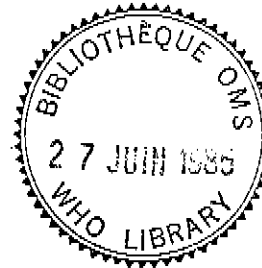




WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTE

CDD/DDM/85.1

ORIGINAL: ENGLISH



DIARRHOEAL DISEASES CONTROL PROGRAMME

- PCS  
Diarrhoea - *compil*  
title

## PERSISTENT DIARRHOEA IN CHILDREN - RESEARCH PRIORITIES

The Diarrhoeal Diseases Control (CDD) Programme of the World Health Organization is interested in supporting research to define the problem of persistent diarrhoea in children of the developing world. Very little information is at present available regarding the incidence, etiology(ies), and treatment of this clinical syndrome. This paper provides background information regarding the problem, and guidelines for developing research proposals. Additional detailed information, including an extensive bibliography, is available from the Programme.

## 1. DEFINITION OF PERSISTENT DIARRHOEA

1.1 Introduction

The term "persistent diarrhoea" is meant to define episodes of diarrhoea that begin acutely, but persist beyond the expected time period for the usual self-limited disease. Many of these prolonged periods of diarrhoea are associated with failure to grow normally, although growth failure is not an inherent part of the definition. The time period covered by the term "persistent" has not been agreed upon and it is hoped that prospective studies will provide a clearer definition. However, diarrhoea lasting for longer than 2-3 weeks is usually considered "persistent".

Certain well-defined, prolonged diarrhoeal illnesses such as coeliac disease, inflammatory bowel disease, genetically-determined illnesses, familial lethal diarrhoeas, and blind loop syndromes due to known causes, will not be included in this research initiative. Other less well-defined diarrhoeal illnesses, such as tropical sprue, intractable diarrhoea of infancy, and chronic non-specific diarrhoea of childhood may fall within the definition of persistent diarrhoea and (although they are thought to be relatively uncommon in children of the developing world) will be included, at least until a more concrete definition of the problem is reached.

1.2 Incidence

Persistent diarrhoea seems to be uncommon in developed countries, with the exception of a few well-defined clinical categories (see preceding section); however, it may be relatively common in developing countries. It has been estimated that 3-20% of children with acute diarrhoeal episodes have prolonged disease, but this has been looked at closely in only a few studies, and then usually in a retrospective fashion. The wide range of reported incidence can be attributed to the use of different case definitions and study methodologies, and the distribution of isolated pathogens. Careful prospective studies are needed to obtain information on the incidence of the syndrome.

1.3 Pathology studies of the small bowel

Many children with chronic diarrhoeas in all parts of the world have had small intestinal biopsies done. All, regardless of suspected etiology, have shown the same histological changes, which are varying degrees of inflammation and/or villous atrophy. Likewise, electron microscopy studies, done on a more limited scale, have shown only non-specific changes. One situation where biopsies can be diagnostic is following milk protein challenge, when "before and after" biopsies must be done to document the effects of milk protein

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intolerance. Biopsies can also be diagnostic in conditions like congenital sucrase isomaltase deficiency and lymphangiectasia. The implications of biopsy findings such as adherent bacteria, or the presence of Cryptosporidia or Giardia, or viral infection of enterocytes have yet to be determined.

## 2. RISK FACTORS FOR PERSISTENT DIARRHOEA

The risk factors for persistent diarrhoea are the underlying characteristics of the patient (host factors), recent or acute illness (pathogenic factors), diet (dietary factors), or therapy (intervention factors) that predispose to the development of persistent diarrhoea. Possible risk factors include:

### 2.1 Host factors

2.1.1 Age: The proportion of all diarrhoeal episodes that become persistent may be related to the age of the child. It is not clear whether this simply reflects the age-specific prevalences of other factors, such as malnutrition, diarrhoea due to specific enteropathogens, or feeding patterns, or whether there are susceptibility factors that are more directly related to age.

