

Treatment of the most common respiratory infections in children

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Abstract

Acute respiratory infections are the most common group of infective diseases in the pediatric population. Although the improvement of health care and vaccination program has led to a significant reduction in the incidence of certain respiratory infections, the combination of a high prevalence in vulnerable pediatric categories and uncritical prescription of antibiotics, due to the inability to adequately distinguish between viruses and bacterial etiology, still represents a significant challenge for the public health system. In order to promote rational antibiotic therapy with an overall improvement of both diagnostic and therapeutic principles, acute respiratory diseases have been the subject of consideration in numerous publications and national guidelines. Nonspecific clinical manifestations with pathogen heterogeneity and both anatomical and physiological characteristics of the child's respiratory system during growth and development have created the need for individualized therapy. Since the guidelines emphasize the undoubtful and crucial benefits of symptomatic therapy (e.g. analgesics in acute otitis media, supplemental oxygen in lower respiratory tract infections with hypoxemia), the use of antibiotics and corticosteroids is indicated in selected cases with a severe clinical picture. The choice of antibiotic depends on the clinical condition, presumed causative agent, and local epidemiologic circumstances. Respiratory support (oxygen therapy and/or artificial ventilation) is reserved for inpatient treatment of cases with a particularly severe clinical picture and associated complications.

Key words: acute respiratory infections, rational antibiotic prescription

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Introduction

Acute respiratory infections in children are the main cause of morbidity worldwide and the leading cause of mortality in developing countries. Numerous initiatives and guidelines have been published, with the primary aim of defining the seriousness of the diseases, presumptive etiology, diagnostic approach, and finally, the necessity of antimicrobial treatment (1).

More than 50% of children have chronic colonization of upper airways with *Streptococcus pneumoniae* (SP), *Haemophilus influenzae* (HI), *Moraxella catarrhalis* (MC), and *Staphylococcus aureus* (SA). With saprophytic flora, these bacteria form its microbiome, with close molecular interactions that may be easily compromised with irrational antibiotic use. Excessive and often unnecessary prescription of antibiotics increases the risk of adverse effects and supports bacterial resistance. Improvements in national vaccination programs have led to a dramatic decrease in invasive bacterial infections, and some diseases, such as acute epiglottitis, have practically vanished.

Serbia is one of the European countries with frequent use of antibiotics, mostly in children up to two years of age (2). The primary aim of this article is to make a short overview of clinical presentation and present current recommendations for medical treatment for the most common respiratory infections in children, in order to improve judicious antibiotic use and avoid polypharmacy.

Acute rhinitis

Acute rhinitis (common cold) is an acute viral infection of the upper respiratory tract with prominent symptoms of rhinorrhea and nasal obstruction with mostly mild nonspecific symptoms (headache, myalgia, and fever). Infection of the nasal epithelium is characterized by the release of inflammatory cytokines and infiltration of the mucosa by inflammatory cells (3). Viral shedding usually peaks 3-5 days after inoculation and often coincides with symptom onset. It may be coupled with concurrent involvement of the sinus mucosa, when the term "rhinosinusitis" is more appropriate (4). A number of viruses can be related to the common cold – the most frequent are *rhinoviruses* (RV), while a huge proportion of cases is caused by respiratory *syncytial virus* (RSV), *human metapneumovirus* (HMPV), *parainfluenza viruses*, *adenoviruses*, *influenza viruses* and *human coronaviruses* (3, 4). Although infection occurs year-round, the peak incidences in the Western hemisphere are in the fall and the spring. Despite its self-limiting character, the common cold remains a significant public health problem due to the diagnostic tool overuse, overtreatment, frequent and unnecessary use of antibiotics, and subsequent financial implications (5, 6). The diagnosis is typically clinical, without the need for additional investigation (5). Treatment goals are symptomatic relief and prevention of both person-to-person spread and complications (7). As rhinorrhea and nasal obstruction are the most prominent symptoms, the main goal is to minimize them. Since these symptoms are often accompanied by local pain and fever, the use of analgesics and antipyretics is useful.

Decongestants

Decongestants have been widely used to reduce the symptoms of nasal obstruction. Stimulation of α 1- adrenergic receptors located on capacitance blood vessels of the nasal mucosa results in vasoconstriction and decreased blood volume, which results in decreased inflammation of the nasal mucosa and decreased mucosal secretions (8). Many preparations licensed for usage in the pediatric population are nowadays available in Europe, either as topical nasal (xylometazoline, oxymetazoline, and naphazoline) or oral preparations (pseudoephedrine and phenylephrine). Although certain positive effects of topical decongestants on nasal congestion have been confirmed in adults with the common cold, there is not enough data that unequivocally supports its use in the pediatric population (9). Since satisfactory effects of oral pseudoephedrine were shown in one study comprised of children aged 6-12 years with an acceptable safety profile, the question regarding the efficacy of oral preparations over topical remains open (10). There is no evidence of the effectiveness of fixed oral combinations of antihistamines, analgesics, and decongestants in young children (11). Additionally, there is no benefit from either inhaled or systemic steroids (12, 13). Given the fact that cough is a frequent symptom of the common cold, the use of antitussives and bronchodilators is widespread. However, their use is ineffective in the common cold and should be avoided (14, 15).

