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Medications and non-pharmacological measures to alleviate the symptoms of respiratory tract infections in the pediatric population

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Abstract

In the pediatric population, acute respiratory tract infections (RTIs) are the most common reason for seeking professional help from a physician or a pharmacist. Alleviation of symptoms is the only therapeutic measure in viral RTIs and is an adjunct to antibiotic therapy in bacterial RTIs. This article discusses pharmacologic and non-pharmacologic options for treating nasal congestion, cough, fever and sore throat in RTIs and clinical evidence on their efficacy and safety in the pediatric population. In general, clinical studies conducted in children for most of these drug groups are few or nonexistent, making it difficult to create evidence-based recommendations. Nasal decongestants, cough suppressants, mucolytics, expectorants, antipyretics/analgesics and sore throat local preparations are available in suitable pharmaceutical forms and strengths for the certain age. As many of them are over-the-counter (OTC) preparations, it is necessary to strictly take into account the age of the child in whom they may be used and dose properly. Multicomponent preparations carry the risk of taking unnecessary medications and of their side effects. The use of multiple OTC medicines is associated with the risk of an overdose of a component that may be present in different preparations. Appropriate non-pharmacological measures (e.g. oral hydration, nasal saline application or irrigation, honey) may be helpful and should be used whenever possible due to their safety.

Key words: symptoms of respiratory tract infections, medications, non-pharmacological measures, pediatric population

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Introduction

In the pediatric population (ages 18 and younger), acute respiratory tract infections (RTIs) are the most common reason for seeking professional help from a physician or a pharmacist. Common RTI symptoms include nasal congestion, runny nose (rhinorrhea), sore throat, ear pain (otalgia) and/or cough, and they are mainly the result of the activation of immune mechanisms in defense against the causative microorganism, i.e. acute inflammatory response. If the inflammation is particularly pronounced at a certain anatomical location, the diseases are referred to as sinusitis, pharyngitis, otitis media, laryngotracheitis (croup), bronchitis/bronchiolitis, and pneumonia. When the symptoms are not predominantly manifested on one part of the respiratory system, they are broadly defined as non-specific respiratory tract infections, which are often referred to as the common cold. Common respiratory infections also include influenza, a syndrome characterized by prominent systemic manifestations and local respiratory symptoms (1-3) (Table I).

Table I Characteristics of common acute respiratory tract infections (RTIs) in children (1-3)
Tabela I Karakteristike najčešćih akutnih infekcija respiratornog trakta (IRT) kod dece (1-3)

RTI	Common signs and symptoms
common cold	nasal congestion and rhinorrhea, sneezing, sore throat, dry cough
sinusitis	nasal congestion and rhinorrhea, face or maxillary tooth discomfort, headache, fever, (daytime) cough
pharyngitis	sore throat, erythema, edema or exudates of the pharynx (in GAS pharyngitis – rapid onset, fever, tonsillar exudates, cervical adenopathy, gastrointestinal manifestations, headache)
otitis media	otalgia (ear pulling, crying, irritability), fever; often accompanied by common cold symptoms
croup	barky cough, hoarseness, dyspnea, inspiratory stridor
bronchitis	cough, wet or dry; often accompanied by common cold symptoms
bronchiolitis	initially rhinorrhea, low-grade fever, cough; later in the disease course cough, tachypnea, wheezing, eventually apnoeic episodes
pneumonia	fever, cough, tachypnea, dyspnea, retractions, wheezing, grunting, crackles
influenza	fever, myalgia, malaise, sore throat, dry cough, rhinorrhea (rapid symptom onset)

GAS - group A β-hemolytic *Streptococcus*
GAS - β-hemolitički *Streptococcus* grupe A

Although, in general, bacteria cause only about 1/4 of cases of RTIs, these infections are the most common reason for prescribing antibiotics in current medical practice. Irrational use of antibiotics in these illnesses has greatly contributed to the development of antimicrobial resistance among common community-acquired pathogens. Since the signs and symptoms of viral and bacterial RTIs are unspecific and largely overlap, clinicians have a demanding task of diagnosing the disease and selecting the patients who really need antimicrobial therapy, i.e. differentiating between those with a bacterial infection and at risk of serious complications, and those with viral, self-limiting infections, in whom antibiotic treatment is ineffective and irrational (3, 4).

Regardless of causal treatment (which, when available, indicated and effective, removes the symptoms), there are medications and non-pharmacological measures that can alleviate the discomfort of patients with RTIs. This article discusses the options for treating nasal congestion, cough, fever and sore throat and some evidence on their efficacy and safety in the pediatric population. It is important to note that this evidence is scarce. The reasons for this are multiple. Most of these drugs were introduced into clinical practice when the requirements to demonstrate efficacy and safety in clinical studies were less demanding compared to today's standards. There are a small number of studies conducted in children. Wide heterogeneity of study design (concerning group size, age, presence of placebo or positive control group, variability of intervention, etc.) and mostly subjective assessment of efficacy (usually by the parent/guardian) makes it difficult to draw conclusions and create evidence-based recommendations for clinical practice.

