ETIOPATHOGENIC AND CLINICAL METHODS IN ACUTE GASTROENTEROCOLITIS IN CHILDREN

RODICA FĂRCĂŞANU

PhD candidate, "Lucian Blaga" University of Sibiu

Abstract: *Acute infectious diarrhoea is called acute gastroenterocolitis. Although it has been considered a benign affection, acute gastroenterocolitis remains a major cause of morbidity and mortality in children all around the world. In infectious etiology, viruses occupy the first position, followed by bacteria, parasites and fungi. The type of disease is defined by the virulence of the germs, through aggressiveness and toxigenity properties. The pathogenic mechanisms of germs' action in enterocolitis may be classified in the following models: enterotoxinic, enteroinvasive, cytotoxic and enteroadherent. Each ethiopathogenic model is responsible for a clinical picture characteristic for secretory or osmotic diarrhoea.*

Keywords: *acute infectious diarrhoea, pathogenic mechanism, ethiopathogenic models.*

Rezumat: *Diareea acută de origine infecţioasă poartă denumirea de gastroenterocolită acută. Deşi considerată o afecţiune benignă, gastroenterocolita acută rămâne în lumea întreagă o cauză majoră de morbiditate şi mortalitate la copii. În etiologia infecţioasă virusurile ocupă prima poziţie, urmate de bacterii, paraziţi şi fungi. Tipul de îmbolnăvire este definit de virulenţa germenilor prin proprietăţile de agresivitate şi toxigenitate. Mecanismele patogenice de acţiune a germenilor în gastroenterocolita acută pot fi încadrate în următoarele modele: enterotoxinic, enteroinvaziv, citotoxic şi enteroaderent. Fiecare model etiopatogenic este responsabil pentru un tablou clinic caracteristic, de diaree secretorie sau osmotică.*

Cuvinte cheie*: diaree de origine infecţioasă, mecanisme patogenice, modele etiopatogenice*

INTRODUCTION

Definition: Acute infectious diarrhoea is called acute gastroenterocolitis. Although it has been considered a benign affection, acute gastroenterocolitis remains a major cause of morbidity and mortality in children all around the world, counting 1,8 million of deaths annually in children under the age of 5 and approximately 17% of the total of infantile deaths.(1)

The infectious **etiology** is given by viruses – 60-80% (rotaviruses, parvovirus-like, coronavirus, adenoviruses, enteroviruses; by bacteria - 20% (Escherichia coli, Salmonella, Shigella, Campylobacter jejuni, Staphylococcus aureus, Clostridium, Yersinia enterocolitica); by ***protozoans*** (Giardia, Entamoeba histolytica); by parasites (Strongyloides, Trichuris) and fungi.(2,3,16)

Gastroenterocolitis etiologic factors are transmitted orally or by faces. Other possible food sources or the contaminated water should also be taken into consideration, as well as the human to human transmission. Salmonella, Sigella or Giardia diarrhoea occur epidemically, while the viral diarrhoea (rotaviruses, caliciviruses or astroviruses) occur endemically, each child being infected according to the type of exposure.(4)

The type of disease is defined by the virulence of the germs, through aggressiveness and toxigenity properties.

The pathogenic mechanisms of germs' action in enterocolitis may be classified in the following models: enterotoxinic, enteroinvasive, cytotoxic and enteroadherent.(5, 6)

I. The enterotoxinic model implies: the multiplication of the germ at the lumen level, mucosal adhesion through fimbriae and pili (CFA), enterotoxins release (proteic substance).(2,5)

Enterotoxinogenesis property depends on the existence of the specific plasmids and occurs only in the strains having it. This is the way of action of Vibrio cholerae, ETEC (E.coli enterotoxigen), Clostridium perfringens, Bacillus cereus, Shigella dysenteriae I, Salmonella.

