

## CONSTIPATION

Constipation is an intestinal dysfunction characterized by infrequent bowel movements or difficult passage of stools that persists for several weeks or longer. Constipation is generally described as having fewer than three bowel movements a week.

Signs and symptoms of chronic constipation include:

- Passing fewer than three stools a week
- Having lumpy or hard stools
- Straining to have bowel movements
- Feeling as though there is a blockage in your rectum that prevents bowel movements
- Feeling as though you cannot completely empty the stool from your rectum
- Needing help to empty your rectum, such as using your hands to press on your abdomen and using a finger to remove stool from your rectum

Constipation may be considered chronic if you have experienced two or more of these symptoms for the last three months.

### Causes

Constipation most commonly occurs when waste or stool moves too slowly through the digestive tract or cannot be eliminated effectively from the rectum, which may cause the stool to become hard and dry. Chronic constipation has many possible causes.

#### Blockages in the colon or rectum

Blockages in the colon or rectum may slow or stop stool movement. Causes include:

- Tiny tears in the skin around the anus (anal fissure)
- Hemorrhoids
- A blockage in the intestines (bowel obstruction)
- Colon cancer
- Narrowing of the colon (bowel stricture)
- Other abdominal cancer that presses on the colon
- Rectal cancer
- Rectum bulge through the back wall of the vagina (rectocele)

#### Problems with the nerves around the colon and rectum

Neurological problems can affect the nerves that cause muscles in the colon and rectum to contract and move stool through the intestines. Causes include:

- Damage to the nerves that control bodily functions (autonomic neuropathy)
- Multiple sclerosis
- Parkinson's disease
- Spinal cord injury
- Stroke

Difficulty with the muscles involved in elimination

Problems with the pelvic muscles involved in having a bowel movement may cause chronic constipation. These problems may include:

- The inability to relax the pelvic muscles to allow for a bowel movement (anismus)
- Pelvic muscles that do not coordinate relaxation and contraction correctly (dyssynergia)
- Weakened pelvic muscles

Conditions that affect hormones in the body

Hormones help balance fluids in your body. Diseases and conditions that upset the balance of hormones may lead to constipation, including:

- Diabetes
- Overactive parathyroid gland (hyperparathyroidism)
- Pregnancy
- Underactive thyroid (hypothyroidism)

Other frequent causes of constipation:

- Bowel diseases (colitis, intestinal atony, large bowel spasms, megacolon, Hirschsprung disease, Crohn's disease, colon polyposis).
- Metabolic disorders (dehydration, adrenal hypofunction).
- Nutrition features: sharp change in diet, lack of dietary fibers in the diet, excess of fat in the diet, insufficient fluid intake, excess of iron in the diet, lack of folic acid in the diet.
- Use of multiple medicines, including antacids, containing aluminum salts, antihistamine medicines, antidepressants, antipsychotics, psychotropic medicines, opiates (codeine), antihypertensive medicines (calcium antagonists), preparations of iron and calcium.

Risk factors:

- Insufficient physical activity;
- Long term use of laxative medicines;
- Frequent use of enemas;

- Being an older adult;
- Being a woman;
- Having a mental health condition such as depression or an eating disorder.

***\*Threatening\* symptoms:***

- Temperature rise;
- Blood traces in feces;
- Severe stomachaches;
- Abdominal distention;
- Vomiting;
- Weight loss.

**Non-medicinal treatment:**

- Intake of food, rich in fibers, pectin, soluble dietary fibers (beet, apples, plums, oat and other whole grain cereals, leaf vegetables, cabbage, wholemeal bread, bran);
- Reduced fat intake;
- Fluid intake at least 1.5 L per day;
- In case of obligatory iron or calcium preparations use preference should be given to vitamin and mineral complexes;
- Physical activity increase;
- Defecation in a quite relaxing environment;
- Hemorrhoids and anal fissures treatment (anus hygiene, emollients and creams use);
- Stop use of cleansing enemas and laxative medicines, stimulating peristalsis.

Defining possible causes of constipation is required before recommending a laxative medicine. Elimination of the cause frequently leads to stool normalization.

In constipated patients appetite is decreased, belching and bad taste in the mouth are frequent. Abdomen heaviness and stomach overflow are common symptoms. Due to permanent intoxication weakness, headaches are developed, mood and performance are reduced (in severe cases – depression), sleep disturbance and memory impairment are observed. In majority of patients skin is affected. Pallor with an earthy tint, dryness, increased peeling, dermatitis manifestations are typical. Nails flake, dandruff, hair loss and split are often observed.

Chronic constipations promote development of secondary colitis, hemorrhoids, anal fissures. They are usually accompanied by dysbiosis, immune system disorders, metabolic disorders. Slow emptying of the intestines leads to blood and lymph level increase of toxins, including carcinogens. Intense straining in

constipation may provoke complications of cardiovascular system diseases (strokes, heart attacks, thromboembolisms).

Constipation treatment success consists of three components:

- Degree of detection and completeness of elimination of stool retention causes;
- Patient's readiness to life style, food habits change, implementation of doctor's and pharmacist's recommendations (full compliance);
- Doctor's and pharmacist's ability to provide complex individual therapy that will not complicate patient's life with side effects.

### **Medicines used in symptomatic constipation treatment and conditions for their rational use**

At the heart of laxative medicines action there is mechanical or chemical irritation of intestinal mucosa. According to the main operating principle laxatives are divided in drugs:

1. Stimulating intestinal motility
2. Softening feces
3. Increasing intestinal contents

The largest group is stimulating intestinal motility. Significant portion of it are herbal preparations that contain anthraglycosides. Anthraquinone glycosides (anthranoids) are contained in:

1. senna – preparations: Xena, Senade, Senadexin, Senna leaves
2. buckthorn – preparations: Buckthorn bark
3. cascara (sold as “Cascara sagrada”)

The non-sugar part of these glycosides includes emodin, chrysofranic acid and other anthraquinone derivatives, irritating receptors, responsible for stretching the lumen of the intestines under pressure, which in its turn excites peristalsis. Laxative medicines of this group are effective 8-12 hours after intake. Senna and buckthorn preparations are not used in spastic constipations as they can cause pain in the colon. Anthraquinone glycosides pass into mother`s milk, so these preparations are not prescribed to feeding mothers. These medicines are not recommended for long term use. Most of the patients taking anthraquinones exhibit dyskinesia, third part of them have an inert colon formed.

Bisacodyl and sodium picosulfate are referred to laxatives that stimulate the intestines functions and do not contain anthraglycosides. Bisacodyl is a derivative of diphenylmethane that stimulates sensitive colon wall receptors by direct contact. As a result mucus secretion in the colon increases, electrolytes and water absorption decreases, peristalsis accelerates and intensifies. Bisacodyl does not pass into breast milk and does not affect uterine tone. In case of long term use in men the development of prostatitis is possible. Preparations of Bisacodyl are sold under the following trade names: Dulcolax, Bisacodyl, Durolax, Muxol, Fleet.

Sodium picosulfate is a prodrug which is activated in the colon due to bacterial sulfatases action. Its active compound stimulates nerve endings of the intestinal mucosa, enhancing its motility. In infants the preparation is not effective due to small amount of bacterial flora and accordingly of sulfatases. Simultaneous treatment with antibiotics can reduce laxative effect. Preparations of sodium picosulfate are sold under the following trade names: Sodipic Picofast, Laxoberal, Laxoberon, Purg-Odan, Picolax.

Castor oil also belongs to this group. In the small intestine it is cleaved by a lipase to form ricinoleic acid and glycerol that irritate colon receptors all along and enhance reflectively its peristalsis. These substances depress water and electrolytes absorption processes, disrupting the activity of the surface epithelium of the intestine, contribute to an increase of intestinal contents volume. Castor oil besides the above given effects, is partially excreted non-metabolized and in a form of glycerol, softening the feces. The laxative effect appears in 5-6 hours.

Feces softeners include liquid paraffin (paraffin oil). Paraffin oil (liquid paraffin) is a mineral substance which is not absorbed in the colon and is not metabolized. It mechanically facilitates the passage of feces and causes their softening. Paraffin oil reduces liquid absorption, accelerating movement of contents in small colon as well. Thus an oil acts all along the whole intestine. In long term use absorption of fat soluble vitamins (A and D) is decreased and risk of malignant tumors in gastrointestinal tract is getting higher, especially in case of gastric and duodenal ulcer. Softening laxative medicines are mainly used in cases when a rapid effect is required, for example in poisonings, patients during the postoperative period, preparation for diagnostic bowel examination.

Plant fibers and hydrophilic colloids are part of the large group of laxative medicines that increase the volume of intestinal contents (osmotic laxatives). Their laxative effect is caused by ability of high molecular weight polysaccharides of plants to swell in gastro-intestinal tract due to binding to water, and thus, increasing in volume, irritate intestinal mucosal receptors, promoting bowel movements.

Preparations increasing volume of feces and thus stimulating colon peristalsis are preparations of plantain ovoid seeds. Plant fibers contained in the preparation have the property to swell, multiplying in volume, that's why one should increase water intake at least up to 1,5 L.

**Osmotic laxatives** are magnesium sulfate, lactulose, macrogol.

Magnesium sulfate is poorly absorbed and creates increased osmotic pressure all along the colon, which prevents reverse water absorption. Volume increase leads to sprain and reflex stimulation of peristalsis, and to increase of cholecystokinin

content released by small intestine mucous membrane, that promotes bowel movements as well.

