Fever

Fever is a typical non-specific reaction of the body that occurs due to the stimulation of the thermoregulation center by pyrogens (thermostable high molecular weight compounds released by microorganisms or by human body tissues).

The body temperature is considered increased when it exceeds 37*C. Depending on the level of fever reaction it can be classified as subfebrile (not over 38*C), moderate (38-39*C), high (39-41*C) or excessive hyperetic (over 41*C).

Moderate temperature increase in infectious diseases promotes organism`s defending powers mobilization, immune system activation. On the opposite, an excessive temperature elevation significantly worsens general performance, promotes a range of adverse shifts in patient's organism: sympathetic nervous system tone increase, tachycardia, respiratory center excitability increase. Thus, body oxygen demand is increased, metabolism intensifies, sodium and chlorides retention occurs with swelling development, skin (skin pallor) and internal organs vessels constrict. Precapillary sphincters spasm occurs, normal blood flow is impaired, centralization of blood circulation develops, leading to organs and tissues hypoxia. Myocardium hypoxia entails weakening of its contractility, brain hypoxia leads to its edema, impaired consciousness, cramps. Internal organs and systems response to temperature elevation is especially intense in children.
All these symptoms determine the necessity of antipyretic preparations prescription as a part of symptomatic treatment of various diseases and pathological conditions.

Temperature elevation symptom can have a lot of «faces» and can manifest in absolute majority of different organs diseases.

Most frequent fever causes in adults:

1. ***Infectious fever***
- viral infections
- bacterial infections
- fungal infections
2. ***Non-infectious fever***
- extensive hemorrhage, including craniocerebral
- autoimmune processes
- allergic reactions
- tissues necrosis
- cancer
3. ***Psychogenic fever***
- central nervous system diseases
- reaction to severe psycho-emotional stress

In adults fever primarily accompanies infectious processes whereas in children hyperthermia frequently has a non-infectious cause. Unlike adults, children often show a temperature elevation after an exposition to non-specific stimuli, including stress.

Most frequent fever causes in children:

4. ***Infectious fever***

- viral infections
- bacterial infections
- fungal infections

5. ***Non-infectious fever***

- overheating
- psycho-emotional stress
- teething
- allergic reactions
- trauma
- water electrolyte balance shift (dehydration of a child`s body).

In all these cases fever is a signal of a trouble in the body. When a patient handles complaints to fever asking him about other symptoms he might have is required.

The main cause of fever is acute respiratory viral diseases (ARVD). Fever is associated to other characteristic complaints that testify to the pathological process in bronchopulmonary system and nasopharynx (rhinitis, sore throat, cough). If subfebrile temperature is associated to these complaints then within 2-3 days after the beginning of the disease, self-treatment with OTC-drugs is allowed. In all the other cases you should contact a doctor.

Any symptom, even if it is insignificant at first sight, may signal the onset of a serious disease or a chronic disease exacerbation.

***Threatening* symptoms** suggesting a serious disease, which require a doctor's consultation:

1. temperature increase over 39*C (high-grade fever).
2. fever associated to severe pain, impaired consciousness, cramps.
3. in ARVI symptoms fever remains over 38,5*C for 3 days or longer.
4. fever remains over 37,5*C for 2 weeks or longer.

If the fever is not associated to an excessive disturbance of performances in ARVD it should be lowered only if it exceeds 38,5*C. Seeking for the normalization of the body temperature is not justified since it decreases the efficacy of the immune system in its fight against the pathogen. In this case it is advisable to apply a symptomatic treatment of sore throat, rhinitis, cough (See previous chapters).

OTC antipyretic drugs, due to their mechanism of action, do not reduce slightly (37,2 – 37,3 *C) elevated temperature.

Recommendations for antipyretic drugs prescription in children:

- in initially healthy children (without concomitant pathology and burdened anamnesis) in fever 38,5*C and above (WHO recommendations are 39 – 39,5*C)
- in children of 2-3 months old and in children with burdened premorbid background (febrile cramps in anamnesis, central nervous system pathologies, cardiovascular system pathologies) – in fever 38*C (WHO recommendations are 38,0-38,5*C).
- if fever threatens child's life (malignant hyperthermia), requires hospitalization, intensive care due to high risk of hemodynamic disturbance, metabolism impairment, disturbance of vital organs functions.
- antipyretic medicines should not be prescribed for regular administration several times a day not depending on temperature level, they should be administered only *if required*, in temperature elevation above 38.5*C
- the decision to use of antipyretics in children taking antibiotics must take into account the pros and cons. Antibiotics are often prescribed empirically and antipyretics may mask their inefficacy since they lower the body temperature.
- strictly stick to the recommended and daily dosages in children.

