



Approach to Common Cold in Children

Çocuklarda Soğuk Algınlığına Yaklaşım

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ABSTRACT

Infections of the upper respiratory tract are very common in children. Clinical features and patterns of disease are different from those in adults. Although infections of the upper respiratory tract often resolve completely without complications, treatment is indicated where it can achieve more rapid resolution of symptoms and prevent the complications. Vast amounts of money are wasted on over-the-counter products for colds. Clinical trials have confirmed their lack of efficacy. This review summarizes the epidemiology, pathogenesis, clinical features, diagnosis and treatment of common cold in children. *The Journal of Pediatric Research 2015;2(1):1-6*

Key words: Respiratory, virus, common cold, rhinovirus

Conflicts of Interest: The authors reported no conflict of interest related to this article.

ÖZET

Çocuklarda üst solunum yolu enfeksiyonuna sık olarak rastlanmaktadır. Hastalığın klinik özellikleri ve seyri erişkindekinden oldukça farklıdır. Üst solunum yolu enfeksiyonu genel olarak komplikasyonsuz iyileşmekle birlikte, semptomların hızla düzeltilmesi komplikasyonları önlemek amacı ile önerilmektedir. Reçetesiz satılmakta olan ilaçlara yüksek miktarda para harcanmaktadır. Klinik çalışmalara ait meta analiz sonuçları, bu ilaçların tedavide etkin olmadıkları yönündedir. Bu derleme çocuklarda soğuk algınlığının epidemiyoloji, patogenez, klinik özellikler, tanı ve tedavi sürecini özetlemektedir. *The Journal of Pediatric Research 2015;2(1):1-6*

Anahtar Kelimeler: Solunum, virüs, soğuk algınlığı, rinovirüs

Çıkar Çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemiştir.

The Common Cold

I love the doctors-they are dears;
But must they study years and years
Investigating such a lot
Of illnesses which no one's go
When everybody, young and old;
Is frantic with the common cold?
And I will eat my only hat
If they know anything about that (1).

The common cold is an acute, self-limited viral infection of the upper respiratory tract. The most common viral pathogens are rhinoviruses, influenza virus A and B, parainfluenza virus and respiratory syncytial virus (RSV).

Adenovirus and enterovirus are rare pathogens of common cold. An estimated 25 million individuals seek medical care for uncomplicated upper respiratory tract infections (URI) annually and it is the 3rd most common reason for hospital admission (2,3). Approximately one third of these visits result in the prescription for antibiotics (4). Compared to previous years, the number of prescriptions for colds and URIs in children decreased; however, approximately one-third of these prescriptions were for broadspectrum antibiotics (5). The prevalence of drug use in children is still as high as %50 in viral infections. In 2011 very well known drugs for cough and common cold were taken off the markets for they had not been FDA (Food and Drug Administration) approved (6).

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Received/Geliş tarihi: 30.04.2014 Accepted/Kabul tarihi: 17.11.2014

Epidemiology

The symptoms of the common cold may be caused by a variety of viruses. The main difference of viruses causing common cold from other viruses is the duration of incubation period. Rhinovirus, RSV, Influenza virus, parainfluenza virus and adenovirus are the most common causative organisms for common cold in pre-school children (7). Rhinoviruses are responsible for at least 50 percent of colds in both children and adults. Common cold symptoms may also be caused by enteroviruses (echoviruses and coxsackieviruses) and coronaviruses. Human metapneumovirus (HMPV) can also be responsible for self-limited upper respiratory infections in addition to pneumonia and bronchiolitis (8,9). Many of these viruses may also cause other characteristic syndromes in children. RSV is mainly responsible for bronchiolitis in children younger than age of two years. Croup is a clinical entity mainly caused by parainfluenza viruses. Herpangina is caused by coxsackie virus A. Pharyngoconjunctival fever is caused by adenoviruses. The common cold may occur at any time of the year, but there is typically a high prevalence during the early fall and lasts until late spring. This season for common cold epidemic begins with the predominance in rhinovirus infections in September (10). Parainfluenza virus is most commonly seen in October or second half of fall. RSV and influenza viruses are most commonly seen starting from december to april. Adenovirus infections are continuously present at a low rate throughout the cold season. The epidemic finally ends with a small wave of rhinovirus infections in April.

