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REVIEW ARTICLE

Finnish guidelines for the treatment of laryngitis, wheezing bronchitis and bronchiolitis in children

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ABSTRACT

Evidence-based guidelines are needed to harmonise and improve the diagnostics and treatment of children's lower respiratory tract infections. Following a professional literature search, an interdisciplinary working group evaluated and graded the available evidence and constructed guidelines for treating laryngitis, bronchitis, wheezing bronchitis and bronchiolitis.

Conclusion: Currently available drugs were not effective in relieving cough symptoms. Salbutamol inhalations could relieve the symptoms of wheezing bronchitis and should be administered via a holding chamber. Nebulised adrenaline or inhaled or oral glucocorticoids did not reduce hospitalisation rates or relieve symptoms in infants with bronchiolitis and should not be routinely used.

INTRODUCTION

Evidence-based clinical practice guidelines for the treatment of lower respiratory tract infections (LRTIs) in children were developed in Finland in 2013–2014. They were devised by an independent interdisciplinary working group, established by the Finnish Medical Society Duodecim and the Finnish Pediatric Society, that included paediatric infectious disease specialists, general paediatricians, a clinical microbiologist, a paediatric radiologist and a general practitioner. The scope of the guidelines was the treatment of acute paediatric LRTIs, excluding severe cases requiring hospital admission or intensive care.

Our professional librarian performed systematic literature searches using selected topics and questions, and then, the group reviewed the literature and evaluated the available evidence. The level of evidence was assessed and marked within guideline statements for the most critical decisions. The following category levels for the evidence were used: level A referred to strong evidence with at least two separate, high-quality studies; level B referred to moderate evidence with at least one high-quality study; and level C referred to weak evidence with at least one satisfactory study. A high-quality study was defined as a study performed in an appropriate population with a strong study design, such as a randomised controlled trial with an appropriate outcome measure. The guideline document was peer-reviewed by 14 experts and clinicians before it was published in the Finnish Current Care Guidelines series in 2014. The process is described in detail on the Current Care Guideline Web pages (www.kaypahoito.fi). The original

Key Notes

- An interdisciplinary working group constructed guidelines to harmonise and improve the treatment of children's lower respiratory tract infections.
- Our review found that currently available drugs were not effective in relieving cough symptoms, but salbutamol inhalations could relieve the symptoms of wheezing bronchitis
- Nebulised adrenaline or inhaled or oral glucocorticoids did not reduce hospitalisation rates or relieve symptoms in infants with bronchiolitis and should not been routinely used.

document included approximately 200 references and more than 50 linked supplementary Web pages presenting the systematic literature review for each statement. This formed the first part of the summary document. The second part presented the treatment of pneumonia and pertussis in children (1). The detailed search description by the professional librarian is presented (Tables S1–S2).

This paper presents the available evidence and the new guidelines for treating laryngitis, wheezing bronchitis and bronchiolitis in children in Finland. The *evidence-based statements*, which appear in italics in this paper, are presented and the reasoning behind the recommendations is discussed. Table 1 summarises the recommendations for the use of antimicrobials, glucocorticoids and sympathomimetics. In addition to the presentation of new guidelines, we have discussed relevant new studies published since 2014 and explained their effect on the present guidelines.

AETIOLOGY AND DIAGNOSTICS OF RESPIRATORY VIRUSES

All known respiratory viruses are capable of causing different LRTIs such as laryngitis, wheezing bronchitis, bronchiolitis or pneumonia. The most important viruses causing LRTIs in children are rhinoviruses, the respiratory syncytial virus (RSV), parainfluenza viruses 1–4, the adenovirus group and influenza viruses A and B. Some viruses, however, are more likely to cause specific LRTIs (2). Rhinoviruses are particularly associated with wheezing bronchitis, RSV with bronchiolitis in infants and parainfluenza viruses with laryngitis. Accordingly, RSV is the most important virus that causes wheezing in children under one year of age and rhinoviruses are the most important in older children (3). All respiratory viruses are capable of causing febrile infections (2), for instance rhinoviruses are associated with fever in 40–50% of children with respiratory tract infections, the parainfluenza virus is associated with fever in 60–80% and influenza A in 90–95%. The most important recently recognised respiratory viruses are the human metapneumovirus, which is associated with bronchiolitis, and the human bocavirus, which is associated with wheezing bronchitis. Bacteria do not usually cause laryngitis, bronchitis, bronchiolitis or wheezing bronchitis in children. The aetiology of pneumonia is presented in the separate guideline document from the same group (1).