Complementary and Alternative Treatments

Some methods of complementary and alternative therapies have been widely used in the pediatric population with the common cold. Nonetheless, some of them – e.g. vapor rub ointment applied to a child's chest and neck before bedtime - may have a useful role in relieving symptoms of nasal congestion and cough (16). The use of menthol alone may also improve perceived nasal patency (17). The effects of nasal saline on nasal secretions are doubtful – since positive effects were reported in one large trial, a review of the Cochrane database failed to confirm a significant difference between nasal saline treatment and routine nasal care (18, 19).

Antibiotic therapy

Taking into account the viral etiology of the common cold, antibiotic treatment is not recommended (20). However, in the case of acute rhinosinusitis, the official recommendations of the American Academy for Pediatrics (AAP) have changed over time (21). In the case of initial presentation with severe symptoms (high fever, purulent nasal discharge) or if symptoms get worse over time, antibiotic therapy is recommended. Observation for 72 hours can be advised in the case of mild persistent symptoms. Routine radiologic assessment is not recommended, and neither is nasal swab examination, because it has been proven that microbiological analysis is unreliable, expensive, and unnecessary for deciding about treatment initiation. The first line of antibiotic therapy is amoxicillin with or without clavulanic acid for seven to ten days.

Acute pharyngitis

Acute pharyngitis is among the most frequent respiratory infections in children, responsible for 1-2% of all visits to the emergency care department yearly (22). As a wide range of viral agents can cause pharyngitis, bacterial etiology is represented in approximately 20-30% of all cases, with the *group A β-hemolytic streptococcus (GABHS)* being the most important agent (22). Bacterial pharyngitis is extremely rare in children younger than three years of age, and these children often have a mild clinical course similar to a viral infection. However, a distinction between viral and bacterial infection is necessary, due to possible complications and different treatment approaches – Table I (23).

Table I Clinical and laboratory differences between bacterial and viral pharyngitis

Tabela I Kliničke i laboratorijske razlike između bakterijskog i virusnog faringitisa

	Bacterial pharyngitis	Viral pharyngitis
Age	> 3 years	all ages
Fever	high fever	no/mild fever
Exudative inflammation	yes	rare
Nasal discharge	no	yes
Cough	no	yes
Throat swab culture	positive	negative
RADT	positive	negative
Complications	possible (e.g. rheumatic fever)	no

Treatment overview

While the disease is self-limited in the case of viral infection, when only symptomatic treatment is needed, antibiotic treatment is recommended for those with confirmed bacterial etiology (24). Treatment of *GABHS* pharyngitis should be initiated only after taking a rapid antigen detection test (RADT) or throat culture (24, 25). These tests are widely available, cheap, and noninvasive, with definitive results within 20 minutes in the case of RADT or 24 hours in the case of throat swab culture. As there are practically no penicillin-resistant *GABHS*, routine susceptibility testing and post-treatment microbiological assessment are not recommended. Antibiotic treatment results in symptom relief and shortening of its duration, reduction of bacterial transmission, and, finally, it decreases the likelihood of complications, especially acute rheumatic fever (23, 26). The role of antibiotic therapy in the prevention of post-streptococcal glomerulonephritis is less clear (27, 28).

Symptomatic treatment

Every patient should be provided with appropriately dosed analgesic and antipyretic medicines and proper oral hydration. Acetaminophen or ibuprofen are indicated for all ages, while aspirin should be avoided in the pediatric population due to a risk of hepatic injury (Reye's syndrome) (29).

Antibiotic treatment

Oral penicillin V and amoxicillin are first-line agents for *GABHS* pharyngitis due to their efficacy and acceptable safety profile (30). According to the Cochrane meta-analysis, there is no sufficient data showing a clinically significant advantage of one antibiotic over another (30). Taking into account its efficacy, lower cost, and absence of *GABHS* resistance, penicillin can be recommended as the first choice therapy, although amoxicillin is more palatable, which is important for use in children (30, 31). Patients nonadherent to an oral regimen can be treated with a single dose of intramuscular penicillin G, whose efficacy is comparable to oral courses (30).

Second-line treatment is used in patients allergic to penicillin. The choice of the antibiotic in these cases depends on the severity of the allergic reaction: while a first-generation cephalosporin may be used in children with a history of non-anaphylactic reactions, it cannot be used in children who have experienced an anaphylactic reaction to penicillin due to the possible cross-reactivity between penicillin and cephalosporins (23, 30, 32). Thus, macrolides such as azithromycin and clarithromycin are efficacious alternatives, despite the emerging reports of *GABHS* resistance to macrolides. Three to six days of oral antibiotics had a comparable efficacy compared to the standard duration 10-day course of oral penicillin in treating children with acute *GABHS* pharyngitis (33). The dosing regimen is listed in Table II.

