Respiratory syncytial virus infection and congenital heart disease

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South Afr J Epidemiol Infect 2008;23(2):17-19

Introduction

Though the role of congenital heart disease (CHD) as a risk factor for respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) has been recognised for over two decades, the extent of this risk and the criteria for prophylaxis for children with CHD still remain controversial. Furthermore, the contribution of CHD to the morbidity from RSV infection in developing countries remains relatively undefined.

Recent studies from South Africa have identified RSV as a significant source of morbidity and mortality in under fives in both community- and hospital-based studies. In a prospective population-based study in rural Agincourt, the incidence of RSV LRTI was found to be nine per 1,000 child years. A second population-based cohort study from Soweto found the rates of hospitalisation for RSV LRTI to be somewhat higher in urban areas (19.4 per 1,000 and 45.0 per 1,000 in HIV-uninfected and -infected children, respectively). A review of hospital-based studies found the incidence of RSV LRTI to vary between 3% to 18%.

Risk factors identified for severe RSV infection requiring hospitalisation include malnutrition, prematurity, age <6 months, vitamin A deficiency, environmental pollution and HIV infection. Madhi et al showed that the case fatality rates from RSV infection was significantly higher in HIV+ children than in HIV- children (7.5% vs 0%, p<0.001). However, there is scant published data on the role of CHD in the causation of severe RSV LRTI from South Africa. We will review the world-wide data on the role of CHD as a risk factor for severe RSV LRTI and the role of prophylaxis in this high risk population.

RSV infection in CHD

There is substantial epidemiological evidence linking congenital heart disease with RSV LRTI. The first definitive study of the effects of RSV LRTI in infants with CHD was reported in 1982. This was a hospital-based cohort study of all infants (n=699) who were admitted during the RSV seasons of 1976 through 1980. The severity of RSV LRTI in children with CHD was significantly greater than those without CHD as measured by requirement for intensive care (63% vs 14% (p<0.001) and assisted ventilation (22% vs 5% p<0.01). The case fatality rate was higher in the CHD group (37% vs 1.5%, p<0.01). Subsequent studies have corroborated this association but show a decreasing trend in mortality (Table 1). However, both medical and surgical morbidity caused by RSV remain significant though it varies with the degree of cardiac compromise as detailed below.

The morbidity caused by RSV LRTI in children with CHD correlates with the severity of the underlying cardiac disease as measured by the degree of compromise of the baseline cardio respiratory status, pulmonary mechanics, degree of cyanosis, level of pulmonary hypertension and extent of ventilation/perfusion mismatch. Pulmonary hypertension in particular is singularly important in causing severe RSV disease in infants with CHD.

RSV infection and cardiovascular surgery

RSV LRTI causes substantial morbidity and even mortality in the immediate period surrounding either palliative or corrective cardiac surgery. Cardiac surgery performed during symptomatic RSV LRTI is associated with a high risk of postoperative complications, especially postoperative pulmonary hypertension. These complications appeared to be more frequent and of greater severity in patients who had surgery earlier in the course of infection as compared with those who had later surgery. RSV is also an important cause of postoperative nosocomial
infection. This is attributed to transient immunological dysfunction following cardiopulmonary bypass and possible dilution of serum neutralising antibodies Preoperative screening for asymptomatic RSV infection has been suggested as a way to reduce this morbidity.13 The epidemiological evidence linking severe RSV LRTI to CHD begs an explanation and also warrants attempts to prevent severe disease in those infants and children.

**Pathophysiology of RSV infection in cardiac disease**

The severe effects of RSV LRTI on the respiratory tract can be attributed to the combined effects of physiological strain on the infant respiratory tree compromised by an abnormal circulation. The smaller diameter of the airways, the lack of effective collateral ventilation, inadequate fluid filtration, endothelial dysfunction and impaired sodium pump function all contribute to respiratory compromise.11 In addition to the physiological haemodynamic abnormalities, putative direct effects of RSV on the myocardium have been observed. This ranges from no detectable electrical or functional abnormality, focal involvement of the conducting system, supraventricular- and ventricular arrhythmias to global myocardial involvement with electrical and mechanical dysfunction. Thus, elevated cardiac troponin levels have been seen in a third to half of all ventilated infants.13

**Prophylaxis of RSV in CHD**

Given that CHD constitutes a significant risk factor for severe RSV LRTI and that an effective vaccine is lacking, a passive immunotherapeutic strategy has been pursued for this group of children.

