	5 mg four times daily; do not exceed 20 mg/day
Loperamide	2 mg/capsule	Initially 4 mg, and then 2 mg after each loose stool; do not exceed 16 mg/day
Paregoric	2 mg/5 mL (morphine)	5-10 mL one to four times daily
Opium tincture	10 mg/mL (morphine)	0.6 mL four times daily
Difenoxin	1 mg/tablet	Two tablets, and then one tablet after each loose stool; up to eight tablets per day
Adsorbents		
Kaolin-pectin mixture	5.7 g kaolin + 130.2 mg pectin/30 mL	30-120 mL after each loose stool
Polycarbophil	500 mg/tablet	Chew 2 tablets four times daily or after each loose stool; do not exceed 12 tablets per day
Attapulgite	750 mg/15 mL 300 mg/7.5 mL 750 mg/tablet 600 mg/tablet 300 mg/tablet	1,200-1,500 mg after each loose bowel movement or every 2 hours; up to 9,000 mg/day
Antisecretory		
Bismuth subsalicylate	1,050 mg/30 mL 262 mg/15 mL 524 mg/15 mL 262 mg/tablet	Two tablets or 30 mL every 30 minutes to 1 hour as needed up to eight doses per day
Enzymes		
lactase	1,250 neutral lactase units/4 drops	Three to four drops taken with milk or dairy product
	3,300 FCC lactase units per tablet	

Management of Diarrhoea

Anti-diarrheal drugs

- Antimotility or Antipropulsive drugs
 - Loperamide (Immodium ®), diphenoxylate/atropine (Lomotil ®),
- Probiotics
- Adsorbents
 - activated charcoal, kaolin, pectin (Bipectinol ®, Gastropect ®, Kaostatex ®), diosmectite (Smecta®),
- Anticholinergics
 - hyoscine (Buscopan ®), mebeverine (Bevespas ®)hyoscyamine and dicycloverine

Zinc in acute diarrhoea

- Reduces duration of diarrhoea episode by up to 25%
- Decrease by about 25% the proportion of episodes lasting more than seven days
- It is associated with a 30% reduction in stool volume
- **Conclusion:** significant beneficial impact on **the clinical course of acute diarrhoea**: reduces both severity and duration

Zinc in persistent diarrhoea

- Zinc-supplemented children had:
 - 24% lower probability of continuing diarrhoea
 - 42% lower rate of treatment failure or death
- **Conclusion:** zinc supplementation **reduces the duration and severity** of persistent diarrhoea

Management of Diarrhoea

Antimotility/Antipropulsive

- Loperamide (Immodium ®), diphenoxylate/atropine (Lomotil ®),

Mechanism of Action

- Delays transit time
- Increases gut capacity by prolonging the contact time and absorption – enkephalins –regulates fluid movements
- Loperamide only acts peripherally and slows gastrointestinal motility by inhibiting contractions both longitudinally and circular muscles partly by local opioid receptors

Antimotility/Antipropulsive

Opioids continue to be used widely

Mechanism of action:

1. Intestinal motility-- μ receptors
2. Intestinal secretion-- δ receptors
3. Intestinal absorption--- μ & δ receptors

All the commonly used opioids act principally via peripheral μ receptors and are preferred over opioids that penetrate central nervous system

Antimotility agents

- **Safety Announcement**
- To foster safe use of the over-the counter (OTC) anti-diarrhea drug loperamide, the U.S. Food and Drug Administration (FDA) is working with manufacturers to use blister packs or other single dose packaging and to limit the number of doses in a package.
- We continue to receive reports of serious heart problems and deaths with much higher than the recommended doses of loperamide, primarily among people who are intentionally misusing or abusing the product, despite the addition of a warning to the medicine label and a previous communication. Loperamide is a safe drug when used as directed.

FDA limits packaging for anti-diarrhea medicine loperamide (Imodium) to encourage safe use

FDA Drug Safety Communication



9/20/2019 Update

To help address loperamide abuse and misuse, FDA approved changes to the packaging for tablet and capsule forms of the brand-name over-the-counter (OTC) anti-diarrheal medicines [Imodium A-D](#), [Imodium Multi-Symptom Relief](#), and [Be Health Loperamide HCl Capsules](#). These changes limit each carton to no more than 48 mg of loperamide and require the tablets and capsules to be packaged in individual doses. FDA continues to work with manufacturers, including those of generic and liquid OTC loperamide products to institute appropriate package sizes and types that support the safe use of these medicines.