Table II Recommended antibiotic treatment for bacterial pharyngitis (107)**Tabela II** Preporučena antibiotska terapija za bakterijski faringitis (107)

First-line treatment			
	Patient's weight < 27 kg	Patient's weight > 27 kg	Duration
<i>Penicillin V</i>	250 mg bid orally	500 mg bid orally	10 days
<i>Amoxicillin</i>	50 mg/kg/once daily (max. 1000 mg) orally		10 days
<i>Benzathine penicillin G</i>	600 000 units IM	1.2 million units IM	Once
Second-line treatment			
	Oral dose		Duration
Oral cephalosporins	depends on chosen agent		10 days
Azithromycin	10 mg/kg day 1; 5 mg/kg days 2-5 (max 500 mg)		5 days
Clarithromycin	15 mg/kg/daily (bid, max 500 mg)		10 days
Clindamycin	20 mg/kg/daily (tid, max 1.8 g daily)		10 days

bid – *bis in die* (two times a day); tid – *ter in die* (three times a day); IM – *intramuscular*
 bid – *bis in die* (dva puta dnevno); tid – *ter in die* (tri puta dnevno); IM – *intramuskularno*

Treatment of recurrent pharyngitis

Various entities come under the umbrella of "recurrent pharyngitis" – viral infections (e.g. infective mononucleosis), autoinflammatory syndromes (e.g. PFAPPA - periodic fever, aphthous stomatitis, pharyngitis, adenitis), macrolide-resistant *GABHS* or poor adherence to therapy (34). The approach to these patients is individual, and treatment depends on the specific etiology. While poor adherence could be overcome by the penicillin G intramuscular treatment, macrolide resistance is eliminated by the introduction of an alternative drug (e.g. clindamycin). PFAPPA is a self-limiting syndrome that usually resolves spontaneously within 5-6 years. However, the course of oral steroids results in relieving symptoms in most cases, while tonsillectomy is viable in virtually all PFAPPA cases, including steroid non-responders (35).

Surgical treatment

With frequent episodes of tonsillopharyngitis – more than seven episodes in the prior year, or five episodes annually in the past two years, or three episodes annually in the past three years, tonsillectomy can be recommended (36). Due to vaccination against HI, peritonsillar and retropharyngeal abscess now predominate as a cause of life-

threatening inflammatory upper airway obstruction. It is caused by the locally aggressive spread of *GABHS*, *Streptococcus anginosus*, *Staphylococcus aureus*, and respiratory anaerobes. What started as acute pharyngitis may progress to cellulitis within a few days, and finally result in abscess formation. Manifested by a defined collection of pus between the tonsillar capsule and the surrounding tissue, it is the most common deep neck infection that requires inevitable surgical incision and parenteral antibiotic therapy. Because of their wide coverage of presumptive bacterial pathogens, β -lactams and clindamycin are mostly used (37).

Acute otitis media

Acute otitis media (AOM) is a common problem in early childhood, with peak age prevalence between 6-18 months and more than two-thirds of children with at least one episode of AOM by school age (38). It affects both genders equally, especially during cold days in autumn and winter. While bacteria (*SP*, *non-typeable HI*, and *MC*) remain the most important causative agents, up to one-fourth of cases are estimated to have a viral etiology (*RSV*, *coronaviruses*, *influenza viruses*, *adenoviruses*, *HMPV*, and *picornaviruses*) (39). The diagnosis should be highly suspected in a child with an abrupt onset of symptoms (ear pain, irritability, fever) accompanied by a bulging of the tympanic membrane, or a new onset of otorrhea not due to acute otitis externa (40). Several risk factors can predispose the development of AOM: the most common are a preceding upper respiratory tract infection, adenoid hypertrophy, allergy, daycare attendance, environmental smoke exposure, immunodeficiency, gastroesophageal reflux, and other genetic predispositions (41). Minimizing or avoiding these factors could lessen the overall burden of AOM.

Symptomatic treatment

Both pain and fever control are the mainstay of a treatment, irrespectively of the need for antibiotics. Since pain is the major symptom of AOM, non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen can be used for these purposes. The role of NSAIDs becomes more important with the fact that antibiotic therapy does not provide symptomatic relief in the first 24 hours (42, 43). The effects of topical agents are less clear; lidocaine and benzocaine offer additional, but brief benefits over acetaminophen in patients older than 5 years (40). However, the administration is contraindicated if the tympanic membrane is perforated. Analgesics doses are listed in Table III. Decongestants, antihistamines, and corticosteroids are not effective in AOM (44).

Table III Dosing regimen of analgesics for AOM (40)

Tabela III Režim doziranja analgetika za AOM (40)

Analgesic	Dose
Acetaminophen	10-15 mg/kg/dose every 4-6 hours as needed
Ibuprofen	10 mg/kg/dose every 6-8 hours
Topical agents (benzocaine)	1-2 drops every 1-2 hours as needed in external ear canal

Antibiotic treatment for AOM

Since a clear clinical distinction between bacterial and viral AOM is often impossible, the decision whether an antibiotic should be prescribed or not is based on clinical circumstances – the patient's age, severity of symptoms, and otoscopic finding (45). Traditionally, two strategies have been used:

1. Starting antibiotic treatment immediately

This approach should be used in each patient with severe signs or symptoms after establishing the diagnosis of AOM (moderate or severe otalgia or fever $\geq 39^{\circ}\text{C}$), irrespective of a child's age. According to AAP guidelines, a course of antibiotics should be offered to patients aged 6-23 months with bilateral AOM, or unilateral AOM, and a severe clinical course (40).

2. The watchful waiting approach

With this approach, symptomatic therapy should be initiated after establishing the diagnosis of AOM. Antibiotic therapy should be initiated only if the child's condition worsens at any time or does not show improvement within 48 to 72 hours of diagnosis, having in mind that most of the affected children have a viral infection. This approach is preferred in the cases of nonsevere unilateral AOM in children aged 6-23 months or nonsevere bilateral AOM in children aged > 24 months (40, 46).

