

Respiratory Syncytial Virus Prophylaxis in Heart Disease: Indication and Limits of Worldwide Administration



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INTRODUCTION

- Respiratory syncytial virus (RSV) is a common pathogen affecting almost all children by the age of 2 years¹
- The morbidity from lower respiratory tract infections results in high rates of hospitalization among those with haemodynamically significant congenital heart disease (hsCHD) during the winter season¹
- Palivizumab (PVZ) is used as standard immune prophylaxis due to the absence of a vaccine against RSV¹

OBJECTIVE

- To understand global variations in the use of PVZ in immune prophylaxis for severe RSV disease

METHODS

DESIGN

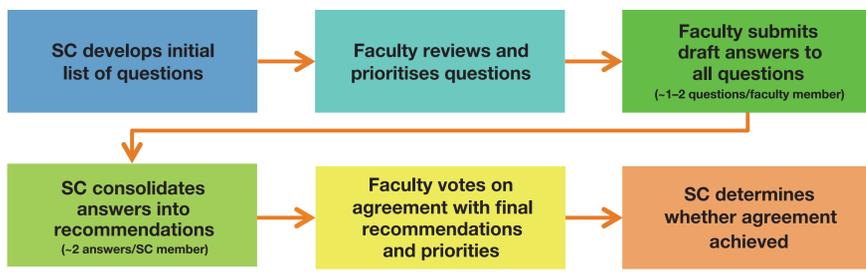
- A quasi-Delphi consensus methodology² was used to develop questions and recommendations aimed at identifying and addressing the unmet needs of paediatric patients with congenital heart disease (CHD) at risk for severe RSV disease who require preventive and management strategies (Figure 1A)
- Strength of evidence (grades and levels) were assessed per standard practice³

STEERING COMMITTEE AND FACULTY

- A steering committee that comprised 5 international paediatric cardiology expert clinicians and additional faculty composed of international experts (eg, paediatric cardiologists, intensivists, and cardiac surgeons) collaborated (Figure 1B)

Figure 1. Study Design and Process

A. Algorithm for step-by-step process**



B. RSV global expert steering committee and faculty members

Steering Committee Members	Faculty Members
Colombia: Dr Claudia Stapper Japan: Prof Naokata Sumitomo Spain: Dr Constancio Medrano-Lopez United Kingdom: Prof Robert Tulloh United States: Dr Paul Checchia	Germany: Prof Matthias Gorenflo Korea: Prof Eun Jung Bae Mexico: Dr Antonio Juanico Spain: Dr Juan Miguel Gil-Juarena Taiwan: Prof Mei-Hwan Wu United Arab Emirates: Dr Talal Farha United States: Dr Ali Dodge-Khatami, Dr Rocky Tsang

SC=steering committee. *The SC developed questions and the faculty answered all questions via an online digital platform; each participant reviewed all comments and uploaded supporting published evidence when available; consolidated answers were summarized into recommendations reviewed by the SC; the faculty agreed or disagreed with the draft recommendations and voted on their order of priority. Evidence-based answers were obtained with regional variations regarding the use of RSV immunoprophylaxis in cardiac disease as well as other indications and regarding obstacles to its use. When there was disagreement with the draft wording, the chairman/SC member contacted the faculty member to understand and clarify the issue; the draft wording was then amended to the member's satisfaction and agreement.

RESULTS

- Through the development process, the group derived 14 questions relevant to the unmet need of RSV immunoprophylaxis in paediatric CHD and the following recommendations (regional variation is indicated where applicable)

RSV immunoprophylaxis in children with CHD

Question 1. Who should be involved in developing the standard of care for the use of immunoprophylaxis against RSV infection in children with CHD?

- Standard of care for RSV immunoprophylaxis should be developed by
 - Cardiologists, cardiac surgeons, infectious disease specialists, intensive care specialists, and neonatologists*
 - National medical societies/associations¹
 - Government health departments and parent associations/regulators

Voting results: agree/disagree 8/0; Evidence grade/level: 1a^{4,5,7-9}

*Supported by epidemiologists, general paediatricians, and primary care physicians. ¹For example, the American Academy of Pediatrics, the British Congenital Cardiac Association, and national guideline groups and health authorities.

Question 2. Who are the key decision makers for the need for prophylaxis against RSV infection in children with CHD already in hospital or outside of a hospital stay?

- A paediatric cardiologist should make the decision for RSV immunoprophylaxis in children with CHD in hospital and community settings*¹

Voting results: agree/disagree 8/0; Evidence grade/level: N/A

NA=not applicable. ¹Supported by cardiac surgeons; infectious disease, intensive care, primary care, and neonatology specialists; epidemiologists; general paediatricians; nursing staff; and anaesthetists. ²Factors affecting who takes role of key decision maker include age of the infant at risk, where and how the patient presents to healthcare services, local practices, and local staffing/departmental arrangements in individual hospitals.

Question 3. Which guidelines do you follow to meet the medical needs of your children with CHD?