Nasal congestion

Non-pharmacological measures for nasal congestion relief

A traditional supportive measure for nasal obstruction is **maintaining adequate oral hydration**. Warm liquids may help to soothe the mucosa and thin secretions, facilitating nasal cleansing (2, 5). Other commonly used supportive measures are **nasal application of saline** and **nasal irrigation with saline**, with or without subsequent **nose cleaning with an aspirator**. Saline nose drops may loosen secretions, making the clearing of nostrils easier (6). In infants and young children this may ease feeding difficulties caused by nasal stuffiness (7). A randomized controlled trial (RCT) on nasal irrigation with a modified seawater solution, involving children (total number, N=401) with uncomplicated cold or flu demonstrated a faster resolution of some nasal symptoms during acute illness and less frequent reappearance of rhinitis in the group that used nasal wash on top of standard treatment (8). In their review, Chirico et al. (9) suggested that nasal saline irrigation significantly improved nasal symptoms in children with acute sinusitis. In children with viral rhinitis, nasal isotonic saline solution followed by suction with a medical device has been shown to lower the risk of developing otitis media and rhinosinusitis, compared with a group treated with saline but without aspiration. No serious adverse events related to these measures were reported (9). **Inhalation of mist or steam** has also been used as a non-pharmacologic measure for nasal obstruction

mitigation. A systematic review of six clinical studies in adults with a common cold (10) concluded that inhalation of warm water vapor (delivered by a particular medical device intended for nasal inhalation) has no beneficial, but also no harmful effects on nasal congestion. However, the risk of burns associated with steam vaporizers and of growing and dispersing the microorganisms associated with cool-mist humidifiers (if they are not cleaned properly, i.e. after each use) should be weighed against potential benefits for children with RTIs (6). **Inhalations containing aromatic constituents** (e.g. menthol or eucalyptus oil) are traditionally used for relieving nasal stuffiness and to ease breathing. The vapor may encourage deliberate inhalation of the warm moist air that can be comforting. Aromatic vapors for external rub (e.g. on chest or on pillow) may create the impression of improved nasal patency, but they don't affect the parameters of spirometry (2, 11). Paul et al. (12) performed a RCT for comparing the effects of vapor rub (Vicks VapoRub containing camphor, menthol and eucalyptus oil), petroleum ointment, and no treatment for children (N=144) with upper RTI symptoms (congestion, rhinorrhea and cough). Subjective parental assessments of their child's symptoms suggested that a single application of vapor rub was associated with a decrease in congestion (and cough) when compared to petroleum ointment or no treatment. Strong aromatic rubs are not recommended for infants under 3 months (7).

Nasal decongestants

These medications reduce swelling and secretion of the nasal mucosa. Either topical (nasal drops or nasal spray) or oral, sympathomimetic agents may be used for nasal obstruction relief in RTIs in children older than 6 years of age (Table II). **Topical nasal decongestants xylometazoline, oxymetazoline** and **naphazoline** are selective α_1 adrenoceptor agonists. They act by inducing local vasoconstriction to reduce edema of the nasal mucosa and rhinorrhea. The recommended duration of treatment with topical nasal decongestants is 3-5 (maximum 7) consecutive days, because with prolonged use (or with an overdose) they can cause rebound nasal congestion (*rhinitis medicamentosa*). It is manifested by mucosal edema after the drug's effect cessation, due to which there is a need for re-applying the drug, resulting in a vicious circle and a kind of "dependence". The efficacy and safety of topical nasal decongestants in children have not been investigated in clinical studies (13). Their use is now restricted to children older than 6 years of age, due to a lack of data on the efficacy and reports of rare, but serious adverse effects in younger children treated with them. For example, cases of central nervous system (excitation, insomnia, convulsions but also overt sedation) or cardiovascular effects (tachycardia) have been reported after the use of oxymetazoline in small children (14). In young infants, who are obligate nose breathers, topical nasal decongestants should not be used due to a risk of rebound congestion (5).