An exception from the aforementioned approach has to be made in risk groups of children with certain underlying defects, such as immunodeficiency, presence of a cochlear implant, Down syndrome, cleft palate and only one hearing ear, in whom antibiotic treatment should be initiated immediately after establishing the diagnosis (47).

Preferred antibiotics for AOM

The choice of a proper antibiotic is related to the most frequent causative bacterial agents of AOM that have to be covered. According to the sensitivity of these agents, amoxicillin is the antibiotic of choice in high-dose for ten days (40, 42, 48). For those whose symptoms do not improve within 48-72h, amoxicillin treatment should be reassessed and high-dose amoxicillin-clavulanate should be given (40, 49, 50). Attention should be paid to children already receiving amoxicillin in the past 30 days, because

amoxicillin/clavulanate is the first-line option in these patients (40, 50). If a child cannot tolerate oral intake, parenteral ceftriaxone is the first-line option (49). Alternatively, parenteral clindamycin can be used (40).

In those allergic to penicillin, the choice of alternative drug depends on the type of hypersensitive reaction – macrolides are preferred with a history of type 1 hypersensitivity, while II and III generation oral cephalosporins can be used in non-type 1 hypersensitivity (50). Antibiotic doses are provided in Table IV.

Table IV Dosing regimen of antibiotics for AOM (40)

Tabela IV Režim doziranja antibiotika za AOM (40)

Antibiotic treatment for children with AOM	
First line	Amoxicillin 80-90 mg/kg/day BID for 10 days
Second line	Amoxicillin-clavulanate 80-90 mg/kg/day BID for 10 days
Antibiotic treatment for children with AOM – penicillin allergy	
	Cefprozil 30 mg/kg/day BID for 10 days
	Or
	<u>Cefpodoxime</u> 10 mg/kg/day BID for 5-10 days
	Or
	Azithromycin 10 mg/kg /day QD first day and then 5 mg/kg /day QD days 2-5

bid – *bis in die* (two times a day); qd – *quater in die* (four times a day)

bid – *bis in die* (dva puta dnevno); qd – *quater in die* (četiri puta dnevno)

Recurrent AOM treatment

The AAP guideline doesn't support the use of prophylactic antibiotics in children with recurrent AOM. In selected cases (three episodes in six months, or four episodes in one year with one episode in the preceding six months), patients may benefit from the insertion of tympanostomy tubes (40).

Myringotomy and tympanocentesis

Myringotomy is a procedure reserved for selected chronic secretory otitis media where the tympanic membrane incision results in an opening that allows a fluid-filled middle ear to drain (51). An additional benefit is in the possibility of identifying the causative pathogen, as it may be useful for patients who have failed multiple courses of antibiotics (52). Depending on the size of the hole, the tympanic membrane usually returns to normal within days to a few weeks. Myringotomy may be coupled with the insertion of tympanostomy tubes in order to secure drainage of the middle ear for an extended period (53).

Acute laryngotracheitis (croup)

Croup is a virus-triggered inflammation that primarily affects the subglottic area, including the larynx and trachea. Croup is mostly caused by viral pathogens, mostly *parainfluenza types 1 and 3*, *RSV*, *HMPV*, *adenovirus*, and *influenza viruses* (54). Typical symptoms often worsen at night and include a rapid onset of barking cough accompanied by hoarseness, dyspnea, and inspiratory stridor, which comes as a consequence of the narrowing of the subglottic space. Nonspecific symptoms of an upper respiratory infection usually precede typical croup symptoms. In moderate to severe cases, respiratory distress can be a part of clinical presentation. The disease mainly affects children between six months and three years of age, with a gradual resolution of symptoms within a few days (54, 55). Although most children with mild croup symptoms can be successfully treated at home, a significant number of children need to be treated in the emergency department (56). According to severity, croup can be classified as mild, moderate, or severe – see Table V (55).

Table V Severity of croup (55)

Tabela V Težina kliničke slike kod krupa (55)

	Mild	Moderate	Severe
Barking cough	occasional	frequent	persistent
Stridor*	none or minimal at rest	audible at rest	prominent and often biphasic
Respiratory rate	mildly increased	moderately increased	markedly increase or decrease
Oxygen saturation rate	normal	normal	< 92%
Consciousness	normal	normal or agitated	substantial lethargy