Pathophysiology

Viral transmission may occur via inhalation of small particle aerosols, deposition of large particle droplets on nasal or conjunctival mucosa, or direct transfer via hand-to-hand contact. Symptoms may occur two days after transmission. In a study investigating finger microbiology during daily public procedures, virus has been shown to be very efficiently transferred from hand-to-hand minimal contact, surface material, ventilation and human behavior (11). Substantial titers of respiratory viruses are present in innate surfaces and also survive up to several days (12,13). The host epithelial barriers and both innate and adaptive immune responses influence the reaction of the host (14). Over 90% of the known rhinovirus (RV) serotypes of the (humanrhinovirus) HRV-A and B families utilize ICAM-1 as their cell entry receptor, while the ruinor group receptor, low density lipoprotein (LDL), is used by 10 serotypes, causing neutrophilic inflammatory response associated with increased vascular permeability and stimulation of mucus secretion (15,16). HRV-C has more recently emerged as a virus of interest, particularly in RV induced exacerbations of asthma (17). Infections with other respiratory pathogens, for instance concomitant infection of rhinoviruses and Streptococcus Pneumoniae (Strept.) show increased adherence of Strept. to human tracheal epithelial cells (18).

After the influx of polymorphonuclear cells (PMNs) in the nasal submucosa and epithelium, inflammatory cytokines are released and infiltration occur in the medium. Increased vascular leakage reflect the ability of viral pathogens ability to disrupt tight junctions (19).

In the absence of pre-existing humoral immunity RV infection will cause an induction in innate immune response with the appearance of type 1 interferon (20). Consistent with the bronchoalveolar lavage (BAL) results, epithelial eosinophils and neutrophil counts are increased in subjects with asthma when compared with normal subjects during acute RV infection (21). During RV infections neutrophils play an important role in neutrophilic asthma where there is destruction of the lung tissue through release of proteases and other mediators (22). Temperature sensitivity is one of the potential barriers to infection of lungs by common cold viruses. Rhinovirus replicates at 33°, which is a lower temperature than that of bronchial epithelium (23). Other inflammatory mediators, are also found in increased amount in the nasal secretions of the infected individuals (24). By an unknown mechanism, viral infection increases vascular permeability in the nasal submucosa and contribute to the symptoms of the common cold. It has been shown in studies that viral replication occurs in only a small number of cells of the nasal mucosa (25,26). In vitro studies have demonstrated that the nasal epithelium remains intact during the course of rhinovirus and coronavirus infections (27). Serotype-specific immune defence occurs against rhinovirus and adenovirus. The reason for recurrent infections by these viruses is that these viruses have many different serotypes. Similarly influenza virus can change surface antigen structure and may cause recurrent infections as if it has many serotypes.

Clinical Features

The presentation of the common cold in children are distinctly different from the illness seen in adults. First complaints are generally sore throat and itching. Immediately after, blocked or runny nose are generally observed complaints. Upper respiratory symptoms usually resolve in few days while nasal symptoms last longer. Cough accompanies in one third of the patients and is usually seen after nasal symptoms. During the course of RSV and adenovirus colds, more fever or similar constitutional symptoms are experienced than rhinovirus or coronavirus colds. Nasal congestion is the most prominent symptom and fever is usually absent.

Children younger than the age of six years average six colds per year. Symptom duration may last as long as 14 days (28). Young children in the daycare appear to be more susceptible to these infections than those cared for at home, but also less vulnerable when they enter primary school. Colored nasal discharge is characteristic, and it does not indicate bacterial superinfection or sinusitis. In infants younger than one year, fever up to 38 C, feeding difficulty, irritability, vomiting and diarrhea is frequent. Physical signs are non-specific, but may include erythema and swelling

of the nasal mucosa, as well as moderate anterior servical lymphadenopathy. Abnormalities of the paranasal sinuses are common during the course of an uncomplicated cold. In a study including young adults, 87% of common cold cases had paranasal sinus pathology (29). These cases were followed up without antibiotherapy and 77% of them was completely fine. In another study, 47% of cases who had CT or MRI evaluation for a reason other than sinus disease, had sinus pathology; and these patients had complaints of upper respiratory tract infection in last two weeks (30). In the course of the disease middle ear involvement may also occur. In a study involving children aged 2 to 12 years, two-thirds had abnormal middle ear pressure by tympanometry at some point during the two weeks after the onset of cold (31). Mucociliary transport defect continues as long as a month in children with common cold, while children with 6 to 8 common cold episodes a year, experience mucociliary transport defect all through winter.