During the laxative medicines administration atrophic and inflammatory changes in the mucous membrane caused by local irritating effect are observed. Saline laxatives are contradicted in pregnancy, since active peristalsis can stimulate uterus contractility.

Lactulose is a synthetic disaccharide which is not cleaved by the small intestine disaccharidase and is not absorbed. It is transformed into low molecular weight organic acids (lactic, acetic) in the large intestine under the influence of intestinal microflora. Thereby osmotic changes that stimulate peristalsis and normalize consistency of feces occur. Lactulose is effective in constipation due to adhesion process in abdominal cavity, in elderly patients, in women after gynecological surgeries.

The special committee of American College Gastroenterology conducted systematic review of preparations used in chronic constipation and has referred lactulose to preparations showing the highest efficacy (grade A).

The trade names are Movelax, Duphalac, Dulose. The original drug of lactulose is Duphalac and has the highest efficacy and safety. Duphalac can be administered in all patients' categories: adults including elderly, newborns, patients after hemorrhoidectomy. The administration is allowed in case of diabetes, pregnancy and lactation, for hepatic encephalopathy treatment. Some data suggest the potential benefit of Duphalac in urinary tract infectious diseases, cholelithiasis treatment, in colon and vagina mycosis treatment, in preventive actions to reduce the risk of colon cancer.

Macrogol is neither absorbed nor metabolized in the gastro-intestinal tract due to its high molecular weight. It induces colon content (feces) volume increase and its softening due to formation of additional hydrogen bonds with water molecules, water retention and its accumulation in the lumen of intestine, which increases intracellular osmotic pressure. Macrogol can be administered in patients with diabetes, pregnant and lactating women, in elderly. The trade names are Movicol, Laxido, CosmoCol, Molaxole

In colon preparation to endoscopic examination complex medicines based on Macrogol are used. Some laxative medicines are administered by direct introduction to the rectum, where they soften feces, and initiate defecation reflex. The effect appears rapidly, in 20 minutes. These preparations contain sodium docusate (Colace, Equate) and glycerol suppositories as well (Zetalate, Fleet). Polyethylene glycol (PEG), sodium phosphate, magnesium citrate and bisacodyl are widely used in bowel preparations. The trade names are Miralax, Enema, Dulcolax.

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A drug of choice in lactulose-containing preparations is Duphalac taking into account its efficacy and safety.

Lactulose and macrogol can be recommended to pregnant and lactating women.

Hypokalemia is developed in long term use of laxatives, that's why laxative medicines administration should be combined with potassium preparations intake.

Laxative medicines containing anthraglycosides are effective in 10-12 hours after administration, thus it is recommended to use them in the evening before going to bed.

Laxative medicines containing anthraglycosides are not used in case of spastic constipation as they can cause pain in the large intestine.

Anthraquinone glycosides pass into breast milk, so they are prohibited in lactating women.

Laxative medicines of anthraglycosides group are not recommended for long term use.

Laxatives of anthraglycosides group can change the urine color to vivid yellow if its medium is acidic and to red if the medium is alkaline.

Sodium picosulfate is not effective in infants.

In long term paraffin oil administration the absorption of fat soluble vitamins (A, E and D) is decreased and the risk of malignant tumor formation in gastro-intestinal tract is increased.

Castor oil is effective in 5-6 hours.

Castor oil is strongly prohibited in pregnant women.

Castor oil is contraindicated in fat soluble poisons poisonings

Magnesium sulfate is effective in 4-6 hours.

Magnesium sulfate is contraindicated in pregnant women since active peristalsis can stimulate uterus contractility.

In administration of laxative medicines containing plant fibers, fluid intake should be increased at least up to 1,5L.

## Algorithm of pharmaceutical care in constipation

Was there a defecation within the last 48 hours?

Yes

**Do you have:**

- fever
- blood traces in feces
- severe stomachache (spastic pain)
- nausea, vomiting
- weight loss
- pain in defecation
- occupational hazards ( work with lead, mercury, etc)

No

Defecation frequency is individual (once in 2-3 days is within physiological norm range).

Yes

To clarify the diagnosis doctor consultation is required.

No

Are u pregnant?

Yes

In early pregnancy intestinal dysfunction is possible. You are recommended to increase the level of your physical activity, increase fluid and fiber, sour milk products intake. Laxative medicines administration is possible only ***after a doctor consultation.***

No

Do you currently take any medicines?

- antacids containing aluminum
- antihistamine drugs
- antidepressants
- neuroleptics and psychotropic medicines
- calcium antagonists
- iron and calcium preparations
- opioids (codeine) and so on?

No

Is the constipation chronic?

Yes

These medicines can cause constipation. You are recommended to consult with your doctor.

No

You can take any laxative medicine. Medicine of choice is a lactulose-containing medicine (Duphalac)

Yes

Besides laxatives administration, you should stick to non-medicament constipation treatment recommendations (diet, physical activity, etc)



## HEARTBURN

Heartburn (pyrosis) is a burning sensation in the epigastric area and behind the sternum which is accompanied by sour taste in the mouth.

Heartburn is actually a symptom of GERD (gastroesophageal reflux disease) and is caused by acid refluxing back into the esophagus. It can be a sign of certain gastrointestinal tract diseases, one of the manifestations of dyspepsia or an independent symptom. The pain is often worse after eating, in the evening, or when lying down or bending over.

Occasional heartburn is common and no cause for alarm. Most people can manage the discomfort of heartburn on their own with lifestyle changes and over-the-counter medications. Heartburn that is more frequent or interferes with your daily routine may be a symptom of a more serious condition that requires medical care.

Heartburn occurs when stomach acid backs up into the tube that carries food from your mouth to your stomach (esophagus). Normally when you swallow, a band of muscle around the bottom of your esophagus (lower esophageal sphincter) relaxes to allow food and liquid to flow down into your stomach. Then the muscle tightens again. If the lower esophageal sphincter relaxes abnormally or weakens, stomach acid can flow back up into your esophagus (acid reflux) and cause heartburn. The acid backup may be worse when you are bent over or lying down.

### **Most frequent heartburn causes:**

1. chronic helicobacter-associated gastritis (type B)
2. stomach and duodenal ulcer
3. chronic cholecystitis
4. gastroesophageal reflux

### **Heartburn in healthy individuals:**

1. irrational diet: overeating; fatty, spicy food abuse
2. intake of large amounts of sweets and of products containing caffeine (coffee, tea, chocolate)
3. food intake \*on the go\*, in stressful environment
4. Individual intolerance to certain products – citrus, onion, garlic, tomato products (juice, pastes, sauces)
5. first half of pregnancy
6. Use of medicines (non steroidal anti-inflammatory drugs -NSAID), steroid hormones, cholinomimetics and some other)

### ***Factors contributing to heartburn appearance:***

1. alcohol abuse;
2. smoking;
3. sleep or rest lying immediately after eating;
4. wearing tight clothes;
5. physical inactivity;
6. obesity.

**\*Threatening\* symptoms in heartburn:**

1. regurgitation of stomach contents mixed with \*coffee grounds\* colored blood or regurgitation of blood only (hematemesis);
2. melena: passage of stools with a black and tarlike appearance caused by the presence of digested blood;
3. persistent heartburn over 3 days;
4. dyspnea, sweating, difficulty swallowing;
5. stomachache;
6. progressing weight loss;
7. heartburn as a consequence of medicines administration.

***General approach to heartburn treatment:***

Heartburn treatment is based on the identification of the cause. In gastritis, peptic ulcer long-term treatment (4-8 weeks and longer) is conducted under the doctor's supervision with preparations that decrease the stomach acidity ( $H_2$  – histamine blockers, proton pump inhibitors, etc). Concomitantly antihelicobacter therapy is conducted, medicines with gastroprotective effect are administered (protecting stomach mucous membrane).

In heartburn caused by gastroesophageal reflux, medicines reducing stomach secretion are also used in combination with antacids and prokinetics preparations that accelerate evacuation of gastric contents (metoclopramide, domperidone).

For heartburn prevention in healthy individuals (with no organic gastro-intestinal tract diseases) it is recommended to stick to healthy regular diet, avoid fatty and spicy food, quit smoking, keep the body weight under control. These dietary measures should be sufficient to prevent this gastro-intestinal tract pathology. However it is not realistic to stick to all the recommendations given above in real life. This is why in a heartburn treatment we have to resort to help of medicines in quite a large number of cases.

***Non-medicinal heartburn treatment:***

1. Do not abuse acid stimulating products such as: spicy food, citrus, tomato pastes and juices, onion, garlic;
2. Avoid overeating, food intake \*on the go\*;
3. Avoid or reduce smoking;

4. Avoid rest lying after eating;
5. Refrain the intake of products containing gases (butter baking, carbonated drinks);
6. In case of heartburn occurring at night it is recommended to sleep with slightly raised headboard;
7. Reduce overweight (final goal: no overweight).

### ***Medicinal heartburn treatment:***

The most widespread OTC group of medicines used in heartburn treatment is antacids.

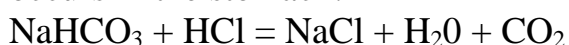
Antacids are preparations that reduce aggressiveness of stomach and duodenum content due to direct chemical interaction. This group of medicines does not have an influence on mechanisms of gastric secretion. Antacids are a class of medicines that neutralize acid in the stomach. They contain ingredients such as aluminum, calcium, magnesium, or sodium bicarbonate which act as bases (alkalis) to counteract stomach acid and make its pH more neutral.

