

State of Respiratory Syncytial Virus Prophylaxis in Congenital Heart Disease Patients and Some of the Questions That Linger

a report by

Timothy F Feltes, MD, FAAP, FACC

Ohio State University and Columbus Children's Hospital

Lower respiratory illness that results from respiratory syncytial virus (RSV) infection has long been recognized as a serious health risk to infants and children with congenital heart disease (CHD).^{1,2} In particular, RSV-triggered pulmonary hypertension, complications in managing heart failure, and prolonged mechanical ventilatory assistance may all delay or jeopardize the successful cardiac surgical palliation or repair of these children. Many of the health concerns for these children mirror those for premature infants. Not surprisingly, the history of prevention of RSV disease in CHD infants and young children parallels that of premature infants with chronic lung disease.

The history of prevention of respiratory syncytial virus disease in congenital heart disease infants and young children parallels that of premature infants with chronic lung disease.

Following an efficacy trial that included premature infants and children with CHD, hyperimmune RSV globulin (RSV-IGIV, RespiGam™ MedImmune Inc., US) was approved by the US Food and Drug Administration (FDA) for the prevention of RSV lower respiratory illness in premature infants.³ Due to the small number of CHD patients and some safety concerns, a subsequent trial tested the safety and efficacy of RSV-IGIV in CHD patients specifically.⁴ This study failed to achieve its primary efficacy end-point of reduced RSV hospitalizations, although it did demonstrate the efficacy of this treatment in CHD patients below six months of age. There were significant safety concerns found in this study as there were an unexpectedly high number of surgically related adverse events in infants with cyanotic cardiac lesions. This was possibly due to altered blood viscosity in the treated patients.

Palivizumab (Synagis™ MedImmune, Inc., US) is a monoclonal antibody (mAb) directed at the F surface glycoprotein of RSV that interrupts viral binding to cells in both RSV subtypes A and B. It was approved by the FDA for the prevention of RSV hospitalization in premature infants following an extensive multicenter clinical trial.⁵ Subsequently, in what remains the largest drug trial conducted in CHD patients, over four RSV seasons (1998–2002) 1,287 CHD patients were randomized to a double-blind, placebo-controlled clinical trial powered to test the efficacy and safety of palivizumab.⁶ The primary efficacy end-point of reduced RSV hospitalizations was met (45% relative reduction in treated group)

and, unlike RSV-IVIG, no serious safety concerns for palivizumab were observed, leading to the addition of infants and children <24 months of age with hemodynamically significant CHD to prophylaxis indications.⁷

Who Is In, Who Is Out?

The American Academy of Pediatrics (AAP) has recommended that CHD candidates for RSV prophylaxis be determined by the presence of physiological cardiovascular compromise.⁷ With this in mind, patients who require medication to control their heart failure (e.g. diuretics, afterload-reducing agents), patients with cyanotic heart disease, and those with pulmonary hypertension are clearly candidates for RSV mAb prophylaxis. In contrast, patients with small left-to-right shunts (e.g. atrial septal defects or small ventricular septal defects) are deemed not to be at an increased risk for the complications of RSV, and therefore should not be prophylaxed. Also included in the AAP recommendations for 'no prophylaxis' are patients with uncomplicated aortic stenosis, pulmonary stenosis, and patent ductus arteriosus.

Even though these are very thoughtful recommendations, there exist some gray areas. As of 2007, it is not unusual for cardiologists to move forward with surgical or interventional treatment during the first few months of life for a child with, for instance, a moderately sized ventricular septal defect rather than initiating medical therapy. If a child is born between the months of October and April (northern hemisphere), should RSV mAb prophylaxis be initiated? Uncertainty also exists for the patient with left-sided obstructive lesions, especially when these lesions occur in series (e.g. subaortic stenosis ± aortic stenosis ± coarctation). Recently, Castelli et al. reported a case of a child with coarctation who died during the peri-operative period due to RSV-triggered pulmonary hypertension.⁸ What should be done with a child born during the RSV season who has small to moderate sized left-to-right shunt who is 35 weeks in gestation?