Testing of influenza A and B virus is recommended to all children with LTRIs during the influenza season if the duration of the acute symptoms is <48 hours (level B). Influenza cannot reliably be diagnosed based on clinical symptoms in children. Antiviral treatment against influenza is effective if the treatment is started within 48 hours of the start of the symptoms (4). However, influenza virus testing may be beneficial for patients admitted to hospital even after 48 hours. Influenza virus testing during an LRTI is likely to decrease antimicrobial consumption (5).

Testing of RSV and other respiratory viruses can be performed on children who are admitted to hospital due to an LRTI (level B) (6,7). Respiratory virus testing may

Table 1 Antimicrobial treatment, corticosteroids and sympathomimetic drug in the treatment of lower respiratory tract infections in children

Clinical condition	Antimicrobial	Corticosteroids	Sympathomimetic drugs
Laryngitis	No antimicrobials	Betamethasone 0.25 mg/kg once orally (water soluble tablets available) Alternative: Dexamethasone 0.15–0.6 mg/kg once orally Add if severe symptoms: Nebulised budesonide (2 mg)	Nebulised racemic adrenaline
Bronchitis	No antimicrobials	No glucocorticoids	No sympathomimetics
Wheezing bronchitis	No antimicrobials	No glucocorticoids	Salbutamol 6 doses (0.1 mg/dose) every 20 minutes via spacer chamber altogether 4 times (emergency room) 2–6 doses every four hours if needed (at home)
Bronchiolitis	No antimicrobials	No glucocorticoids	No sympathomimetics

Antitussives are ineffective in all LRTIs presented above.

decrease the use of antimicrobial treatment after hospitalisation (8). Wheezing bronchitis or bronchiolitis are rarely associated with a bacterial infection of the lower respiratory tract. Nosocomial infections may be decreased with active cohorting of hospitalised patients based on viral testing. Wheezing associated with a rhinovirus infection is a risk factor for later asthma in children (3). The sensitivity of point-of-care antigen tests is lower than that of polymerase chain reaction (PCR) performed in laboratory, but their sensitivity and specificity in detecting influenza viruses and RSV is rather good (9). The accuracy and feasibility of point-of-care tests for other respiratory viruses than influenza viruses and RSV is largely unknown.

LARYNGITIS

Laryngitis can be classified into upper respiratory tract or lower respiratory tract infections. Our working group decided to include laryngitis in the present LRTI guideline as laryngeal symptoms are caused by subglottic oedema, dyspnoea is common and laryngitis can be treated with drug inhalations. Typical symptoms of laryngitis are inspiratory wheezing and a barking cough. Bacterial tracheitis is rare, and epiglottitis is very rare in the era of *Haemophilus influenzae* B immunisation, but they can also cause inspiratory difficulties and should be remembered in the differential diagnostics. The occurrence of laryngitis is highest among children aged six months to three years. These days, children with laryngitis are mainly treated in emergency departments and other outpatient clinics and hospitalisation due to laryngitis is rare.