Most of antacid preparations reduce the acidity of gastric medium, creating a uniform protective layer in the stomach that prevents gastric juice from contact with inflamed areas of stomach wall.

There is still no consensus on whether alginic acid salts are referred to antacids or they are an independent group of medicines. Alginates are referred to antacids and adsorbents according to pharmacological formulary. The alginates mechanism of action consists in interaction with HCl of the gastric juice and creating gel-like layer that prevents further contact of the acid and pepsin with esophagus mucosa. By forming a mechanical barrier sodium alginate provides anti-reflux effect with no selectivity to reflux type, meaning it prevents both acid reflux from the stomach and alkaline reflux from duodenum to esophagus. Alginates anti-reflux mechanisms of action can be marked as universal not only according to level of significance and effective time interval (up to 4 hours) but also according to quality of achieved effect. Alginic acid salts trade names are among others Heartburn Antacid Extra Strength, Gaviscon Extra Relief Formula, Alenic Alka.

### **1. Absorbable antacids.**

**Sodium bicarbonate.** An irreversible one way reaction with hydrochloric acid occurs in the stomach:



The main advantage of this preparation is an instant neutralization of hydrochloric acid. Due to its properties soda is called \*heartburn nitroglycerine\*.

However, sodium bicarbonate has a short duration of action. In 15-20 minutes a sharp alkalization of the medium occurs (up to pH 7 and above), that in

combination with stomach wall stretching by carbon dioxide causes secondary secretion increase (\*rebound\* syndrome).

If carbon dioxide overstretches the wall of a stomach ulcer there is an increased risk of perforation. Excess of endogenous alkali as well as unreacted amount of sodium bicarbonate administered by the patient are absorbed, and alkaline blood plasma reserve increases. It explains the systemic effect of this antacid. This phenomenon occurs especially fast in patients with impaired renal function. Systemic alkalosis is accompanied by loss of appetite, nausea, vomiting, fatigue, stomachache, muscle spasms, sometimes cramps.

The excretion of an excessive amount of sodium bicarbonate in urine leads to its alkalization, which promotes phosphate stones formation in urinary tract. In case of long term sodium bicarbonate administration, sodium ions accumulation occurs. This induces hypertension and swelling.

**Calcium carbonate.** The following reaction occurs in the stomach:



The calcium carbonate suspension reacts with the hydrochloric acid quite slowly. Calcium carbonate induces a secondary hydrochloric acid secretion which is more intense compared to all the other antacids because it directly stimulates gastrin secretion by the mucous gastric membrane cells.

About 10% of calcium chloride is absorbed. In case of constant calcium carbonate administration hypercalcemia may occur, especially in patients with impaired kidney function. Long term calcium carbonate administration may lead to constipation.

## **2. Unabsorbable antacids.**

**Aluminum hydroxide** has an enveloping and an absorbing effect. It is capable of binding pepsin. The effect is developed very slowly.

Even the excess of the preparation cannot cause total hydrochloric acid neutralization. This is extremely important for the preservation of the pepsin activity, which is required in proteins digestion. The preparation absorbs bile salts. This decreases their damaging effect on the gastric mucous membrane. It increases the prostaglandins synthesis in the gastric mucosa. As a consequence blood supply of mucosa improves and protective mucus secretion is increased. It does not disturb blood acid-base equilibrium.

Long term administration in patients with impaired kidney function may induce aluminum accumulation in tissues (bones, muscles, brain), which leads to muscles and bones pain, Alzheimer disease. It can cause hypophosphatemia (fatigue, mental disorders, loss of appetite), hyperphosphaturia, hypercalciurea and calcium nephrolithiasis. Due to the decreased calcium absorption in the intestine and the

calcium bones resorption, the risk of osteoporosis is high. Long term administration of aluminum hydroxide also inhibits gastrointestinal motility and promotes constipation.

**Aluminum phosphate** possesses buffer antacid (reduces hyperacidity to norm, does not cause acidic “rebound”) and adsorption properties: binds to bacteria, endogenous and exogenous toxins and gases released during pathological fermentation and decay in the colon. It does not cause constipation, acid-base equilibrium shift, does not interfere with phosphate absorption.

**Magnesium oxide** does not cause secondary gastric juice hypersecretion (“rebound” phenomenon). It does not shift the acid-base equilibrium. The preparation stimulates gastro-intestinal peristalsis that provides a laxative effect. This is related to the osmotic ability of magnesium ions and their property to induce cholecystokinin secretion, which stimulates intestine peristalsis.

Neurologic and cardiovascular disturbances are possible in case of impaired kidney function.

**Bismuth nitrate** has an astringent and anti-inflammatory effect. It does not shift the acid-base equilibrium. The administration of bismuth-containing preparations can lead to black-colored stools. This has to be taken into account during the differential diagnosis (see melena and its causes).

There is a lot of combination drugs that combine positive effect and leveling negative effects of the ingredients on the market.

Preparation	Ingredients	Special features
Gaviscon	Sodium alginate Potassium bicarbonate	Provides local physical action. Dose correction is not required in elderly. Administration in pregnant and lactating women is allowed.
Maalox	Aluminum hydroxide Magnesium hydroxide	
Rennie	Calcium carbonate Magnesium carbonate	Preparation can be administrated in case of diabetes (contains saccharin and 400 mg of sorbitol)
Phosphalugel	Aluminum phosphate pectin agar agar with correcting substance	Preparation can be administrated in case of diabetes as it does not contain sugar. Constipation may occur.