Update Probiotics: rationale

- Probiotics are microorganisms given to reestablish normal colonic microflora. This supposedly restores normal intestinal function and suppresses the growth of pathogenic microorganisms.
- There is conflicting evidence on whether *Saccharomyces boulardii*, *Lactobacillus* GG, and *Lactobacillus acidophilus* decrease the duration of infectious and antibiotic-induced diarrhea in adults and children.
- Probiotics may prevent antibiotic-associated diarrhea (AAD).
- However, a randomized control trial in hospitalized patients over the age of 65 years found no difference in cases of AAD between a probiotic preparation (two strains of lactobacillus acidophilus and Bifidobacterium) and placebo.
- The dosage of probiotic preparations varies depending on the brand used. Intestinal flatus is the primary patient complaint experienced with this modality.

Collinson S, Deans A, Padua-Zamora A, et al. Probiotics for treating acute infectious diarrhoea. *Cochrane Database of Systematic Reviews*. 2020;(Issue 12). Art. No.: CD003048. doi: 10.1002/14651858.CD003048.pub4. Accessed July 1, 2021.

Blaabjerg S, Artzi DM, Aabenhus R. Probiotics for the prevention of antibiotic-associated diarrhea in outpatients: A systematic review and meta-analysis. *Antibiotics (Basel)*. 2017;6(4):21. 10.3390/antibiotics6040021.

Allen SJ, Wareham K, Wang D, et al. A high-dose preparation of lactobacilli and bifidobacteria in the prevention of antibiotic-associated and *Clostridium difficile* diarrhoea in older people admitted to hospital: A multicentre, randomised, double-blind, placebo-controlled, parallel arm trial (PLACIDE). *Health Technol Assess*. 2013;17(57):1–140.

Adsorbents

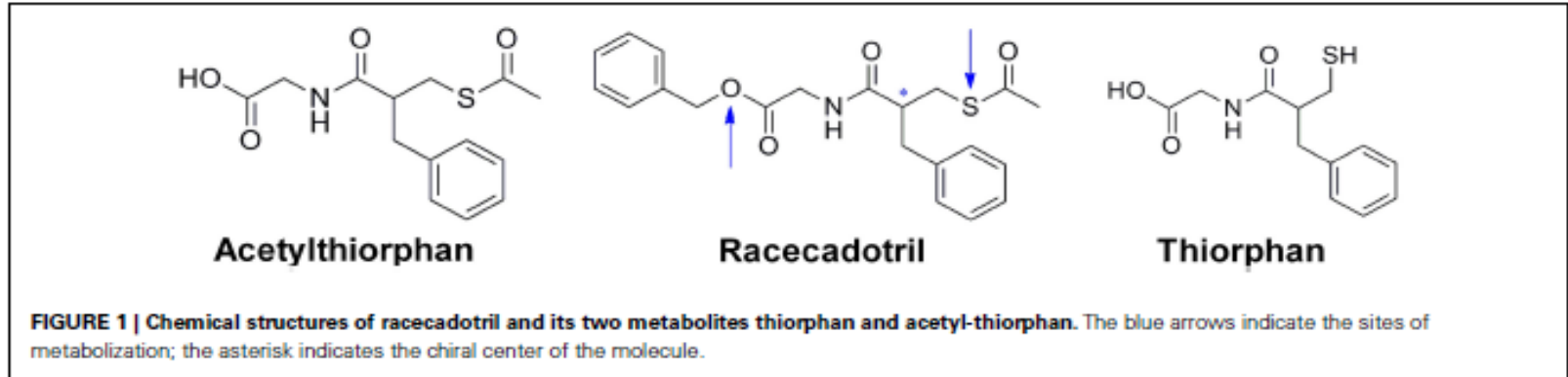
- Adsorbents are used for symptomatic relief.
- These products, many not requiring a prescription, are nontoxic, but their effectiveness remains unproven.
- Adsorbents are nonspecific in their action; they adsorb nutrients, toxins, drugs, and digestive juices.
- Polycarbophil absorbs 60 times its weight in water and can be used to treat both diarrhea and constipation.
- This hydrophilic, nonabsorbable product is safe and may be taken four times daily, up to 6 g/day in adults.