Table II Nasal decongestants for use in the pediatric population (7, 15, 16)

Tabela II Nazalni dekongestivi za primenu u pedijatrijskoj populaciji (7, 15, 16)

Drug	Pharmaceutical form	Age, dosage and duration
xylometazoline hydrochloride	nasal drops and nasal spray	**6-11 years (0.05% concentration):** 1-2 drops or one spray actuation in each nostril, 3 times daily **Treatment duration:** up to 5 days **12-17 years (0.1% concentration):** 1-2 drops or one spray actuation in each nostril, 3 times daily **Treatment duration:** up to 7 days
oxymetazoline hydrochloride	nasal drops and nasal spray	**6-11 years (0.025% concentration):** 2-3 drops or 1-2 spray actuations in each nostril, 2-3 times daily **Treatment duration:** up to 5 days **12-17 years (0.05% concentration):** 1-2 drops or 1-2 spray actuations in each nostril, 2-3 times daily **Treatment duration:** up to 5 days
naphazoline hydrochloride	nasal drops	**7-11 years (0.05% concentration):** one drop in each nostril, 3 times daily **Treatment duration:** up to 5 days **12-17 years (0.05% concentration):** 1-2 drop in each nostril, 3-4 times daily **Treatment duration:** up to 5 days
pseudoephedrine hydrochloride*	oral solution, tablet	**6-11 years:** 30 mg, up to 4 times daily **12-17 years:** 60 mg, up to 4 times daily
phenylephrine hydrochloride**	capsule	**12-17 years:** 12 mg, up to 4 times daily

* Also available in combination with antipyretic/analgesic drugs, cough suppressants, expectorant drugs and/or antihistamines, see Table VII

** Also available in combination with antipyretic/analgesic drugs, expectorant drugs, antihistamines and/or other substances (cetylpyridinium chloride, caffeine, ascorbic acid), see Table VII

* Takođe dostupno u kombinaciji sa antipireticima/analgeticima, antitusicima, ekspentoransima i/ili antihistaminicima, videti Tabelu VII

** Takođe dostupno u kombinaciji sa antipireticima/analgeticima, ekspentoransima, antihistaminicima i/ili drugim supstancama (cetilpiridinijum hloridom, kofeinom, askorbinskom kiselinom), videti Tabelu VII

Oral nasal decongestants are **pseudoephedrine** (a stereoisomer of ephedrine, a mixed sympathomimetic agent that directly stimulates α and β receptors and increases the release of norepinephrine from sympathetic nerve endings) and **phenylephrine** (α_1 adrenoceptor agonist). The use of these agents is not associated with rebound congestion, but carries the risk of systemic (cardiovascular and/or central nervous system) side effects and drug interactions (17, 18). In a recent multicenter, double-blind, placebo-controlled study, Gelotte et al. (19) randomized 568 children (aged 6 to 11 years) with nasal congestion due to the common cold to evaluate the efficacy and safety of pseudoephedrine hydrochloride. Pseudoephedrine provided temporary congestion relief and was superior to placebo. Multiple pseudoephedrine doses given "as needed" were generally well tolerated. Pseudoephedrine-containing preparations are currently approved for children older than 6 years of age and phenylephrine preparations for children above 12 (Tables II and VII).

The benefits of **antihistamines** for nasal congestion due to infection are doubtful, particularly after topical application, so their use for RTIs symptom relief in either adults or children is not justified (5, 6, 17).

Cough

The symptomatic treatment of cough depends on whether the cough is dry or wet. Upper RTIs are usually accompanied by dry, non-productive cough, which serves no beneficial purpose for the patient. It is only a source of discomfort, so cough suppressants (antitussives) can provide some relief, which is particularly important when the cough interferes with night sleep. One should have in mind that, although unpleasant, cough is a useful symptom that usually leads to further investigations. Dry cough is also a symptom of pneumonia or asthma exacerbation, so cough suppressants should be used carefully. Lower RTIs are mostly accompanied by a productive (wet) cough, characterized by the presence of sputum. Unlike non-productive cough, productive cough is useful, as it serves to expel secretions and clear the airways. Thus, the use of cough suppressants is inappropriate, as it could cause mucus retention and increase the risk of superinfection. In productive cough, expectorants are used on the grounds that enhancing the volume of respiratory secretions facilitates its removal by ciliary mechanism and coughing. Mucolytics (secretolytics) can reduce sputum viscosity, which is thought to ease its clearance.

Non-pharmacological measures for cough relief

A common non-pharmacological approach for *dry cough relief* is the use of **demulcent agents** such as honey, sucrose-based syrups or glycerol (20). They are harmless and inexpensive and may temporarily relieve dry, irritating cough. Demulcents are thought to act by creating a protective layer that coats the sensory receptors in the pharynx, reducing the possibility of their activation and triggering the cough reflex. In a 2018 Cochrane review, Oduwole et al. (21) analyzed six RCTs (involving 899 children aged 12 months to 18 years) which assessed the effects of **honey** on acute cough due to

upper RTIs (22-27). In the studies covered by this review, different types of honey (e.g. buckwheat, eucalyptus, citrus honey) in an amount that ranged from 5 to 10 g were given with a beverage (e.g. water, tea), before bedtime. The authors concluded that honey is probably better than "no treatment" or placebo for symptomatic cough relief (21). Given the safety and availability of honey, it might be a useful home remedy for the relief of cough in the pediatric population. However, honey should be avoided in infancy, due to the risk of allergic reactions and botulism (2, 6). **Throat lozenges or hard candy** may be temporarily efficacious against dry cough. They are safe in children older than six years of age, in whom they do not carry a risk of aspiration (2, 6). Adequate **oral hydration or inhalation of moist air** helps to liquefy mucus, so it is commonly used as a supportive measure for *wet cough treatment*. It also has a demulcent effect (2, 17).