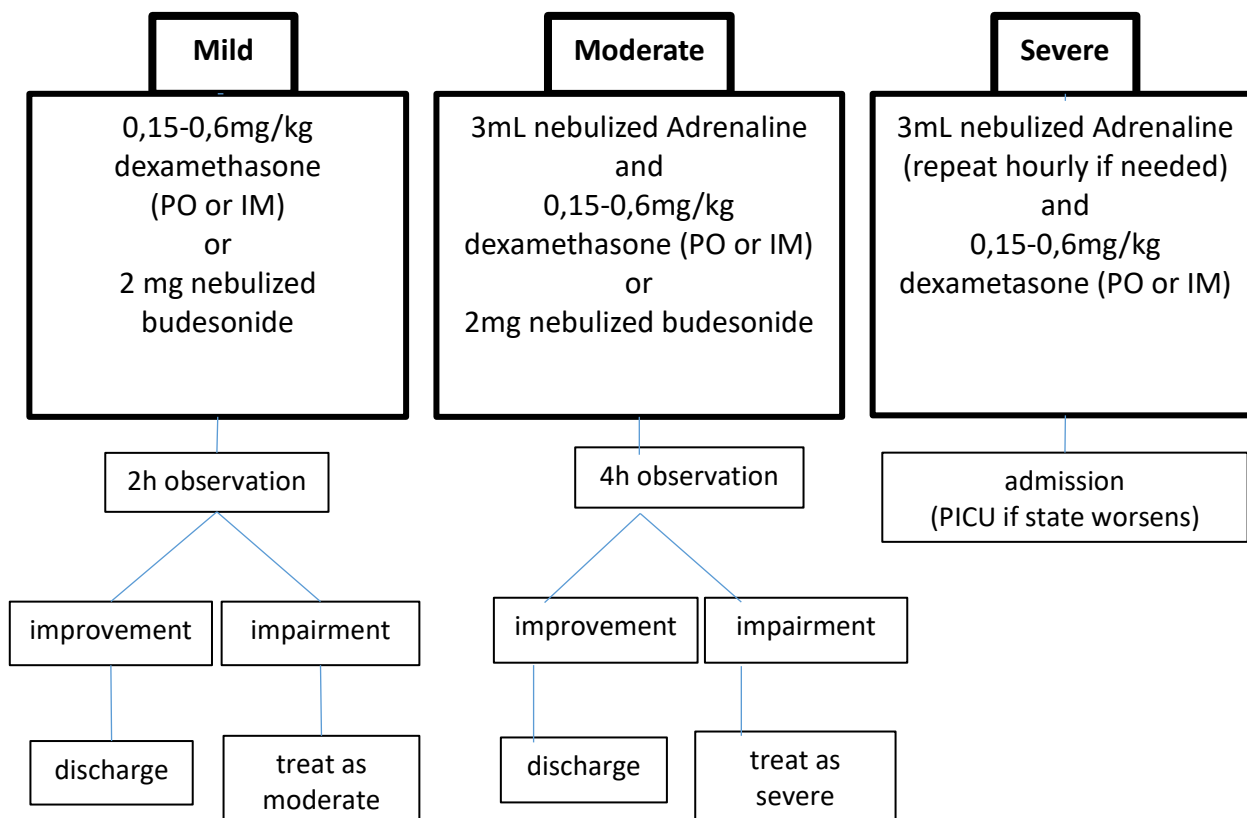
* Decrease of intensity of stridor in the presence of acute respiratory distress and cyanosis may be a sign of severe airway obstruction and imminent respiratory insufficiency.

* Smanjenje intenziteta stridora uz prisustvo akutnog respiratornog respiratornog distresa i cijanoze može biti znak ozbiljne opstrukcije disajnih puteva i nastupanja respiratorne insuficijencije.

Treatment of laryngitis

A general approach to each patient includes minimal handling with a comfortable position. Pharmacological management is guided by the severity of the disease. Severe croup requires systemic corticosteroids with the eventual need for supplemental oxygen. Admission to the intensive care unit (ICU) is reserved for children with symptoms of

severe croup and impending respiratory failure (55, 57). An algorithm for the treatment of children diagnosed with croup is given in Figure 1.



PO – *per os*; IM – *intramuscular*; PICU – *pediatric intensive care unit*

PO – *per os*; IM – *intramuskularno*; PICU – *pedijatrijska jedinica za intenzivnu negu*

Figure 1. Treatment of acute laryngitis (55)

Figure 1. Lečenje akutnog laringitisa (55)

Systemic corticosteroids

Corticosteroids are beneficial in children with croup due to their anti-inflammatory action and consequent decrease of laryngeal mucosal edema without significant adverse effects (58). The benefit of corticosteroids in croup is well-known, and is the cornerstone of both outpatient and inpatient management (59). Corticosteroid treatment significantly reduces return medical visits to an emergency department in mild cases, as well as admission rates in children with a moderate to severe clinical course (60, 61). Furthermore, patients admitted due to severe croup experience a shorter length of stay (62). Additionally, corticosteroid treatment decreases the endotracheal intubation rate in these patients (63).

Published studies have underlined the effects of different types of corticosteroids and modes of administration (61, 62). A single dose of dexamethasone (0.15-0.6 mg/kg) has shown the same efficacy if administered intravenously (IV), intramuscularly (IM), or orally (PO) (64, 65). Improvement after a single oral dose of dexamethasone begins within 2 hours and persists for one to two (66).

Inhaled therapy for acute croup

Inhaled therapy with either nebulized budesonide or adrenaline has substantially improved outpatient treatment. The mechanism of budesonide's action differs from systemic steroids and has been ascribed to both α 1-adrenergic vasoconstriction and anti-inflammatory mucosal effects (67). Nebulized budesonide in the dose of 2 mg is as effective as both oral and parenteral dexamethasone (68). However, certain authors stress prolonged agitation and crying with budesonide nebulization, as well as the time required to deliver the drugs, which all potentially worsen the child's respiratory distress (69).