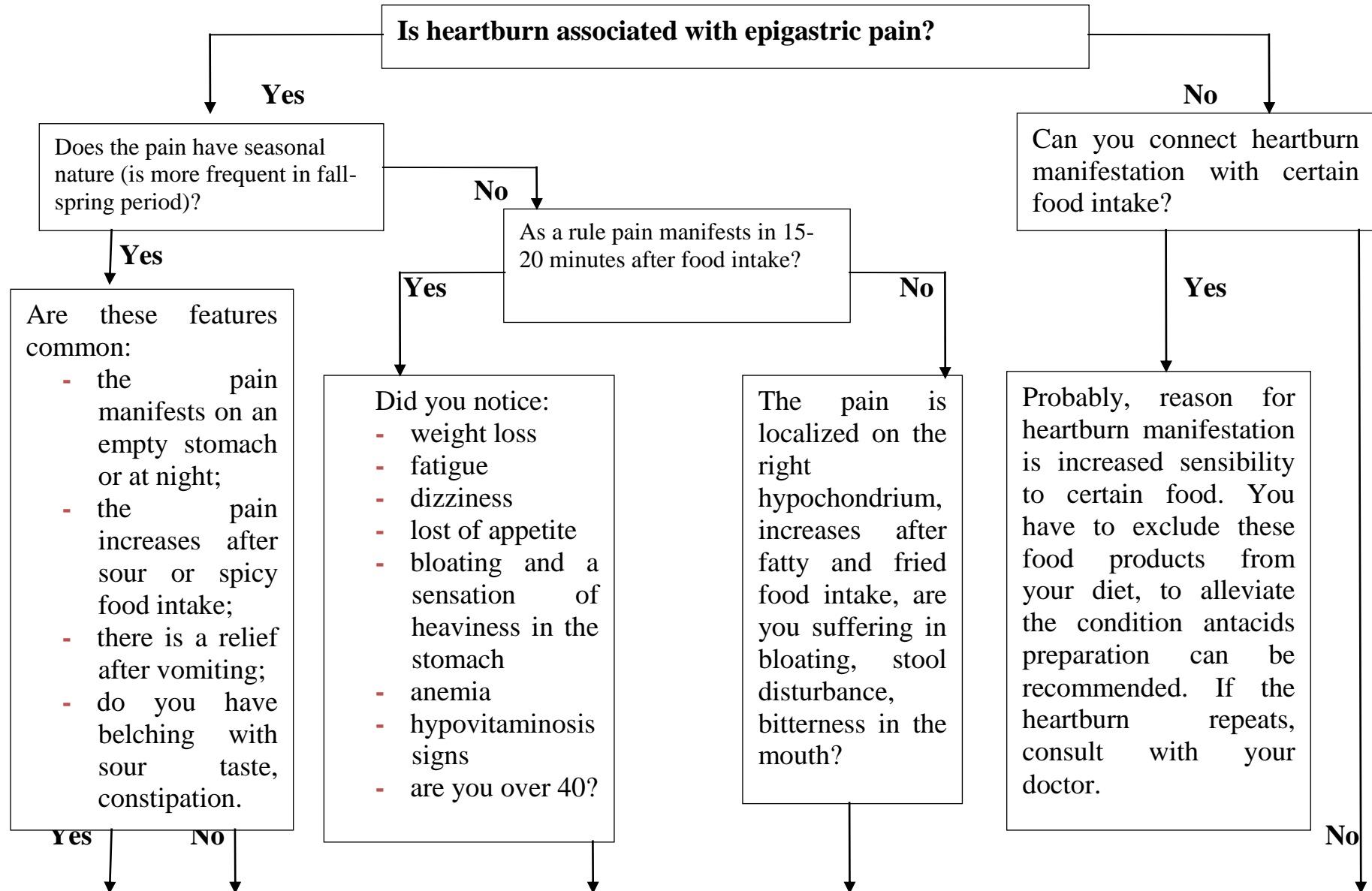
PHARMACEUTICAL CARE IN OTC - MEDICINAL SYMPTOMATIC  
TREATMENT OF HEARTBURN

1. All antacids preparations are administered orally in one hour after food intake.
2. Unabsorbable antacids slow down absorption of some medicines such as tetracyclines, norfloxacin, cardiac glycosides, corticoids.
3. To prevent drug – drug interactions antacids should be administered 2 hours before or 2 hours after any other drugs administration.
4. Aluminum-containing antacid are indicated in propensity for diarrhea and magnesium-containing antacid are indicated in propensity for constipation.
5. All aluminum-containing antacids disturb phosphorus absorption, forming insoluble salts of aluminum phosphate.
6. Increase of aluminum content in the organism due to excess preparations administration can cause encephalopathy. The first symptoms are speech impairment, muscle twitching, cramps. Dementia occurs later.
7. Aluminum excess in unabsorbable antacids administration accumulates in renal glomeruli, which leads to kidney failure.
8. Absorbable antacids preparations administration is frequently associated to a “rebound” syndrome (secondary hydrochloric acid hypersecretion after primary neutralizing effect).
9. Absorbable antacids in large doses can cause systemic metabolic disorders such as alkalosis and lactic syndrome.
10. Sodium bicarbonate is contraindicated in patients with hypertonic disease, cardiac and impaired kidney function, liver cirrhosis. As a result of a chemical reaction with hydrochloric acid, sodium chloride is formed. It induces water retention in the body.
11. Silicon-containing (magnesium trisilicate) antacids are contraindicated in patients with urolithiasis. Magnesium trisilicate is excreted in urine and promotes stones formation in the urinary tract.
12. Long term antacids administration increases the risk of gastro-intestinal tract infections as a result of decreased hydrochloric acid protective effect.
13. Antacids cannot be combined with De-nol and Sucralfate (pharmacodynamics incompatibility).
14. The only OTC-drug of pantoprazole (inhibitors of proton pump group) is Tecta, which is indicated for reflux disease and its symptoms treatment.
15. Small doses of H<sub>2</sub>-histamine blockers can be administered in symptomatic heartburn treatment, e.g. ranitidine at a 75 mg, 150 mg or 300 mg dose (Zantac) and famotidine at a 20 mg or 40 mg dose (Pepcid, Act, Fluxid), which are OTC-drugs in Ukraine.
16. Alginic acid is not an antacid, but because of its unique mechanism of action, it is added to some antacid preparations to increase their effectiveness in the treatment and relief of the symptoms of GERD. Gaviscon contains alginic acid. In the presence of saliva alginic acid reacts with sodium bicarbonate to form sodium alginate. Gastric acid causes this alginate to precipitate, forming a foaming, viscous gel that floats on the surface of the gastric contents. This provides a relatively pH-neutral barrier during episodes of acid reflux and enhances the efficacy of drugs used to

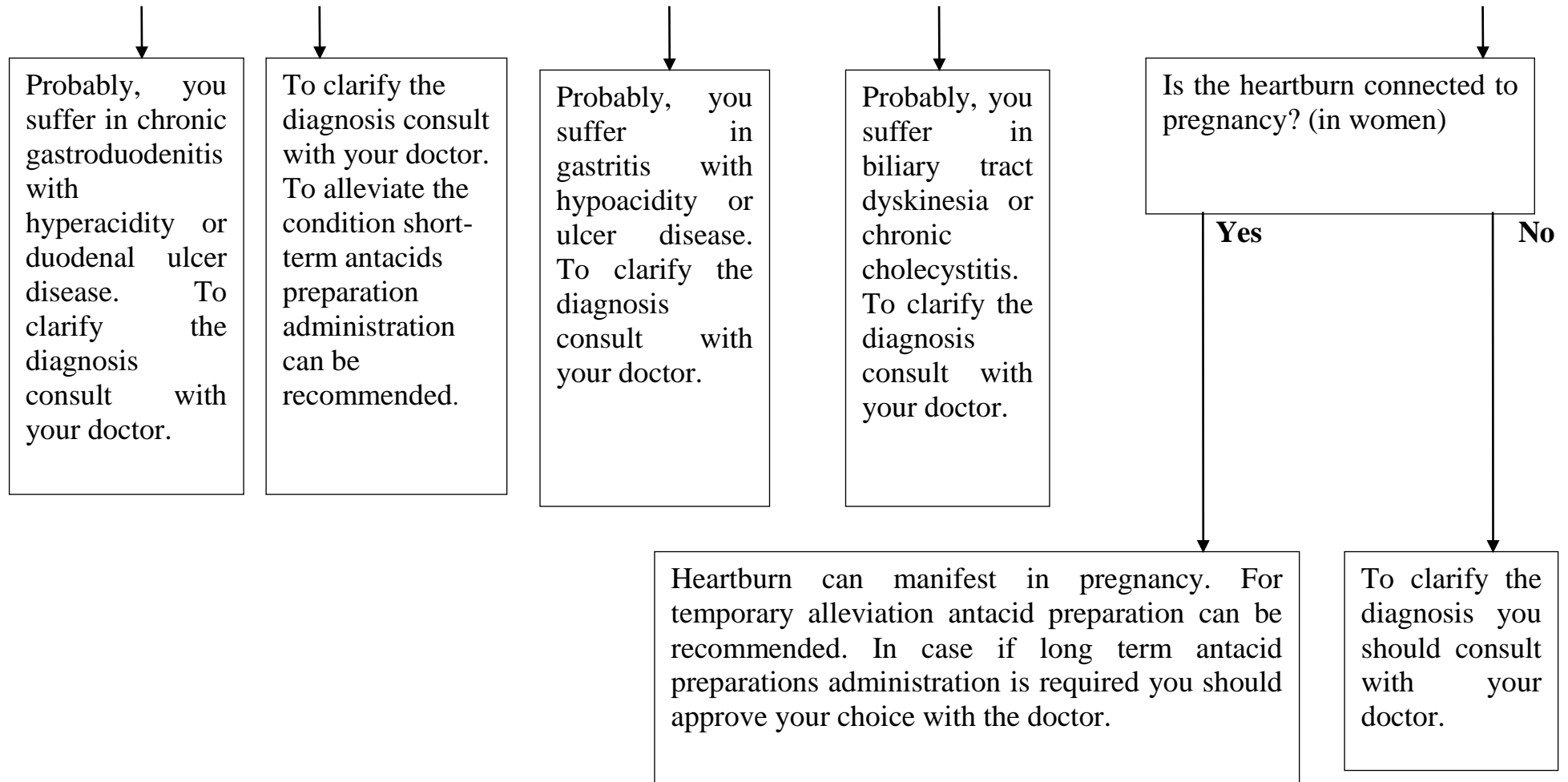
treat GERD. The preparation has local effect with no systemic effects and no drug interactions. Administration can be recommended in pregnant and lactating women, kids of age of 6 and older.

17. In symptomatic treatment of a heartburn OTC-drug Pepsan is administered as well. Guaiazulene, one of its ingredients inhibits hydrochloric acid secretion, exhibits anti-inflammatory and regenerative effect. The second ingredient, dimethicone, provides absorbing and enveloping effects.

## Algorithm of pharmaceutical care in heartburn







## DIARRHEA

The average stool weight in adults is approximately 200 g per day. If a patient has high intake of fiber-containing foods, stool mass may increase up to 500 g per day. According to the traditional notion normal defecation frequency is once per day in the morning hours. This is far from reality. Defecation is quite variable and is subject to numerous extraneous influences. This colon function changes greatly with age and is under influence of individual physiological, dietary, social and cultural factors. In healthy individuals defecation frequency varies from 3 times per day to 3 times per week. Volume and consistency changes, the appearance of impurities (blood, food leftovers) are the symptoms of a pathology.

Diarrhea is defined as more frequent (over 3 times per day) defecation and/or more liquid stool consistency, and/or stool volume increase.

Diarrhea is based on water-electrolyte balance shift in the colon. Average water intake in human is approximately 2 L, whilst 8 to 12 L of liquid pass through duodenum. Water absorbed in the colon repeatedly enters as saliva and digestive juices. Water absorption occurs mainly (90 %) in the small intestine, and only about 1-1,5 L reach large intestine, where it continues to be absorbed, and the rest (about 100 mL) is excreted with feces. Up to 5 L of water can be absorbed in the large intestine. This is why if the liquid amount coming from small intestine exceeds 5 L, diarrhea occurs. Such disorders may occur in case of indigestion, or impaired absorption, secretion and motility in the colon. Small and large intestines should be seen as one physiological unit. Diarrhea can occur due to small intestine damage (enteritis) or large intestine damage (colitis). An infectious agent causing an enteritis does not penetrate into the intestinal epithelial cells, causing only their toxic damage, which is accompanied by the loss of large amounts of salts and water. In infectious colitis the infectious agent penetrates the cells, causing mucosal ulceration, there are blood and mucus in the feces, whilst amount of water is significantly lower than in enteritis.

A diarrhea can be acute or chronic. The causes of each one are different. Diarrhea is considered to be acute when it does not last more than 2-3 weeks and there is no previous similar episode during the anamnesis.

### **Most frequent acute diarrhea causes:**

- infection (viral, bacterial);
- parasitic infestation;
- sharp diet changes and/or nutritional errors;
- unripe fruits intake;
- sudden fright/anxiety;
- medicines administration
  - laxatives
  - magnesium containing antacids
  - antibiotics ( clindamycin, lincomycin, ampicillin, cephalosporins)

- antiarrhythmic medicines (quinidine, propranolol)
- cardiac glycosides (digoxin)
- potassium preparations
- sulfasalazine
- anticoagulants
- chenodeoxycholic acid
- sugar substitutes (sorbitol, xylitol).