Antipyretic OTC- drugs

Active ingredient	Pharmacological characteristics
Paracetamol (Acetaminophen) Dafalgan, Panadol, Efferalgan	➢ Provides antipyretic, mild analgesic, mild anti-inflammatory effects. ➢ Does not have a damaging effect on the gastro-intestinal mucosa. ➢ It is contraindicated in hypersensitivity, erosive ulcerous lesions of gastro-intestinal tract and duodenum, asthma, progressive kidney and liver diseases. ➢ It does not affect platelets aggregation. ➢ It can be recommended in children over 1 month. ➢ It can increase the risk of asthma manifestation and other allergies. ➢ It increases the risk of functions disturbances of liver, kidneys, and cardiovascular system in simultaneous administration with ethanol. It is recommended to decrease the dose in patients abusing alcohol. ➢ It is not recommended in 3rd pregnancy trimester.

Ibuprofen Nurofen, Advil, Nalgesic	➢ Provides anti-inflammatory, analgesic, antipyretic effects (up to 6-8 hours). It increases non-specific organism resistance, possesses immunostimulating effect. ➢ It can be recommended in children over 3 months (dosage forms for children). ➢ It is not recommended in case of stomach and/or duodenal ulcers, bleedings in anamnesis, severe kidney, liver, heart functions disturbances. ➢ It is not recommended in pregnant women. ➢ Simultaneous administration with other NSAID is not recommended.

Clinical pharmacological characteristics of medicines containing antipyretic active ingredients

Along with traditional tablets form, new improved dosage forms, liquid and solid, were developed for symptomatic fever treatment.

Advantages	Disadvantages
Tablets	
1. Convenience and simplicity of administration. 2. Dosage accuracy. 3. Absorption regulation of active ingredients in localization (stomach, colon) and time. 4. The ability to combine several active ingredients. 5. The ability to correct unpleasant taste and odor.	1. Not all the patients, especially children, are able to swallow the tablets. 2. Relatively slow effect (25-30 minutes). 3. High concentration of active ingredient in the dissolution spot is possible. Thus, there is an irritating action on the gastro-intestinal mucosa.
Instant effervescent tablets	
1. Simplicity of administration in different categories of patients, including children. 2. Rapid absorption and fast effect (up to 10 minutes). 3. Reduced impact of food on preparation absorption. 4. Significant irritating effect decrease on gastrointestinal mucosa.	1. Higher price compared to usual tablets. 2. Limited administration in children practice (starting the age of 6-12). 3. Necessity to take into account sodium amount in patients maintaining salt-free diet.
Capsules with microgranules or	

the liquid active ingredient	
1. Better solubility and better absorption of active ingredients compared to tablets. 2. The ability to combine several active ingredients. 3. The ability to correct unpleasant taste and odor 4. Minimal irritating effect on gastrointestinal mucosa. 5. Prolonged action.	1. Higher price compared to usual tablets.
Syrups/suspensions	
6. Simplicity of administration in different categories of patients, including children. 7. Rapid absorption and fast effect development (up to 10 minutes). 8. Pleasant odor and taste. 9. Reduced impact of food on preparation absorption.	1. Lower dosage accuracy.
Suppositories	
1. Convenience of administration in immobilized (bed) patients, in children, in elderly. 2. The ability to administer in impaired swallowing process. 3. Relatively fast speed of absorption and effect development (10-15 minutes). 4. Absence of food influence on preparation absorption. 5. Absence of stomach enzymes impact on active ingredients. 6. The ability to prescribe unpleasant-tasting ingredients. 7. Lower impact of active ingredients on liver function.	1. Mild irritating effect on the colon mucosa (in some categories of patients stimulation of bowel movements is possible). 2. Psychological discomfort (in certain patients). 3. Absorption in the large intestine is up to 65-90%. Hence decrease of pharmacological effect is possible. 4. Diarrhea is quite common in children, so suppositories use may be difficult and not sufficiently effective.

Both safety and convenience of administration should be taken into account when choosing an antipyretic in children. Hence only dosage forms for children should be used.

Ibuprofen and paracetamol are first-line preparations for symptomatic fever treatment in children. Since 2011 according to WHO, ibuprofen is considered to be more effective, because its effect lasts longer and it also has significant anti-inflammatory and analgesic effects.