Cough suppressants

Antitussives affect the cough reflex by increasing the triggering threshold of the neurons in the cough center of the medulla oblongata (central antitussives) or by increasing the activation threshold of cough receptors in the proximal airways (peripheral antitussives) (28, 29). Opioid (codeine, pholcodine) and opioid-like cough suppressants (dextromethorphan), as well as butamirate, have central action; levodropropizine acts peripherally (Table III).

Table III Cough suppressants for use in the pediatric population (7, 15, 16)
Tabela III Antitusici za primenu u pedijatrijskoj populaciji (7, 15, 16)

Drug	Pharmaceutical form	Age, dosage and duration
pholcodine	oral solution, syrup, capsules	**6-11 years:** 4 mg, 3 times daily **12-17 years:** 5-20 mg, 3-4 times daily (maximal dose: 60 mg/day) **Treatment duration:** up to 5 days
dextromethorphan	oral solution, syrup, lozenges	**Lozenges** **6-11 years:** up to 17.5 mg/day **12-17 years:** up to 25 mg/day **Oral solution/syrup** **12-17 years:** 15 mg, 4 times daily **Treatment duration:** up to 5 days (6-12 years) or 7 days (12-17 years)
butamirate	oral solution, syrup, modified-release tablet	**Oral solution/syrup** **3-5 years:** 8 mg, 3 times daily **6-11 years:** 12-16 mg, 3 times daily **12-17 years:** 12-16 mg, 4 times daily **Treatment duration:** up to 7 days **Modified-release tablet** **6-11 years:** 20 mg, 2 times daily **12-17 years:** 20 mg, 2-3 times daily or 50-100 mg once daily **Treatment duration:** up to 7 days
levodropropizine	syrup	**2-11 years:** around 1 mg/kg body weight, 3 times daily (10-20 kg – 18 mg, 3 times daily; 20-30 kg – 30 mg, 3 times daily) **12-17 years:** 60 mg, 3 times daily

In a RCT that included 57 children with acute cough due to upper RTI, **codeine** was no more effective than placebo (30). It seems that no clinical studies on the properties of **pholcodine** in children are available. Four double-blind RCTs (30-33) evaluated the effects of **dextromethorphan** in overall 327 children with acute cough due to RTI and did not report a significant effect on cough frequency, child/parental sleep and symptom scores recorded by parents (analyzed in detail in a 2014 Cochrane review) (34). Opioid and opioid-like cough suppressants can cause sedation and respiratory depression (in high doses); codeine is also constipating (7). An additional concern with codeine is that there are "ultra-rapid CYP2D6 metabolizers" i.e. patients that convert codeine to morphine faster than normal, who have a higher risk of toxic effects such as life-threatening respiratory depression (20). Pholcodine and dextromethorphan have fewer side effects than codeine (35). However, dextromethorphan can cause hallucinations at higher doses; thus, it has a high abuse potential (28, 36). Available antitussives for use in pediatric population are pholcodine and dextromethorphan, in mono- and poly-component preparations (for age limitations, see Tables III and VII). **Butamirate** is available in some countries (including Serbia, Table III). It is claimed to be effective and safe (37), but no data from placebo-controlled RCTs neither in adults nor in children with cough due to RTIs are available.

Zanasi et al. (38) performed a meta-analysis of studies dealing with the properties of **levodropropizine** for cough treatment in adults and children. In general, levodropropizine has been shown to be an effective cough suppressant, with statistically significant better overall efficacy outcomes in comparison with central antitussive drugs. When considering only the studies performed in children with cough due to RTIs (one RCT in 77 children with bronchitis [39] and two observational studies including in total 773 children and adolescents with upper RTIs [40, 41]), levodropropizine was effective in reducing cough severity and exerted greater efficacy than codeine or dextromethorphan. Levodropropizine has a favorable safety profile and is advantageous to opioid and similar antitussives, as it does not cause sedation, has no potential to induce respiratory depression and no potential for abuse (20). Currently, levodropropizine can be used in children older than two years of age for short-term symptomatic relief of acute cough (Table III). It has good tolerability (gastrointestinal side effects, tachycardia and palpitations have been reported) (16).

