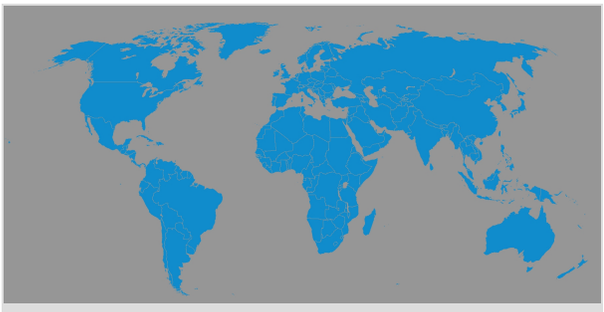
Background

Global Burden | Causative Agents & Transmission | Pathogenesis | Current Control Strategy | Existing Products | Get Involved

What are Diarrheal Diseases?

Diarrheal diseases are a collection of diseases caused by multiple viral, bacterial, and parasitic organisms that share the common symptom of diarrhea, defined as the passage of three or more loose or liquid stools per day. The diarrheal diseases cholera, ETEC, rotavirus, shigellosis, and typhoid are also profiled separately, but we have grouped them together with other forms of infectious diarrhea in this profile to discuss general diarrhea treatments. Irrespective of the underlying cause of the diarrhea symptoms, diarrheal diseases can lead to severe dehydration or even death when left untreated.

Global Burden



Diarrheal diseases are prevalent around the globe.

Diarrheal diseases affect people of all ages throughout the world. Children, however, are the most vulnerable; diarrhea is the second leading causes of death worldwide in children under the age of five, accounting for approximately 1.5 million deaths per year.[1] More than 80% of these deaths occur in Africa and Southeast Asia.[2]

Back to Top

Causative Agent and Transmission

Diarrheal disease can be caused by a variety of pathogens including viruses, bacteria, and parasites. Examples of the spectrum of diarrheal diseases are summarized in the table below. The relative frequency of each of these organisms as the cause of diarrhea varies significantly geographically.

Bacterial	Viral	Parasitic
Campylobacter	Rotavirus	Amoebic dysentery (e.g *Entamoeba hystolicai*)
Cholera	Calciviruses	Cryptosporidium
ETEC	Noroviruses (e.g. Norwalk virus)	Giardia
Shigellosis		

Typhoid		

Infectious organisms that cause diarrhea are primarily transmitted by the oral-fecal route, such as when fecal matter contaminates food or water or from person-to-person contact in situations with poor hygiene.

Back to Top

Pathogenesis

Diarrhea is caused by poor absorption of fluids in the large intestine or from increased secretion of water into the small intestine, resulting in excess fluid in the stool.

Diarrhea is generally characterized as:[1]

- Acute watery diarrhea - caused by secretion of a toxin that disrupts the balance of electrolytes in the intestine resulting in excess water secretion.
- Acute bloody diarrhea - primarily caused by bacteria that invade the intestinal lining resulting in damage.
- Persistent diarrhea – diarrhea episode that lasts for more than 14 days commonly seen in children with poor nutrition and a history of diarrheal disease.

Current Control Strategy

UNICEF and WHO recommend a seven point plan to improve diarrheal disease control, focusing on:[2]

1. Fluid replacement to prevent dehydration
2. Zinc treatment
3. Rotavirus and measles vaccinations
4. Promotion of early and exclusive breastfeeding and vitamin A supplementation
5. Promotion of handwashing with soap
6. Improved water supply quantity and quality, including treatment and safe storage of household water
7. Community-wide sanitation promotion

Existing Products

Drugs

Diarrheal diseases are generally managed by oral or intravenous rehydration therapy. However, only 33% of children in developing countries currently receive standard oral rehydration salt (ORS) therapies to treat diarrheal episodes.[2] Additional supportive therapy including continued feeding and zinc are also recommended. Use of drugs beyond ORS to treat the underlying causes of diarrhea is addressed under individual disease profiles for cholera, ETEC, rotavirus, shigellosis, and typhoid.

Vaccines

Vaccines are available to prevent several forms of infectious diarrhea including rotavirus, cholera, and typhoid. These vaccines are discussed in more detail under the individual disease profiles for cholera, ETEC, rotavirus, shigellosis, and typhoid.