Timothy F Feltes, MD, FAAP, FACC, is a Professor of Pediatrics and Chief of Pediatric Cardiology at Ohio State University. He is Co-Director of the Heart Center and the Andy Paxton Chair in Cardiology at Columbus Children's Hospital. Prior to this, he was Director of Critical Care Cardiology and Inpatient Services at Texas Children's Hospital and Baylor College of Medicine. Dr Feltes is a cardiac intensivist whose research has focused on the care of congenital heart disease patients in the clinical setting. He was one of the principal investigators of the Cardiac Synagis Study, a blinded placebo-controlled trial establishing the efficacy and safety of palivizumab prophylaxis in children with hemodynamically significant congenital heart disease. Dr Feltes trained and served as a cardiology attending and researcher at Baylor College of Medicine.

E: feltest@pediatrics.ohio-state.edu

The relative contributions of comorbid factors in the CHD patient have not been determined. Since the publication of the AAP guidelines for CHD patients, physicians from other countries have published guidelines for RSV mAb prophylaxis (the UK, Spain, Canada, and Japan), including a consensus statement from representatives of multiple European countries.⁹⁻¹³ Unsurprisingly, there are subtle differences in these reports that attempt to address confounding variables. For instance, in the Japanese guidelines it is recommended that children <24 months of age with Down syndrome and DiGeorge syndrome (22q11.2 deletion) with asymptomatic CHD should be included in the RSV prophylaxis.¹⁰ These recommendations seem to be logical, but given the relatively small number of such 'orphan disease' patients, it is unlikely that any study will be able to substantiate mAb prophylaxis effectiveness. Other patients who were not included in the Cardiac Synagis Trial but who would seemingly benefit from mAb prophylaxis include patients with cardiomyopathies (restrictive, dilated), patients with significant arrhythmias on medication, and Kawasaki disease patients with coronary artery involvement. These patients have been included in other published guidelines, recognizing that unanimous consensus was not always reached among participants.^{9,10}

When to Stop Respiratory Syncytial Virus Prophylaxis in Congenital Heart Disease Patients?

If the cardiac surgery performed for CHD is merely palliative, there is a consensus that prophylaxis should continue for the duration of an RSV season. However, a significant difference in opinion and practice exists when determining when RSV prophylaxis should be stopped in CHD infants who undergo complete surgical correction. Most agree that the patient should be re-prophylaxed immediately after surgical repair because of evidence that mAb titers decrease significantly as a result of the dilutional effect of cardiopulmonary bypass.⁶ In France, it is not unusual for prophylaxis to be discontinued two weeks after surgery. In the UK this is often four to six weeks after surgery, while in the US three or more months or the end of the RSV season is thought to suffice.⁹ On one side of the argument there are those who contend that the lung of

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the child with CHD is abnormal and time is needed for remodeling to occur, thus arguing for the continuation of prophylaxis. Others say that the shunt or obstruction has been relieved and therefore, assuming normal hemodynamics, the patient is not at risk for RSV complication and prophylaxis can be stopped. Unfortunately, no data exist in the literature in favor of either stance. There is a 'soft' consensus (better to compromise) that as long as the post-operative patient requires medications (e.g. diuretics, digoxin, afterload-reducing agents), this probably reflects significant residual disease.

Can Anti-respiratory Syncytial Virus (RSV) Polyclonal, Monoclonal Antibodies Be Used as a Treatment for Active RSV Illness or RSV Exposure?

Few treatment options exist for active illness from RSV infection other than providing supportive care. The antiviral agent ribavirin, previously approved for treatment of active RSV illness, is now rarely used. Speculation that high titers of neutralizing antibody might attenuate RSV illness led to several studies in which polyclonal RSV-IGIV was used as a treatment for active RSV illness. A Cochrane review of these studies was recently reported and concluded that there was no beneficial effect from use of RSV-IGIV.¹⁴ RSV mAb treatment has been shown to reduce RSV in the trachea of infected infants.¹⁵ A phase I/II multicenter, placebo-controlled trial using two doses of

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intravenous palivizumab (5mg/kg, 15mg/kg) was conducted in a small group of infants (n=59) with active RSV illness.¹⁶ Intravenous palivizumab was well tolerated but had no benefit as measured by days of RSV hospitalization, days of supplemental O₂, and days with increased severity score. Similar testing is planned using the more potent motavizumab (see below) in low-risk patients.

