INTRODUCTION

Diarrheal diseases are the leading cause of death among children in developing countries. Diarrhea leads to estimated 1.4 to 2.5 million deaths per year ***(Gregorio et al., 2007).***

In industrialized countries, although death from diarrhea are uncommon occurrences, diarrheal disease remains an important cause of morbidity and increase substantial health care costs. In addition to its direct health burden, consequences of diarrhea include malnutrition, diminished growth, and impaired cognitive development are added increase the magnitude of the problem. In recent years, advances in diagnostics have led to the identification of new causative agents and have improved our understanding of etiologic role of previously recognized pathogens, guidelines for the management of diarrhea have been refined, and new strategies for prevention and control have been identified ***(Niehaus et al., 2002).***

AIM OF THE WORK

The aim of this work is to estimate the incidence, seasonality, and distribution of diarrheal diseases as well as to find out the commonest enteric pathogens causing diarrhea in Egyptian children and try to evaluate the economic burden of diarrheal diseases and the need for the future enteric diseases vaccines.

DIARRHEA

Definition

Diarrhea is an increase in daily stool weight above 200 gm, for most individuals eating western diet, normal stool weight ranges between 100 and 200 gm ***(Soffer, 2001)***.

In clinical practice the term diarrhea is used to describe an alteration in normal bowel movement characterized by an increase in water content (liquidity of stools), volume, or frequency (more than 3 times per day), This is applied more in adult but as regards frequency in children, it is normal for young infant to have up to three to ten stools per day, although this varies depending on the child's diet (breast milk versus formula), older infants, toddlers, and children normally have one to two motion/ day so it is considered diarrhea if stool frequency increases to twice the usual number**.** According diarrhea could be summarized as stool that contains blood or mucous, or is watery or less formed with greater occurrence than usual, and is not contained by diapers or toilet use ***(Guerrant et al., 2001)***.

On the basis of clinical and epidemiologic parameters, episodes of diarrhea are classified into four categories:-

Acute diarrhea is defined as a episode of diarrhea of less than 14 days in duration. ***Persistent diarrhea*** is diarrhea of more than 14 days in duration. ***Chronic diarrhea*** is considered if illness persists for more than 4 weeks and ***dysentery*** is refers to presence of blood and mucous in diarrheal stool ***(Soffer, 2001)***.

Causes of acute diarrhea

I. Infectious diarrheas *(Gadewar and Fasano, 2005)*

Most of them are acquired through the feco-oral route by way of food or water contamination.

Viruses:

* Adenovirus (type 40, 41)
* Calcivirus
* Astrovirus
* Rotavirus
* Narwalk virus
* Cytomegalovirus

Bacterial

* Escherichia coli.
* Vibriocholera.
* Yersinia spp.
* Bacillus cereus
* Staphylococcus aureus
* Clostridium difficile
* Campylobacter spp.
* Shigella spp.
* Clostridium perfringes
* Salmonella spp.

Parasitic, protozoal

* Entamoeba histolytica
* Cryptosporidium parvum
* Microsporidium
* Giardia lamblia
* Cyclospora cayetanensis
* Isosporabelli

II. Non infectious diarrhea *(Scheidler and Giannella, 2001)*

* Medications
* Inflammatory bowel diseases
* Pelvic inflammation (e.g., rectosigmoid abscess)
* Recent ingestion of poorly absorbable sugars (e.g., lactulose)

Table (1): The major gastroenteritis syndromes and most common etiologic agents

Syndrome	Bacteria	Viruses	Parasites	Comments
Inflammatory diarrhea, including dysentery	*Shigella* spp., enteroinvasive *E. coli*, enterohemorrhagic *E. Coli, Salmonella enteritidis, Campylobacter jejuni, Vibrio parahaemolyticus, Clostridium difficile*	None	*Entamoeba histolytica*	Involves colon; fecal leukocytes often present
Non-inflammatory diarrhea	Enterotoxigenic *E. coli*, Enteroaggregative *E. Coli, Vibrio cholerae, clostridium perfringens, Bacillus cereus, Staphylococcus aureus*	Norovirus, Rotavirus, enteric adenovirus, astrovirus, etc.	*Giardia lamblia, Cryptosporidium parvum, Isospora belli, Cyclospora cayetensis,* microsporidia	Involves proximal small bowel; fecal leukocytes usually absent
Diarrhea with systemic disease, including enteric fever	*Salmonella typhi,* other *Salmonella spp., Yersinia enterocolitica, Campylobacter* spp.	None	None	Involves distal small bowel; fecal mononuclear leukocytes may be present