2.1.2 Malnutrition: Diarrhoeal episodes in general, as well as those due to specific agents, such as Shigella and enterotoxigenic Escherichia coli (ETEC) are of longer duration in children of poorer nutritional status (as assessed by anthropometry). It is believed that malnutrition is associated with gastrointestinal and/or immunological abnormalities that alter the host's response to infectious agents, resulting in a prolongation of illness. Specific micronutrient deficiencies (e.g., of specific vitamins or trace metals) could also predispose to persistent diarrhoea.

2.1.3 Gastric acid and gastric emptying time: Gastric acid is an important defense against ingested micro-organisms. A reduction in the level of acid could result in greater numbers of both enteropathogens and other organisms, such as may be found in children with small bowel colonization, reaching the intestine.

2.1.4 Immunological status: Passively acquired maternal IgG and breast-milk IgA, actively acquired systemic or local antibody, cell-mediated immune functions, and other factors such as opsonization and neutrophil chemotaxis must play a role in limiting infectious diarrhoeal illnesses; defects in these functions may contribute to persistent diarrhoea.

2.1.5 Intestinal motility: Abnormal motility of the small intestine may predispose to persistent diarrhoea. Increased motility could lead to rapid transit of ingested nutrients and malabsorption, while slowed motility could predispose to bacterial colonization of the small bowel. This may be particularly important in young infants, in whom coordinated peristaltic activity is not fully developed.

2.1.6 Pancreatic exocrine function: Malabsorption can result from deficiencies in pancreatic digestive enzymes (e.g., chymotrypsin, lipase, amylase).

2.1.7 Intestinal cell integrity and replacement rate: Recovery from acute diarrhoea due to infectious organisms that invade the epithelium or produce toxins that bind to the epithelial cells is, in part, due to replacement of these cells by dividing crypt cells. A lower rate of cell division and slower cell replacement have been found in malnutrition and could partially explain persistent diarrhoea in this condition. It is not known whether such alterations are associated only with young age or with other circumstances as well.

2.1.8 Intestinal mucins and glycoproteins: The intestinal mucous layer forms a relatively impermeable blanket that protects the mucosa from damage due to acid, bile salts, proteases, peptidases, and lipases and inhibits bacteria from binding to the mucosa. A diminished or abnormal mucous layer could predispose to mucosal damage or bacterial colonization, leading to persistent diarrhoea.

## 2.2 Pathogenic factors

2.2.1 Etiology of acute diarrhoea: Persistent diarrhoea may occur more frequently following acute illnesses caused either by specific enteropathogens, or perhaps by mixed infections with multiple enteropathogens.

2.2.2 Previous morbidity: Previous episodes of acute diarrhoea or systemic illnesses, such as measles, could result in persistent intestinal or immunological abnormalities that predispose the child to more prolonged illness during subsequent acute diarrhoeal episodes.

## 2.3 Dietary factors

2.3.1 Feeding patterns: The type and quantity of food that a child receives may play a role in the acquisition of diarrhoea - e.g., certain foods may more often be vehicles for enteropathogens or certain dietary components, such as lectins and enzyme inhibitors, may lead to mucosal alterations or inhibition of digestive enzymes, predisposing to diarrhoea.

2.3.2 Feeding during diarrhoea: The quantity of certain foods or nutrients (glucose polymers, disaccharides, etc.) that a child receives during acute diarrhoea may, in part, determine the degree and consequences of malabsorption. Likewise, there is a possibility that the feeding of certain proteins (animal milks, soya, etc.) may result in later intolerance of such proteins.

## 2.4 Intervention factors

2.4.1 Treatment: Treatment of the illness with antibiotics, antimotility agents or other drugs may be a risk factor. While a shortening of the duration of a few types of diarrhoea (e.g., shigellosis) would be expected with appropriate antibiotic therapy, a prolongation could occur if inappropriate drug therapy were used.

