

Management of acute diarrhea: current and future trends

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Abstract. – Acute diarrhea is a very common symptom, which may recognize different causes and is basically the expression of an altered homeostasis of the bowel, which overcame current classifications. When approaching patients with acute diarrhea, we should firstly check body temperature and vital parameters and secondly provide a general medical examination mainly focused on the abdomen, in order to exclude surgical causes of diarrhea, such as acute appendicitis, diverticulitis, intestinal occlusion and others. Another important aspect is the assessment of the level of hydration in order to provide the right amount of fluids. There is no current indication for the administration of loperamide in infectious diarrhea, but there is a strong rationale for new class of drugs, which may be defined as “mucous regenerators”, such as gelatin tannate. Further studies are needed on this matter in order to test the effect of gelatin tannate in adult patients with acute diarrhea.

Key Words:

Diarrhea, Infection, Gelatin, Probiotic.

Introduction

Acute diarrhea is a very common symptom, which may recognize different causes¹. In developed Countries acute diarrhea is more prevalent in children or older patients affected by a greater number of diseases or taking many drugs at the same time. It may also appear quite often in travelers. In contrast, in developing Countries infectious diarrhea or antibiotic associated diarrhea are the most common causes¹.

A full knowledge of the pathological processes behind acute diarrhea is the key to establish an adequate treatment². Diarrhea is basically the expression of an altered homeostasis of the bowel,

which overcame current classifications³. In fact, during diarrhea, all components of the so called gut barrier fail to exert their physiological action and, among different mechanisms, some antigens or components of microorganisms composing the normal “gut microbiota” may penetrate the intestinal mucosa triggering the activation of the immune and non immune system³.

In this article we illustrate how to manage acute diarrhea based on the most recent findings and we provide an overview on future trends.

Causes of diarrhea

Acute gastroenteritis is a frequent cause of diarrhea; additional symptoms such as vomiting, abdominal pain or even fever may also occur⁴. Gastroenteritis may be generated from a number of infectious or not-infectious factors, including viruses (especially norovirus, rotavirus and adenovirus), bacteria (*Campylobacter spp*, *Escherichia coli*, *Salmonella spp*, *Shigella spp*, *Vibrio cholerae*, and others), bacterial toxins, even in the absence of producing bacteria (contaminated food by toxins produced by *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*), parasites (*Cryptosporidium*, *Entamoeba histolytica*; *Giardia lamblia*, *Anisakis* and others) and food allergy⁵.

While it is estimated that acute diarrhea may affect 20% of the population at least once in a year, an infectious origin may be recognized in 30-40% of the subjects with a higher prevalence of viruses⁵. Sometimes, the infectious origin may be only supposed. Anyway, there are several risk factors related with this condition, including lack of personal hygiene, consumption of not properly refrigerated or cooked food, deficit of the immune system, hypochlorhydria and achlorhydria⁵.

The anamnesis, together with the evaluation of the initial symptoms, may be very useful in terms of defining a possible infectious origin⁵. In fact,

while incubation period of viruses is 24 hours, it is much longer in case of bacteria (4-5 days) or parasites (7-10 days).

At the same time, is very important to know whether people exposed to the same food developed the same symptoms⁵. Fever often reflects an infectious origin, whereas bloody diarrhea may be related to bacterial causes or to infection sustained by *Entamoeba histolytica*⁵.

Diarrhea may also occur in other diseases either systemic or localized in the GI tract. Inflammatory bowel diseases, such as Crohn disease or ulcerative colitis are very often clinically characterized by diarrhea, as well as acute appendicitis or diverticulitis. In these cases diarrhea is usually bloody with or without mucous or urgency and tenesmus, and it could represent the clinical presentation of a first episode. Traveler' diarrhea is also quite frequent in the general population together with irritable bowel syndrome and paradoxical diarrhea in constipated patients. Finally, diarrhea may also occur in patient with Addison' disease or with food allergies, as well as in patients under radiation therapy and chemotherapy^{6,7}.

How to manage a patient with acute gastroenteritis in the Emergency Room

First of all we should check body temperature and vital parameters⁸. Secondly patients should undergo general medical examination particularly focused on the abdomen, in order to exclude surgical causes of diarrhea, such as acute appendicitis, diverticulitis, intestinal occlusion and others⁸.

Another important aspect is the assessment of the level of hydration; this issue is particularly important in children as well as in older patients. In particular, dehydration may be clinically classified as follow⁹:

1. Mild dehydration: asthenia, anorexia, nausea, mild postural hypotension
2. Moderate dehydration: apathy, asthenia, vertigo, muscle cramps, dryness of mouth and skin, sunken eyes, hypotension, tachycardia, oliguria
3. Severe dehydration: marked asthenia, mental confusion, signs of hypovolemic shock, anuria.

In all patients, blood tests including blood cell counts should be performed, in order to obtain useful information about the origin of diarrhea. In particular, in bacterial diarrhea we will observe a rise in neutrophils while in viral diarrhea we will frequently observe a relative lymphocytopenia sometimes accompanied by a rise in alanine and aspartate aminotransferase levels¹⁰. Whenever is possible, and especially in older patients previous-

ly treated with antibiotics, a rapid test for the detection of *Clostridium difficile* toxin should also be performed followed by culture¹¹.

Finally, imaging should be only reserved to selected patients in whom we suspect a possible surgical disease underline diarrhea¹².