**\*Threatening\* symptoms** suggesting a serious disease in a patient and requiring a doctor's intervention in acute diarrhea are:

1. life-threatening disorders associated to diarrhea;
2. diarrhea lasting over 48 hours;
3. diarrhea accompanied by fever;
4. a lot of mucus is excreted and/or there is blood in the feces;
5. tenesmus and painful defecation;
6. diarrhea is accompanied by vomiting;
7. signs of general dehydration (intense thirst, mouth dryness, wrinkled skin, oliguria/anuria).

A diarrhea that lasts over 3 weeks is defined as chronic. It is observed in inflammatory intestine diseases (non-specific ulcerative colitis, Crohn's disease, AIDS), other stomach cavity organs diseases (liver, pancreas), some general diseases (thyroid gland dysfunction, emotional stress), motility disorders (irritable bowel syndrome or "IBS"). Long term diarrhea is quite frequently a consequence of an impaired absorption of some substances contained in food products (lactose and other sugars, gluten, cow milk proteins, fat), or food allergy (milk, cereals), pancreatic undersecretion or malabsorption syndrome. Chronic diarrhea treatment must be implemented by a doctor after diagnostics of the cause.

***Non-medicinal diarrhea treatment:***

1. dehydration prevention by large amount of liquid intake. In watery diarrhea one should drink one glass of water after each defecation. Sweetened tea, juices, slightly salted vegetable decoctions, soups can be used as well.
2. avoidance of spicy, fried products and caffeine and alcohol containing drinks.
3. sour milk products.

**General approach to diarrhea treatment:**

Since the etiological agent that causes diarrhea in most cases remains unclear, treatment should start with symptomatic remedies (Loperamide sold under the trade name Imodium). There are always several factors contributing to diarrhea; this is why symptomatic diarrhea treatment must be complex.

## **Clinical and pharmaceutical characteristics of main groups of medicines used in symptomatic diarrhea treatment**

### **Medicines for diarrhea treatment**

#### **1. Preparations for symptomatic diarrhea treatment**

1. Antiperistaltic preparations
2. Oral rehydration preparations
3. Sorbents
4. Enzymes preparations
5. Antimicrobial preparations, probiotics

#### **2. Preparations for etiological diarrhea treatment**

1. Antibacterial preparations (antibiotics, sulfonamids, nitrofurane derivatives, antiseptics) are prescribed only by the doctor. Metronidazole and Tinidazole are used to treat parasitic infections. There is often no specific medical treatment for diarrhea caused by viruses. Antibiotics are not effective against viruses, and overusing them can contribute to the development of antibiotic-resistant strains of bacteria. Treatment initially consists of self-care measures.

### **Oral rehydration preparations.**

Replenishment of increased water and salts loss is provided orally in most cases. Solutions containing balanced amount of sodium, potassium, chlorine, bicarbonate, citrate, as well as glucose, sucrose or dextrose are administrated. Administration of these preparations is based on the fact that in case of diarrhea of any origin, including infectious, parietal hydrolysis and parietal absorption processes in the intestine mucosa are still ongoing. Oral rehydration mixtures are preparations of substitutional action for electrolyte blood composition. They provide rapid effect, do not have any contraindications and side effects. These preparations are available in the form of powders, from which solutions can be quickly and easily prepared, and ready-to-use solutions as well.

Name	Ingredients
Gastrolite	Sodium chloride, potassium chloride, sodium bicarbonate, glucose, chamomile extract
Normohydron	Sodium chloride, potassium chloride, sodium citrate, glucose
Rehydron	Sodium chloride, potassium chloride, sodium citrate, glucose, anhydrous dextrose

### **Medicines reducing peristalsis**

Loperamide. The effect is caused by its binding to the intestinal wall opioid receptors, inhibition of acetylcholine and prostaglandins release. This process is associated with the intestines tone and motility decrease, inhibition of water secretion into the colon lumen. Loperamide is contraindicated in children under 5 years, during the first pregnancy trimester and lactation. Loperamide trade names are Imodium, Kaopectate II, Maalox Anti-Diarrheal, Pepto Diarrhea Control. Some combination preparations also exist: Imodium Multi-Symptom Relief (loperamide + simethicone), Bendiar (loperamide + furazolidone + metronidazole).

*Uzara* is antidiarrheal herbal preparation. Its mechanism of antiperistaltic action is based on sympathetic nervous system stimulation, and as a result colon motility is inhibited. Besides inhibiting gastrointestinal motility, *Uzara* shows spasmolytic, antisecretory, astringent and enveloping effects. The trade name is *Uzara*.

### Enterosorbents

Enterosorbents prescription promotes endogenous intoxication syndrome prevention and treatment. Preparations of this group actively absorb different toxic metabolites from the intestines (and some preparations even from the blood – transmembrane absorption from the capillaries of the villi of the intestinal mucosa).

Some enterosorbents are even able to absorb microorganisms including viruses.

International name	Trade name	Clinical and pharmaceutical characteristics
Diosmectite	Smecta, Smeccral	Possesses great enveloping ability towards the mucous membrane of the gastrointestinal tract, prevents water-electrolyte losses. It interacts with mucous membrane glycoproteins, protects it from adverse effects of intestinal microorganisms, their toxins and other irritants. It is able to absorb bacteria.
Polyphepan	Filtrum-STI	Preparation obtained in lignin processing, which is a hydrolysis product of carbohydrate components of wood. Possesses great absorptive ability, is able to absorb bacteria in the gastrointestinal tract. It has a hypocholesterolemic effect. Fatigue, sensation of heaviness in the epigastrium, constipation are rare side effects.
Methylsilicic acid		It is not absorbed by oral route, absorbs (transmembrane absorption from the capillaries of the villi of the intestinal mucosa) different toxic substances from intestinal contents and excretes them, has an enveloping effect on intestinal mucosa.

		<p>It has a sorption selectivity – absorbs middle molecular weight toxic metabolites, while high molecular weight compounds (such as proteins, immunoglobulins, etc.) and ions are not absorbed. It is selective in microorganisms absorption, absorbs only conditionally pathogenic and pathogenic flora, this is why it does not cause dysbiosis.</p> <p>No contraindications.</p>
Activated charcoal	CharcoalAid, Insta-Char, Liqui-Char	<p>Prolonged enterosorbent. It physically absorbs toxic substances that enter intestinal tract from the outside, from the blood or formed in the gastrointestinal tract. It is not metabolized in the organism and is fully excreted within 36-48 hours. The dosage is 2 – 4 g, three to four times a day.</p>

### Enzyme preparations

Enzyme preparations are administrated when diarrhea is caused by enzymes dysfunction. They can also be a part of a complex therapy.

### Preparations for correction of physiological intestinal flora equilibrium

Probiotics normalize microflora in the host organism. These are substances of microbial and non-microbial origin, which have a beneficial effect on the intestinal flora homeostasis. They are taken orally. In order to correct physiological colon microflora deficiency preparations containing live *Lactobacillus* (Lacteol), *Bifidobacteria* (Bifidumbaterin forte), *Escherichia coli* Nissle 1917 (Mutaflor) and their combinations – Bificol (*Lactobacillus rhamnosus* and *Bifidobacterium bifidum*), Bifi-form (*Bifidobacterium BB-12*, *Lactobacillus rhamnosus GG*, *Lactobacillus acidophilus LA-5*), Linex (*Lactobacillus acidophilus*, *Bifidobacterium animalis*) are recommended.

### Herbal preparations

Herbal preparations administered for diarrhea treatment are known for quite a long time. Their main effect is astringent. Tannins and polyphenols contained in them have the ability to form dense albuminates on the cells surface by interacting with proteins of cells and tissues, proteins of tissues fluids enzymes. Besides, herbal preparations have an anti-inflammatory effect. Herbal preparations exhibit an intestinal cytoprotective effect to a certain extent. It maintains and repairs intestinal mucous barrier.

Despite their low specificity in diarrhea syndrome, herbal preparations are recommended in mild conditions, and as a part of complex therapy as well. They

are administered as decoctions, herbal teas, which is inconvenient and does not guarantee active ingredients stability. Chamomile flowers, blueberries, bird cherry, burnet rhizomes with roots, alder fruits, oak bark, St. John's wort grass, bloodroot rhizomes, etc. are recommended for diarrhea treatment.

Enzyme preparations are administered in diarrhea, caused by enzymes dysfunction. They can also be a part of complex therapy.

### **Preparations for the correction of physiological intestinal flora equilibrium**

Probiotics normalize microflora in the host organism. These are substances of microbial and non-microbial origin, which have a beneficial effect on the intestinal flora homeostasis in case of natural route of administration.

In order to correct physiological colon microflora deficiency preparations containing live lactobacilli (Lactobacterin dehydrated), bifidumbacterias (Bifidumbacterinum dehydrated, Bifidumbacterin forte), E. coli (Colibacterin) and their combinations – Bificol, Bifi-form, Linex are recommended.