Complications

Otitis Media

Is the most frequent complication of common cold in children (32). Fluid in the middle ear or inflammation of tympanic membrane is the typical feature (33). Age has been found the most important risk factor among children in a study (34). Bacterial or suppurative otitis media, defined as a bulging tympanic membrane with purulent material behind it or purulent otorrhea from perforation of the tympanic membrane (35). Otitis media occurs in 5 to 15 percent of colds in young children (36).

Asthma

Viral URIs are the most important reason for asthma attacks in children. There is no evidence that cold medications protect from asthma attacks.

Sinusitis

Persistent nasal symptoms greater than 10 to 14 days may signify a secondary bacterial infection of the paranasal sinuses. Bacterial sinusitis during the course of common cold is generally selflimited and is estimated to complicate approximately 6 to 13 percent of viral URIs in children.

Lower Respiratory Tract Disease

New-onset fever with the first few days of cold symptoms often may be pointing out to bacterial lower respiratory tract infection. Prolonged cough in the absence of a new fever may signify viral lower respiratory tract infection. Complications of the comon cold in children may include epistaxis, conjunctivitis, and pharyngitis.

Diagnosis

The most important aim of the physician should be to make the differential diagnosis of similar clinical entities that would be close to common cold appropriately. The infectious and noninfectious ethiologies in the differential diagnosis of the common cold are, allergic rhinitis, foreign

object, sinusitis, streptococcal nasopharyngitis, pertusis and congenital syphilis. Most of the diseases for example pertusis, epiglottitis, measles and diphtheria have very similar begining symptoms that is similar to common cold. But immediately after, characteristic features of the disease settles. Common cold has no spesific diagnostic laboratory test. Nasal eosinophilia may be used to exclude alergic rhinitis while polymorphonuclear (PMN) predominance indicate noncomplicated common cold rather than bacterial infection. The identification of the pathogens responsible for common cold can be made by culture tests, antigen tests and serology. The patients eligibility for antiviral therapy should first be evaluated by these tests. Bacterial cultures should be performed when group A Streptococcus, Bordetella pertusis or nasal diphtheria are suspected. Other pathogens identified from nasal mucosa does not indicate that they are the responsible microorganisms (37).

Treatment

Supportive therapy is the only recommended treatment of the common cold since the main reason for common cold are viruses (37).

Antiviral Treatment

There is no spesific antiviral treatment for rhinovirus infections. Ribavirin can be used in RSV infections but it is not recommended in treatment of the common cold. Oseltamivir and Zanamivir which are neuroaminidase inhibitors are known to have mild effect on influenza virus infection. Oseltamivir can prevent otitis media during the course of influenza virus infection. Drug is most effective when used in first 48 hours of the disease so the diffrential diagnosis must be made very carefully. Supportive treatment is the main treatment method in common cold. Antihistamines, decongestants, antitussives, and expectorants, singly and in combinations, are all marketed for symptomatic relief in children. However, there have been few clinical trials of these products in infants and children and none that demonstrate benefit for treatment of the symptoms of the common cold (38). In addition, for children younger than two years of age, prescription and over-the-counter cough and cold medications have been associated with fatal overdose. Common cold and cough medications are among the first twenty chemicals that cause death below age 5 (39). These infants were prescribed medications containing pseudoephedrine (decongestant), carbinoxamine (antihistaminic), dextromethorphan (antitussive.) By the removal of non FDA approved common cold drugs from the markets, the emergency admissions due to side effects among children below age 2, was decreased as much as fifty percent (40). In 2008, the FDA issued a public health advisory recommending that over-the-counter cough and cold medicines not be used to treat children younger than two years (41). The FDA in continuing to review the information regarding the safety of these products for children two through 11 years of age (41). In october 2008, makers of over-the-counter cough and cold medicines voluntarily added a warning against their use in children younger than four years (42). Because these products lack

proven efficacy, have the potential for enhanced toxicity since metabolism, clearance, and drug effects vary by age, and dosing recommendations have not been established, it is not recommended in infants and children under 6 years.