- Healthcare professionals should refer to international guidelines (eg, AAP), and their national guidelines

Voting results: agree/disagree 8/0; Evidence grade/level: 1a^{4,5,7-9}

Regional variation (country-specific guidelines)

- Germany: DGPK
- Japan: JSPCCS guidelines
- Korea: Korean guidelines from the Society of Paediatric Cardiology and the Society of Neonatology
- Mexico, Spain: SECPCC guidelines based on the Spanish clinical consensus document
- Taiwan: Taiwanese guidelines from the Society of Paediatric Cardiology and the Society of Neonatology
- United Kingdom: BCCA and JCVI guidelines

AAP=American Academy of Pediatrics; BCCA=British Congenital Cardiac Association; DGPK=Deutsche Gesellschaft für Pädiatrische Kardiologie [German Society for Pediatric Cardiology]; JCVI=Joint Committee on Vaccination and Immunisation; JSPCCS=Japanese Society of Pediatric Cardiology and Cardiac Surgery; SECPCC=Spanish Society of Paediatric Cardiology and Congenital Heart Disease.

RSV immunoprophylaxis in children with CHD (specific populations)

Question 4. Based on the benefit shown, and from your own clinical experience, in which children with unoperated* CHD do you recommend immunoprophylaxis against RSV infection?

- The following groups of children with unoperated CHD are candidates for RSV immunoprophylaxis
 - Children with hsCHD (eg, <2 years of age with left-to-right shunt requiring therapy for CHD, pulmonary hypertension, single ventricle physiology, or cyanotic heart disease [oxygen saturations below 85% on room air])¹
 - Children with symptomatic airway abnormalities associated with vascular rings, absent pulmonary valve syndrome, evidence of airway obstruction due to cardiovascular causes, and congenital tracheal stenosis

Voting results: agree/disagree 7/1; Evidence grade/level: 1a^{7,8,11}

*hsCHD as defined by Feltes et al¹⁶ (Cyanotic stratum, previous cardiac surgery or interventional catheterization, hypercyanotic episode, receiving cardiac medications, congestive heart failure, pulmonary hypertension [PH], and increased pulmonary blood flow).

Question 5. Based on the benefit shown and from your own clinical experience, in which children with operated CHD do you recommend immunoprophylaxis against RSV infection?

- RSV immunoprophylaxis should be administered for the first year of life in children with surgically operated hsCHD if aged 1–2 years, for up to 6 months postoperatively; or on a case-by-case basis.

Voting results: agree/disagree 8/0; Evidence grade/level: 1a, 1b^{4,5,14}

Regional variation (reflects differences in opinions of individual experts)

- Germany, Korea, Spain, and the United States: use prophylaxis in children with
 - hsCHD after surgery*
 - Palliated CHD¹
 - Operated CHD with significant residual defects/airway abnormalities^{4,5}
 - hsCHD surgery planned during RSV season, reducing the number of doses as RSV season ends
- Mexico: prophylaxis in all of the at-risk groups listed above; also consider preventive use of PVZ for children with heart disease scheduled for a therapeutic diagnostic procedure (eg, catheterization) during RSV season or at risk during the first 2 years of life
- United Arab Emirates: use clinical judgment on a case-by-case basis in patients with hsCHD with partially corrected CHD, recommending immunoprophylaxis for remainder of RSV season or for 2 months (whichever is longer) to allow maximum recovery from surgery
- United States: prophylaxis in children <2 years of age (at beginning of RSV season) with residual lesions: surgically palliated for augmentation of pulmonary blood flow; palliated with single ventricle physiology; systolic or diastolic heart failure requiring therapy for CHF

CHF=congestive heart failure. ¹Germany: would continue for 6 months, even if the haemodynamic cause is resolved, to allow time to recover. ²Germany: would continue for 6 months after palliative surgery, and ideally for the first 2 years of life. ³Spain: prophylaxis up to 2 years of age (ideally up to 2 years of age). ⁴Korea: prophylaxis in patients <24 months of age or with body weight <12kg.

Questions 6-10: On the basis of benefit shown and from your own clinical experience, in which children with the following conditions do you recommend immunoprophylaxis against RSV infection?

During the RSV season, children with PH

- RSV immunoprophylaxis for all children <2 years of age diagnosed with or being treated for idiopathic PH
- RSV immunoprophylaxis for PH associated with congenital heart disease or CLD,* or PH secondary to cardiomyopathy

Voting results: agree/disagree 8/0; Evidence grade/level: 1a, 1b^{4,5,15-18}

CLD=chronic lung disease. ¹In PH due to CLD (eg, due to prematurity) or neuromuscular disorders, evidence for RSV immunoprophylaxis is generally lacking; however, advise RSV immunoprophylaxis for patients continuing on oxygen therapy.