Diagnostics

Diarrheal disease is primarily diagnosed by clinical symptoms. As diarrheal disease is treated by supportive rehydration therapy rather than medications, specific diagnosis is generally not considered essential. Immune-based, nucleic acid amplification-based, and culture-based diagnostic techniques are available for multiple specific causes of diarrhea. However, all of these diagnostics require access to sophisticated laboratory facilities.

Back to Top

References

1. WHO Diarrhoeal Disease Fact Sheet.
2. WHO and UNICEF (2009) Diarrhoea: Why children are still dying and what can be done.

Get Involved

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Pipeline & Analysis

Drugs | Vaccines | Diagnostics | Get Involved

Drugs

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Crofelemer	Glenmark Pharmaceuticals Ltd. Luye Pharma Napo Pharmaceuticals, Inc. Salix Pharmaceuticals					
iOWH032	Galapagos NV Institute for OneWorld Health Roche					
Second-generation synthetic CFTR chloride channel inhibitors	Napo Pharmaceuticals, Inc.					
Discovery program for anti-diarrheal agents	Anacor Pharmaceuticals, Inc. Institute for OneWorld Health Novartis AG Roche					

ANALYSIS

Drugs in development for specific underlying causes of diarrhea are not profiled here or in the individual disease profiles as they primarily consist of general antibiotics or antivirals. The drugs included in the pipeline above are instead general antidiarrheal agents that target the physiological symptoms of diarrhea rather than the underlying infectious cause.

The two products in clinical stage development target chloride channels in the intestine that regulate water flow. Crofelemer, a natural product derivative in phase II clinical development by Napo Pharmaceuticals, targets the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel and calcium activated chloride channel (CaCC). By stabilizing the ion channel in a closed position, the rate of fluid loss is slowed.[1] One World Health (OWH) recently launched a phase I clinical trial for its new CFTR inhibitor, iOWH032.[2]

Both Napo and OWH also have backup programs for novel CFTR inhibitors in discovery/pre-clinical development.

	Strengths	Weaknesses	Opportunities	Risks
Ion channel inhibitors				
Most advanced program: Crofelemer, Phase II (iOWH032, Phase I)	General mechanism of action stops diarrhea regardless of cause of diarrhea Oral formulation of Crofelemer is not absorbed in the intestine avoiding	Malfunctioning CFTR is the cause of cystic fibrosis, therefore inhibition of CFTR outside the intestine poses a risk for severe side effects	Potential to treat multiple forms of watery diarrhea without need for diagnosing underlying cause Potential commercial	The standard of care for diarrhea is currently oral rehydration therapy, so introduction of the drug will require changes in treatment policy

	systemic inhibition of ion channels Crofelemer has positive Phase III safety and efficacy data available for use in HIV/AIDS antiretroviral-related diarrhea		market for treatment of irritable bowel syndrome or other non-infectious conditions that cause diarrhea in the developed world	

Back to Top

Vaccines

Vaccines in development for specific organisms that cause diarrhea are discussed under individual disease profiles. Vaccines that prevent general diarrhea symptoms are not being pursued. However, diarrheal diseases represent an interesting opportunity for multi-disease combination vaccines.

The ability of live attenuated Salmonella Typhi vaccines for the prevention of typhoid fever to be delivered orally, to be taken up by phagocytic cells, and to elicit robust serum antibody, mucosal, and cell mediated immune response also makes them potential candidates for vectors to express heterologous antigens. For example, Emergent BioSolutions is developing an attenuated *Salmonella Typhi* vector to express other bacterial, viral, and cancer cell antigens. The *Salmonella Typhi* vector may represent a way to elicit a robust immune response to multiple enteric pathogens using a single vaccine.

Diagnostics

Because the treatment of diarrhea is generally not specific to the underlying cause of diseases, diagnostics are not a high priority for diarrheal disease. However, a rapid test to differentially diagnose the cause of diarrhea, particularly between bacterial, viral or parasitic causes, currently in early-stage development, has the potential to change the treatment paradigm for this class of diseases.