For fever treatment in children the recommended dose of paracetamol is 10-15 mg/kg, the maximal daily dose is 60 mg/kg. The recommended daily dose of ibuprofen is 5-10 mg/kg, the maximal daily dose is 30 mg/kg of a child's body weight (WHO recommendations 2011).

It is always necessary to recommend to the parents to follow the medicine instruction.

Currently the pharmaceutical companies sell a wide range of complex OTC-drugs for cold treatment. Their characteristic features are defined by their composition and pharmacological properties of each ingredient in their composition. Detailed characteristics of the active ingredients is given in previous articles.

Antipyretic medicines comparative characteristics of adverse effects

Adverse effects	Ibuprofen	Paracetamol
Bleedings	+	-
Stomach mucosa damage	+	-
Bronchospasm	+/-	-
Brain edema	-	-
Na^+ Cl^- retention	+	-
Toxins retention	-	-
Reye's syndrome development	-	-
Negative impact on the fetus	3rd trimester	-
Hemolytic anemia	-	-
Allergic reactions	+	+/-
Kidney damage	Large doses and prolonged administration	Large doses and prolonged administration
Liver damage	-	Large doses and prolonged administration

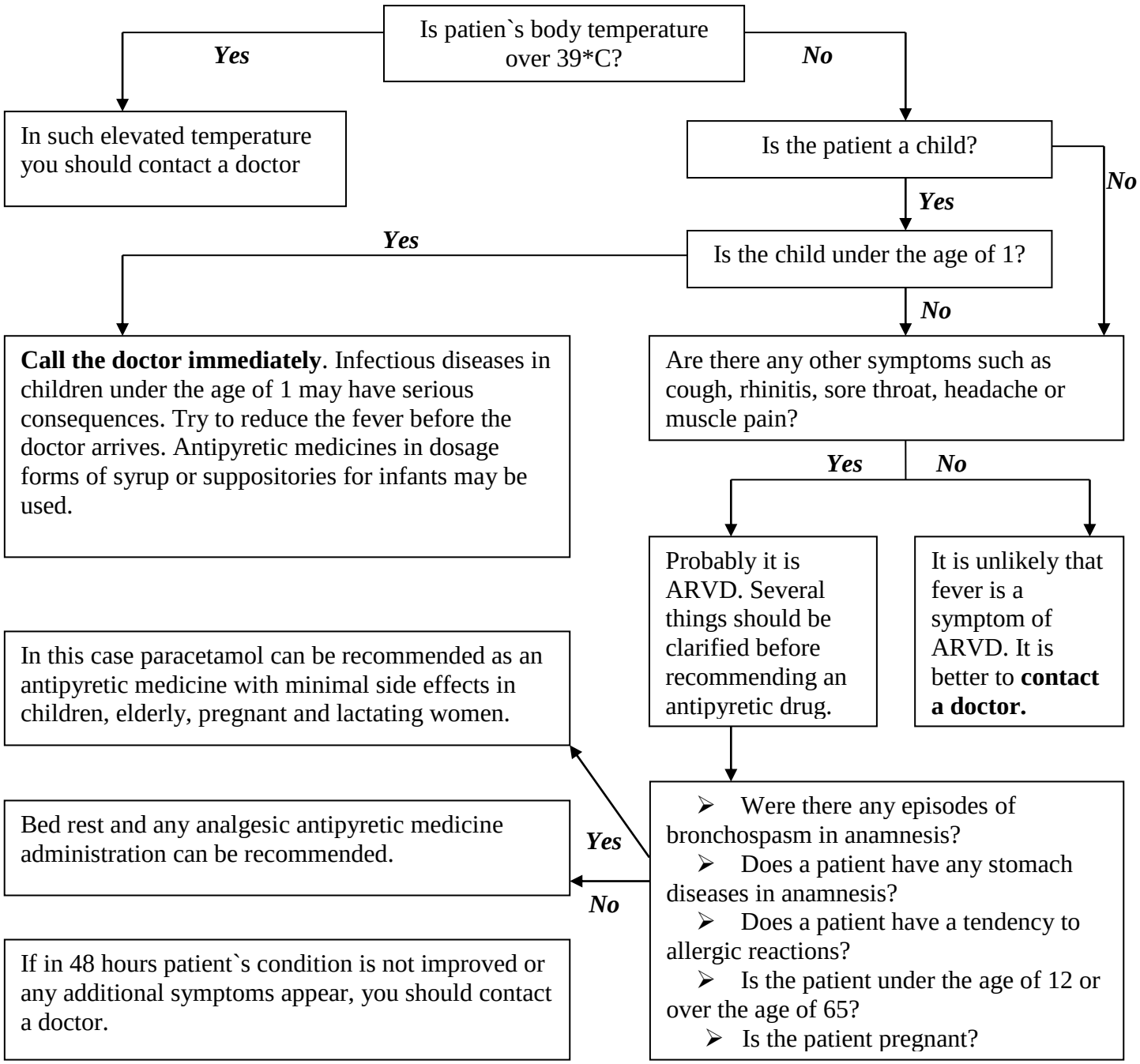
PHARMACEUTICAL CARE IN ANTIPYRETIC MEDICINES ADMINISTRATION