(Guernant, 2001)

Incidence:

Infectious diarrhea is one of the most common causes of death in children. About 4 billion episodes of diarrhea/ year cause 1.5 million deaths mostly in children less than 5 years (13-21% of all death of children aged < 5 years)

(Lorgelly et al., 2008). For children under 5 years of age in developing countries, there is a median of 3.2 episodes of diarrhea/ child/ year. The mortality study revealed that 4.9 children per 1000 per year died as a result of diarrheal illness in the first 5 years of life ***(Billoo and Ahmed, 2000).***

The total number of deaths from diarrhea has been reduced substantially. Although the total number of deaths from diarrhea is still unacceptably high, these numbers have been reduced in 1982, an estimated 5 million deaths/ year occur, and in 1992, the estimated annual declined to 3 million / year ***(Synder and Merson, 1992).***

Table (2): Estimates of mortality from Diarrheal diseases among children of developing countries.

Source	Year of estimate	Year of publication	Deaths per year (millions)
Rohde	1976	1984	5
Snyder and Merson	1982	1982	4.6
Institute of Medicine	1986	1986	3.5
Martines and Phillips	1990	1990	3.2
Bern et al.	1992	1992	3.3
World development report	1993	1993	2.5
Murray and Lopez	1997	1997	2.4-2.9
Kosek et al.	2000	2003	2.1-4.7
Parashar et al.	2000	2003	1.7-3.0
World Health Organization	2001	2002	1.4
World Health Report	2002	2003	1.6

(WHO, 2003)

Predisposing factors of acute infectious diarrhea

Infectious diarrhea is related to environmental conditions including:

- Close living and working condition
- Poor sanitation and hygiene
- Unsafe water supplies
- Poor education
- Inadequate sewage disposal

(Gadewar and Fasano, 2005)

Table (3): Association of gastrointestinal infections with specific factors

Factor	Infectious agent(s)
Backpacking and drinking from mountain streams	Giardia lamblia
Dairy products	Salmonella, campylobacter, Yersinia, Listeria
East coast and gulf coast	Halophilic vibrios; e.g., vibrio parahaemolyticus, vibrio vulnificus
Egg and potato salads, pastries	Staphylococcus aureus
Eggs	Salmonella spp.
Fresh fruit	Cryptosporidium spp., Cyclospora spp.
Fried rice	Bacillus cereus
Hamburger	Escherichia coli O157:H7
Immunosuppressed patients	Cryptosporidium, Isosporabelli, Mycobacterium avium, strongyloides stercoralis, cytomegalovirus, candida.
Shellfish	Vibrio spp., noroviruses, hepatitis A virus

(Koneman et al., 2006)

Pathophysiology

Most of the fluids in the intestine are absorbed in the small intestine, and only about one to two liters are presented to the colon, most of this are absorbed as it passes through the colon, leaving a stool out put of about 100 to 200 gm daily. Water is absorbed passively in the gut, dependent on the osmotic gradient. Consequently, diarrhea is due to excess osmotically active substances in the stool, the result of either decreased absorption of nutrients and electrolytes or excess secretion of electrolytes, or both ***(Sellin, 1998)***.