## 3. KNOWN CAUSES OF PERSISTENT DIARRHOEA

### 3.1 Persistent infection

Persistent infection and diarrhoeal illnesses have been associated with nearly all of the known bacterial and parasitic etiologies of acute diarrhoea, but their direct causal role is not always certain. The most common agents in this category are enteropathogenic *E. coli*, *Shigella*, *Campylobacter*, *Aeromonas*, *Clostridium difficile*, and *Giardia lamblia*. Since each of these infectious agents is capable of inducing mucosal damage and/or deranged intestinal function, additional pathological mechanisms for prolonged diarrhoea need not be invoked. Nevertheless, it has been hypothesized that small intestinal colonization by the infecting agent - as occurs with ETEC, for example - may favour further small intestinal colonization with other aerobic and anaerobic bacteria. Viral agents of acute diarrhoea have rarely shown this association, except in immunosuppressed hosts.

### 3.2 Carbohydrate malabsorption

Malabsorption, particularly of carbohydrates, during and following an episode of acute diarrhoea has been well described. Most common is lactose malabsorption, but temporary sucrose and even glucose malabsorption have also been found. Reduced intestinal disaccharidase concentrations and loss of mucosal surface area together may account for the decreased amount of available brush border digestive enzymes during diarrhoea. Rapid transit time can further limit the contact between carbohydrate substrates and the mucosal surface.

### 3.3 Protein intolerance

Feeding of cow's milk (or soya protein) during acute diarrhoeal illnesses has been thought to lead to milk (or soya) protein intolerance, although the diagnosis is often difficult to make and its frequency as a cause of persistent diarrhoea is not known.

#### 4. POSSIBLE CAUSES OF PERSISTENT DIARRHOEA

##### 4.1 Abnormal colonization of the upper gastrointestinal tract (see 3.1)

Colonization of the small intestine and possibly the stomach with aerobic and anaerobic bacteria has been associated with prolonged diarrhoea. The factors that determine whether colonization occurs and persists are not known, but the etiology of the initial infection and the host's nutritional status may be important (see section 2 for other possible risk factors).

##### 4.2 Abnormal bile salt or fat metabolism

Deconjugation of bile acids due to colonization with an abnormal microbial flora or malabsorption of bile acids due to terminal ileal dysfunction can result in steatorrhea and diarrhoea. In addition, an increase in faecal bile acids in the colon may directly lead to diarrhoea. Bacterial flora colonizing the small bowel may metabolise ingested long-chain fatty acids into toxic products which increase the secretion of fluids in the colon.

##### 4.3 Abnormalities of digestive enzymes

Deficits of enzymes, such as amylase, lipase, or trypsin, from pancreatic insufficiency or alteration in these enzymes by bacteria colonizing the intestine, could lead to malabsorption and diarrhoea.

##### 4.4 Small intestinal or colonic mucosal damage

Continuing damage, impaired renewal, or alteration in function because of persisting infection or post-infectious processes could result in an illness of long duration.

##### 4.5 Antibiotic usage

Indiscriminate use of antibiotics may prolong diarrhoea either by a direct toxic effect on the intestinal mucosa or by permitting the emergence of pathogenic bacteria that are otherwise suppressed by the normal flora.

#### 5. TREATMENT

There is presently no uniformly effective therapy for persistent diarrhoea, except for patients with known etiologies (see section 3). Among the treatment modalities evaluated have been antimicrobials, cholestyramine, antimotility agents, and diverse diets. The results with these different agents have been conflicting. It should be pointed out that hospitalization alone will sometimes bring about a cessation of diarrhoea.

#### 6. RESEARCH RECOMMENDATIONS

The ultimate goal of research into persistent diarrhoea is to answer questions that can lead to control of the problem through prevention and/or treatment. Since the importance of persistent diarrhoea is not known, an initial research priority is to define and quantify the problem and to identify children at high risk. An additional priority is to determine the pathophysiological mechanisms that cause persistent illness and develop specific treatment. A later research priority will be to test specific interventions in an operational setting.