Symptomatic Therapy

Symptomatic therapy may include antipyretics, saline nasal irrigation, adequate hydration, and use of a humidifier. In children with reactive airway disease or asthma beta-agonist medications should be used to relieve associated bronchospasm.

Antipyretics: Acetaminophen or ibuprofen may be used to alleviate fever during the first few days.

Saline Irrigation: In infants, bulb suction with saline nose drops may help to temporarily remove nasal secretions. In the older child, a saline nose spray may be used. It is found that the use of saline nasal irrigation was associated with fewer physician visits and less reliance on other medications (43). In a study involving children between ages 6 and 10 the use of saline irrigation was associated with a modest improvement of symptoms, decreased use of other therapies, decreased recurrence of symptoms, and decreased school absence (44).

Antihistamines: The anticholinergic effects of the first generation antihistamines may help reduce the secretions associated with the common cold. However, in controlled trials, antihistamines have been ineffective in relieving the symptoms of children with URI, when administered in combination with decongestants or as monotherapy (45-47). Two randomized controlled trials evaluated the effects of antihistamine-decongestants in young children with ages between six months and five years (45,46). The first trial compared three antihistamine-decongestants to placebo and no treatment and found no differences in symptom score changes or parental perception of improvement (45). A second trial compared an antihistamine-decongestant to placebo and found no improvement in symptoms (rhinorrhea, nasal congestion, cough) (46). In another meta-analysis concerning 72 studies there was little support for the effectiveness of these medications for acute cough or common cold in children (47). All of the children were fully improved on the second day. Neither study drug was superior to placebo. Drowsiness was reported in 3 of 33 children in the diphenhydramine group and none of the children in the other groups. In addition to sedation, side effects of antihistamines may include paradoxical excitability, respiratory depression, and hallucinations.

Antitussives: Cough is a common complaint during the course of the common cold, and parents frequently seek out a cough suppressant. For many children, especially those with reactive airway disease triggered by viral URI's, effective cough suppression could result in mucus plugging and worsening of respiratory symptoms. No cough suppressants have proven effective in children. Combination cold medications, including antihistamine/decongestant/analgesic, antihistamine/decongestant, antihistamine/analgesic and analgesic/decongestant formulations provide modest symptom relief in older children but not effective in

young children (48). Effectiveness of both dextrometorphan and codein has not been demonstrated in children with common cold (49). Because of potential serious toxicities and the lack of proven efficacy, these medications are not recommended for pediatric use.

Decongestants: Decongestants are sympathomimetic medications that cause vasoconstriction of the nasal mucosa. They are available in oral and topical formulations. Commonly used decongestants include pseudoephedrine hydrochloride, and phenylephrine hydrochloride, and oxymetazoline. In adults, such medications have been shown to decrease nasal congestion and increase patency, but there are no studies demonstrating the effectiveness of these medications in children. Side effects of decongestants may include tachycardia, elevated diastolic blood pressure, palpitations (50).

Zinc: Zinc not only modulates cell-mediated immunity, but is also an antioxidant, anti-inflammatory agent decreasing incidence of infections and oxidative stress (51). In a study involving 200 children, zinc sulphate has been found to be effective for the prevention and treatment of common cold in children (52). In another study, when initiated in first 24 hours, zinc had been found to be associated with shorter duration of common cold in healthy individuals with common cold (53).

Echinacea: In a 2006 Cochrane collaboration, reviewers suggested that when 16 studies were evaluated, due to methodological limitations there were no sufficient data to suggest the effectiveness of echinacea in children with common cold (54).

Vitamin C: A recent review shows that vitamin c used in children and adults show no benefit (55).