The way of action of ET enterotoxins supposes:(5)

1. Reception of the pathologic information
   - Existence of membrane receptors specific for ET at the level of small intestine
   - Adherence of the germ to this receptors due to the CFA-factor of colonization, fimbriae or pili (filament-like proteic structures)
   - ET release
2. Stimulation of the cell mediators
   - Cyclic nucleotides and calcium
   - Acetylcholine and serotonin
   - (Metabolites of the arahydonic acid – do not intervene in this model)
3. Alteration of the absorption mechanisms and physiologic secretion

ET action on the cell mediators leads to the increase of permeability to Cl- and to the inhibition of

neutral NaCl and of the HCO3- secretion. At lumen level, an increased secretion of Cl-, Na+, HCO3- and water may be observed, which is diffused through osmosis. As a result, secretory diarrhoea will occur, which exceeds the absorption capacity of the colon, resulting in aqueous diarrhoea. CT induces a secretion of 5-HT by the enterocromafine cells, that stimulate ENS (enteric nervous system) and increases the intestinal peristaltis.(7,8) ET acts through a number of mechanisms.

Table no. 1. ET distribution according to the mechanism of action.

ET – increase the production of AMP	ET – increase the production of GMPc	ET - affect Ca++ - calmodulin	ET - stimulate 5-HT serotonin
•V.cholerae CT •E.coli LT (labile toxin) •Salmonella •Aeromonas Spp •Shigella dysenteriae	•E.coli ST (stabile toxin) •Klebsiella pneumonie •Yersinia enterocolitica	•Clostridium difficile	•V.cholerae CT

Clinically, we will have aqueous diarrhoea with AIDS and acidosis, abdominal dystensia and mild fever.(9)

II. The enteroinvasive model implies: penetration in the intestinal mucosa, the multiplication of the germ in the intestine structures, morphological alterations ± enterotoxins release. This is the way of action of Shigella, Salmonella, EIEC (E.coli enteroinvaziv), Yersinia enterocolitica, Campylobacter jejuni, Entamoeba histolitica, viruses.(10,11)

Regarding bacteria, the germ is included in the interior of the epithelial cell. Germs multiplication takes place in different structures. Thus, in:

- **Shigella** and **E. coli enteroinvasive EIEC (O28,O112,O124,O136,O143)**, the vesicles containing the germs are divided in the interior of the cytoplasm; the multiplication of bacteria takes place locally, destruction of the epithelium also occurs, as well as the ulceration of the mucosa.(14,15,22)
- **Salmonella**, the vesicles containing the germs traverse the enterocytes, the germ being localised in lamina propria.(10,13)
- **Yersinia enterocolitica serotypes O3,O8,O9,** the germ is multiplied and affects the small lymphatic intestinal noduli and the Peyer plates, which bring about to microabcesses. **O3 and O8** stereotypes elaborate a thermostable enterotoxins that activates guanylate cyclase.(11)
- **Vibrio parahaemolyticus,** release a cytotoxin – thermostable haemolysin.(12)

The multiplication of the germ at the level of mucosa produces:(16)

- Acute inflammation with kynin release (bradykinin, kallydin) and metabolites of the arahydonic acid (prostaglandin PGL, leukotriene LCT).
- Hypersecretion, through the increase of adenylate and guanylate cyclase and through the activation of the Ca-calmodulin system.
- Stimulation of the peristalsis through the increase of 5-HT.

The consequence of damaging the epithelium with inflammation and ulceration and of the PGL and LCT release, will turn in diarrhoea through intestinal exudate and hypersecretion and in an inflammatory syndrome.(18,21)

Clinically, we will notice *fever, abdominal pains* and *a dysentery-like syndrome* – tenesmus, frequent stools (quantitatively reduced), pathologic elements: mucus, blood, pus.(8, 9)

In viruses (rotavirus, astrovirus, parvovirus and parvovirus like), the production mechanism is the following:(19, 20)

- Rotaviruses invade the mature absorbing cells, become fixed on the specific receptors (decapsidation enzymes) and lose their capsid.
- The viral replication takes place in viroplasma.
- NSP4 non-structural viral proteins lead to the increase of the intracellular Ca by ER (endoplasmic reticule)
- NSP4 act on the enterocromafin cells and bring about the 5-HT release, which stimulates ENS and increases Ca.
- Chemokines and PGL released by the infected enterocytes stimulate ENS.
- NSP4 has also toxin like activity.