Nebulized adrenaline has been recommended for moderate to severe croup. The two preparations of nebulized adrenaline used have been racemic adrenaline and L-adrenaline aerosols. While the former has not been licensed for use in some countries (including Serbia), the latter is just as effective, but less expensive (70). Pharmacologic treatment of nebulized adrenaline is based on α 1-receptor activity, with subsequent vasoconstriction of the blood vessels in inflamed mucosa and better patency of the subglottic area (55, 57). Adrenaline quickly improves signs of respiratory distress - within 10 to 30 minutes of initiating treatment, but the effects cease after two hours. Importantly, it lowers both the admission and intubation rate (55). As nebulized adrenaline has been used frequently in combination with dexamethasone in outpatient settings, there have been certain concerns regarding the possible rebound effects with subsequent clinical worsening. However, no evidence supports this presumption, and safety discharge after the administration of adrenaline has been documented (71).

Acute bronchiolitis

Acute viral bronchiolitis is characterized by the inflammation of the lower parts of the respiratory tract in children less than two years of age, with resultant tachypnea, wheezing, crackles, and occasionally poor oral intake. *RSV* is responsible for the vast majority of cases, with peak prevalence from October to March (72). Other agents include *HMPV*, *rhinovirus*, *parainfluenza virus*, *influenza virus*, *coronaviruses*, and *adenovirus* (73). Viral-mediated mucosal inflammation leads to mucosal edema and the obstruction of airways by cellular debris and mucus plugs (73). Although mild in most cases, bronchiolitis has the potential to cause significant respiratory distress and is still the leading cause of hospital admission for respiratory disease in infancy (74). Even though there is no specific treatment, symptomatic treatment is crucial in minimizing both potential complications and hospital admission rates.

Outpatient treatment

Infants with bronchiolitis are often mildly dehydrated due to a decreased fluid intake and increased insensible fluid losses (75). As patients with mild symptoms may require only observation if feeding remains unaffected, adequate outpatient treatment is based on adequate nutritional support and hydration. To the maintenance of regular oral intake, exclusive breastfeeding in the first six months of life should be encouraged (76). Except for the fact that respiratory infections are shown to be significantly less common in breastfed children, some authors emphasize a favorable influence on the severity of acute bronchiolitis (77). Frequent small portions of a meal can reduce the potential of vomiting triggered by bouts of coughing.

As human infants are obligate nasal breathers, maintenance of the nostrils' passability is necessary for outpatient treatment (75). Nasal irrigation of nostrils with normal saline may be useful.

Although a significant proportion of cases diagnosed with bronchiolitis are advised to use bronchodilators in outpatient settings, most randomized controlled trials have failed to show clear benefits from either β -agonists or anticholinergics regarding disease resolution, need for hospitalization, or length of stay in hospital (78–80). Moreover, despite some inconsistent reports, neither independent bronchodilator inhalation nor the addition of either normal or hypertonic saline (3%) has been recognized as efficacious in prehospital treatment (75, 79, 80).

Inpatient treatment

The decision regarding hospital admission has to be considered in patients with signs of significant respiratory distress (cyanosis, oxygen saturation rate (SpO_2) on room air $< 90\%$, signs of respiratory distress), in those with an inability to maintain oral intake and in those with clinically significant comorbidities such as prematurity, congenital heart, lung or neurometabolic disease (81). Management is primarily supportive and aimed at maintaining oxygenation and proper hydration (75, 80). Supplemental oxygen administration should be offered to each patient with $SpO_2 < 90\%$ (80). Hydration should be maintained through a nasogastric tube or via intravenous access (73, 80, 82). In contrast with these steps, the benefits of pharmacological treatment are controversial, to say the least.

Bronchodilators

Despite the widespread usage of nebulized bronchodilators, particularly adrenaline (both α and β -agonist) and salbutamol (β -agonist), there is not enough data that unequivocally supports the concept of efficacious use of these agents. Although a relatively small proportion of infants may have reversible bronchial obstruction due to bronchoconstriction - and thus may benefit from β -agonists - routine use of bronchodilators cannot be recommended (75, 79, 80). The decision on introducing nebulized β -agonists into therapy is often related to the individual basis.

Mucolytic therapy

Guidelines have shown a considerable variability in terms of highlighting the role of hypertonic saline in the treatment of bronchiolitis. Recent AAP guidelines recommend the administration of nebulized hypertonic saline to infants and children hospitalized for bronchiolitis (80). The presumption of the beneficial effect of hypertonic saline came from its ability to enhance rehydration of the airway surface and the proposed pathophysiology of the disease that includes mucus plugging (83). It was stated that hypertonic saline improves symptoms and shortens the length of stay only when it is longer than three days, although there are opposite reports (84, 85). According to the assumption that mucus secretions in distal airways partly originate from upper airways, the use of deep suctioning with nasopharyngeal catheters has been widely adopted in clinical terms. However, deep suctioning can cause mucosal edema and irritation, so it is to be avoided (86). None of the chest physiotherapy techniques has been proven beneficial in acute bronchiolitis (80).

Corticosteroids

Despite the theoretical benefit of systemic corticosteroids in reducing airway inflammation and mucosal edema, which are important determinants of the bronchiolitis pathophysiology, its routine use is not recommended in either outpatient or inpatient settings (80). While several studies have highlighted beneficial results of corticosteroids alone or in combination with nebulized adrenaline, a Cochrane Review failed to show improvements in shortening the length of stay or reducing hospital admission rates (87, 88). Inhaled corticosteroid treatment has not been proven efficacious even if high doses were given, and its use should be avoided (89).