References

1. Tradtrantip L et al. (2010) “Crofelemer, an antisecretory antidiarrheal proanthocyanidin oligomer extracted from Croton lechleri, targets two distinct intestinal chloride channels.” *Mol Pharmacol* **77**: 69-78. PMID: 19808995
2. One World Health press release, available here.

Back to Top

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Tools

Because product development tools are generally organism specific, please refer to profiles for the specific diarrhea-causing organisms, including cholera, ETEC, rotavirus, shigellosis, and typhoid, for more information.

Product Details

Crofelemer

Synonyms:
Crofelemer
NP-303
SP-303

Disease:
Diarrheal diseases

Specific Indication:
Infectious diarrhea

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Ion channels

Mechanism of Action:
Cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel and calcium activated chloride channel (CaCC) inhibitor

Molecule Class:
Natural product-derived oligomer

Administration Route:
Oral

Notes:	Clinical Trials:	Publications:
More information can also be found on this product at [Napo Pharmaceuticals]. Crofelemer is also in development for HIV/AIDS antiretroviral treatment-related diarrhea (Phase III) and irritable bowel syndrome (Phase II).		9886979

Discovery program for anti-diarrheal agents

Synonyms:
Discovery program for anti-diarrheal agents

Disease:
Diarrheal diseases

Specific Indication:
Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) chloride channel inhibitor; Calcium activ

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Ion channels

Mechanism of Action:

Molecule Class:

Administration Route:
Oral

Notes:	Clinical Trials:	Publications:

Disposable enterics card (DEC)

Synonyms:

Disease:
Diarrheal diseases

Specific Indication:

Technology:
Rapid Diagnostic Test (RDT)

Sample of Type:
Stool

Portability:
Handheld

Training Required:
Minimal

Notes:

For more information, see PATH's website

Clinical Trials:

Publications:

iOWH032

Synonyms:
3-(3,5-dibromo-4-hydroxyphenyl)-N-(4-phenoxybenzyl)-1,2,4-oxadiazole-5-carboxamide
iOWH032
Anti-secretory treatment for diarrheal disease

Disease:
Diarrheal diseases

Specific Indication:
Secretory diarrheas (cholera and other watery diarrhea)

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Ion channels

Mechanism of Action:
Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) chloride channel inhibitor

Molecule Class:

Administration Route:
Oral

Notes:

More information on this product is available from iOWH].

Clinical Trials:

Publications:

Second-generation synthetic CFTR chloride channel inhibitors

Synonyms:
Second-generation synthetic CFTR chloride channel inhibitors

Disease:
Diarrheal diseases

Specific Indication:
Infectious diarrhea

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Ion channels

Mechanism of Action:
Cystic fibrosis transmembrane conductance regulator (CFTR) inhibitor

Molecule Class:
Hydrazide derivatives

Administration Route:
Oral

Notes:

Clinical Trials:

Publications:

Developer Details

PATH (United States)

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Diarrheal diseases	Disposable enterics card (DEC)	Pre-clinical

University of Washington (United States)

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Diarrheal diseases	Disposable enterics card (DEC)	Pre-clinical

Micronics, Inc.

Type	Disease	Product/Research Program	Current Phase
Diagnostic	Diarrheal diseases	Disposable enterics card (DEC)	Pre-clinical

Galapagos NV (Belgium)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	iOWH032	Phase I

Institute for OneWorld Health (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	iOWH032	Phase I

Institute for OneWorld Health (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	Discovery program for anti-diarrheal agents	Discovery

Roche (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	iOWH032	Phase I

Roche (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	Discovery program for anti-diarrheal agents	Discovery

Glenmark Pharmaceuticals Ltd. (India)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	Crofelemer	Phase III

Napo Pharmaceuticals, Inc. (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	Crofelemer	Phase III

Napo Pharmaceuticals, Inc. (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	Second-generation synthetic CFTR chloride channel inhibitors	Pre-clinical

Luye Pharma (China)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	Crofelemer	Phase III

Salix Pharmaceuticals (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	Crofelemer	Phase III

Novartis AG (Switzerland)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	Discovery program for anti-diarrheal agents	Discovery

Anacor Pharmaceuticals, Inc. (United States)

Type	Disease	Product/Research Program	Current Phase
Drug	Diarrheal diseases	Discovery program for anti-diarrheal agents	Discovery