Sedating antihistamines (e.g. diphenhydramine, chlorphenamine, promethazine, triprolidine) are thought to have some antitussive activity. Cough suppression is mostly attributed to their anticholinergic and/or sedative effects. In their systematic review, Smith et al. (34) analyzed 3 RCTs focused on antihistamines in the treatment of acute cough associated with RTIs in pediatric population. Studies evaluated chlorpheniramine (N=143, [42]), diphenhydramine (N=100, [33]) and promethazine (N=120, [31]) and didn't detect a significant difference concerning cough severity/frequency, child or parental sleep over placebo. The main side effect reported was drowsiness. They are often a constituent in combined cough and cold preparations (Table VII).

Mucolytics and expectorants

Acetylcysteine and **carbocisteine** are mucolytic drugs widely prescribed for reducing mucus viscosity and facilitating expectoration in productive cough, for both adults and children, older than two years of age (Table IV). Letosteine and erdosteine are newer cysteine derivatives, so far not approved for use in children. The mechanisms that may contribute to actions of these medications are the reduction of disulfide bridges that bind glycoproteins and thus break the mucus chains; antioxidant properties that may reduce the inflammation in the airways; restoration of mucus viscoelastic properties by resetting the balance between sialomucins and fucomucins, and several others (28, 29). In the only RCT addressing efficacy/safety of cysteine derivatives versus placebo, **letosteine** significantly decreased the cough score in children (N=40) with bronchitis (43). Cysteine derivatives are relatively well tolerated. Common side effects are GI disturbances (epigastric pain, nausea, vomiting, diarrhea). They can disrupt the gastric mucosal barrier and cause hemorrhage. Hypersensitivity reactions (bronchospasm, angioedema, rash, pruritus) have been reported in patients receiving acetylcysteine; it should be used with caution in children with asthma (15-17). Acetylcysteine is also available in some countries as a nasal spray (in combination with tuaminoheptane, a sympathomimetic amine) for the relief of nasal symptoms associated with acute/subacute rhinitis and sinusitis.

Mucolytics **bromhexine** and its active metabolite **ambroxol** are synthetic derivatives of vasicin originating from the Indian shrub *Adhatoda vasica*. They induce hydrolytic depolimerization of mucoprotein fibers and modulate the activity of mucus-secreting cells (20, 29, 44). Besides oral preparations, bromhexin is also formulated as a concentrate for nebulization solutions, and ambroxol as a throat lozenge (due to its local anesthetic action) (Tables IV and VII). It seems that only a few small, open studies in children with productive cough in RTIs have been performed so far. In these, ambroxol was effective in improving cough and expectoration, and showed either greater efficacy or faster onset of action than acetylcysteine (20, 44). In a RCT involving children with lower RTIs (N=120), ambroxol was tested as an adjunct to antibiotic treatment. A more rapid improvement (concerning remission of the cough and lung radiological picture) was observed in antibiotic and ambroxol group compared to group that received antibiotic and placebo (45). Bromhexine and ambroxol are generally well tolerated. Common side effects are GI system related (nausea, vomiting, diarrhea). Ambroxol may induce oral/pharyngeal hypoaesthesia. Hypersensitivity reactions have been reported. If inhaled bromhexine is intended for patients with asthma, prior use of bronchodilators is advised. Caution and treatment cessation is necessary if skin reactions (e.g. rash) occur, as there are reports of severe skin reactions related to use of either ambroxol or bromhexine (16, 17).

Table IV Mucolytics for use in the pediatric population (7, 15, 16)

Tabela IV Mukolitici za primenu u pedijatrijskoj populaciji (7, 15, 16)

Drug	Pharmaceutical form	Age, dosage and duration
acetylcysteine	oral solution, powder/granules for oral solution, tablets, effervescent tablets	**2-5 years:** 100 mg, 2-3 times daily (200-300 mg/day) **6-13 years:** 200 mg, 2 times daily (400 mg/day) **14-17 years:** 200 mg, 2-3 times daily (600 mg/day) **Usual treatment duration:** 4-5 days
carbocisteine	oral solution, syrup, capsules	**2-5 years:** 62.5-125 mg, 4 times daily **6-11 years:** 250 mg, 3 times daily **12-17 years**: initially 750 mg, 3 times daily (when symptoms improve 500 mg, 3 times daily) **Usual treatment duration:** 7-10 days
bromhexine	oral solution, syrup, tablets	**2-5 years:** 4 mg, 3 times daily **6-13 years (and patients weighing < 50 kg):** 8 mg, 3 times daily **14-17 years:** 8-16 mg, 3 times daily **Usual treatment duration:** 4-5 days
	concentrate for nebulization solution	**2-5 years:** 1.33 mg (10 drops of 2 mg/mL solution), 2 times daily **6-13 years:** 2 mg, 2 times daily **14-17 years:** 4 mg, 2 times daily **Usual treatment duration:** 4-5 days
ambroxol	oral solution, syrup, tablets lozenges	**2-5 years:** 7.5 mg, 3 times daily **6-11 mg:** 15 mg, 2-3 times daily **12-17 years:** initially 30 mg, 3 times daily (when symptoms improve 30 mg, 2 times daily) **Usual treatment duration:** 4-5 days

Expectorants available for use in the pediatric population, in multicomponent preprations, are guaifenezin and terpin (Table VII). **Guaifenezin** originates from the bark of the guaiac tree (*Guaiacum officinale*) and is thought to act by influencing the cholinergic innervation of airway mucous glands, thus promoting an increase in the volume of bronchial secretions. There is, in general, little or no evidence for the efficacy of expectorants (28, 29).