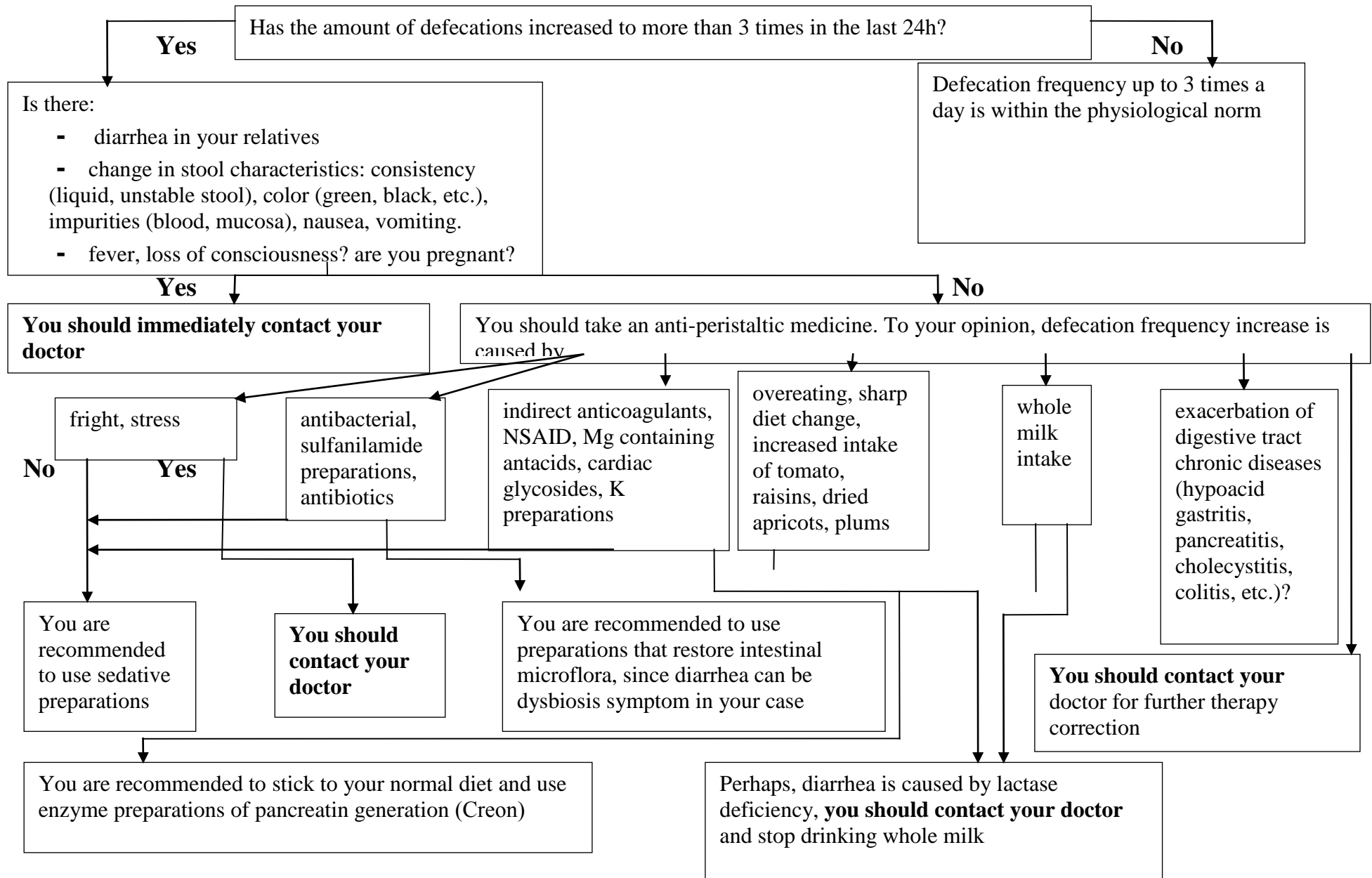
## **PHARMACEUTICAL CARE IN OTC - MEDICINES ADMINISTRATION IN DIARRHEA SYMPTOMATIC TREATMENT**

1. Antiperistaltic medicines are used for the elimination of diarrhea of any origin.
2. In patients with impaired liver function loperamide benefit/risk balance has to be taken into account. Indeed, liver disease or reduced liver function may cause this medication to build up in the body, causing side effects. This medication may also decrease the liver function.
3. Spasms of the lower abdomen are a side effect of loperamide.
4. Heavy liquid and electrolytes losses occur in diarrhea, so oral rehydration is key.
5. Uncontrolled administration of saline oral rehydration preparations may lead to water-electrolyte imbalance.
6. It is unacceptable to add sugar into the solutions for oral rehydration because the osmolarity of the solution increases and hence diarrhea intensifies.
7. Due to their absorption properties preparations of sorbent group can reduce efficacy of other preparations administered simultaneously.
8. It is recommended to keep the interval between adsorbents and any other medicines administration.
9. In case of prolonged administration of adsorbents a depletion of vitamins, proteins, fats occurs.
10. Adsorbents, due to their moderate constipating effect, in case of prolonged use (or/and administration in large doses) may promote constipation.
11. If activated charcoal is used then feces are black colored. (Beware: differential diagnosis versus melena).
12. Diosmectite can be administered in early childhood, including premature babies.
13. Enzyme preparations should be administered while eating or right after a meal.
14. Enzyme preparations tablets must not be chewed.

15. Pancreatin preparations in the form of minimicrospheres in an enteric capsule are preferable (Creon).
16. Minimicrospheres of pancreatin preparations (Creon) must not be chewed or shredded, they must not be added to food which pH is higher than 5,5, because this would lead to the dissolution of the shell that protects them from the gastric juice activity.
17. If the capsule cannot be swallowed (kids, elderly patients), it can be open and minimicrospheric granules can be added to liquid food, that does not require chewing. The mixture must be administered immediately and must not be stored for later use.
18. In case of constipation anti-peristaltic medicines administration must be stopped immediately.
19. During antimicrobial therapy probiotics administration or Linex or Bifiform preparations administration is allowed since they contain antibiotic resistant intestinal flora strains.
20. It is not recommended to administer Hylak and Hylak forte concomitantly with milk and other dairy.
21. Hylak and Hylak forte must not be administered concomitantly with antacids.
22. Probiotics preparations are compatible with dairy and sour dairy.



## Algorithm of diarrhea pharmaceutical care



## FLATULENCE

Flatulence is a bloating due to increased gas formation in the gastrointestinal tract (stomach and intestines) that may be associated to stomachaches, belching, dyspnea.

### **Most frequent flatulence causes**

The most frequent cause of flatulence is the decomposition of food, containing proteins and carbohydrates, or air swallowing while chewing during food intake or in chewing gum use.

Other causes of flatulence are:

- intolerance to some food products (dairy and carbohydrates of certain types of food: mushrooms, soybeans, sweets, beans, nuts, cabbage, plums, some grains, fruit juices);
- overeating;
- unusual food or diet change (business trips, vacation, vegetarianism);
- smoking;
- gastritis and stomach ulcer;
- cholelithiasis;
- dysbiosis;
- abnormal peristalsis (colon contractions);
- premenstrual period;
- post-surgery period.

**\*Threatening\* symptoms** in flatulence that require doctor's intervention:

1. severe stomachaches;
2. nausea and vomiting;
3. jaundice of the skin and eyes sclera;
4. sharp and pronounced weight loss;
5. bloating after medicines administration.

### **Non-medicinal flatulence relief:**

1. identification and avoidance of food products causing flatulence;
2. restriction of foods containing sugar substitutes that promote bloating and pain due to gases accumulation;
3. physical activity increase;
4. stop chewing gums;
5. quit or reduce smoking;
6. food intake in small portions 4-5 times a day;
7. intake of food products containing acidophilic cultures.

### **Medicinal flatulence treatment:**

For the symptomatic flatulence treatment administration of next pharmacotherapeutic groups of medicines is recommended:

**Enterosorbents.** They efficiently absorb different toxic metabolites from the intestines. Organism detoxification due to absorbents administration prepares organs and tissues and improves the interaction between biologically active substances (including herbal preparations) and body receptor apparatus. Enterosorbents promote flatulence and other dyspeptic disorders reduction. They can be successfully administered as a part of complex therapy, in combination with herbal preparations in particular.

Silicones are chemically inert surface-active substances obtained on the basis of silicon. They act as defoamers, reducing the surface tension of the gas bubbles formed in the intestines. Bubbles burst and/or are resorbed and excreted naturally. Silicones act exclusively on the gas bubbles surface, do not affect the intestinal mucosa, are not absorbed in the intestines. Preparations of this group are practically non-toxic. They can be prescribed to pregnant and lactating women, children.

#### Comparative characteristics of silicones

International name	Trade name	Clinical and pharmaceutical characteristics
Simethicone	Infacol Espumisan Alka-Seltzer Anti Gas, Colic Drops, Colicon, Degas, Flatulex Drops, Gas Aide, Gas-X	Chemically inert substance that is not absorbed in the gastrointestinal tract, is excreted unchanged (non-metabolized) in the feces. It does not contain sugar so it can be administrated in patients with diabetes. It is contraindicated in intestinal obstruction, obstructive gastrointestinal tract diseases. There is no common or important side effects reported with this medicine.

Enzyme preparations. In symptomatic flatulence treatment enzymes preparations prescription the goal is not substitutional therapy but to reach a \*functional rest\* of excessively stimulated by plentiful food pancreas. Administration of preparations that contain moderate amounts of lipolytic and sufficient amount of proteolytic enzymes is advisable.

Carminative herbal preparations: dill fruits, fennel fruits, caraway seeds, chamomile flowers.

Probiotics. Preparations of this group inhibit the activity of putrefactive and gas-forming microorganisms. This effect promotes flatulence elimination, digestion and absorption processes normalization.