There are 4 mechanisms of diarrhea, the major ones are osmotic and secretory diarrhea ***(Sellin, 1998)***

I. Osmotic diarrhea

This type of diarrhea is due to the presence of an un-absorbable or poorly absorbable solute that exerts an osmotic pressure effect across the intestinal mucosa, resulting in excessive water output. Because the diarrhea is caused by the solute, it tends to stop during fasting. In addition, there is an increased stool osmotic gap. The total stool osmolality is close to the serum osmolality, i.e., 290 mOsm/kg. Normally, most of the stool osmolality is accounted for by the sum of stool sodium and potassium concentrations multiplied by two. Products of colonic fermentation, such as short chain fatty acids, account for

the remaining osmolarity, i.e., osmostic gap. Stool osmotic gap is calculated as follows: Osmotic gap = 290 – [2 (stool Na + Stool K)]. In osmotic diarrhea, the presence of un-absorbable solute contributes significantly to the stool osmolality and the concentrations of electrolytes is lower, resulting in an increased osmotic gap. The osmotic gap in all forms of osmotic diarrhea is greater than 50 mOsm/kg ***(Schiller, 2000).***

Causes of osmotic diarrhea

1. Disaccharidase deficiency (lactose intolerance)
2. Malabsorption.
3. Poorly absorbed sugars (lactulose, sorbitol, mannitol)
4. Laxatives (magnesium, sodium citrate, sodium phosphate)
5. Mg containing antacids

(Schiller, 2000)

II. Secretory diarrhea

In this type of diarrhea there is abnormal ion across the intestinal epithelial cells, which results in increased secretion, decreased absorption, or both. There is no osmotic gap or decreased, and as the diarrhea is not related to intestinal contents, it typically does not stop with fasting ***(Scheidler and Giannella, 2001)***.

Causes of secretory diarrhea

Acute secretory diarrhea

- Cholera as a classic example
- Enterotoxigenic E. coli (ETEC)

Chronic secretory diarrhea

- Celiac sprue
- Collagenous colitis
- Hyperthyroidism
- Stimulant laxatives (phenolphthalein, senna, bisacodyl)

(Scheidler and Giannella, 2001).

III. Altered motility

Enhanced motility, resulting in rapid gut transit and decreased contact time between luminal contents and absorptive epithelial cells. Causes include hyperthyroidism, irritable bowel syndrome and post-gastrectcomy and post-vagotomy status. **Slow motility,** may result in bacterial overgrowth, which causes deconjugation of bile acids and results in steatorrhea. Altered motility as the primary cause of diarrhea is mostly seen in cases of chronic diarrheas. It is often a diagnosis of exclusion ***(Soffer, 2001)***.

IV. Exudative diarrhea

Extensive injury of the small bowel or colon mucosa may result in fluid and protein loss into the intestinal lumen

and ensuing diarrhea. Causes include invasive bacterial infections and inflammatory bowel diseases.

It is important to note that more than one mechanism may coexist. For example, in infectious and inflammatory conditions, malabsorption leading to osmotic diarrhea and active secretion ***(Soffer, 2001).***

Pathogenic mechanisms

Enteric bacteria produce clinical disease by two primary mechanisms: the production of toxins and invasion of the enteric mucosa. A variety of toxins are produced by enteric pathogens. Some agents, such as V. cholera and ETEC produce enterotoxins that cause diarrhea by activation of secretory mechanisms in the intestinal mucosa. ETEC produces both heat stable and heat labile toxins. Others, such as S. dysenteriae and Vibrio para hemolyticus, produce cytotoxins that lead to destruction of the intestinal epithelium ***(Podewlis et al., 2004).***

Dysentery results form either the production of cytotoxins or from direct invasion of the intestinal mucosa by pathogens such as shigella and enteroinvasive E.coli. Some pathogens, such as salmonella typhi and yersenia, can penetrate the intestinal mucosa and disseminate through the lymphatics so enter the blood stream, resulting in systemic manifestations ***(Morris et al., 2003).***