Fever

Fever (pyrexia) is a controlled increase in body temperature, due to elevated set-point temperature in the thermoregulatory center in hypothalamus. It is a physiological response to endogenous (cytokines, interferons) or exogenous pyrogens (microbial products or whole microorganisms). Cytokines (IL-1, IL-6, TNFα) released by immune/inflammatory cells in infection act as endogenous pyrogens by inducing cyclooxygenase-2 (COX-2) in the hypothalamus. Released prostaglandin E_2 (PGE_2) sets

the thermoregulatory center to a higher point (46). Rectal temperature ≥ 38 ºC is considered a fever (2).

Fever is a beneficial mechanism that stimulates the immune response to a pathogen; it does not worsen the course of the disease and does not cause long-term neurologic complications or other bodily harm (except in rare cases of febrile status epilepticus and heatstroke). Thus, its lowering in otherwise healthy children is justified if there is significant discomfort of the child (decreased oral intake, altered activity, sleep and behavior), if fever is associated with headache/myalgia, or if the temperature is high (> 39 ºC) (2, 17, 47). Both non-pharmacological treatments and antipyretics may be used to lower body temperature in fever.

Non-pharmacological measures for fever

Appropriate fluid intake is the first step towards replacing the fluids that are lost due to increased metabolic demands of fever. **External cooling measures** (e.g. removal of clothing, reducing the ambient temperature, tepid sponging) are often used, but they do not affect the set-point in the hypothalamus and cause shivering or the other side effects as the body tries to maintain the higher set-point temperature. Thus, their value is questionable. Cold baths may actually increase body temperature by inducing vasoconstriction, so they should not be used (17).

Antipyretics

Antipyretics work by inhibiting prostaglandin synthesis in the thermoregulatory center of the hypothalamus, thereby returning elevated set-point to normal. They do not affect normal body temperature (17, 48, 49). **Paracetamol (acetaminophen)** and **ibuprofen** are the antipyretics used in children in modern clinical practice (Table V). Owing to their analgesic effect, they can also relieve pain that accompanies RTIs (otalgia, myalgia, headache, sore throat etc.). Acetylsalicylic acid is contraindicated in children under 12 (e.g. in the United States) or 16 years of age (e.g. in Serbia and United Kingdom) with pyrexia caused by viral infection, due to the risk of Reye's syndrome (7, 17, 49). The antipyretic efficacy of paracetamol and ibuprofen is well established. Increasing evidence suggests that ibuprofen is superior to paracetamol concerning antipyretic efficacy and duration of action (17, 47, 50). There is also some evidence that alternation or combination of paracetamol and ibuprofen may be more effective than either alone (51). Current National Institute for Health and Care Excellence (NICE) guidelines for treatment of fever in children under five years of age do not favor any of the two and suggest alternating these agents only if the distress persists or recurs before the next dose is due. These guidelines advise against the use of both agents simultaneously (52). The use of paracetamol and ibuprofen is generally safe. An analysis of the outcome of treatment of more than 80,000 children found that the risk of hospitalization due to GI bleeding, renal failure or anaphylaxis was no greater in febrile children treated with ibuprofen than in those treated with paracetamol (53). More recent meta-analyses also corroborate that the safety and tolerability of paracetamol and ibuprofen in managing

children's fever (and pain) are similar and favorable (54). If overdosed, paracetamol can cause severe liver damage.

Table V Antipyretics for use in the pediatric population (7)
Tabela V Antipiretici za primenu u pedijatrijskoj populaciji (7)

Drug	Pharmaceutical form	Age, dosage
paracetamol	oral suspension, oral solution, capsules, tablets, effervescent tablets, suppositories	**Oral use** **1-2 months:** 30-60 mg, 3 times daily (60 mg/kg maximal daily dose) **3-5 months:** 60 mg, 4 times daily **6-23 months:** 120 mg, 4 times daily **2-3 years:** 180 mg, 4 times daily **4-5 years:** 240 mg, 4 times daily **6-7 years:** 240-250 mg, 4 times daily **8-9 years:** 360-375 mg, 4 times daily **10-11 years:** 480-500 mg, 4 times daily **12-15 years:** 480-750 mg, 4 times daily **16-17 years:** 500-1000 mg 4 times daily **Rectal use** **1-2 months:** 30-60, 3 times daily (60 mg/kg maximal daily dose) **3-11 months:** 60-125 mg, 4 times daily **1-4 years:** 125-250 mg, 4 times daily **5-11 years:** 250-500 mg, 4 times daily **12-17 years:** 500 mg, 4 times daily
ibuprofen	oral suspension, syrup, granules for oral solution, effervescent granules, tablets, capsules	**Oral use** **1-2 months:** 5 mg/kg, 3-4 times daily **3-5 months (> 5 kg):** 50 mg, 3 times daily **6-11 months:** 50 mg, 3-4 times daily **1-3 years:** 100 mg, 3 times daily **4-6 years:** 150 mg, 3 times daily **7-9 years:** 200 mg, 3 times daily **10-11 years:** 300 mg, 3 times daily **12-17 years:** 200-400 mg, 3-4 times daily