Honey: It has been suggested that a single dose of honey at bedtime may be effective in reducing nocturnal cough in children with URI. In paired comparisons honey was significantly superior to no treatment or honey-flavoured-dextrometorphan for cough frequency and severity as reported by parents (56).

Antibiotic Therapy: There is no role for antibiotics in the treatment of common cold (57). Antibiotic therapy does not prevent secondary bacterial infection and may cause significant side effects, as well as contribute to increasing bacterial antimicrobial resistance (58). The use of antibiotics should be reserved for clearly diagnosed secondary bacterial infections, including bacterial otitis media, sinusitis and pneumonia.

Prevention: Frequent handwashing is the mainstep in prevention. Infected individuals are recommended to prevent themselves from touching nose and eye contact.

References

1. Herbert AP. The common cold. In: Look Back and Laugh. London, Methuen, 1960; pp 115-117 cited in Heikkinen T, Jarvinen A. The common cold. Lancet 2003; 361: 51-60.
2. Hsiao CJ, Cherry DK, Beatty PC, Rechsteiner EA. National Ambulatory Medical Care Survey: 2007 summary. Nat Health Stat Report 2010; 27: 1-32.
3. Heikkinen T, Jarvinen A. The common cold. Lancet 2003; 361: 51-60.

4. Lee GM, Friedman JF, Ross-Degnan D, Hibberd PL, Goldmann DA. Misconceptions about colds and predictors of health service utilisation. *Pediatrics* 2003; 111: 231-7.
5. Steinman MA, Gonzales R, Linder JA, Landefeld CS. Changing use of antibiotics in community-based outpatient practice. 1991-1999. *Ann Intern Med* 2001; 138: 525-58.
6. FDA prompts removal of unapproved drugs from market. Silver Springs, Md, U.S. Food and Drug Administration 2011.
7. Handley JO. Epidemiology, pathogenesis and treatment of the common cold. *Semin Pediatr Infect Dis* 1998; 9: 50-5.
8. Boivin G, Abed Y, Pelletier G, Ruel L, Moisan D, Cote S, Peret TC, Erdman DD, Anderson LJ. Virological features and clinical manifestations associated with human metapneumovirus: a new paramyxovirus responsible for acute respiratory-tract infections in all age groups. *J Infect Dis* 2002; 186: 1330-4.
9. Esper F, Boucher D, Weibel C, Martinello RA, Kahn JS. Human metapneumovirus infection in the United States: clinical manifestations associated with a newly emerging respiratory infection in children. *Pediatrics* 2003; 111: 1410-7.
10. Monto AS. The seasonality of rhinovirus infections and its implications for clinical recognition. *Clin Ther* 2001; 24: 1987-97.
11. Sze-To GN, Yang Y, Kwan JK, Yu SC, Chao CY. Effects of surface material, ventilation and human behaviour on indirect contact transmission risk of respiratory infection. *Risk Anal* 2014; 34: 818-30.
12. Jacobs JA, Van Ranst MJ. Biometric fingerprinting for visa application: device and procedure are riskfactors for infection transmission. *Travel Med* 2008; 15: 335-43.
13. Sattar SA, Jacobsen H, Springthorpe VS, Cusack TM, Rubino JR. Chemical disinfection to interrupt transfer of rhinovirus type 14 from environmental surfaces to hands. *Appl Environ Microbiol* 1993; 59: 1579-85.
14. Kennedy JL, Turner RB, Bracilae T, Heyman PW, Borish L. Pathogenesis of Rhinovirus infection. *Curr Opin Virol* 2012; 2: 287-93.
15. Bella J, Rossman MG. ICAM-1 receptors and cold viruses. *Pharm Acta Helv* 2000; 74: 291-7.
16. Vlasak M, Roivainen M, Reithmayer M. The minor receptor group of human rhinovirus (HRV) includes HRV23 and HRV 25, but the presence of a lysine in the VP1 HI loop is not sufficient for receptor binding. *J Virol* 2005; 79: 7389-95.
17. Bizzintino J, Lee WM, Laing IA. Association between human rhinovirus C and severity of acute asthma in children. *Eur Respir J* 2011; 37: 1037-42.
18. Ishizuka S, Yamaya M, Suzuki T. Effects of rhinovirus infection on the adherence of *Streptococcus pneumoniae* to cultured human airway epithelial cells. *J Infect Dis* 2003; 188: 1928-39.
19. Yeo NK, Jang YJ. Rhinovirus infection-induced alteration of tight junction and adherens junction components in human nasal epithelial cells. *Laryngoscope*. 2010; 120: 346-52.