Adsorbents

- Kaolin & Pectin - Useful in mild diarrhoea
- Diosmectite - Natural adsorbent clay formed of fine sheets of aluminomagnesium silicate
 - Non-systemic gastrointestinal tract muco-protective agent
 - Interacts with mucus molecules, to strengthen the mucosal barrier and protect the apical pole of the enterocytes and tight junctions against bacteria and toxin present within the lumen
 - It has also been shown to have a specific binding action for rotavirus, one of the main causes of diarrhoea in children

Antisecretory Drugs

Antisecretory drug that exerts its antidiarrhoeal effects by inhibiting intestinal enkephalinase



Bismuth Subsalicylate

- Bismuth subsalicylate have antisecretory, anti-inflammatory, and antibacterial effects.
- As a non-prescription product, it is marketed for indigestion, relieving abdominal cramps, and controlling diarrhoea, including traveler's diarrhea.
- **WARNING** - Bismuth subsalicylate contains multiple components that might be toxic if given in excess to prevent or treat diarrhea. For instance, an active ingredient is **salicylate**, which may interact with anticoagulants or may produce salicylism (tinnitus, nausea, and vomiting). Bismuth reduces tetracycline absorption and may interfere with select GI radiographic studies. Patients may complain of a darkening of the tongue and stools with repeat administration. Salicylate can induce gout attacks in susceptible individuals.

Racecadotril : A Novel Antidiarrheal

Lt Col N Singh*, Lt Col S Narayan*

MJAFI 2008; 64 : 361-362

Key Words: Diarrhea; Anti secretory drugs; Racecadotril

Introduction

Diarrhea is among the commonest of illnesses affecting people from all age groups and causes enormous loss of money and man working hours [1]. The present modalities of treatment aim at restoring the fluid and electrolyte loss, the use of antimicrobials to eliminate the pathogens and antimotility agents to reduce the number of diarrheal days.

Oral rehydration has been the mainstay of treatment of diarrhea, however it does not reduce the frequency of stools or the number of diarrheal days. Antimotility drugs like loperamide have a limited role because of side effects. Potentiation of the effects of endogenous enkephalin activity by enkephalinase inhibition has produced a safe and effective anti secretory drug, Racecadotril [2].

Pharmacological Properties

[3-acetylmercapto-2-benzylpropanoyl] - glycine, benzyl ester, is a lipophilic derivative of thiorphan. Racecadotril is rapidly converted in the body to thiorphan, a potent enkephalinase inhibitor. Enkephalins are endogenous opioid peptides secreted by myenteric and sub mucosal neurons in the digestive tract. The enkephalins by activating the δ opioid receptor, inhibit the secretion of Cl^- and fluids thus reducing the loss of fluids and electrolytes during diarrhea [3,4]. The anti-secretory mechanisms are independent of effects on intestinal motility, differentiating this compound from μ -opioid receptor agonists like loperamide and diphenoxylate. Experimental studies in rodents and human volunteers demonstrated no delay on gastrointestinal transit or increase in experimental bacterial proliferation in small bowel of germ free piglets with racecadotril as compared to loperamide [5].

to its active metabolite thiorphan. Peak plasma levels are attained in about an hour and half life of the drug is three hours. Data on safety in pregnancy, lactation and renal/hepatic insufficiency is inadequate, which requires care in the usage.

Clinical Uses

Racecadotril is the first truly intestinal antisecretory drug to gain approval for treatment of diarrhea. The drug is available as 100 mg capsules and 10, 15 and 30 mg sachets. The recommended dosage is 100 mg three times a day for adults and 1.5 mg/kg three times a day for children. It improves the patient's perception of the effectiveness of therapy due to reduced number of stools. Studies have shown that racecadotril reduces the frequency and duration of acute diarrhea of both infectious and noninfectious origin [6-8].

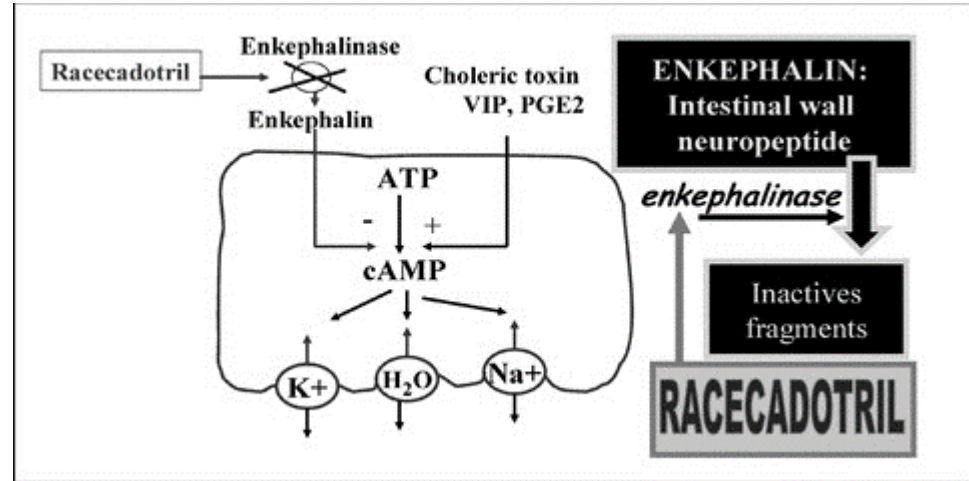
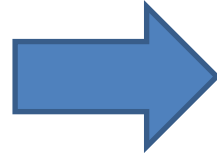
Adverse Effects