As a result, the following are produced:

- The tearing of the cellular junctions, which will lead to an exudation of electrolytes and water.
- The destruction of the microvilli skeleton, villus aplatisation – the absorption area for sodium and water and for disaccharides decreases (through the destruction of disaccharides of the brush border).

It results: *malabsorption of electrolytes, water and malabsorption of disaccharides,* which will lead to *osmotic diarrhoea.*

Clinically, we will observe: nausea, vomiting, osmotic diarrhoea and the decrease to disaccharides – lactosis. **Parasites: Entamoeba histolytica** – protozoan, traverses the colonic mucosa, reaches the sub-mucosa, where it multiplies and produces inflammatory, ulcerative lesions and cellular infiltration (due to the enzymatic equipment: hyaluronidasis, proteases, mucopolysaccharides). (13)

It results:

- Mucus hypersecretion
- Lose of serum protein in lumen, which will lead to exudation.
- PGL release, which induce secretion through the stimulation of the cyclic nucleotides.

Clinically, we will notice a dysentery-like syndrome, fulminant ulcerative colitis, toxic megacolon and perforation.

III. The cytotoxic model involves the release of cytotoxins and cell affection and death. Is the way of action of: Shigella, EPEC (enteropathogenic E. coli), EHEC (enterohemoragic E.coli), EaggEC (enteroaggregative E. coli), Clostridium difficile.(5,6,7)

The mechanism of production: **Shigella dysenteriae 1** releases **– Shigella toxin STx**

- Strong inhibitor of the protein synthesis at ribosome level.
- Leads to the intracellular increase of Ca, of proteinkinase, inositol triphosphate

- Act on ENS
- Alters the transportation of Na+ and Cl-
- Neurotoxic action (explaining the convulsions at the debut of the disease)

EHEC O157: H7 releases a violent toxin – verotoxin, with similar action as Shiga toxin: It produces hemorrhagic colitis and hemolytic uremic syndrome SHU (thrombocytopenia, platelet activation and microthrombs formation)

EAggEC releases - **Shiga toxin like** and **haemolysin:** Produces persistent diarrhoea

Clostridium difficile releases **– toxin:** At the level of the colon cells, it produced the desegregation of the actin filaments with the tearing out of the junctions; Increases the pro-inflammatory activation of cytokines by the intestinal epithelium.

IV. Enteroadherent model supposes: *adherence to the enterocytary mucosa and cytostructural alterations.* It is the way of action of EPEC, EAEC (Enteroadherent E. coli), Giardia. (5,11,17)

EPEC (O26, O55, O111, O125….O128)

- It adheres to the intestinal epithelium through an extramembrane protein, **Intimin**, produced by gena eae A and produces lesions of the brush border of the microvilli "attaching and effacing" (attachment and erasure).
- The re-arrangement of the actin filaments will occur, which form pedestals in cup-shape, near the adherence place of the bacterium.
- The lose of integrity of the cellular junctions and of the mitochondrial function, which will lead to the lose of electrolytes, even cell death.

Clinically, *aqueous diarrhoea in the new born up to the age of 2 may occur*. Increased susceptibility of the new born is due to the fact that IgM is not transferred from mother to foetus. Mention must be made of the fact that naturally fed new born are immune to EPEC - IgA from colostrum and the mother milk prevents the adherence.

Giardia lamblia. Trophozoite adheres to the mucosa area in intimate contact with the enterocytes glycocalix. The following are resulting:(23)

- Minor lesions of the microvilli and of the brush border.
- Reduces the activity of the membrane enzymes activity, leading to the *osmotic diarrhoea.*
- Unabsorbed disaccharides produce an afflux of water in jejunum and their incomplete resorption in colon.
- The fermentation of disaccharides in colon by the intestinal bacteria brings about the accumulation of acetic acid and lactic acid
- Motility disorders altering water absorption.