Mist is not effective in relieving the symptoms of laryngitis (level A) (10,11). In two randomised controlled trials (RCTs), mist administration did not decrease clinically evaluated symptoms of laryngitis. *Nebulised racemic adrenaline is effective in relieving the symptoms of laryngitis* (level A) (12). The effect is short term and lasts for one to two hours. Nebulised levo-adrenaline, an isomer used in systemic adrenaline products, was used in one small study. There was no statistically significant difference in symptom scores between children receiving nebulised racemic adrenaline and levo-adrenaline, but the sample size of the study was too small to confirm equal efficacy. *Oral glucocorticoids are effective in relieving the symptoms of laryngitis* (level A) (13). Different doses of glucocorticoids appear to be equally beneficial and oral glucocorticoids as effective as intramuscular glucocorticoids. Possible drug alternatives include a single oral dose of betamethasone 0.25–0.4 mg/kg (Betapred®, water soluble tablets) or dexamethasone 0.15–0.6 mg/kg. Nebulised budesonide (2 mg) may provide additional efficacy in children treated with systemic glucocorticoids (14).

ACUTE BRONCHITIS

Acute cough in children is usually caused by viral respiratory infections. The duration of cough is usually less than three weeks, but in 10% of cases, the cough may continue longer. Antimicrobials are ineffective in treating cough in children. *Antitussive drugs* (15–21) *and beta-sympathomimetic agents* (18,22) *are ineffective in relieving acute cough in children and may cause serious adverse events* (level A). This is in line with an earlier statement by the U.S. Food and Drug Administration recommending that antitussives should not be used for infants due to serious adverse events. *Honey may relieve acute nocturnal cough during an LRTI in children older than one year of age* (level C) (23–26). Dosing of honey in RCTs has ranged from a single dose of a few millilitres to 10 g given orally approximately 30 minutes before sleep in children with an acute viral LRTI. Honey should not be given to infants younger than one year of age due to the risk of infant botulism. Chronic wet cough, which is also called presumed protracted bacterial bronchitis in the literature and lasts for several weeks, is a less frequent condition in children than acute bronchitis. More commonly, a child suffers from recurrent viral LRTIs and is asymptomatic between LRTI episodes. If chronic bacterial bronchitis is suspected in children, other diagnoses such as tuberculosis, foreign body aspiration, cystic fibrosis or primary immunodeficiency should be excluded. *Antimicrobial treatment may be effective in treating chronic wet cough in children* (level C) (27–29).

ACUTE WHEEZING UNDER THREE YEARS OF AGE

Acute wheezing in children under three years of age covers two clinical conditions, wheezing bronchitis and bronchiolitis, that are different in terms of causative agents, clinical symptoms and outcomes. However, in the literature we examined, both conditions were often included together in the same trials. The term bronchiolitis is used for children under 24 months of age with wheezing in the United States, but in Europe, it is restricted to children under 12 months of age experiencing their first wheezing episode. The European definition of bronchiolitis is used in this guideline. However, RSV bronchiolitis during the first months of life differs from rhinovirus-induced wheezing in older infants who are under 12 months of age. In future trials, RSV infection in infants younger than six months of age and rhinovirus-induced wheezing in infants older than six months of age would ideally be assessed separately.

WHEEZING BRONCHITIS

Wheezing bronchitis is most frequently triggered by a rhinovirus and is defined as wheezing in children aged 12 to 36 months during acute respiratory viral infection or repeated wheezing in children aged six to 12 months. Rhinovirus-induced wheezing in children is a clear risk factor for asthma in later childhood (3). The border between repeated episodes of wheezing bronchitis and childhood asthma is sliding. In most cases, children with wheezing grow out of this tendency before school age, but there are no reliable means to assess, early in life,

who will stop and who will continue wheezing. Risk factors for recurrent wheezing are passive smoking, parental asthma, atopic disease in the child and wheezing starting when the child is more than 12 months of age.