Homeopathic preparations. Enterokind, Gastrokind, Gastritol preparations are used in functional intestinal disorders. Gastritol (drops for oral administration) are used in functional dyspepsia, flatulence.

### **Comparative characteristics of carminative herbal preparations**

<b>Plant name</b>	<b>preparations</b>	<b>Clinical and pharmaceutical characteristics</b>
Dill fruits	Dill fruit	Provides spasmolytic, anti-inflammatory, choleretic and carminative effects, stimulates digestive glands secretion, reduces decay and fermentation processes in the intestines. It is contraindicated in pregnancy. Hypersensitivity to the preparation is possible.
Caraway fruits	Caraway fruit	Normalizes the tone and the motility of the gastrointestinal tract. It provides spasmolytic, antiseptic, choleretic effects, stimulates digestive glands secretion, reduces decay and fermentation processes in the intestines. Hypersensitivity to the preparation is possible.
Fennel fruits	Fennel fruits	Provides spasmolytic, anti-inflammatory, carminative and antibacterial effects. It regulates intestines motility function. Hypersensitivity to the preparation is possible.
	Plantex	Contains fennel fruits, glucose and galactose. It improves digestion, stimulates gastric juice secretion and intestinal motility activity, prevents gas formation and relieves spasms caused by flatulence. It can be recommended for kids under 1 year Hypersensitivity to the preparation is possible.
	Carminativum-hetterich	Contains liquid alcohol extracts of bitter fennel, coriander, chamomile flowers.

		<p>Provides carminative and spasmolytic effects. Prevents and relieves stomach and intestine spasms caused by flatulence. It can be recommended for kids under 1 year.</p> <p>Hypersensitivity to the preparation is possible. Due to alcohol content (36%) prolonged use is not recommended (up to several weeks).</p>
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Gastrokind (tablets) is recommended in gastrointestinal disorders in children, including infants.

Enterokind (oral solution) is recommended for the treatment of functional intestinal disorders associated with flatulence.

#### PHARMACEUTICAL CARE IN FLATULENCE SYMPTOMATIC TREATMENT

1. Due to sorption properties medicines of sorbents group decrease the efficacy of any oral preparations administered simultaneously.
2. It is recommended to keep an interval between adsorbents and any other medicines administration.
3. Prolonged administration of adsorbents leads to vitamins, proteins, fats depletion.
4. Due to their moderate constipating effect in prolonged use (or/and administration in large doses) adsorbents may promote constipation.
5. If activated charcoal is used then feces are black colored. (Beware: differential diagnosis versus melena).
6. It is recommended to administer simethicone with a small amount of water after every meal and before bedtime.
7. Herbal carminative preparations are administered as decoctions and infusions.
8. Dill, caraway and fennel infusions stimulate breast milk secretion.
9. Infusions and decoctions should be kept in the fridge for no longer than 3 days.
10. Plantex tea cannot be sweetened.
11. Carminativum-hetterich prolonged administration is not recommended (up to several weeks) due to alcohol content (36%).
12. Enzymes preparations should be administered during a meal or right after.
13. Tablets and capsules containing enzyme preparations should not be chewed or broken.

#### DYSBIOSIS

Dysbiosis is a quantitative (decrease in the content of useful and increase in the content of pathogenic microflora) and qualitative (intestinal flora biological properties change, reduced performance of useful functions and increased toxicity) changes in intestinal microflora.

According to recent epidemiological researches, about 90% of the world population suffer of dysbiosis to different extents. It is caused by irrational diet, stresses, decreased immune reactivity, ecological and physical-chemical factors of the environment, unjustified and uncontrolled use of medicines. All of these negatively impacts the organism microflora. After suffering from an acute intestinal infection, in absence of adequate therapy, dysbiotic changes in the intestines may persist up to 2-3 years.

In children of first year of life (70 – 80 %) and newborns (80 – 100 %) dysbiosis is often observed. In children over the age of one dysbiosis is observed in 60 – 70 %, in healthy children of age 3 and older in 30 - 50% .

### **Basic composition and functions of normal intestinal microflora**

The human gastrointestinal tract is an habitat for a large amount of microorganisms, which quantitative and qualitative composition differs in various sections of gastrointestinal tract. The greatest number of microflora is detected in the large intestine, where 3 species proliferate the most: bifidobacteria and bacteroides (main group), lactic acid bacteria and Escherichia coli strains (concomitant group), staphylococci, fungi and Proteus (residual group). Microflora composition in adults is quite stable in physiological conditions and is characterized by certain proportions between its representatives. Temporary microflora disturbances may occur depending on diet changes, life style conditions. The digestive tract microflora contributes to non-specific immunity.

### **Main functions of the normal intestinal microflora:**

- detoxification (inactivation of alkaline phosphatase enterokinase)
- fermentation (hydrolysis of proteins, lipids, carbohydrates metabolism products)
- synthesis (synthesis of vitamins, antibiotic and other biologically active substances)
- digestion (increase of the digestive tract physiological activity)
- antianemic (promotes iron absorption)
- antirachitic (promotes calcium and vitamin D absorption)
- immunity (immune system activation, immunoglobulins and interferon synthesis)
- intermicrobial antagonism.

### Microorganisms contents in healthy adult feces

<b>Bacteria</b>	<b>Number of bacteria per 1 g of stool</b>
Bifidobacteria	$10^7$ - $10^9$
Bacteroides	$10^7$ - $10^{10}$
Lactobacilli	$10^6$ - $10^9$
Clostridia	$10^3$ - $10^5$
Escherichia coli	$10^5$ - $10^8$
Proteus	$10^4$
Klebsiella	$10^5$
Lactic Streptococcus	$10^5$ - $10^8$
Staphylococcus aureus	$10^3$
Enterococcus	$10^5$ - $10^6$
Fungi	$10^4$

Factors leading to microflora disturbance are numerous and diverse.

#### **Main factors promoting dysbiosis:**

Exogenous:

1. industrial poisons;
2. violation of sanitary standards in everyday life and at work;
3. ionizing radiations;
4. climatic and geographical factors;
5. gastroenterological surgery.

Endogenous:

1. immune disorders;
2. stress;
3. non-infectious gastrointestinal tract diseases (intestine and gall bladder pathologies, peptic ulcer);
4. infectious diseases;
5. diabetes;
6. rheumatic diseases;
7. starvation;

8. irrational diet;
9. old/senile age;
10. irrational medicines administration.

Except for the given above factors, in children factors promoting dysbiosis are:

1. anatomic disorders;
2. food allergies;
3. errors in the diet;
4. antibacterial therapy (even if it is rational).

Clinical symptoms are diverse and are largely determined by the degree of violation of the normal intestinal biocenosis. In some cases there is no symptom of dysbiosis, but most often the following complaints are reported by the patients:

- unstable stool (constipation, diarrhea, alternation of constipation and diarrhea);
- bloating and rumbling;
- pain in the lower abdomen decreasing after the discharge of gases;
- nausea, belching, bitter taste in the mouth.

Besides as result of long-lasting dysbiosis a whole series of pathological conditions arise:

- asthenoneurotic syndrome (caused by hypovitaminosis and intoxication);
- anemia;
- hypoproteinemia;
- weight loss;
- hypovitaminosis (mostly deficiency of fat soluble vitamins).

In young children showing dysbiosis belching, vomiting, decrease in the rate of increase in body weight, anxiety, sleep disturbance are observed. The stool may be plentiful, liquid and mushy, frothy, greenish with sour and putrefaction odor.

Pains in the abdomen are paroxysmal, appear within 2-3 hours after the meal and are associated to bloating and urges to defecate.

Four clinical stages of dysbiosis are distinguished:

**Stage 1.** Compensated (latent) dysbiosis which is characterized by quantitative composition change in aerobic microorganisms in normal proportion of bifidobacteria and lactobacilli. There are no clinical manifestations.



**Stage 2.** Subcompensated (localized) dysbiosis. There is a decreased amount of *Escherichia coli* and a moderate decrease of bifidobacteria quantity associated with a simultaneous increase of conditionally pathogenic microorganisms quantity. There is a mild inflammatory process in the intestine (enteritis, colitis).

**Stage 3.** Extended dysbiosis which is characterized by significant changes in quantitative and qualitative composition of the microflora. The severity of the clinical symptoms varies.

**Stage 4.** Generalized (decompensated) dysbiosis. Along with a significant increase in the content of *Escherichia coli* it is characterized by an almost complete lack of bifidobacteria and a sharp decrease in lactobacilli amount. Clinical symptoms are severe intestinal dysfunction, bacteremia, septic complications, dystrophic changes in the internal organs.

### **Main principles of intestinal dysbiosis treatment**

Intestinal dysbiosis treatment is complex. Its goal is to address the cause of the dysbiosis, eliminate pathogenic and conditionally pathogenic microorganisms and to recover normal colon microflora. Recovering normal colon microflora is achieved through the use of probiotics.

Ambulatory treatment is only possible in case of latent (compensated) form of intestinal dysbiosis. A microbiological stool examination must be done and it is necessary to consult a doctor.

### **Non-medicinal intestinal dysbiosis treatment**

Non-medicinal dysbiosis treatment is based on rational diet. In dysbiosis diet must be full-fledged chemically, thermally and mechanically gentle and its goal should be to provide full-fledged good nutrition, improvement of intestine and other digestive organs functional condition, regeneration process stimulation and immunity increase. In dysbiosis lean boiled meat, fish, porridges (buckwheat, oat, rice), low-fat cottage cheese, white stale bread, large amounts of fruits and vegetables (as fiber-containing products) are recommended.