20. Ngamtruakulpanit LVJ, Nguyen A, Urban P, et al. Exhaled breath condensate acidification during Rhinovirus colds. American Throat Society 99th International Conference, Seattle. 2003.
21. Zhu J, Message SD, Qiu Y, Mallia P, Kebabdz T, Contoli M, Ward CK, Barnathan ES, Mascelli MA, Kon OM, Papi A, Stanciu LA, Jeffery PK, Johnston SL. Airway inflammation and illness severity in response to experimental rhinovirus infection in asthma. *Chest* 2014; 145: 1219-29.
22. Smith JA. Neutrophils, host defence and inflammation: a double-edged sword. *J Leukoc Biol* 1994; 56: 672-86.
23. Turner RB, Weingand KW, Yeh CH, Leedy DW. Association between interleukin-8 concentration in nasal symptoms of experimental rhinovirus colds. *Clin Infect Dis* 1998; 26: 840-6.
24. Rajan D, Gaston KA, McCracken CE, Erdman DD, Anderson LJ. Response to human rhinovirus infection by human airway epithelial cells and peripheral blood mononuclear cells in an in vitro two-chamber tissue culture system. *PLoS One* 2013; 8: e66600.
25. Bardin PG, Johnston SL, Sanderson G, Robinson BS, Pickett MA, Fraenkel DJ, Holgate ST. Detection of rhinovirus infection of nasal mucosa by oligonucleotide in situ hybridization. *Am J Respir Cell Mol Biol* 1994; 10: 207-13.
26. Arruda E, Boyle TR, Winther B, Pevear DC, Gwaltney JM Jr, Hayden FG. Localization of human rhinovirus replication in the upper respiratory tract by in situ hybridization. *Am J Respir Dis* 1995; 171: 1329-33.
27. Winther B, Farr B, Turner RB, Hendley JO, Gwaltney JM Jr, Mygind N. Histopathologic examination and enumeration of polymorphonuclear leucocytes in the nasal mucosa during experimental rhinovirus colds. *Acta Otolaryngol Suppl* 1984; 413: 19-24.
28. Pappas DE, Hendley JO, Hayden FG, Winther B. Symptom profile of common colds in school aged children. *Pediatr Infect Dis J* 2008; 27: 8-11.
29. Gwaltney JM Jr, Philips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. *N Eng J Med* 1994; 330 :25-30.
30. Manning SC, Biavati MJ, Philips DL. Correlation of clinical sinusitis signs and symptoms of imaging findings in pediatric patients. *Int J Pediatr Otorhinolaryngol* 1996; 37: 65-74.
31. Winther B, Hayden FG, Arruda E, Dutkowski R, Ward P, Hendley JO. Viral respiratory infection in schoolchildren: effects on middle ear pressure. *Pediatrics* 2002; 109: 826-32.
32. Elkhatieb A, Hipskind G, Woerner D, Hayden FG. Middle ear abnormalities during natural rhinovirus colds in adults. *J Infect Dis* 1993; 168: 618-21.
33. Winther B, Alper CM, Mandel EM, Doyle WJ, Hendley JO. Temporal relationship between colds, upper respiratory viruses detected by polymerase chain reaction, and otitis media in young children followed through a typical season. *Pediatrics* 2007; 119: 1069-75.
34. Revai K, Dobbs LA, Nair S, Patel JA, Grady JJ, Chonmaitree T. Incidence of acute otitis media and sinusitis complicating upper respiratory tract infection: the effect of age. *Pediatrics* 2007; 119: 1408-12.
35. Hendley JO. Clinical practice. Otitis media. *N Eng J Med* 2002; 347: 1169-74.
36. Chonmaitree T, Revai K, Grady JJ, Audra C, Patel J. Viral Upper Respiratory Tract Infection and otitis media complication in young children. *Clin Infect Dis* 2008; 46: 815-23.
37. Arroll B, Kenealy T. Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database Syst Rev* 2005; (3): cd001107.
38. Smith MB, Feldman W. Over-the-counter cold medications. A critical review of clinical trials between 1950 and 1991. *JAMA* 1993; 269: 2258-63.
39. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Giffin SL. 2009 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila)* 2010; 48: 979-1178.
40. Shebab N, Schaefer MK, Kegler SR, Budnitz DS. Adverse events from cough and cold medications after a market withdrawal of products labeled for infants. *Pediatrics* 2010; 126: 1100-7.
41. U.S. Food and Drug Administration. Public Health Advisory. Non prescription cough and cold medicine use in children. FDA recommends that over-the-counter (OTC) cough and cold products not be used for infants and under 2 years of age. Available at: <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafety>.