Clinically, we will record: diarrhoea with stinking stools, flatulence, epigastric pains, nausea, vomiting and transitory intolerance to disaccharides.

REFERENCES

1. Adam Levine, MD, MPH, Staff Physician, Department of Emergency Medicine, Brigham and Women's Hospital & Massachusetts General Hospital). Pediatrics, Gastroenteritis - Last Updated June 16, 2008.
2. Conte MP, Schippa S, Zamboni I, Penta M, Chiarini F. Gut-associated bacterial microbiota in paediatric patients with inflammatory bowel disease. Gut, Dec. 2006;55(12).
3. Gherghina I. Actualităţi în diareea acută la sugar şi copilul mic. Medical Business, nr.29-30, 2006.
4. Ford A.C, Forman D. Who consults with dyspepsia? Results from longitudinal 10 years follow-up study. The American Journal of Gastroenterology, May 2007;105(5).
5. Maiorescu M, Anca I. Bolile diareice acute ale sugarului şi copilului mic. Ed.Academiei, Buc.1985.
6. Ciofu E, Ciofu C. Esenţialul în pediatrie. Ed.Amaltea, Bucureşti 2002.
7. Georgmaneanu M. Tratat de pediatrie vol. 2.Nutriţie şi alimentaţie raţională. Boli ale tractului digestiv. Ed. Med. Bucuresti 1984.
8. Neamţu M. Cazan Corina. Patologie digestivă la copil. Ed. ULB Sibiu, 2005.
9. Ţurcanu L. Simedrea I. Bolile digestive la copil. Ed. Med. Bucuresti 1988.
10. Wyllie R, Williams JS, Hyams SJ. Pediatric Gastrointestinal and Liver Disease. Third Edition. Saunders Elsevier, June 2006.
11. Diskin A, MD Chair Department of Emergency Medicine, Mount Sinai Medical Center. Gastro- enteritis Medicine, Last Updated April 10, 2007.
12. Gardiner J, Brown Ch. Gastroenteritis. Last Editorial Rewiew 8.10.2005. Department of Emergency Medicine, Pitt Country Memorial Hospital, East Carolina University.
13. Levine A, Santucii Karen. Paediatrics Gastroenteritis Medicine, Last Updated June 14, 2006.
14. Lynn Jennifer, MD, Department of Internal Medicine, Division of Gastroenterology, Lennox Hill Hospital. Gastroenteritis. Medicine, Last Updated August 17, 2006.
15. Kojimo Keishi, Muschi MV, Ropeleski MJ et all. Escherichia coli LPS induces shock protein 25 in intestinal cell trough MAP kinase activation. American Journal of Physiology 2004;286(4).
16. Iusan Mirela. Etiopatogenia sindromului post enteritic la copil. Medicina Moderna 2006;13(2).
17. The Merck Manual of Medical Information: Gastroenteritis. Second Home Edition, Febr 2003.
18. Otte JM, Podolsky D. Functional modulation of enterocytes by gram positive and gram negative Microorganism. American Journal of Physiology 2004;286(4).
19. Mayo Clinic.com.Viral Gastroenteritis. March 10 2006.
20. National Digestive Diseases Information Clearinghouse. Viral gastroenteritis. NIH Publication No. 06-5103, Febr 2006.
21. Leon AJ, Gomez E, Garrote JA, Arranz E. The pattern of cytokine expression determines the degree of mucosal damage. Gut March 2007;56(3).
22. Rhodes MJ. The role of Escherichia coli in inflammatory bowel disease. Gut Mai 2007;56(5).
23. Buret AG. Mechanism of epithelial dysfunction in giardiasis. The American Journal of Gastroenterology, Mai 2007;105(5).