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Respiratory syncytial virus infection in children with congenital heart disease: global data and interim results of Korean RSV-CHD survey

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Respiratory syncytial virus (RSV) is a main cause of hospitalization for bronchiolitis and pneumonia in infants worldwide. Children with hemodynamically significant congenital heart disease (HS-CHD), as well as premature infants are at high risk for severe RSV diseases. Mortality rates for CHD patients hospitalized with RSV have been reported as about 24 times higher compared with those without RSV infection. Recently with advances in intensive care, mortality rates in CHD patients combined with RSV have decreased below 2%. The requirements of intensive care and mechanical ventilation for CHD patients with RSV infection were still higher than those without RSV infection or with non-CHD children. RSV infection has frequently threatened CHD infants with congestive heart failure, cyanosis, or with pulmonary hypertension. As a progressive RSV pneumonitis in those infants develops, the impairment of oxygen uptake, the breathing workload gradually increases and eventually causes to significant pulmonary hypertension, even after the operation. Preventing RSV infection as much as possible is very important, especially in infants with HS-CHD. A humanized monoclonal antibody, palivizumab, has effective in preventing severe RSV disease in high-risk infants, and progressive advances in supportive care including pulmonary vasodilator have dramatically decreased the mortality (<1%). Depending on the global trend, Korean Health Insurance guidelines have approved the use of palivizumab in children <1 year of age with HS-CHD since 2009. Korean data are collected for RSV prophylaxis in infants with CHD.

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Introduction

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection in infants and toddlers worldwide, including Korea. According to the biweekly reports of Korea Centers for Disease Control and Prevention, the seasonal outbreaks of RSV infection occur during the winter months, September through March, even in Korea. Almost all children have RSV infection until the age of 2 years, and nearly half of those will be infected two episodes on the average[1-3]. About half the children may develop bronchiolitis and pneumonia which might require hospitalization. Often for some cases, an intensive care with mechanical ventilation is necessary. RSV infection in particular pediatric groups produces significant morbidity and mortality: especially in premature infants with <35 weeks gestational age and in patients with chronic lung disease, such as bronchopulmonary dysplasia (BPD) or hemodynamically significant congenital heart disease (HS-CHD)[4,5].

CHD patients with RSV infection were more likely to be hospitalized, and had greater morbidity and mortality associated with bronchiolitis than non-CHD infants, particularly associated with undertaking corrective surgery in CHD patients with a history of recent RSV bronchiolitis. In Korea, there were a few of initial reports for intervening in serious and fatal cases with CHD superimposed by RSV infection, and those still remains as painful memories for some pediatric cardiologists[4-6]. For the past 10 years, with advances in operative skills as well as transcatheter intervention and intensive care, RSV prophylaxis with palivizumab were introduced for these high-risk infants[7,8]. This review is to describe about the impact of RSV infection on infants with CHD and the recent trends according to global and Korean standardization.

Impact of Respiratory Syncytial virus on infants with hemodynamically significant congenital heart diseases

Lung compliance and airway resistance contributes to how much effort a patient needs for breathing. The airways of infants have greater resistance compared with the older children due to their smaller diameter. Increased peripheral resistance affects the distribution of air ventilation, and makes infants more vulnerable to hypoxemia. Spontaneous ventilation is characterized by a functional residual capacity, that is relatively small in infants and then the infant is prone to potential ventilation-perfusion mismatch and is at higher risk for respiratory compromise[5,9-12].

Depending upon the types of cardiac defect which is present, the lung of the infant may be over-circulated, as in the setting of ventricular septal defect, or under-circulated as with tetralogy of Fallot with pulmonary stenosis[9,10].

Pulmonary over-circulation associated with left-to-right shunting may result in mucosal edema, and luminal narrowing, as well as vascular or cardiac compression of the large bronchuses. During the typically delayed transition of the circulation in infant with CHD, usually occurring within the first few months, decreased pulmonary arteriolar resistance leads to increasing left-to-right shunt (LR shunt). There is a decrease in lung compliance and an increase in respiratory rate. Infants also may have significantly increased pulmonary blood flow, capillary wedge pressure and left atrial pressure. The result may be pulmonary edema, which leads to further decreases in functional residual capacity, potentiating ventilation-perfusion mismatch and become susceptible to hypoxia. In addition increased alveolar edema will lead to decreased lung volume and decreased compliance of the lung bed[9,12].

In the under-circulated lung, as seen with right-to-left shunting, those patients with cyanotic congenital heart disease typically include tetralogy of Fallot. The basic physiology is obstruction to pulmonary outflow due to stenosis. These patients are prone to increased hypoxemia because the degree of pulmonary stenosis increases over time, and there may be reduced lung volume and airway hypoplasia. Where there is increased ventilation compared with perfusion, dead space ventilation may lead to further hypoxemia. With decreased alveolar saturation, compliance of the lungs may be increased. However, small airway obstruction may also be present, leading to increase airway resistance. At baseline, these cyanotic patients are at risk for increasing hypoxemia, and RSV infection can precipitate significant cyanosis[5,9].

Many infants with complex CHD have both manifestations of cyanosis and relatively increased pulmonary blood flow. Examples of such patients include those with most forms of single ventricle including hypoplastic left heart syndrome and hypoplastic right heart of tricuspid atresia, or pulmonary atresia. The majority of infants with complex univentricular heart will have undergone palliative surgery early period with risk of increasing ventilation-perfusion mismatch, which is potentiated by RSV infection. Compromised ventricular function may contribute to higher pulmonary venous pressures, which may lead to capillary leak and pulmonary edema. In addition, those patients with oxygen saturations 85% have a relatively large amount of pulmonary blood flow, which can contribute to risk for respiratory complications in this setting. The result of this mixed physiology may be the reason for the poor tolerance in a superimposed respiratory infection, such as with RSV[5,9,10,12].

Global Trends of Respiratory Syncytial virus infection with congenital heart diseases

The development of the recent innovative interventions is expected to change RSV infection treatment in infants with CHD. Earlier studies in RSV infection on CHD patients revealed that lower respiratory infection by RSV was potentially lethal leading to increased mortality and morbidity in HS-CHD infants[1-6,12].

On the effects of RSV infection during late 1970's in infants with CHD reported in 1982, the severity of RSV bronchiolitis in children with CHD for a hospital based cohort study of all infants (n=699) was significantly greater than those without CHD, categorized by those who require intensive care (63% vs. 14%, $P<0.001$) and assisted ventilation (22% vs. 5%, $P<0.01$). These fatality rate was higher in the CHD group (37% vs. 1.5%, $P<0.01$). In infants with RSV and pulmonary hypertension, the mortality rate was extraordinarily high (73%)[4]. In these subgroup, nosocomial infection was associated with mortality rate, compared with children without CHD (44% vs. 5%)[4].

A review in Canada between 1988 and 1991 was evaluated for 260 children with CHD, hospitalized with RSV disease at 12 pediatric tertiary care centers, and 87 (33%) required intensive care and 49 (19%) required mechanical ventilation[13]. Other reports released in 1992 and 1995 revealed that pulmonary hypertension in particular was the single most important factor in causing severe RSV infection in infants with CHD[14].

The morbidity caused by RSV infection in children with CHD correlates with the severity of the underlying cardiac disease, represented by the degree of compromise of the baseline functional status in cardio-pulmonary system, pulmonary flow/ventilation mechanics, degree of cyanosis, level of pulmonary hypertension and extent of ventilation/perfusion mismatch[14,15].

In 1990 through 1995, a retrospective review for 25 infants with CHD showed that RSV bronchiolitis and pneumonia causes substantial morbidity and even mortality in the immediate period surrounding either palliative or corrective cardiac surgery[15]. Cardiac surgery performed during symptomatic RSV bronchiolitis and pneumonia is associated with a high risk of postoperative complications. In particular, postoperative pulmonary hypertension can cause immediate postoperative mortality. These complications in CHD patients appeared to occur more frequently and sometimes fatal in patients who had undertaken earlier surgery, while bronchiolitis due to RSV infection continues as compared with those who had later surgery. Therefore, to obtain complete and safe results after congenital heart surgery, procedures should not be performed in an infant who has not fully recovered from an acute RSV infection. In addition, RSV is also an important cause of postoperative nosocomial infection. It may be due to a transient immunologic dysfunction following cardiopulmonary bypass and a possibility for dilution of serum neutralizing antibodies. Preoperative screening for asymptomatic RSV infection has been suggested as a main key to reduce this morbidity. This was the basic idea in the development of RSV vaccination, to prevent severe RSV infection in high-risk infants [12,14,15].

For recent 10 years with advances in intensive care, mortality rates in CHD patients combined with RSV has decreased to below 2% of the population[11,12]. Nevertheless the requirements of intensive care for CHD patients with RSV infection in progress, were much higher as almost 2.5 times compared with those without current RSV infection, and as up to 1.7 times than those for non-CHD children with RSV infection. The need of mechanical ventilation for RSV infection in CHD patients was recognized as about 2.4 times higher than in non-CHD patients[1,4-6,12]. This infection is further threatening to particular conditions of CHD patients: infants with congestive heart failure, cyanosis, or pulmonary hypertension. Under these cardiac conditions there are severely restricted capacity of cardiac function to increase cardiac output and oxygen delivery. As RSV pneumonitis progresses in those infants with compromised cardiac performance, oxygen uptake was markedly impaired and the work of breathing was gradually increased[5,14,15].

Non-sustained immunity and difficulties to develop the effective vaccines made RSV management directed toward a passive immunotherapy for these high risk children[16-18]. Palivizumab is one of the first humanized murine monoclonal antibody targeting the RSV envelope F glycoprotein, and in a Phase III clinical trial palivizumab through randomized double-blind study of 1,287 patients from 1998, significantly reduced RSV hospitalization in children with HS-CHD safely[8]. Study results showed a 45% relative reduction in RSV hospitalization among children receiving palivizumab prophylaxis (9.7% vs. 5.3%, $P=0.003$). Other information was that serum palivizumab levels were reduced to 58% after cardiopulmonary bypass due to diluted effect. The American Academy of Pediatrics (AAP) revised its indications for palivizumab to include less than 24 month aged children with HS-CHD in 2003[19]. In addition, the AAP recommended redosing of CHD patients following cardiopulmonary bypass to reach adequate serum concentration of neutralizing antibody to protect the vulnerable postoperative infant. Many countries including Japan have followed their own guidelines that identify high-risk patients and define the appropriate timing of vaccination, usually 5 doses during winter[19-23]. Its guidelines for CHD patients in Japan were approved for children less than 24 month of age at the start of RSV season in October 2005

similar to those of AAP[22].

However, RSV hospitalization has not been eliminated in CHD patients receiving prophylaxis, as palivizumab tends to attenuate but not eradicate RSV disease[21-25]. Significant controversy remains regarding the cost effectiveness of palivizumab prophylaxis in high-risk patients, including those with CHD[25,26]. Eventually this may be considered as the limitation of passive immunization.

Even subsequent studies have a decreasing trend in mortality, both medical and surgical morbidity, e.g. RSV hospitalization requiring intensive care and oxygen supply and need for mechanical ventilation, caused by RSV remain significant high though it varies with the degree of cardiac compromise[21,22,24,25]. In infant with HS-CHD, major issues by result of RSV infection are considered as the compromised cardio-pulmonary function during perioperative period, caused by pulmonary hypertension, bi-ventricular functional failure, and deoxygenation. Recently as to the development of intensive care, including brand-new mechanical ventilation and selective pulmonary vasodilators, it looks impossible to make the treatment available even in serious RSV infected infants[5].

The chronic effects of RSV infection on lung are not only confined to acute morbidity, but there may also be long-term sequelae[5,9]. A long-term prospective study for 7.5 years, provide strong evidence that RSV bronchiolitis in infancy is associated with a higher risk of developing subsequent bronchial obstructive disease in the development of asthma and allergy at least in some children.

Korean experiences of Respiratory Syncytial virus infection with congenital heart diseases

Similarly in Korea, there were a few of initial reports for intervening in serious and fatal cases with CHD superimposed by RSV infection, and still remains as a painful memories for some pediatric cardiologists[27]. According to a Korean study reported in 2010, 76 children with 45 CHD and 31 non-CHD patients infected by RSV were evaluated, just before palivizumab era, from 2003 to 2006[27]. Of total 71 patients, 22 (48.9%) were treated in intensive care in 3 of non-CHD patients (9.7%), 12 (26.7%) were required mechanical ventilation but none in non-CHD patients, and 2 (4.4%) mortalities of CHD patients were noticed none in non-CHD patients.

Korean public health insurance guidelines recommend the use of palivizumab in children less than 1 year of age with HS- CHD since 2009. The categories of theses HS-CHD include pulmonary hypertension, cyanotic heart diseases, and CHD treated by medication for congestive heart failure.

Since palivizumab was introduced to premature infants of Korea in 2007, the total number of infants receiving palivizumab has more than doubled annually. A preliminary survey for pediatric cardiologists done after 2009 RSV season revealed that 40% thought that palivizumab was quite effective; another 40% thought that it may be effective in Korea. In addition, about 1.8 doses of palivizumab were used in limited pediatric centers. Current data has been collected on the effectiveness of RSV prophylaxis with palivizumab in infants with CHD in Korea.

Conclusion

Infants with CHD represent a group that is at a higher risk for morbidity from RSV infection. RSV infection is further threatening to particular conditions of CHD patients: infants with congestive heart failure, cyanosis, or pulmonary hypertension. Under these cardiac conditions, CHD patients are severely restricted in capacity of cardiac function to increase cardiac output and oxygen delivery. As RSV pneumonitis progresses in those infants with compromised cardiac performance, oxygen uptake is markedly impaired and the work of breathing is gradually increased.

A few reports of RSV experiences in Korea were similar to those of global data. Eventhough fatal cases with CHD superimposed by RSV infection are still under concern, RSV prophylaxis using palivizumab and powerful advances in intensive care has been shown to reduce RSV mortality and morbidity in infants with HS CHD, particularly those with palliated complex disease, unrepaired serious CHD and those with significant residual defects after cardiac surgery.

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