The efficacy of racecadotril in acute diarrhoea is not associated with adverse gastrointestinal effects and fewer patients on racecadotril therapy suffered from abdominal distension following treatment (5.6 vs 18.2% on placebo) [9]. It caused significantly less constipation after resolution of diarrhea than loperamide. Incidence of itching was higher in racecadotril than loperamide group [10]. Racecadotril does not enter the central nervous system (CNS) thus it lacks any potential for neurotoxicity; however in children below two years of age where blood brain barrier is immature it can cause depression. Caution is also advocated in using racecadotril in disorders of carbohydrate intolerance due to the presence of saccharose as an excipient.

Conclusion

The pure antisecretory action of racecadotril, its high

Racecadotril



Tormo R, Polanco I, Salazar-Lindo E, Goulet O. Acute infectious diarrhoea in children: new insights in antisecretory treatment with racecadotril. Acta Paediatrica (Oslo, Norway : 1992). 2008 Aug;97(8):1008-1015. DOI: 10.1111/j.1651-2227.2008.00830.x. PMID: 18462465; PMCID: PMC7159603.

MOA: Racecadotril

Racecadotril is a prodrug that needs to be hydrolysed to its active metabolite thiorphan, which is an inhibitor of enkephalinase, a cell membrane peptidase located in the epithelium of the small intestine. Racecadotril protects enkephalins from enzymatic degradation, thereby prolonging their action at enkephalnergic synapses in the small intestine and reducing hypersecretion.⁴

Racecadotril decreases intestinal hypersecretion of water and electrolytes induced by cholera toxin or inflammation, exerting a rapid antidiarrhoeal action, without modifying the duration of intestinal transit.⁴ The bioavailability of racecadotril is not modified by food, but peak activity is delayed by about 90 minutes. The biological half-life of racecadotril is approximately 3 hours.

Racecadotril Indications

- Racecadotril is indicated for the symptomatic treatment of **acute diarrhoea in adults, children and infants over 3 months** old when causal treatment is not possible.
- If causal treatment is possible, then it can be administered as a complementary treatment.
- For children and infants, racecadotril is **used together with oral rehydration** and the usual support measures, when these measures alone are insufficient to control the clinical condition, and when causal treatment is not possible.
- To initiate therapy in adults, one capsule (containing 100mg of racecadotril) is taken regardless of the time of day; after that, one capsule is taken three times daily, preferably before the main meals.
- Racecadotril is also available in 10mg and 30mg sachets containing granules to produce an oral suspension.
- For both adults and children, treatment should be continued until two normal stools are recorded. Treatment should not exceed 7 days and long-term treatment with the drug is not recommended.
- The recommended dose is determined according to body weight:

Table 1 | Efficacy of racecadotril in the treatment of acute diarrhea in adults.