In dysbiosis associated with diarrhea it is recommended to temporarily exclude rye bread, whole milk, raw vegetables and fruits, spices. Intake of mashed rice and oat soups, porridges, jellies, boiled vegetables, carrot, blackberry, quince, garnet jelly and juice is recommended.

In dysbiosis associated with constipation products rich in fibers and providing laxative effect should be incorporated into the diet: bran bread, vegetable vinaigrette, buckwheat, raw vegetables and juices, highly mineralized mineral waters.

In case of severe flatulence intake of beans, cabbage, high glucose products such as honey, jam, sweets, grape should be restricted. It is recommended to increase boiled meat and fish intake.

In children it is advisable to use traditional sour dairy products and special fermented milk mixtures (dry powders used to prepare milk for babies), that are close to breast milk in their composition.

### **Medicinal intestinal dysbiosis treatment**

In compensated dysbiosis for microflora normalization and pathogenic and conditionally pathogenic germs growth inhibition probiotics, containing components or metabolite products of over 20 types of microorganisms are used.

Probiotics (eubiotics) are freeze dried live weakened strains of normal intestinal microflora that colonize the intestines after being taken orally. In the intestine these bacteria produce acetic and lactic acid, creating an acidic medium, which inhibits putrefaction and gas-forming microorganisms (Clostridium, Proteus, bacteroids). They release anti-bacterial substances that inhibit multiplication of various conditionally pathogenic microorganisms and pathogens involved in intestinal infections such as Salmonella and Shigella.

Probiotics are not prescribed as a substitute therapy but as remedies providing proper conditions for microflora composition recovery.

The inhibition of putrefaction and fermentation processes by eubiotics eliminates flatulence, normalizes digestion and absorption processes in the intestines. The normal microflora recovery promotes organism immunization and increases its resistance to infections.

Eubiotics are administrated for the treatment and prevention of dysbiosis, especially in children.

In dysbiosis prevention and treatment along with probiotics functional nutrition products are used. It is a special type of probiotics, which is represented by food products of natural origin, intended for daily intake and providing regulatory effect on physiological functions and biochemical reactions of human body.

Prebiotics are indigestible food ingredients that promote health improvement through selective growth and/or metabolic activity stimulation of one or several bacteria groups living in the colon. A food component can be classified as prebiotic only if it is neither hydrolyzed by human digestive enzymes nor absorbed in upper sections of digestive tract. It must be a selective substrate for growth and/or metabolic activation of one type or certain group of microorganisms, living in the colon, normalizing their proportions. Nutrition ingredients meeting these criteria are low molecular weight carbohydrates. Prebiotics are fructose oligosaccharides (FOS), inulin, galactose oligosaccharides (GOS), lactulose, lactitol. They are present in dairy, corn flakes, groats, bread, bulb onion, field chicory, garlic, beans, peas, artichoke, asparagus, bananas and many other products.

Regular intake of food containing lactobacilli, bifidobacteria, fibers and natural antioxidants contributes to health maintaining, mitigates the adverse environment impact and promotes increase of life expectancy.

### **Probiotics and prebiotics.**

#### ***Lactobacilli.***

Lactobacillus acidophilus

Bacid

Culturelle

#### ***Others.***

Bifidumbacterin

Subalin

Enterojermina

LitterGuard

Escherichia coli bacterin Toxoid J-VAC

### **Other microorganisms and their combinations.**

Bifiform

Bificol

#### **Lactobacilli and their combinations.**

Acipol

Linex

Acidolac

Probio`vit Granions

Yogurt

#### **Prebiotics**

Hylak

Duphalac (lactulose)

Probilac

#### **Saccharomyces bulardii**

Enterol 250

Normagut

## PHARMACEUTICAL CARE IN PROBIOTICS AND PREBIOTICS ADMINISTRATION

The most efficient medicine for dysbiosis correction is the complex multicomponent preparation Linex.

Linex capsule can be opened and mixed with teaspoon of liquid such as tea, water or juice if required (children). The mixture is a water suspension. It should be used immediately and not stored.

During antimicrobial therapy Linex or Biform administration is possible, since they contain antibiotics resistant strains of intestinal flora.

It is not recommended to administer Hylak and Hylak forte concomitantly with milk and other dairy.

Hylak and Hylak forte must not be administered concomitantly with antacids.

Hylak and Hylak forte should be administered only after dilution in water.

Enterol 250 administration should not be combined with oral antifungal medicines.

Lactobacilli preparations should be administered with milk

It is not recommended to administer any probiotics with hot drinks.

It is not recommended to administer any probiotics with alcohol.

For dysbiosis prevention food products for functional nutrition are recommended.

Simultaneous administration of probiotics and lactulose increases treatment efficacy.

## FUNCTIONAL DYSPESIA

Functional dyspepsia is a presence of one or more dyspeptic symptoms that originates from the gastroduodenal area (feeling of heaviness after a meal, feeling of early satiety, epigastric pain, burning sensation in epigastrium) in absence of any organic changes (according to endoscopy results), system or metabolic changes, that could explain this symptom.

Depending on the predominance of one or another clinical symptom there are 3 variants of functional dyspepsia. In epigastric pain syndrome (ulcer-like variant) there are night and \*hungry\* pains in the stomach pit that relief after a meal. In the postprandial distress syndrome (dyskinetic variant) the symptoms are heaviness and feeling of overflow in the stomach pit after a meal, early satiety. In the mixed type (non-specific variant) patient's complaints cannot be referred to one or another group. The most frequent variant of functional dyspepsia is the dyskinetic variant.

Dyspepsia may be a symptom of another disease and may be an independent disease itself as well (functional dyspepsia).

Dyspepsia is said to be functional if it meets the following criteria:

- presence of persistent or intermittent dyspepsia at least 12 weeks per year;
- absence of organic gastrointestinal tract diseases with similar symptoms;
- dyspepsia does not relieve after defecation and is not associated with the frequency or the characteristics of the stool (no signs of irritable bowel syndrome).

### **Most common functional dyspepsia causes**

Pathophysiological changes in intestinal motility are the cause of functional dyspepsia. Physiological reaction of the stomach to the ingestion of the food lump is relaxing its proximal section. Then, there is a relaxation of the lower part and the body of the stomach, which is required for large amount of food intake without increase of gastric wall tension. Through contractions of the lower part of the stomach its content moves to the distal section. Food fragments leave the stomach when their diameter is 1 mm or less. In physiological conditions contractions of various sections of the stomach are strictly sequenced and synchronized in time.

Motility disturbances may occur due to stomach accommodation disturbances (capability to relax in food lump ingestion), sequence (synchronization) disturbances of different stomach sections, decreased motility with subsequent relaxation and complete stopping of the stomach contractions.

### ***Factors promoting functional dyspepsia development:***

- overreaction to normal intensity irritation (visceral hypersensitivity);
- psycho-emotional stress;
- decrease of sensitivity threshold of stomach wall mechanoreceptors to stretching;
- individual intolerance to certain food components;
- *Helicobacter pylori* can cause stomach motility function disturbance, although a clear relation between these factors has not been shown.

**\*Threatening\* symptoms** that suggest a serious condition in patient and requires a doctor's consultation are:

1. sharp pains in the upper abdomen;
2. gradual pain intensity increase or increasing discomfort in the epigastrium;
3. heartburn manifestation that lasts over 3 days
4. hematemesis;
5. black colored feces;
6. progressive weight loss;

7. dyspepsia symptoms may occur during medicines administration (consult your doctor before considering any medication change).

### ***General approaches to functional dyspepsia treatment by OTC-drugs***

Taking into account that gastro-intestinal tract motility disturbances are basis for disease development, medicines of choice in this case are peristalsis stimulators (prokinetics). According to their mechanism of action they are dopamine receptors antagonists. Gastrokinetic effect is caused by peripheral dopamine receptors blockade and by their impact on the hypothalamus and parasympathetic nerves. Preparations have anti-nausea and antiemetic effect, that is connected to both gastrokinetic action and to inhibition of trigger zone of the brainstem receptors. As a result sensitivity of the nerves transmitting the impulse from the stomach and duodenum to emetic centre is decreased. Due to given above effects duration of stomach antrum and duodenum peristaltic movements increases, lower esophageal sphincter tone increases. Prokinetics do not affect gastric secretion.

Preparations: Motilium, Neoperidys, Permotil, Motilium Pédatrie, Domperidon-Teva, Domperidon Sandoz.

Empirical therapy with spasmolytic, carminative, polyezyme, antacid preparations is recommended.

### **PHARMACEUTICAL CARE IN FUNCTIONAL DYSPEPSIA SYMPTOMATIC TREATMENT**

1. Prokinetics should be administered 15-20 minutes before meal. In case of its administration after meal absorption is inhibited.
2. In case of domperidone and antacids or anti-secretion preparations complex therapy, antacids or anti-secretion medicines should be administered after meal.
3. It is not recommended to administer simultaneously domperidone and cholinoblockers, since they neutralize its antidyspeptic effect.
4. Domperidone is contraindicated in pregnant and lactating women.
5. Domperidone does not affect the speed of psychomotor reactions, that is why it can be approved in drivers.

Decrease of contractions



Food overflow of the stomach



Excessive irritation of receptors in the stomach

Pain

Discomfort

Bloating

Nausea

Early satiety

Food overflow sensation in  
the stomach