Compliance to Prophylaxis Guidelines

It is one thing to define guidelines for prophylaxis, but it is quite another to ensure compliance. Who takes responsibility for identifying CHD candidates and assuring prophylaxis compliance? In the US, pediatric cardiologists often serve as gatekeepers in determining CHD candidates for prophylaxis. Thus, it is often the cardiologist's service that manages palivizumab injections. At our center we have identified nursing personnel whose role is to maintain a database of candidates for prophylaxis and to arrange with either the primary care physician or our hospital-based outpatient center the scheduling of mAb monthly injections.

In a recent paper by Afghani et al., an interventional program designed to improve compliance with AAP guidelines for RSV prophylaxis in at-risk children was reported.¹⁷ The authors noted an improvement in the capture of candidates of more than 50%. Unfortunately, the baseline capture of 39% (improved to 61%) indicates much room for improvement. The authors were also able to reduce the number of late injections from 14 to 2% in this at-risk cohort. In countries where CHD patients are entered into national databases, compliance has the potential for greater success.¹⁸

The Cost-effectiveness of Prophylaxis

A very appropriate concern for mAb prophylaxis is cost. A number of cost-benefit analyses for RSV prophylaxis in CHD patients have been published in recent years with varying conclusions.¹⁹⁻²³ Cost-benefit testing is difficult and often oversimplified from the perspective of direct costs, namely how many prevented RSV hospitalizations it takes to justify

treating the pool of CHD patients. There are also indirect costs that need to be considered. From a societal perspective, simple factors such as lost parental production due to the hospitalization of their child need to be considered. There is evidence to support a link between RSV in infancy and health issues such as reactive airway disease later in childhood. The long-term cost of this disease should also be considered.

In a recent publication, Ashburn et al. reported that roughly only half of patients born with forms of hypoplastic left heart syndrome survive (or avoid cardiac transplant) all three staged palliations (I-Norwood operation, II-cavopulmonary anastomosis, and III-Fontan procedure).²⁴ Needless to say, there are many reasons for failure to progress along this treatment algorithm, but an infant with a single ventricle depends on very low pulmonary resistance to sequence along this surgical pathway, and a significant delay in surgical intervention (especially at stages I and II palliation) may greatly affect long-term survival and health. An RSV illness may be cause for a delay and a potentially significant risk for loss of candidacy for the sequence of repair. If the cost of successful palliation of the child with a single ventricle seems high, imagine the cost to society of a failed palliation. There are significant long-term consequences of any disabilities created and the potential emotional cost of a lost child.

What Is Next?

Various host immunological factors account for previous failures to develop an effective vaccine for RSV. Therefore, RSV prevention will probably remain in the realm of passive immunization for some time. The next-generation RSV mAb closest to widespread clinical use is motavizumab (MedImmune, Inc., US). This mAb has a much greater binding affinity to

the F glycoprotein compared with palivizumab, and is 50–100 times more potent than palivizumab in animal studies.²⁵ A phase III clinical trial testing the efficacy and safety of motavizumab (versus palivizumab control) in high-risk infants has recently been completed.²⁶ Preliminary results were presented at the annual meeting of the Society for Pediatric Research (SPR) in Toronto May 2007. The primary efficacy end-point of the non-inferiority of motavizumab compared with palivizumab was achieved with a relative

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reduction of RSV hospitalization by 26%. Motavizumab showed superiority over palivizumab in a reduction of medically attended lower respiratory infections, a secondary end-point, by 52%. A phase III safety trial of motavizumab is currently being conducted in infants and young children with hemodynamically significant CHD.

Synthetic small molecules such as the peptide-based inhibitors of viral fusion proteins are making their way into antiviral treatment strategies. Future development of anti-RSV small-molecule inhibitors may become a viable antiviral treatment in interrupting the RSV life-cycle either alone or in combination with a mAb. ■

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