42. Centers for disease control and Prevention (CDC). Revised product labels for pediatric over-the-counter cough and cold medicines. *MMWR Morb Mortal Wkly Rep* 2008; 57: 1180.
43. Papsin B, Mc Tavish A. Saline nasal irrigation: Its role as an adjunct treatment. *Can Fam Physician* 2003; 49: 168-73.
44. Slapak I, Skoupa J, Strnad P, Hornik P. Efficiency of isotonic nasal wash (seawater) in the treatment and prevention of rhinitis in children. *Arch Otolaryngol Head Neck Surg* 2008; 134: 67-74.
45. Hutton N, Wilson MH, Mellits ED, Baumgardner R, Wisow LS, Bonuccelli C, Holtzman NA, DeAngelis C. Effectiveness of an antihistamine-decongestant combination for young children with the common cold: a randomised, controlled clinical trial. *J Pediatr* 1991; 118: 125-30.
46. Clemens CJ, Taylor JA, Almquist JR, Quinn HC, Mehta A, Naylor GS. Is an antihistamine-decongestant combination effective in temporarily relieving symptoms of the common cold in preschool children? *J Pediatr* 1997; 130: 463-6.
47. Isbister GK, Prior F, Kilham HA. Restricting cough and cold medicines in children. *J Paediatr Child Health* 2012; 48: 91-8.
48. Salisbury-Afshar E. Oral antihistamine/decongestant/analgesic combinations for the common cold. *Am Fam Physician* 2011; 86: 812-3.
49. Simasek M, Blandino DA. Treatment of the common cold. *Am Fam Physician* 2007; 75: 515-20.
50. Morales-Carpi C, Torres-Chazarra C, Lurbe E, Torro I, Morales-Olivas FJ. Cold medication containing oral phenylephrine as a cause of hypertension in children. *Eur J Pediatr* 2008; 167: 947-8.
51. Prasad AS. Impact of the discovery of human zinc deficiency on health. *J Trace Elem Med Biol* 2014; 28: 357-63.
52. Kurugöl Z, Akilli M, Bayram N, Koturoglu G. The prophylactic and therapeutic effectiveness of zinc sulphate on common cold in children. *Acta Paediatr* 2006; 95 :1175-81.
53. Das RR, Singh M. Oral zinc for the common cold. *JAMA* 2014; 311: 1440-1.
54. Linde K, Barrett B, Wölkart K, Bauer R, Melchart D. Echinacea for preventing and treating the common cold. *Cochrane Database Syst Rev* 2006; (1): CD000530.
55. Douglas RM, Hemila H, Chalker E, Treacy B. Vitamin C for preventing and treating common cold. *Cochrane Database Syst Rev* 2007; CD000980.
56. Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A comparison of the effect of honey, dextrometorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. *Arch Pediatr Adolesc Med* 2007; 161: 1140-6.
57. Shields MD, Bush A, Everard ML, McKenzie S, Primhak R; British Thoracic Society Cough Guideline Group. BTS guidelines: Recommendations for the assessment and management of cough in children. *Thorax* 2008; 63 Suppl 3: iii1.
58. Del Mar C, Glasziou P. Upper respiratory tract infection. *Clin Evid* 2003; 7: 1391-400.