Other therapy

Routine administration of antibiotics is not recommended (80). Although fever, respiratory distress, and consolidations on X-ray may mislead clinicians into starting antibiotics, their use is justified only in selected cases - in those who require mechanical ventilation for respiratory failure or in case of complications, such as bacterial pneumonia or AOM (79, 80).

Antiviral therapy for cases of bronchiolitis is controversial and is not routinely recommended. High costs and toxicity with a lack of clear benefits limit the wider use of ribavirin in clinical practice (79).

Treatment of severe cases

Severely ill infants often require additional respiratory support. Recent data suggest beneficial effects of high-flow nasal cannula (HFNC), which combines the administration of oxygen with the application of positive airway pressure, all of which decreases work of breathing and improves gas exchange. HFNC therapy should be performed in high-dependency units or ICU (90).

Noninvasive ventilation (NIV) and eventually invasive mechanical ventilation are reserved for the most serious cases mainly drafted from the group of infants with chronic lung disease or congenital heart disease. Infants with progressive hypoxemia despite conventional ventilation may benefit from high-frequency ventilation or extracorporeal membrane oxygenation (ECMO) (91).

Once enthusiastic reports regarding the role of heliox, a breathing gas mixture of helium and oxygen have nowadays come into question (92, 93). Despite theoretical benefit over atmospheric air in terms of lower density that facilitates flow through the airways, latest studies suggest that heliox treatment did not have an impact on clinically important endpoints, such as the need for continuous positive airway pressure (CPAP) or invasive mechanical ventilation (93).

Pneumonia

Pneumonia is a leading cause of morbidity and mortality in children younger than five years. While the vast majority of deaths occur in the developing world, pneumonia remains a significant health care problem in developed countries as well (94, 95). It is often hard to distinguish infants with bacterial pneumonia from those with viral illnesses since clinical presentation may be almost the same, as it is labeled by nonspecific symptoms (poor feeding, lethargy, tachypnea, temperature instability, dehydration). Toddlers and older children often show a more typical appearance with cough, fever, and tachypnea (96). Therefore, it is not unusual for children with a viral infection to be treated with antibiotics and, on the contrary, those with mild bacterial pneumonia are often treated only symptomatically (97). Having in mind the prevalence of different pathogens in different age groups, initial antibiotic therapy is empiric. Viruses are the most frequent causative agents up to the age of two years (*RSV*, *influenza virus*, *HMPV*, *adenovirus*) with an important note that bacterial agents (*Streptococcus agalactiae*, *Escherichia coli*, *Chlamydia trachomatis*, and *Listeria monocytogenes*) prevail in neonatal age. As age increases, the incidence of bacterial pathogens becomes more prevalent (96). In children older than five years, atypical agents (*Mycoplasma pneumoniae* and *Chlamydia pneumoniae*) have an important role (96). Since immunocompromised children are particularly susceptible to unusual viral, fungal, and protozoal agents, such as *cytomegalovirus*, *Pneumocystis jirovecii*, and *Aspergillus species* with an atypical clinical pattern, special attention is paid to their treatment (98, 99).

Table VI Empirical antimicrobial therapy for pneumonia in children (96)

Tabela VI Empirijska antimikrobna terapija za pneumoniju kod dece (96)

Age group	Outpatients	Inpatients
		intravenous penicillin (100 000–250 000 U/kg/day Q4–6h) or intravenous ampicillin (200 mg/kg/day QID)
<u>1-3 months</u>	<u>not recommended as initial step</u>	*intravenous azithromycin (10 mg/kg QD on days 1 and 2 of therapy; transition to oral therapy if possible) or azithromycin orally 10 mg/kg QD on day 1, followed by 5 mg/kg/day QD days 2–5
	amoxicillin orally (90 mg/kg/day in 2 doses or 45 mg/kg/day TID) or amoxicillin clavulanate orally (45 mg/kg/day TID or 90 mg/kg/day BID)	intravenous ampicillin (150–200 mg/kg/day QID) or intravenous penicillin (200 000–250 000 U/kg/day Q4–6 h) or ceftriaxone (50–100 mg/kg/day every BID)
<u>3 months – 5 years</u>		
	amoxicillin orally (90 mg/kg/day in 2 doses or 45 mg/kg/day TID) or *azithromycin orally (10 mg/kg QD on day 1, followed by 5mg/kg/day QD on days 2–5);	intravenous ampicillin (150–200 mg/kg/day every 6 hours) or ceftriaxone (50–100 mg/kg/day every BID) or intravenous azithromycin (10 mg/kg QD on days 1 and 2 of therapy; transition to oral therapy if possible)
<u>5-18 years</u>		

bid – *bis in die* (two times a day); tid – *ter in die* (three times a day); qd – *quarter in die* (four times a day); IM – *intramuscular*; U – *unit*

* *Atypical pneumonia* (e.g. *Chlamydia trachomatis*)

bid – *bis in die* (dva puta dnevno); tid – *ter in die* (tri puta dnevno); qd – *quarter in die* (četiri puta dnevno); IM – *intramuskularno*; U – *jedinica*

* *Atipična pneumonija* (npr. *Chlamydia trachomatis*)

Treatment of pneumonia – an overview

Questions that have to be answered before the initiation of treatment are:

1. Is the patient suitable for inpatient or outpatient treatment?
2. What is the probable causative pathogen?

Since the presumption about a specific pathogen is made according to the child's age and local epidemiologic situation, the vast majority of children are successfully managed ambulatory. In both scenarios, supportive and symptomatic management is important and includes antipyretics for fever and fluids for dehydration (94). Supplemental oxygen is needed to achieve targeted SpO₂ > 92% (94).