Local treatment of the inflamed pharyngeal mucosa

Preparations for local relief of pain/inflammation of the pharynx often contain analgesics/anti-inflammatory drugs (flurbiprofen, benzidamine), local anesthetics (lidocaine) or other drugs with local anesthetic action (benzidamine, ambroxol). They are often combined with antiseptics (2,4-dichlorobenzyl alcohol, chlorhexidine, amylmetacresol) or local antibiotic (tyrothricin). The available pharmaceutical forms are lozenges, oropharyngeal mucosal sprays and rinsing/gargling solutions (Table VI).

Flurbiprofen and **benzidamine** are non-steroidal anti-inflammatory drugs (NSAIDs) (17). NSAIDs exert their analgesic and anti-inflammatory effect by inhibiting COX and consequently suppressing prostaglandin synthesis (49). For both drugs

administered locally, there are favorable reports from clinical studies conducted in adults with sore throat, concerning their efficacy in relieving pain, sensation of swollen throat, difficulty swallowing, and other associated symptoms, as well as their safety (55, 56). Following administration to the oral mucosa, **lidocaine** has a rapid onset of action, reaching its maximum within 5 minutes (57). It is a result of a blockade of voltage-gated sodium channels in the peripheral terminals of sensory neurons. Evidence on its efficacy in infectious pharyngitis seems to be lacking. **Ambroxol** belongs to the group of mucolytics but applied to the oropharyngeal mucosa it exerts a local anesthetic effect, probably due to its sodium channel blocking properties (44). De Mey et al. (58) performed a pooled analysis of seven placebo-controlled RCTs that investigated ambroxol-containing lozenges; ambroxol was well tolerated and efficacious for pain relief in acute uncomplicated sore throat in adolescents and adults.

Table VI Drugs for local treatment of the pharyngeal mucosa for use in the pediatric population (7, 15, 16)

Tabela VI Lekovi za lokalnu terapiju faringealne sluznice za primenu u pedijatrijskoj populaciji (7, 15, 16)

Drug	Pharmaceutical form	Age, dosage and duration
flurbiprofen	lozenges	**12-17 years:** 8.75 mg every 3-6 hours (up to 43,75 mg/day) **Treatment duration:** up to 3 days
ambroxol	lozenges	**12-17 years:** 20 mg, up to 6 times daily **Treatment duration:** up to 3 days
benzydamine	lozenges, mouthwash/ gargle, oromucosal spray	**Lozenges** **6-17 years:** 3 mg, 3-4 times daily **Treatment duration:** up to 7 days **Oromucosal spray (0.15%)** **3-5 years:** 1 spray activation/4 kg body weight, 2-6 times daily **6-11 years:** 4 spray activations, 2-6 times daily **12-17 years:** 4-8 spray activations, 2-6 times daily **Treatment duration:** up to 7 days **Mouthwash/gargle (0.15%)** **12-17 years:** 15 mL of solution, 2-3 times daily **Treatment duration:** up to 7 days
lidocaine*	lozenges (1-10 mg of lidocaine)	**12-17 years:** dosing is product specific **Treatment duration:** usually up to 3-4 days

*Available only in combination with antiseptic (2,4-dichlorobenzyl alcohol, chlorhexidine, amylmetacresol) and antibiotic drugs (tyrothricin)

*Dostupno samo u kombinaciji sa antisepticima (2,4-dihlorbenzil alkoholom, hlorheksidinom, amilmetakrezolom) i antibioticima (tirotricinom)

Combined cough and cold preparations

There are a number of combined non-prescription (i.e. over-the-counter, OTC) preparations for relieving symptoms of common RTIs containing analgo-antipyretics, nasal decongestants, antihistamines, antitussives and/or expectorants. Some of them are approved for use in the pediatric population (Table VII), although there is no direct evidence to support their use. Multicomponent preparations carry the risk of taking unnecessary medications and their side effects. The use of multiple (either mono- or poly-component) OTC medications is associated with the risk of an overdose of a component that may be an ingredient in different preparations (17). This is particularly important for paracetamol (risk of severe liver damage), opioid cough suppressants (risk of respiratory depression) and antihistamines (overt sedation). Due to a lack of direct evidence of efficacy and adverse effect risks, medicine authorities in Europe and USA have restricted the use of multicomponent cough and cold preparations to children older than 6 years of age (2, 59). The decision on whether to use these preparations in older children should be based on the consideration of the likelihood of beneficial and adverse effects.