Outcome parameter	Number of patients	Racecadotril	Comparator	Reference
DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES IN ADULTS WITH ACUTE DIARRHEA				
Time to recovery, h	54–55 per group vs. 49 ⁵	65.0–69.9	72.0	data on file
% Probability for recovery on day 4	95 vs. 98	75*	37	Baumer et al. (1992)
Stool weight, g	32 vs. 38	355 ± 35*	499 ± 46	Hamza et al. (1999)
DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES IN ADULTS WITH CHOLERA				
Total stool output, g	54 vs. 56	315 ± 31	280 ± 21	Alam et al. (2003)
STUDIES IN ADULTS WITH ACUTE DIARRHEA ASSOCIATED WITH CANCER CHEMOTHERAPY (5-FLUORO-URACIL)				
Number of stools per day	15 (sequential racecadotril vs. no treatment)	4.9*	6.3	Dorval et al. (1995)
STUDIES IN ADULTS WITH DELAYED DIARRHEA DUE CANCER CHEMOTHERAPY (IRINOTECAN)				
Treatment responder	11	36%	–	Saliba et al. (1998)
Prophylaxis of diarrhea	68 vs. 68 no treatment	55%	59%	Ychou et al. (2000)
OCTREOTIDE-CONTROLLED STUDIES IN ADULTS WITH TREATMENT-RESISTANT DIARRHEA IN AIDS PATIENTS				
Stools/day	13 (cross-over)	–2.4*	–1.4	Beaugerie et al. (1996)
DOUBLE-BLIND, LOPERAMIDE-CONTROLLED STUDIES IN ADULTS WITH ACUTE DIARRHEA				
Time to diarrhea resolution, days	37 vs. 32	2.2 ± 0.2	2.3 ± 0.2	Roge et al. (1993)
Number of stools	82 vs. 75	3.5 ± 0.5	2.9 ± 0.4	Vetel et al. (1999)
Duration of diarrhea, h	473 vs. 472	55.0	55.0	Prado (2002)
Duration of diarrhea, h	31 vs. 31	19.5	13.0	Wang et al. (2005)
Time recovery, h	30 vs. 31	36 ± 4*	63 ± 6	Gallelli et al. (2010)

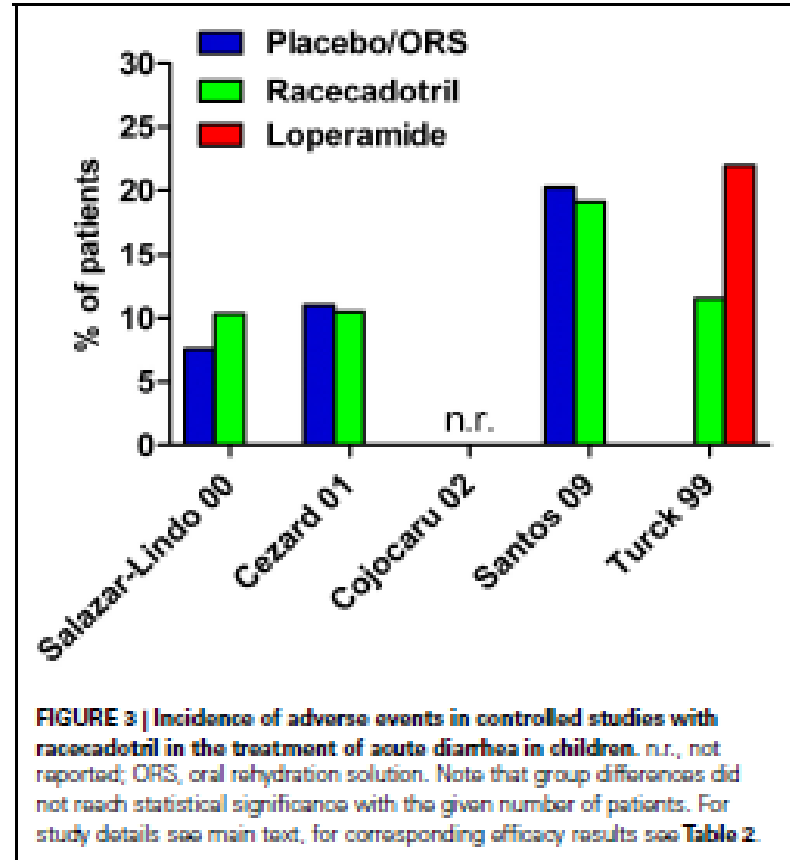
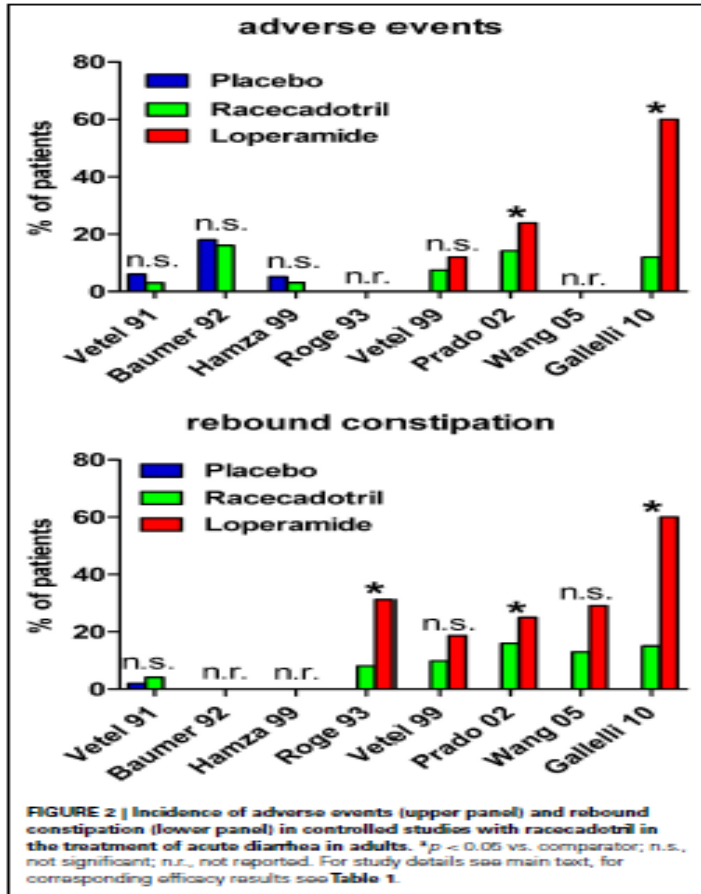
**p* < 0.05 vs. comparator; ⁵dose-ranging study using 30, 100, and 300 mg racecadotril thrice daily. For details on individual studies see main text Section “Studies in the Gastro-Intestinal Tract.”