Antibiotic treatment

Neonatal pneumonia is treated inpatient (94). Neonates should receive both ampicillin and either aminoglycoside or third-generation cephalosporin (ceftriaxone is not recommended due to its effects on the bilirubin metabolism and possible kernicterus) (94, 100). As atypical pneumonia caused by *Chlamydia trachomatis* is not uncommon in infants up to three months of age, an additional benefit is provided by adding macrolides - azithromycin or erythromycin (94, 100). Amoxicillin is recommended as first-line therapy for previously healthy appropriately immunized preschool-aged children with mild to moderate community-acquired pneumonia (CAP), given the fact that even penicillin-resistant strains of *Streptococcus pneumoniae* - the most prominent invasive bacterial pathogen causing pneumonia – show sensitivity to high doses of amoxicillin (101, 102). Although amoxicillin remains the cornerstone for outpatient management of pneumonia for all school-aged children and adolescents, a number of patients from these groups with findings compatible with CAP caused by atypical pathogens benefit from macrolide antibiotics (102). Preschool and school-aged children with severe pneumonia are to be treated inpatient with ampicillin or penicillin G as a first-line treatment in fully immunized individuals (96, 102). Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be used in incompletely immunized children, as well as in regions with penicillin-resistant pneumococcal strains (102). Although frequently used in inpatient settings – especially intensive care units – vancomycin has not been shown to be more effective than third-generation cephalosporins in the treatment of penicillin-resistant pneumococcal pneumonia (102). However, vancomycin is inevitable in the management of necrotizing pneumonia due to its effects on *Staphylococcus aureus* as a common causative agent (103). Since the strategy of vancomycin monotherapy in these circumstances is doubtful, it is recommended to combine it with β-lactams (or even clindamycin) if clinical, laboratory or imaging characteristics are consistent with an infection caused by *S. aureus* (102,104).

The duration of the treatment is individual and depends on the severity of the disease. Shorter courses (e.g. 3 or 5-day) may be just as effective as longer ones (e.g. 10-day courses). However, complicated infections (necrotizing pneumonia or pneumonia with pleural empyema) may require much longer treatment, up to six weeks (105, 106). Furthermore, the shortest effective duration minimizes the selection of resistant strains, leads to a reduced number of adverse effects, and decreases the financial burden on the public health care system (105, 106).

Conclusion

The majority of acute respiratory infections in childhood are caused by viruses, so antimicrobial therapy should be used wisely, following national and international guidelines for rational use of antibiotics in pediatrics. In severe infections, empirical therapy should be initiated immediately, having in mind the age of the patient, clinical status, and presumptive etiology of the disease.

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Lečenje najčešćih respiratornih infekcija kod dece

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Kratak sadržaj

Akutne respiratorne infekcije predstavljaju najčešću grupu infektivnih oboljenja u pedijatrijskoj populaciji. Iako su unapređenje zdravstvene zaštite i program vakcinacije doveli do značajnog snižavanja incidence pojedinih respiratornih infekcija, zbog zastupljenosti u naročito vulnerabilnim pedijatrijskim kategorijama kakve su odojačka i predškolska populacija, uz čestu nemogućnost adekvatnog razlikovanja virusne i bakterijske etiologije, koja rezultuje nekritičkom upotrebom antibiotika, akutne respiratorne infekcije ostaju značajan javnozdravstveni izazov. U cilju racionalne primene antibiotika i sveukupnog unapređenja dijagnostičkih načela i terapijskog pristupa, akutna respiratorna oboljenja su predmet razmatranja brojnih publikacija i vodiča dobre kliničke prakse. Nespecifičnost kliničkog ispoljavanja, uz heterogenu distribuciju uzročnika bolesti i različita anatomska i fiziološka svojstva dečijeg respiratornog sistema tokom različitih perioda rasta i razvoja, stvorili su potrebu za individualizacijom terapijskog pristupa, koji može značajno da se razlikuje među različitim slučajevima. Dok smernice nacionalnih vodiča ističu nesumnjivu i ključnu korist od širokozastupljene simptomatske terapije kod mnogih pacijenata, primena antibiotika i kortikosteroidne terapije biva indikovana u odabranim slučajevima sa teškom kliničkom slikom. Odluka o izboru antibiotika donosi se u zavisnosti od kliničkog stanja, pretpostavljenog uzročnika i lokalne epidemiološke slike. Respiratorna potpora (kiseonična terapija i/ili arteficialna ventilacija) rezervisane su za pacijente koji se zbog posebno teške kliničke slike i pridruženih komplikacija leče u bolničkim uslovima.

Ključne reči: akutne respiratorne infekcije, racionalna primena antibiotika