Enteric viruses cause diarrhea through multiple mechanisms, including interfering with gastrointestinal motility or destroying the intestinal epithelium and reducing brush border enzymes, consequently, produces osmotic diarrhea. Studies in mice indicate that a non structural protein of Rotavirus, NSP4, acts as an enterotoxin and causes secretory diarrhea by altering epithelial cell function and permeability ***(Estes et al., 2003).*** In addition, Rotavirus may evoke fluid secretion through activation of the enteric nervous system in the intestinal wall. Recent data indicate that Rotavirus antigen and RNA are present in serum of children with Rotavirus infection, suggesting that Rotavirus possibly escapes the intestinal tract in children, resulting in antigeniemia and viremia ***(Blutt et al., 2003).***

Prognostic factors:

The synergistic relationship between malnutrition and diarrhea is well recognized ***(United Nations Children's Fund, 2003)***. Diarrhea has prolonged duration and is more severe in children with macronutrient or micronutrient deficiencies, and persistent diarrhea often results in malabsorption and significant weight loss, further promoting this cycle. Children with poor nutritional status have an elevated risk for diarrheal death. Zinc deficiency suppress immune system function ***(Rice et al., 2000)***, similarly, children with immunosuppression secondary to infection with HIV or other chronic conditions may have an increased risk for the development of clinical illness and frequent recurrence of diarrheal episodes ***(Mitra et al., 2001).***

PRACTICE GUIDELINES FOR THE MANAGEMENT OF INFECTIOUS DIARRHEA

Introduction

Two converging factors highlight the growing need for clear guidelines for the diagnosis and management of infectious diarrhea. ***First***, there is increasing recognition of a widening array of enteric pathogens associated with illnesses of the gastrointestinal tract. With the rapid globalization and industrialization of our food supply and with multiplicity of recognized pathogens and diagnostic tools, the challenges of determining optimal, cost effective means for appropriate diagnosis, clinical management and public health control of diarrheal illnesses are great ***(Guerrant et al., 2001).***

The ***second factor*** we entered an era when health care is increasingly managed with an eye to cost containment. Critical to developmental cost effective approach to the evaluation and management of infectious diarrhea is the selective use of available diagnostic methods, therapies, and preventive measures. These must be targeted to the clinical scenarios in which they will yield the greatest benefits, certain factors must be taken into account: the patient's history, exposure, and immune status, and the nature of the illness: its severity and duration and whether the process is inflammatory or hemorrhagic ***(Vernacchio et al., 2006).***

Table (4): Summary of recommendations for managing infectious diarrhea

Recommendation	Ranking[a]
Initiate rehydration (oral whenever possible)	A-I
Perform a thorough clinical and epidemiological evaluation for any significant diarrheal illness (profuse dehydrating, bloody or febrile diarrhea, or illness in infants, elderly, or immunocompromised patients). That is, ascertain how the illness began; stool characteristics (frequency and quantity); symptoms or signs of hypovolemia; travel history; whether the patient attends a day care center; whether the patient has ingested raw or undercooked meat, raw seat food, or raw milk; whether the patient's contacts are ill; the patients sexual contacts, medications, and other medical conditions, if any	A-II
Perform selective fecal studies	B-II
Institute selective therapy for Traveler's diarrhea Shigellosis Campylobacter infection	 A-I A-I B-II
Avoid administering antimotility agents with bloody diarrhea or proven infection with Shiga toxin producing Escherichia coli	E-I
Selectively administer available vaccines[b] and for travelers to (or residents of) areas where typhoid is endemic, administer typhoid vaccine (parenteral Vi or oral Ty21A)	B-II

[a] Letters indicate the strength of the recommendation and Roman numerals indicate the quality of evidence supporting it, respectively.

[b] Oral live (103 HgR) and killed (WCBS) cholera vaccines are available outside the United States for travelers to areas where cholera is endemic, although diarrhea is uncommon in careful travelers (B-II)

(Guerrant et al., 2001)

Table (5): Categories indicating the strength of recommendations and the quality of evidence on which they are based

Category	Definition
Strength of evidence	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least 1 well designed clinical trial without randomization, from cohort or case controlled analytic studies (preferably from more than one center), from multiple time series studies, or from dramatic results in uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience descriptive studies, or reports of expert committees

(Guerrant et al., 2001)