Current concepts of therapy

The first therapeutic action to be considered in case of diarrhea is rehydration¹³: the amount of fluids to be replaced mostly depends on the grade of dehydration. Anyway, the administration of an oral rehydrating solution is the best option, while intravenous administration of normal saline solution has to be considered only in compromised patients or in whom home help may not be guaranteed¹³. Electrolyte imbalances may be corrected using an intravenous administration or even orally, depending on the severity of the deficit¹⁴. Acetaminophen is the best option in case of fever, especially when the body temperature is higher than 38.5°C¹⁵. Fasting is strongly recommended, at least during the acute phases and in case of vomiting; fluids and food should then be reintroduced gradually, depending on the clinical course of the disease^{16,17}.

Antiemetic can be considered in case of vomiting, while antibiotics are not recommended at all unless there is evidence of defined bacteria or parasites in the stool^{18,19}. From this point of view, a viral origin has always to be presumed in case of an infectious diarrhea⁵.

Another important issue when considering acute diarrhea in the Emergency Room is the use of antidiarrheal drugs, such as loperamide²⁰. Indeed, loperamide has not to be considered in the treatment of acute diarrhea when an infectious origin may be presumed²⁰. This is due to the fact that diarrhea exert a protective role in this case, by contributing to the elimination of the infectious agent. On the other hand, there is a strong rationale for the administration of a new class of drugs, which may be defined as "*mucous regenerators*". In order to better understand this issue, we have to consider that mucus is the first physical barrier that bacteria or other microorganisms meet in the intestinal tract, providing protection from harmful microorganisms or antigens. It is organized into two different layers: an inner, stratified mucus layer that is firmly adherent to the epithelial cells and an outer unattached one. The inner mucus layer is dense and does not allow bacteria to penetrate, thus, keeping bacteria away from the epithelial cell surface. The normal bacterial flora resides in the loose mucus, whereas the inner at-

tached mucus is impervious to bacteria and functions as a protective barrier for the epithelial cell surface²¹. During infection, there is a significant reduction of the mucosal barrier. The final effect is that the infectious agent comes in contact with the epithelial barrier increasing the inflammatory response and symptoms. This is the reason why mucosal protectors, such as gelatin tannate, which is able to reproduce a protective muco-adhesive film in the intestine, are effective in reducing intestinal inflammation in infectious diarrheas. Gelatin tannate, in fact, has been found to reduce inflammation and to have antibacterial properties in children with acute diarrhea²².

Finally, specific probiotics, may be recommended in case of infectious acute diarrhea, by contrasting the replication of pathogens and/or reducing local inflammation^{23,24}. The final effect is a significant reduction of diarrhea duration. Indeed, previous studies have clearly demonstrated that Lactobacilli and Bifidobacteria produce bactericidal acids, such as lactic acid, bacteriocins, and short-chain fatty acids (SCFA), which suppress *Salmonella enterica typhimurium* growth in animal models^{25,26}. A recent study demonstrated that a mixture of *Bacteroides thetaiotaomicron* and *Eubacterium rectale* is able to induce the production of mucosal glycans in the host that are utilized only from these 2 bacterial strains and not from pathogens, which are not able to proliferate²⁷. Interestingly, several Lactobacillus species increase mucin expression in *in vitro* and *in vivo* models, thus, blocking *Escherichia coli* invasion and adherence^{28,29} and enhance total and pathogen-specific mucosal IgA levels upon infection^{30,31}. The only contraindication for the administration of probiotics other than a previous demonstrated allergic reaction is the acute pancreatitis³². Conversely, when acute diarrhea is the expression of an intestinal or extra-intestinal disease, like in the IBD, together with this general approach, a quick and specific treatment is also be mandatory.

Under which circumstance should not the patient leave the hospital?

The majority of the patients with acute diarrhea may leave the hospital, after appropriate treatment. However, there are some patients needing additional cures and investigations³³:

- Patients without home help.
- Subjects in whom hydration has not been restored to a normal level.
- Elderly patients or those living under poor hygienic conditions.

- Immune-compromised patients, including diabetics or patients under treatment with immunosuppressant medications.
- Patients with hemorrhagic diarrhea or in whom symptoms persist over 10 or more days (particularly if patients are assuming diuretics, ace inhibitors or steroids).
- Patients travelling from Countries at a higher risk of parasitic infections.
- Patients experiencing severe complications, including hypovolemic shock, sepsis, hemolytic uremic syndrome, arthritis, Henoch-Schoenlein purpura, myocarditis, pericarditis, endocarditis, skin rash, erythema nodosum, conjunctivitis, Reiter's syndrome, especially during infections caused by *Salmonella*, *Shigella*, *Campylobacter*, or *Yersinia enterocolitica*. Other complications are systemic infections sustained by *Salmonella* spp (abdominal aortic aneurysm, arthritis, meningitis, cholecystitis, etc.), toxic megacolon, malnutrition, reduced absorption of drugs (i.e. anticonvulsants, oral contraceptive and others) or inability to retain oral medications, and Guillain Barré syndrome (*Campylobacter jejuni*).

Conclusions

Diarrhea may be considered as the result of an altered intestinal homeostasis³⁴. The removal of the intestinal cause, whenever is possible, together with the rehydration and the correction of electrolyte imbalance, represents the key points for a correct therapeutic strategy. Moreover, strengthening either intestinal barrier or protective microbial component is another important point to be considered³⁴. Indeed, some probiotics have shown a strong efficacy in reducing the duration of symptoms in infectious diarrhea²⁴. On the other hand, there is a strong rationale for the introduction of gelatin tannate, a new drug classifiable as a "mucous regenerator", in the treatment of acute diarrhea in adults²². However, further studies are needed to assess the effect of gelatin tannate, alone or in combination with probiotics.

Conflict of Interest

None of the Authors has potential conflict of interests. No funds have been received for the production of this manuscript.

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