The first product to be tested for the prevention of severe RSV LRTI in children with CHD was RSV immune globulin (RSV-IGIV; RespiGam). The initial study conducted between 1989-1991 was a randomised, multicentre, controlled trial which compared 249 high risk children (BPD, prematurity and CHD) who were divided into two groups (high- and low dose immunoglobulin) to controls (n=89).14 This study showed that children treated with high dose RSV-IGIV(750 mg/kg given every 7 vs 20 in the control group; p=0.01), fewer hospitalisations (6 vs 18 in the control group; p=0.02), fewer hospital days (43 vs 128 in the control group; p=0.02) and fewer days in the intensive care unit (p=0.05). The protective effect of RSV-IGIV was clear in children with bronchopulmonary dysplasia or prematurity, but efficacy among the 87 children with CHD was less impressive. Five of the six children who died during the course of the study had CHD.

Although none of the deaths in the study were considered related to the infusions or to RSV infection, a further study to specifically determine the safety and efficacy of RSV-IGIV prophylaxis in CHD was conducted between 1992-1995.9 Children younger than 4 years of age were randomly assigned to a treatment group receiving RSV-IGIV, 750 mg/kg, monthly or to a control group not receiving infusions. Thirty-two of 214 (15%) control children were hospitalised with RSV as compared to 21 of 202 (10%) of the children receiving RSV-IGIV, a 31% relative risk reduction (p=0.16). However, in infants younger than 6 months of age at study entry, 20 of 82 (24%) in the control group and 10 of 96 (10%) in the RSV-IGIV group had RSV hospitalisations (58% reduction, p=0.01). Among 77 children with cyanosis, eight instances of unanticipated increase in cyanosis occurred leading directly to a cardiac intervention in the RSV-IGIV group as compared with none in the 83 control patients (p=0.03). This was attributed to the possible hyper viscosity caused by high dose IGIV. The authors concluded that RSV-IGIV did not reduce hospitalisation in all children with CHD, but it was effective in preventing RSV hospitalisation in infants younger than 6 months of age and that RSV-IGIV should not be used in children with cyanotic heart disease.8

The development of palivizumab, a humanised murine monoclonal anti-F glycoprotein antibody preparation with specific RSV action and without the systemic side effects of IGIV opened up a new avenue in prophylaxis. A multicentre, randomised, double-blind, placebo-controlled phase III clinical trial was conducted in 1,287 children (639 vs 648 controls) between 1998-2002 with haemodynamically significant CHD, demonstrated a 45% reduction in RSV hospitalisations (9.7% vs 5.3%, p=0.003). The study was not powered for subgroup analysis between the groups but reductions in hospitalisation were seen in both cyanotic and the acyanotic strata. In the cyanotic stratum RSV hospitalisations were reduced by 29% (7.9% vs 5.6%, p=0.235) while in the other group there was a 58% relative reduction (11.8% vs 5.0%, p=0.003). The reduction was greatest in children <6 months of age (12.2% placebo vs 6.0%).

Children who received palivizumab had significantly fewer total days of RSV hospitalisation per 100 children (56% reduction; 129.0 days placebo vs 57.4 days palivizumab, p=0.003) and less, RSV hospital days with increased oxygen requirement per 100 children (73% reduction; 101.5 days placebo vs 27.9 days palivizumab, p=0.014). This study concluded that palivizumab significantly reduced the rate of hospitalisation for RSV infection in children 24 months or younger with haemodynamically significant cardiovascular disease.10

Based on this pivotal trial, palivizumab was recommended for use in the US by the American Academy of Pediatrics in children who are 24 months of age or younger with haemodynamically significant cyanotic and acyanotic congenital heart disease.16 Currently in South Africa, palivizumab prophylaxis is recommended for infants of any gestation with any of the following who are <12 months of age at the start of the RSV season:

- Cyanotic congenital heart disease
- Moderate to severe pulmonary hypertension
- Receiving medication to control congestive cardiac failure

However, a proposed expansion of these guidelines to include children <24 months of age is under consideration by the South African Paediatric Association.
**Newer therapies**

A more potent second-generation anti RSV monoclonal antibody, motavizumab, is currently under study in phase III clinical trials. Compared with palivizumab, this antibody has an 80-fold greater binding affinity for the RSV F protein and is 23 times more potent at neutralising RSV in vitro in a cotton rat model. A multinational, randomised, double-blind, phase III clinical trial in premature infants has shown that motavizumab was noninferior to palivizumab (p<0.01) with a 26% relative reduction in RSV hospitalisations (1.4% vs 1.9%, respectively; relative risk: 0.740; 95% CI: 0.503, 1.083). Motavizumab also demonstrated superior efficacy to palivizumab with a 50% relative reduction in RSV-specific outpatient medically attended LRTIs, (2.0% vs 3.9 %, (p<0.01).17

Current trials underway in the Navajo and Apache Native American population are evaluating the long and short term outcomes of motavizumab therapy. A multicentre trial is also assessing the role of motavizumab prophylaxis in children with CHD.

In conclusion, though current epidemiological evidence supports the association and clinical trials support the role of prophylaxis, further studies need to be done to tailor prophylaxis and better define the epidemiology of RSV infection in children with CHD in developing countries.

**References**