- In elevated body temperature it is recommended to reduce physical activity, in high-grade fever bed rest is recommended.

- The room should be regularly ventilated to keep moderate air temperature (*comfortable temperature*). During temperature elevation when a patient has ague (chills) it is recommended to make him/her feel warm. At the temperature peak when it does not elevate any more, cooling is allowed by wiping with water of room temperature.
- In case of elevated temperature and absence of contraindications it is recommended to drink a lot of liquid (3-4 L per day). Supplementation with vitamins should be provided, fatty food should be restricted.
- In children fever reducing should start with physical cooling methods (wiping with water of room temperature, room ventilation).
- Antipyretic drugs should be used only in high-grade fever (38,5*C and over). Antipyretic medicines are not effective in low-grade fever (37,5*C and lower)
- All antipyretic preparations should be administered short-term only (up to 3 days). If the fever sustains over 3 days, the patient should contact a doctor.
- Preparations of paracetamol and ibuprofen in standard adult dosages may be recommended to elderly patients.
- Paracetamol containing preparations have more sparing impact on gastrointestinal mucosa. Hence their administration is possible in patients with gastro-intestinal tract pathologies. Administration in patients with asthma, liver, kidney pathologies, in case of alcohol abuse should be done with caution.
- Liquid ibuprofen dosage form and ibuprofen sodium salt are absorbed faster. Hence the effect is developed faster, maintaining safety criteria.
- Ibuprofen effectively relieves pain associated with fever such as back pain, joints pain (arthralgia), muscles pain (myalgia) due to its anti-inflammatory effect.
- Ibuprofen and paracetamol are first-line preparations in fever treatment in children.
- The antipyretic preparations should be administered after meal. Antipyretic preparations excretion is significantly increased in case of urine alkalization, which leads to drug efficacy decrease and a shorter therapeutic effect. Urine may be alkalized in dairy, plant-based diet, by alkali mineral waters, citrates, sodium bicarbonate, sodium lactate. Urine is acidified by predominance of meat products, ascorbic acid, calcium chloride, ammonium chloride.
- The antipyretic drugs should be used with caution in patients with asthma, erosive ulcerous gastro-intestinal tract damages, bleeding tendency (hemorrhagic diathesis), liver diseases, impaired kidney function.
- Simultaneous administration of ibuprofen and anticoagulants, antihypertensive preparations, thiazide diuretics should be prescribed with caution.
- In pregnant women ibuprofen, mefenamic acid are forbidden.
- The antipyretic medicines should not be combined with alcohol (sharp increase of ulcers, stomach bleeding risk and liver toxicity).

- Complex anti-cold preparations are contraindicated in pregnant and lactating women, in children under the age of 6. In these patients it is more advisable and safe to provide symptomatic treatment of separate cold symptoms.
- It is advisable to combine antipyretic medicines administration with preparations for symptomatic treatment of sore throat, rhinitis, cough.
- Independent administration of antipyretic medicines (without a doctor's consultation) during antibiotics treatment is not advisable since antipyretic drugs may hide inefficiency of antibacterial treatment.
- Medicines used for fever reduction relieve muscle pain and headache.
- Antipyretic medicine administration in low-grade fever is recommended only in case of severe ague, tendency to cramps.

Algorithm of fever pharmaceutical care



Warning

1. If the body temperature is over 38*C for more than 48 hours or elevated over 40*C, you should **immediately contact a doctor**.
2. If episodes of fever repeat **without any certain reason, especially in association with fatigue, you should immediately** contact a doctor. These symptoms may be caused by chronic infections, blood diseases, and a number of diseases requiring as early as possible medical help.