Table 2 | Efficacy of racecadotril in the treatment of acute diarrhea in children.

Outcome parameter	Number of patients	Racecadotril	Comparator	Reference
DOUBLE-BLIND, PLACEBO-CONTROLLED STUDIES IN CHILDREN WITH ACUTE DIARRHEA				
Stool output, g/kg	68 vs. 65	157 ± 27*	331 ± 39	Salazar-Lindo et al. (2000)
Stool output, g/h	84 vs. 82	9*	15	Cezard et al. (2001)
OPEN-LABEL CONTROLLED STUDIES (VS. REHYDRATION ALONE) IN CHILDREN WITH ACUTE DIARRHEA				
Medical exams within 1 week of treatment	81 vs. 83	14*	27	Cojocaru et al. (2002)
Number of stools in first 48 h	88 vs. 91	3.8 ± 2.4	4.1 ± 2.7	Santos et al. (2009)
OPEN-LABEL OBSERVATIONAL STUDIES IN CHILDREN WITH ACUTE DIARRHEA				
Time to relief, h	3873	18.5 ± 12.5	n.a.	Chacon (2010)
DOUBLE-BLIND, LOPERAMIDE-CONTROLLED STUDIES IN CHILDREN WITH ACUTE DIARRHEA				
Number of diarrhoic stools until recovery	52 vs. 50	2.7 ± 0.4	2.1 ± 0.4	Turck et al. (1999)

n.a., Not applicable; **p* < 0.05 vs. comparator.

Adverse events with racecadotril



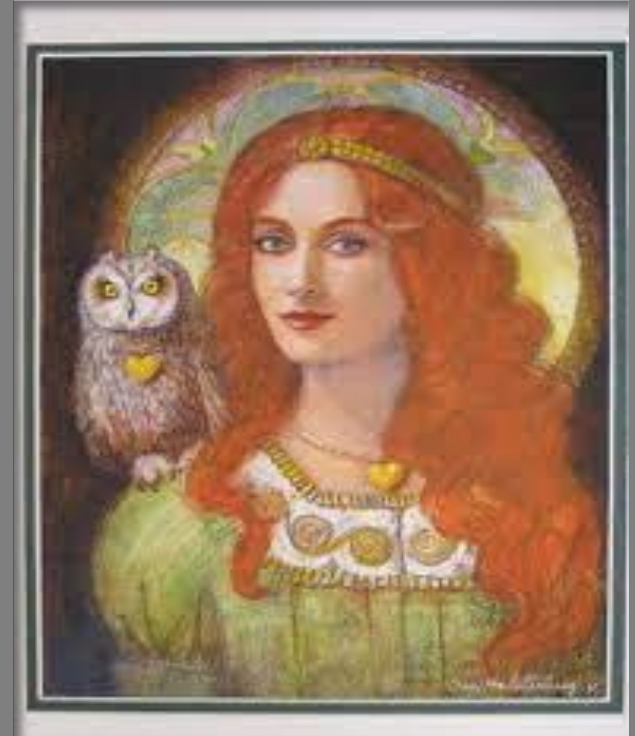
Management of Diarrhea in children

- Use of antimicrobials - on a patient-by-patient basis
- **Even when a bacterial cause is suspected, antimicrobial therapy is NOT usually indicated** among children because most cases of acute diarrhea are self-limited and their duration is not shortened by the use of antimicrobial agents. Exceptions to these rules may involve:
 - Premature infants, children who are immune compromised or have underlying disorders) or Suspicion of sepsis
 - In the context of an outbreak of shigellosis, cryptosporidiosis, or giardiasis.
- Anti-emetics & antimotility agents should be avoided

