

VIRUS-INDUCED WHEEZE IN YOUNG CHILDREN

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Virus-induced wheeze (VIW) can be defined as wheezing that occurs only in association with viral infections. Wheeze is defined as a continuous high-pitched sound with musical quality emitted from the chest during expiration. It generally occurs in children between 6 months and 5 years of age. The prevalence declines over time, and usually disappears by age 6 years old. It has few or no interval respiratory symptoms and is also known as episodic wheeze. Ten-to-twenty percent of all children experience at least two wheezing episodes during the first year of life, and about 2% of all infants suffer from wheezing severe enough to warrant hospitalization. As preschool children have 6-10 episodes of upper respiratory infections annually, recurrent viral-induced wheezing is associated with considerable distress and use of healthcare services.

Despite its prevalence, the optimal preventive management for virus-induced wheezing remains elusive. Many recent studies have examined therapeutic strategies to reduce the frequency and/or severity of virus-induced wheezing in young children, but these remain controversial. A study during 1998-1999 at Patheingyi General Hospital of acute respiratory infection found that prevalence of wheezing in these cases was 14.97% (Saw Win, personal data).

The problem with these studies was that at the time there was no consensus on what constituted virus-induced wheez-

ing; therefore no definite numbers could be stated for its prevalence in Myanmar. It is suspected that true values exceed the values found in these studies, as many virus-induced wheezing cases may have been diagnosed as bronchitis with wheezing or asthma.

Many clinical trials demonstrate various degrees of benefit associated with daily use of inhaled or oral corticosteroids or leukotriene receptor antagonists. Similar benefits are also demonstrated with episodic therapy with high-dose inhaled corticosteroids or leukotriene receptor antagonists in terms of episode prevention and attenuation. Panickar *et al* (2009) mentioned that oral corticosteroids did not change the outcome of VIW, while Csonka *et al* (2003) showed that a short course of oral corticosteroids effectively reduced disease severity, length of hospital stay, and duration of symptoms amongst children with VIW. In clinical practice in Myanmar, there is a good response when such practices are used in cases of severe VIW.

Viruses can be detected in the airways of the majority of wheezing infants, with respiratory syncytial virus (RSV) and rhinovirus being the most dominant agents. These viruses interact with host factors to promote virus-induced wheezing and asthma exacerbations. Respiratory symptoms with viral infections are believed to result from virus-induced damage of the airway epithelium, followed by airway inflamma-

tion, in which case anti-inflammatories are often helpful.

Parasympathetic hyperresponsiveness is another contributing factor towards the pathogenesis of virus-induced wheeze. Immune responses triggered by viral respiratory tract infections include enhanced allergic inflammation, increased granulocyte recruitment, promotion of cytokine production, and upregulation of the parasympathetic response.

Pathogenesis

Following exposure to viruses, there is airflow limitation and reduced antiviral activity, and poor regulation of inflammation, which leads to a wheezy lower respiratory tract infection. Airway remodeling then ensues, with reduced alveolarization and epithelial programming, leading to recurrent wheeze and asthma.

There is also a relationship between childhood asthma and infection. In animal studies in guinea pigs and rats, viral respiratory infections impair inhibitory M2 muscarinic receptor function, producing parasympathetic hyperresponsiveness, which leads to bronchoconstriction. This effect may persist for weeks after resolution of the acute infection.

Wheezing due to a viral infection in children under 2 years of age

A first episode of wheezing in association with a viral respiratory infection leads to an outpatient visit for about 15% of all infants in the United States, and 3% are hospitalized with this presentation (Shay *et al*, 1999). RSV is the commonest cause, with metapneumovirus, coronavirus, bocavirus and influenza viruses also being causes. Factors that increase the risk of a child wheezing are exposure to cigarette

smoke, maternal smoking during pregnancy, a history of bronchopneumonia, daycare attendance, and early exposure to pets (Chong *et al*, 2010).

Treatment of virus-induced wheezing in young children

There is a good consensus for suggestions for management of recurrent wheezing and asthma for children over 5 years old. However, for children below this age group this is less clear. Episodic therapy includes inhaled short-acting Beta2-agonist bronchodilators, intermittent use of inhaled glucocorticoids, systemic glucocorticoids, intermittent leukotriene receptor antagonists, as well as antiviral agents for rhinoviruses and immunostimulants. Inhaled short-acting Beta2-agonist bronchodilators are considered first-line therapy for treatment of VIW and are an effective rescue treatment for symptomatic treatment, particularly in children with established asthma. However, short acting inhaled bronchodilators have not been shown to improve clinical outcome, decrease the rate of hospital admissions, or decrease the duration of hospitalization in children with bronchiolitis (Gadomski and Bhasale, 2006).

Use of inhaled and systemic glucocorticoids intermittently has been shown to prevent virus-induced wheezing in young children. This has been examined in several randomized control trials, and a systematic review (Svedmyr *et al*, 1999; McKean and Ducharme, 2000, Bacharier *et al*, 2008; Ducharme *et al*, 2009; Papi *et al*, 2009). However, there is still some controversy over this, and some suggest that such use has effects on growth suppression and have advised against it. Most

studies mentioned suggested that intermittent high-dose inhaled glucocorticoids should be started at the onset of an upper respiratory tract infection and continued for approximately one week. This may reduce asthma-type symptoms and rescue oral glucocorticoid use in preschool children with viral associated wheezing. Slight deficits in growth are shown in some children, although data on this is limited.

Ducharme *et al* (2009) found that inhaled glucocorticoid use was not effective in the prevention of VIW; however, others (Bisgaard *et al*, 2006; Bacharier *et al*, 2008; Papi *et al*, 2009) have found good outcomes with its use. Most studies reviewed (Csonka *et al*, 2003; Oommen *et al*, 2003; Vuillermin *et al*, 2006; Jartti *et al*, 2007; Panickar *et al*, 2009), found that use of systemic glucocorticoids were not effective in the treatment of VIW, whilst a good outcome with its use was only found by one study (Brunette *et al*, 1988). Leukotriene receptor antagonists have been found to reduce the severity of acute illness and reduce recurrence (Bacharier *et al*, 2008).

With the question of an antiviral agent for rhinoviruses, as many serological types of these viruses exist, the production of a single vaccine is impractical. What is currently known is that capsid-binding agents and soluble ICAM-1 (intercellular adhesion molecule 1) can prevent viral binding.

In daily therapy, daily inhaled glucocorticoids and daily leukotriene receptor antagonists are used. Daily use of inhaled glucocorticoids has been found to be effective in the prevention of episodic virus-induced wheezing in younger children. Castro-Rodriguez and Rodrigo (2009) found that children had significantly fewer

wheezing and asthma exacerbations as a result of use. Although there are concerns of its effects on linear growth, the majority of studies show minimal to no effect (Bisgaard *et al*, 2006).

There has been one study that has suggested that children younger than 3 years of age are at greater risk for growth effects, but further studies are needed to substantiate this. A study by Robertson *et al* (2007) found that daily use of leukotriene receptor antagonists such as montelukast might be helpful in preventing virus-induced asthma exacerbations. Over 12 months of treatment, montelukast was found to decrease the average rate of exacerbations. The need for systemic corticosteroids was not significantly different between treatment and placebo groups.

The optimal management of acute episodes of VIW in infants and preschool children has yet to be determined, in part because of the heterogeneity of wheezing phenotypes. The specific therapy for each patient needs to be individualized. In the near future, it is hoped that studies will discover more effective treatment options for the management of VIW, with clearer answers for the current international debate over the benefits of use of corticosteroids in VIW.

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