##### 6.1 Epidemiological studies

These would be used to describe and measure the incidence of persistent diarrhoea and to determine the important risk factors. Specific types of epidemiological studies are:

6.1.1 Community-based: In this type of study, a group of children under five years of age are followed with routine household visits at least weekly for one year or longer. The information collected for the children in the study should include: occurrence of diarrhoea and other illnesses, enteropathogens associated with diarrhoeal episodes, growth (by anthropometric measurements - e.g., weight and length), dietary intake, treatments, the presence of specific risk factors and the consequences of prolonged diarrhoea on subsequent morbidity and growth. It may be efficient to add specific observations or tests related to prolonged diarrhoea (e.g., anthropometry) into ongoing community-based studies of acute childhood diarrhoea. In the analysis, the magnitude of the problem of persistent diarrhoea (e.g., incidence, proportion of all diarrhoeas that persist, effect on growth) can be described and individual risk factors evaluated, with appropriate statistical control for other potentially important factors. With prospective field studies of this type, it may be necessary to refer children with persistent diarrhoea to a health facility for clinical studies and/or therapeutic management. This type of linkage would provide ideal subjects for evaluation of the possible causes of persistent diarrhoea, as well as furnish an ethical safeguard for children with persisting illness.

6.1.2 Hospital-based (or clinic-based): In this type of study, children under five years of age who come to the health facility early in their acute diarrhoeal illness would be studied for their clinical characteristics and treatment practices during illness, and the presence of risk factors. Because one cannot predict during the acute phase which children will develop prolonged disease, acutely ill children must either be selected randomly or according to specific risk factors such as age, nutritional status, and/or acute diarrhoeal etiology. A specific time, e.g., 14 days after onset of diarrhoea, could be selected for a clinic or a home revisit to determine whether or not diarrhoea persisted during the interval between onset and follow-up. Children with abnormal outcome and/or continued diarrhoea would remain under observation for an additional period of time and then would be restudied.

This type of study would provide information on the proportion of cases of acute diarrhoea that persist beyond certain times, but it would not allow the true incidence of persistent diarrhoea to be calculated, since only acute diarrhoea cases that come to the health facility would be studied. The information on risk factors and on whether or not the acute episode persisted can be analysed to determine the relative importance of various risk factors in the development of persistent diarrhoea.

## 6.2 Clinical studies

These would be used to evaluate specific pathophysiological mechanisms as possible causes of persistent diarrhoea.

6.2.1 Observational: Patients are studied during the natural history of their disease by selected tests, e.g.:

- (a) Identification of known enteric pathogens, which would include agents that have been reported to be associated with persistent diarrhoea, as well as, in some studies, organisms that are not currently recognized as pathogens, e.g., adhering strains of E. coli.
- (b) Carbohydrate digestion and absorption studies which could include lactose, glucose, and complex carbohydrates. These could be done using the breath hydrogen test or direct blood sampling.
- (c) Nutrient balance studies on defined diets to describe and quantify malabsorption. These may include the development of non-invasive tests that can more easily be used to assess absorptive function or mucosal integrity in a field or clinical setting.
- (d) Measurement of faecal protein loss (e.g., by determining alpha 1 anti-trypsin in stool).

- (e) Evaluation of protein intolerance - e.g., milk or, less likely, soya proteins.
- (f) Measurement of gastric acid.
- (g) Evaluation of small bowel microbiology through closed, anaerobic tube sampling; both qualitative and quantitative studies are important. Organisms found should be assayed for enteric pathogenicity.
- (h) Measurement in small bowel fluid of bile acids, pancreatic enzymes, and specific secretory immunoglobulins.
- (i) Studies of entero-adherent organisms and intestinal antibodies by small intestinal biopsy studies.

6.2.2 Intervention-oriented: These studies would evaluate the efficacy of specific therapy targeted at the interruption of a hypothetically important pathophysiological mechanism. For example, studies could be directed towards eliminating a suspected pathogen (or "toxin") from the upper gastrointestinal tract based on the results of small bowel microbiology. If possible, they should be double-blind, placebo-controlled studies. Other studies could be directed towards dietary treatment regimes that would be carefully defined.

In any treatment intervention study, the patients can be selected either early during diarrhoeal illness or later, depending on the pathophysiological mechanism to be tested. In most studies, however, it will be preferable to begin studying patients during the acute phase of illness. Patients must be selected on the basis of certain pathological conditions identified during the initial evaluation, (e.g., presence of bacterial colonization of the small intestine) and entered into the study either randomly or on the basis of certain risk factors such as age, stool pathogen, and nutritional status. The clinical management of patients in the treatment and control groups should be similar, except for the specific treatment to be tested.

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