Vaccination and Diarrhoea

Cassandra's philosophical approach

Cassandra, princess of Troy
Could see the future, but were cursed that no-
one would believe her prophecies



Vaccine pipeline for antimicrobial-resistant pathogens

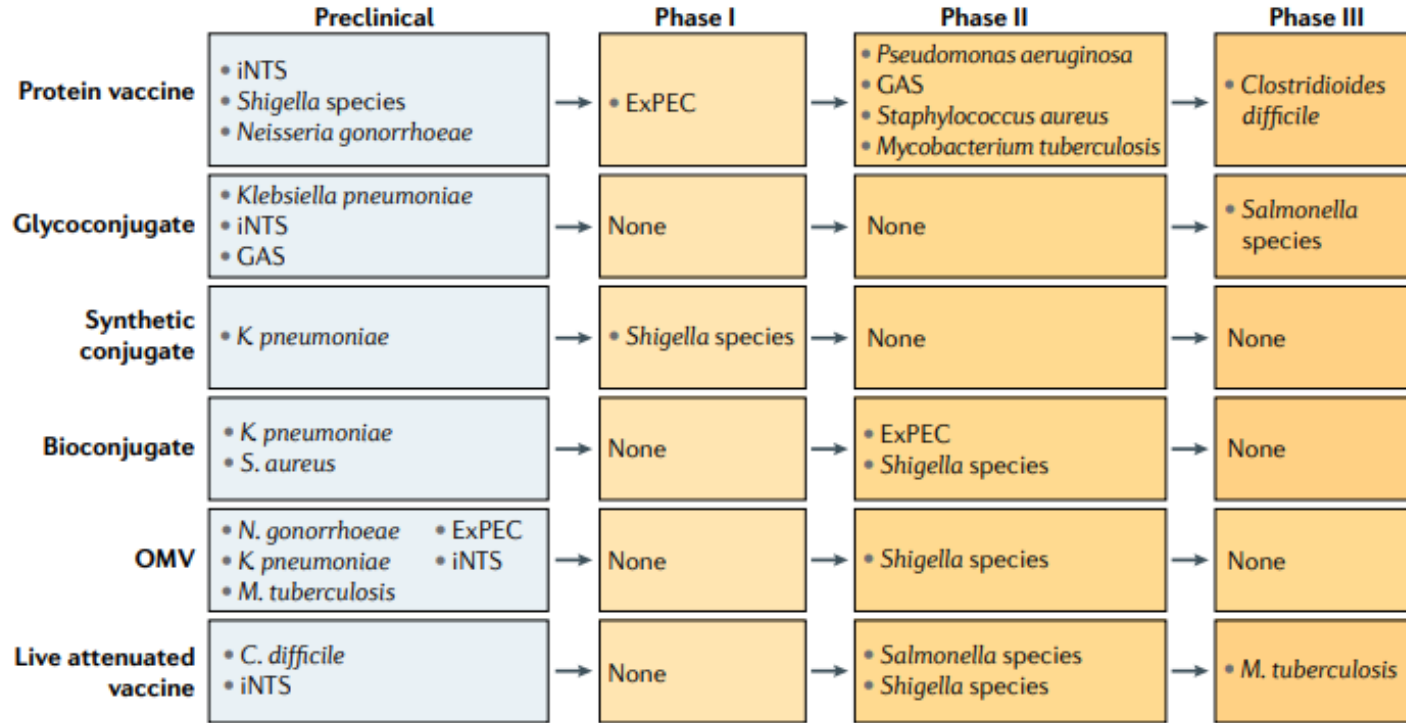


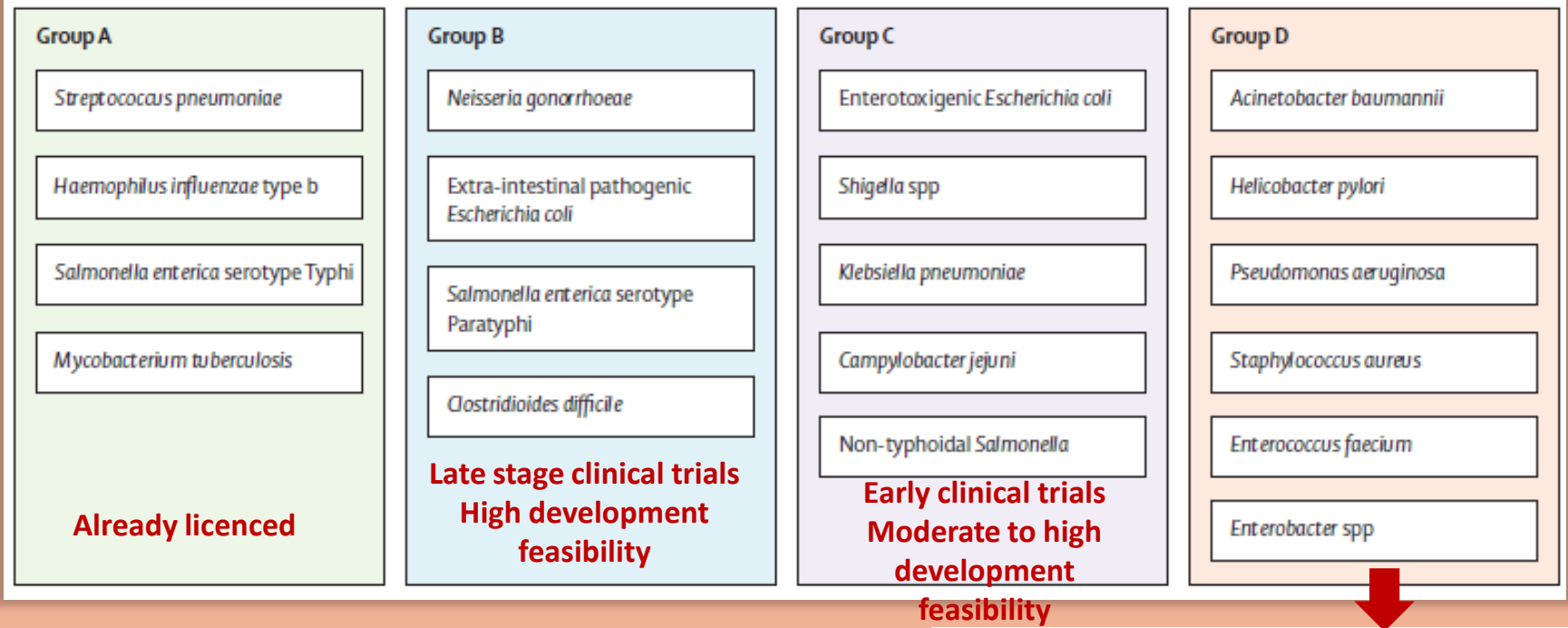
Fig. 3 | Vaccine development for antimicrobial-resistant pathogens. Shown are vaccine candidates that are currently at different stages of development. Various vaccine technologies and platforms (protein vaccine, glycoconjugate, synthetic conjugate, bioconjugate, outer membrane vesicles (OMVs) and live attenuated vaccines) are being applied to identify and develop such vaccines, as indicated. (see also Supplementary Table 1). ExPEC, extraintestinal pathogenic *Escherichia coli*; GAS, group A *Streptococcus*; iNTS, invasive non-typhoidal *Salmonella*.

The role of bacterial vaccines in the fight against antimicrobial resistance: an analysis of the preclinical and clinical development pipeline

Isabel Frost, Hatim Sati, Pilar Garcia-Vello, Mateusz Hasso-Agopsowicz, Christian Lienhardt, Valeria Gigante, Peter Beyer

Vaccine candidates in development against pathogens on 2017 WHO bacterial priority pathogen list

- 94 active preclinical vaccine candidates
- 61 active development vaccine candidates



Concluding Statements

- Diarrhea is caused by many viral and bacterial organisms. It is most often a minor discomfort, not life-threatening, and usually self-limited.
- The four pathophysiologic mechanisms of diarrhea have been linked to the four broad diarrheal groups, which are secretory, osmotic, exudative, and altered intestinal transit.
- The three mechanisms by which absorption occurs from the intestines are active transport, diffusion, and solvent drag.
- Management of diarrhea focuses on preventing excessive water and electrolyte losses, dietary care, relieving symptoms, treating curable causes, and treating secondary disorders.



Thank You



UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA