WHEEZE ASSOCIATED RESPIRATORY SYNCYTIAL VIRUS INFECTION AND ITS PREVENTION

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ABSTRACT

Wheeze associated respiratory infection is an important cause of morbidity and mortality in both the developed and the developing worlds. The commonest causative agent is the Respiratory Syncytial Virus (RSV). Lower respiratory infection with this virus is assuming great proportions and hence much work is being done to find a cure or at least a suitable vaccine that will be available to everyone even in the poorer countries. This article reviews the latest literature and attempts to set out some guidelines to help in reduction of the problems associated with lower respiratory infection caused by RSV in developing countries.

Key Words : *Lower respiratory infection, Respiratory Syncytial Virus.*

INTRODUCTION

Viral respiratory infections are a global phenomenon affecting people from every walk of life, rich and poor alike. Children in the age group of 2 months - 6 years are most prone to this illness incapacitating them from attending school regularly. It is an added problem in the developing countries due to uncongenial environmental conditions like overcrowding, overpopulation, improper housing facilities and a lack of substantial medical care. The low per capita income in these underprivileged areas make the parents unable to afford costly hospitalization.

Virus infections other than smallpox and hepatitis have been extensively studied in the last two centuries. Acute Lower Respiratory Infections (ALRI) which occur in children are predominantly viral in nature barring a few of bacterial aetiology, namely *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Staphylococcus aureus*. Respiratory Syncytial Virus (RSV) is the most common viral cause of ALRI in both the developed and developing countries.

EPIDEMIOLOGY

RSV is a single strand RNA virus belonging to the family of 'Paramyxoviridae'. It is a pneumovirus

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with genome size (kb) 16-20, has a lipid bilayer envelope from which several surface proteins project and with a helical capsid symmetry. Among the surface proteins the most important is the transmembrane glycoprotein 'F' which facilitates viral entry into host cells. It stimulates cell to cell fusion ultimately forming a 'syncytium' in the cells. RSV destroys the epithelial cells of the respiratory tract by forming 'syncytia' and hence the name.

Epidemics are annual and occur in late fall, winter or in spring and last up to 5-6 months. Peak attacks in children are seen in infants in the age group of 2-4 months. In hospital admissions for respiratory illnesses, RSV accounts for 20-25% of cases of Pneumonia and 75% of cases of Bronchiolitis in the pediatric age group. In older children the infection is milder than in infancy. Transmission is by close contact with contaminated fingers or fomites and by self-inoculation of the anterior nares or conjunctiva. Droplet infection is another method of spread. Incubation period is about 4-6 days. Viral shedding may be present for 2-3 weeks in children and for a shorter period in adults. To diagnose RSV infection one should

- a) have a high index of suspicion by knowing the epidemiology of community infection
- b) isolation of the virus from respiratory secretions like sputum, throat swab and nasopharyngeal swab
- c) ELISA
- d) immunofluorescence technique of nasal scrapings
- e) complement fixation antibody technique

MORBIDITY AND MORTALITY

Around 3.7 million deaths occur from acute respiratory infections in under-fives annually: of which 3 million are due to ALRI.² Mortality rate in children admitted to hospital with RSV is low in developed countries; yet a considerable number

of children with low birth weight get repeated wheeze associated respiratory infections.³ On the other hand ALRI is one of the major causes of morbidity and death in the third world assuming huge proportions and is responsible for 20-25% of all infant deaths. RSV being the major pathogen, the link between acute infantile RSV infection and subsequent respiratory tract pathology in older children is ill understood. Increased RSV hospitalization and deaths have been attributed to certain risk factors like congenital heart disease, chronic lung disease and immuno-compromised state, especially in the developed world.^{4,5,6} 50-70% of infants are supposed to develop RSV infection in the first year of life and virtually all by the third year, either primary infection or re-infection. Unlike many other viral infections, RSV infection does not give rise to prolonged immunity and seasonal re-infection is very common.

REVIEW OF LITERATURE

Sims et al⁷ in a controlled study, published an article in 1978 illustrating a very disturbing fact that severe RSV lower respiratory infection (LRI) in the first two years of life were associated with subsequent recurrent wheezing in childhood. These workers have taken inspiration from an earlier article published in 1959 by Wittig and Glaser⁸ about relationship between acute bronchiolitis and childhood asthma. For the next twenty years or so no substantial study was done to add to this very intriguing revelation. Children by and large experience one or more attack of RSV infection by 2-3 years of age and report for treatment of wheeze in the pre-school period.

Martinez et al⁹ and Pullan and Hey,¹⁰ in their study established that frequent viral LRI in the age group 0-3 years is mainly due to diminished lung function (in relation to airway size and length) early in life and such babies have a tendency to wheeze

subsequently. This could be a transient wheeze for about 5-7 years. On the other hand a child who continues to have a persistent wheeze as asthma could have normal lung function.¹¹ The first group of children with transient wheeze has no history of atopy, asthma and has normal IgE: whereas the second group with persistent wheeze has a positive history of allergy, asthma and elevated IgE levels.

Development of the airway tract in the fetus is completed before birth and is influenced by prenatal factors such as young maternal age, low socio-economic strata and prematurity. Maternal smoking too has a deleterious effect on pulmonary functions in the infant.¹² Barker et al¹³ suggested a close relationship between low birth weight per se and development of bronchiolitis and pneumonia later and they could even develop chronic obstructive lung disease in adolescence and adulthood. Weber et al¹⁴ in their study in Gambia suggested that children with RSV LRI in early life had a higher incidence of transient wheeze associated symptoms for the next three years or so and the periodicity comes down with advancing age. However this study did not correlate birth weight, gestational age and maternal smoking as additional factors in the etiology of acute RSV LRI. Maternal smoking in pregnancy is the largest population-attributable factor for intra-uterine growth retardation in the developed countries. Other prenatal factors are more prevalent in the developing world.

Many queries were raised and theories postulated as to the etio-pathology of acute wheeze syndrome:

- 1) Is RSV LRI a predisposing factor or a marker causing atopic asthma.^{15,8}
- 2) Are children with a family history of atopy more prone to severe RSV LRI and subsequent wheezing¹¹ or not.¹⁶
- 3) Is RSV itself responsible for causing abnormal airway reactivity by damaging the airway¹⁷

- 4) Does RSV induce an atypical immune response with an imbalance of TH-1 and TH-2 cells and therefore induce asthma.¹⁸

Whatever may be the etiological factor the most important sequelae of severe RSV infection is an increased susceptibility to wheeze associated LRI in the pre-school period. Hence increased morbidity due to LRI could be prevented by an anti-RSV vaccine, the benefit of which both in health and economics may be substantial. This would definitely reduce further wheezy attacks that are impediments to growth and development and lead to better scholastic performance. It could reduce injudicious antibiotic usage resulting in development of resistant strains of bacteria. It would also reduce hospitalization thereby drastically cutting down the enormous medical expenditure to a poor person.

PREVENTION OF RSV INFECTION

Clinical trials using inactivated formalin treated intra-muscular RSV vaccine were undertaken in children as early as 1960.¹⁹ The recipients showed an early immune response but experienced more alarming LRI in subsequent infections and greater risk of hospitalization and deaths. Further studies with the virus itself were abandoned and attention was directed to evolve a passive immunity status. As per the recommendations of the American Academy of Pediatrics, RSV IVIG (Respigam) was licensed by the Food and Drug Administration (FDA) in the year 1996 for prevention of RSV LRI in children below 24 months of age with chronic lung disease or a history of premature birth <35 weeks of gestation. Two dosage schedules of RSV IVIG -150mg/kg/dose and 750mg /kg /dose, five infusions in total, were tried by a study of the National Institute of Allergy and Infectious Diseases (NIAID) on 2 different groups of children. In the higher dose group, there was a 62 %

reduction in incidence of further LRI. Period of hospitalization was reduced as compared to the lower dosage group. There was also a six-fold reduction in complications like otitis media in the higher dosage group. Although RSV IVIG prophylaxis showed an overall efficacy of 41% reduction in RSV infection, the disadvantages were too many. RSV IVIG benefit in congenital heart disease (CHD) was not established. Moreover such babies, immunized with RSV IVIG were found to have increased surgical mortality when subjected to cardiac surgery.²⁰ Cyanosis in CHD worsened probably due to increase in the baseline hyperviscosity of serum. RSV IVIG requires monthly IV injections/infusions throughout the RSV season which is neither cost effective nor convenient. This paved the way for development of a more powerful and less inconvenient preventive therapy in the form of an anti -RSV monoclonal antibody namely PALIVIZUMAB.

PALIVIZUMAB

Palivizumab is a humanized monoclonal antibody directed against 'F' glycoprotein of RSV—a surface protein that is highly conserved among RSV isolates.²¹ Humanized monoclonal antibody is a genetically engineered chimerical molecule that grafts an antigen - recognition site derived from a mouse monoclonal antibody on to human immunoglobulin backbone. Mouse monoclonal antibody recognizes and counteracts a protective epitope of 'F' protein that promotes fusion of the viral envelope with host cell membrane during early stage of infection. Thus palivizumab is not derived from human immunoglobulin and hence safe from transmission of dangerous infectious agents. It can be given by intramuscular route, is well tolerated, is less costly and 50-100 times more potent.

A major double blind, randomized clinical trial called impact study enrolling 1502 children was

done in three countries (USA, UK, Canada) in the year 1996.²² Palivizumab 15 mg/kg/dose was administered intramuscularly monthly once for five months. There was a 55% reduction in hospitalization rate of RSV related illness compared to the previous study with RSV IVIG with only 41% reduction. Maximum benefit was found in preterm born children with or without chronic lung disease, in 1998 Palivizumab was approved for use in a targeted high-risk population.

Comparative Study of Passive RSV IVIG and Palivizumab

S.N.		RSV IVIG	PALIVIZUMAB
1	Source	Derived from human donors screened for high doses of neutralizing RSV antibody (polyclonal)	Humanized monoclonal antibody (a pure antibody in cell culture)
2	Transmission of Pathogen	Transmission of unsuspected human pathogen is possible	No such possibility
3	Route of administration	Needs intravenous infusion	Given intramuscularly
4	Potency	Potency is less than Palivizumab	Potency 50-100 times more than RSV IVIG
5	Allergic reactions	Allergic reaction to human serum can take place	Well tolerated and no allergic reactions
6	Cost factor (in a 3 kg infant)	RSV IVIG -5 infusions US\$3621	5 IM injections US\$ 2378
7	Reduction in hospitalization rate	41% reduction in hospitalization	55% reduction in hospitalization
8	Interference with other immunization	Measles, MMR, Varicella vaccines should be delayed for about 9 months after the last dose	Does not interfere with other vaccine administration

RECOMMENDATIONS

Developing countries, where 90% of the world's children are born each year, cannot afford the exorbitant cost of RSV IVIG or Palivizumab. The Alma Ata Declaration of 1978 emphasized the need for Primary health care with supportive National policies for comprehensive intersectoral health systems. National Acute Respiratory Infection (ARI) Programmes have been established in all regions of the world.

LOW COST STRATEGY FOR THE THIRD WORLD FOR PREVENTING ARI

The following measures could be taken at home or in the community to reduce mortality and morbidity due to ALRI.

- 1) Isolation of close contacts: older children and adults can be encouraged to wear anti-pollution cloth masks during epidemics and while handling infants and children.
- 2) Teach mothers to recognize early danger signs like respiratory distress, stridor, grunting and chest indrawing, thereby seeking early medical aid.
- 3) Adequate distribution of essential drugs through health workers to start first level of treatment at home.
- 4) Vitamin A prophylaxis: Vit A stabilizes the structure and function of the mucosal surface, involving T-Cell function and mucus production. Mortality and morbidity in ARI are increased in deficiency of Vit A. Single dose of 2,00,000 IU Vit A per year has been found to decrease childhood mortality by 50%.
- 5) Counteract malnutrition and further vitamin deficiencies.
- 6) Encourage breast-feeding. Breast milk provides adequate Vit A through the first 6 months and even partly upto 1-11/2 years.
- 7) Zinc supplementation: Zn normalizes the function of cells in many tissues. It can enhance a child's ability to combat disease states. Therefore zinc supplementation is more economically feasible than vaccines directed against a number of specific organisms. Researches are underway to prove me efficacy of Zinc in combating diarrhoea and pneumonia— the two major killers. The recommended daily dosage of Zinc is 2mg/kg/day.

CONCLUSION

Both Palivizumab and RSV IVIG will have a positive impact on pediatric clinical setting for years to come. Developed countries can well afford the exorbitant cost of the vaccine. Cost factor analysis shows that hospitalization charges for every visit with RSV LRI will ultimately outweigh the immunization cost. So why not to try and reduce the number of hospitalizations by at least 55%. As regards developing countries like India, Nepal, Sri Lanka etc, the affluent class only can afford the vaccine. It is next to impossible to introduce this in the national immunization programme. However the future is not bleak. Continued research and advanced medical technology could bring out cheaper vaccines for the underprivileged whose RSV infection rate is much higher than in the upper strata of society. There is always a ray of hope—a silver lining to any dark cloud.

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