Table VII Combined oral preparations for RTI symptom relief in the pediatric population (7, 15, 16)

Tabela VII Kombinovani oralni preparati za ublažavanje simptoma IRT u pedijatrijskoj populaciji (7, 15, 16)

Antipyretic/ analgesic drug	Decongestant drug	Antihistamine drug	Antitussive or expectorant drug	Age
paracetamol	pseudoephedrine	-	-	6 years and older
		diphenhydramine	-	10 years and older
		chlorphenamine	-	12 years and older
		-	dextromethorphan	12 years and older
		-	pholcodine	16 years and older
		promethazine	dextromethorphan and pholcodine	16 years and older
	phenylephrine	-	-	12 years and older
		chlorphenamine	terpin	12 years and older
		-	terpin	12 years and older
		-	guaifenesin	12 years and older
	-	diphenhydramine	-	16 years and older
	-	promethazine	dextromethorphan	12 years and older
ibuprofen	pseudoephdrine	-	-	12 years and older
	phenylephrine	-	-	12 years and older
-	pseudoephedrine	triprolidine	-	6 years and older
		triprolidine	dextromethorphan	12 years and older
		-	guaifenesin	12 years and older

Note: Some of these preparations contain additional active substances, such as ascorbic acid, caffeine and/or cetylpyridinium.

Napomena: Neki od ovih preparata sadrže dodatne aktivne supstance, kao što su askorbinska kiselina, kofein i/ili cetilpiridinijum.

Conclusion

Alleviation of symptoms is the only therapeutic measure in viral RTIs and is an adjunct to causal (antibiotic) therapy in bacterial RTIs. Nasal decongestants, cough suppressants, mucolytics, expectorants, antipyretics/analgesics and sore throat local preparations are available, in suitable pharmaceutical forms and strengths for children of a certain age. Clinical studies conducted in the pediatric population for most of these drug groups are few or nonexistent. The available studies are characterized by heterogeneous designs, making it difficult to create evidence-based recommendations for clinical practice. As many of these medications are available as non-prescription, it is necessary to strictly take into account the age of the child in whom they may be used and use proper dosing. Multicomponent preparations carry the risk of taking unnecessary medications and their side effects. The use of multiple OTC medicines is associated with the risk of an overdose of a component that may be an ingredient in different preparations. Appropriate non-pharmacological measures (e.g. oral hydration, nasal saline application or irrigation, honey) may be helpful and should be used whenever possible due to their safety.

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Conflict of interest

The authors declared no conflict of interest.

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Lekovi i nefarmakološke mere za ublažavanje simptoma infekcija respiratornog trakta u pedijatrijskoj populaciji

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Kratak sadržaj

U pedijatrijskoj populaciji, akutne infekcije respiratornog trakta (IRT) su najčešći razlog traženja stručne pomoći od lekara ili farmaceuta. Ublažavanje simptoma je jedina terapijska mera kod virusnih i dodatak je antibiotskoj terapiji kod bakterijskih IRT. Ovaj članak govori o farmakološkim i nefarmakološkim opcijama za lečenje nazalne kongestije, kašlja, povišene telesne temperature i upale grla kod IRT i kliničkim dokazima o njihovoj efikasnosti i bezbednosti u pedijatrijskoj populaciji. Uopšteno govoreći, kliničke studije sprovedene kod dece za većinu ovih grupa lekova su malobrojne ili ih uopšte nema, što otežava pripremu preporuka zasnovanih na dokazima. Dostupni su nazalni dekongestivi, antitusici, mukolitici, ekspektoransi, antipiretici/analgetici i lokalni preparati za ublažavanje simptoma upale grla, u odgovarajućim farmaceutskim oblicima i jačinama za određeni uzrast. Kako se mnogi od njih izdaju bez lekarskog recepta (OTC), potrebno je striktno voditi računa o uzrastu deteta u kome se smeju koristiti i pravilnom doziranju. Višekomponentni preparati nose rizik od primene nepotrebnih lekova i njihovih neželjenih efekata. Primena više OTC lekova nosi rizik od predoziranja komponente koja može biti sastojak različitih preparata. Odgovarajuće nefarmakološke mere (npr. oralna hidratacija, primena fiziološkog rastvora u nos ili ispiranje nosa, med) mogu biti od pomoći i treba ih koristiti kad god je to moguće zbog njihove bezbednosti.

Ključne reči: simptomi infekcija respiratornog trakta, lekovi, nefarmakološke mere, pedijatrijska populacija