TREATMENT OF WHEEZING BRONCHITIS

Salbutamol inhalations may relieve the symptoms of wheezing bronchitis (level C) (30). *Salbutamol administered via a holding chamber (spacer) is likely to be more effective than salbutamol administered via a nebuliser* (level B) (31,32). The side effects caused by salbutamol appear to be more prevalent when salbutamol is administered using a nebuliser than if it is administered using a holding chamber (31,32). For these reasons, most wheezing bronchitis episodes are currently treated using space chambers in Finland. *Oral beta-sympathomimetic agents are ineffective and are not recommended for the treatment of wheezing bronchitis* (level A) (33–35). *Glucocorticoid inhalations are ineffective and are not recommended for the prevention of expiratory wheezing episodes induced by viral infections in children* (level A) (36–41). Glucocorticoid inhalations administered either continuously or just during respiratory infections were ineffective in preventing wheezing episodes. Children attending glucocorticoid prevention trials had suffered from two or more wheezing episodes, but were asymptomatic between the episodes, in other words children with persistent asthma symptoms were not included in the studies.

BRONCHIOLITIS

Bronchiolitis is most often seen in infants under six months of age during RSV epidemics. Crepitations (fine crackles) on chest auscultation are characteristic of bronchiolitis. Young infants may present with apnoea. In total, 2–3% of children are hospitalised due to bronchiolitis during their first year of life (42). The mortality rate due to bronchiolitis was two to three per 100 000 during the first year of life in the United Kingdom and the United States in the 1990s (42). Risk factors for severe bronchiolitis are being younger than two months of age, prematurity and bronchopulmonary dysplasia in preterm infants (42). In addition, children with congenital heart defects, neurological diseases or immunodeficiency are prone to severe diseases. RSV is the main causative agent of bronchiolitis. RSV epidemics used to follow a biannual pattern in Finland, with the highest incidence starting in October–December every second year. However, during the last two to four years, the epidemiology of RSV has changed in Finland and RSV epidemics appear to happen every winter from December to February.

TREATMENT OF BRONCHIOLITIS

Nebulised adrenaline is not effective in reducing the hospitalisation rate of infants with bronchiolitis (level B) (43–46). *Nebulised salbutamol is not effective in relieving symptoms in infants with bronchiolitis* (level B) (44,47). *Inhaled or oral glucocorticoids are not beneficial in relieving symptoms, reducing hospitalisation rates or reducing the duration of hospitalisation in infants with RSV bronchiolitis* (level B) (48–53). *It has been suggested that high-flow nasal oxygenation with a warmed and humidified oxygen–air mixture can decrease the intubation rates in bronchiolitis, but randomised controlled trials are not yet available* (level C) (54–56). *Nebulised hypertonic saline may reduce the duration of hospitalisation, but is not effective in relieving acute symptoms in infants with bronchiolitis* (level B) (57,58).

Evidence regarding nebulised hypertonic saline in the treatment of bronchiolitis is conflicting. In most RCTs, hypertonic saline has been compared to normal saline which has been presumed to be suitable as placebo. Nebulised adrenaline or saline, however, appears to increase the duration of hospitalisation if given regularly, compared to on-demand dosing (46). It is notable that, after the Finnish guidelines were published in the form presented above, several new high-quality studies questioned the efficacy of hypertonic saline inhalations in the treatment of bronchiolitis (59–61). Thus, the recommendation to use hypertonic saline in the treatment of bronchiolitis is no longer valid and will be updated accordingly in the Finnish electronic guideline document.

INDICATIONS FOR HOSPITALISATION OF INFANTS WITH BRONCHIOLITIS

A child should be admitted to hospital if their general condition is poor or the oxygen saturation is decreased. Infants who experience bronchiolitis during the first weeks of life should usually be treated in hospital to arrange proper monitoring as bronchiolitis can lead to severe apnoea and the respiratory symptoms of bronchiolitis can deteriorate for five to seven days after the beginning of the disease.

CONCLUSION

Evidence-based guidelines have been developed to harmonise and improve the diagnosis and treatment of children‘s lower respiratory tract infections. The drugs that are currently available are not effective in relieving cough symptoms. Salbutamol inhalations may relieve the symptoms of wheezing bronchitis and should be administered via a holding chamber. Nebulised adrenaline or inhaled or oral glucocorticoids do not reduce hospitalisation rates or relieve symptoms in infants with bronchiolitis and should not be routinely used.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. The databases and terms used in the systematic literature search.
Table S2. Detailed description of search strategies.