During the RSV season, children with cardiomyopathies

- Children with cardiomyopathies requiring medical treatment including therapy for CHF, who are on oxygen support, and who are <1 year of age are candidates for RSV immunoprophylaxis*
- Review the need for prophylaxis on a case-by-case basis and favor prophylaxis in infants <1 year of age

Voting results: agree/disagree 8/0; Evidence grade/level: 2a, 2b^{4,5,14,19,22}

Regional variation (reflects differences in opinions of individual experts)

- Germany and Mexico: consider prophylaxis in infants with cardiomyopathies requiring medical treatment
- Mexico: consider prophylaxis in hospitalized infants with decompensated cardiomyopathy as well as in mild, unmedicated cases in which infants are aged <1 year
- United States, Taiwan, and Korea: Prophylaxis for infants (<1 year of age) with haemodynamically significant cardiomyopathy (ie, diuretic dependent, inotrope dependent, or oxygen dependent) consistent with AAP guidance on infants this age with CHD
- United States¹: no prophylaxis for mild cardiomyopathy in asymptomatic infants not requiring anticongestive therapy

*There are currently no formal, published recommendations for RSV immunoprophylaxis in infants with cardiomyopathies, despite some evidence that this may be of benefit in symptomatic children. ¹One of the US experts held this opinion.

Children with arrhythmias (including Brugada or long QT syndrome)

- Children with recurrent arrhythmias and channelopathies are not usually candidates for RSV immunoprophylaxis, but it is recommended that those with other risk factors (ie, hsCHD, cardiomyopathies) receive RSV immunoprophylaxis during the RSV season*¹

Voting results: agree/disagree 7/1; Evidence grade/level: 3, 4^{4,5,7,12,23,26}

*There is no evidence-based, published guidance on RSV immunoprophylaxis in those with arrhythmias or channelopathies; further research is needed in this area. ¹Use standard antipyretics to protect from fever because febrile illness is an important precipitating factor for paediatric arrhythmias.

Children undergoing heart transplantation

- Consider RSV immunoprophylaxis for children who are on a waiting list for heart transplant or in their first year after heart transplant

Voting results: agree/disagree 7/1; Evidence grade/level: 3^{27,30}

*There are very few published data (1) to guide clinical decisions regarding the need for severe RSV disease immunoprophylaxis in children requiring heart transplant and (2) on the need for/importance of checking donor hearts from RSV-positive donors.

Children with associated risk factors

- Children with a genetic condition or associated condition, regardless of the primary diagnosis, and with hsCHD should receive RSV immunoprophylaxis*
- There is no evidence for giving RSV immunoprophylaxis to those with 22q11.2 microdeletion or insignificant CHD

Voting results: agree/disagree 7/1; Evidence grade/level: 2a^{4,6,8,27,30-33}

Regional variation (reflects differences in opinions of individual experts)

- Colombia and Spain: consider prophylaxis in all children with Down syndrome

*A number of genetic conditions, such as Down syndrome or having a chromosome 22q11 microdeletion, may be associated with CHD; many infants and children with primary or acquired immunodeficiency may also be at risk for or experience CHD.

Question 11. Based on the benefit shown and from your own clinical experience, in which CHD children do you recommend immunoprophylaxis for the prevention of nosocomial RSV infection, if the patient is not previously covered?*

- In children <12 months of age with CHD, use RSV immunoprophylaxis during a nosocomial RSV outbreak if
 - Hospitalized for surgery/interventions/other medical reasons in a general paediatric area or a specific paediatric cardiology area
 - Hospitalized in either a mixed PICU/NICU or cardiac ICU in the perioperative period
- In children >12 months of age with CHD, consider RSV immunoprophylaxis during a nosocomial RSV outbreak for the following (if not previously covered)
 - Infants meeting criteria for CLD of prematurity needing ongoing care
 - Children with CHD (cyanotic or noncyanotic), whether noncorrected or partially corrected, or complex heart diseases (palliative intervention) who have haemodynamic sequelae (moderate to severe pulmonary hypertension, heart failure, hypoxemia)
 - Children with surgically corrected CHD with residual lesions with haemodynamic sequelae
 - Children with surgically corrected congenital heart defects, with a history of severe lung complications that have required prolonged mechanical ventilation
 - Children with immediate postoperative haemodynamic sequelae
 - Children 12–24 months of age undergoing treatment for cardiomyopathy
 - Children with heart disease with planned therapeutic diagnostic procedure (eg, catheterization)

Voting results: agree/disagree 6/2; Evidence grade/level: 3, 4^{4,31,34,38}

ICU=intensive care unit; NICU=neonatal ICU; PICU=paediatric ICU. ¹Some clinicians recommend prophylaxis for all inpatients, whereas others recommend it for only those undergoing cardiac surgery.

Question 12. In which children with CHD >2 years of age should you consider immunoprophylaxis against RSV infection?

- It is essential to continually update recommendations on RSV immunoprophylaxis, to take into account both the latest evidence and the professional judgment of expert cardiac care providers to reduce variations and inequity in clinical practice
- More evidence and gathering of further experience is required for populations not described in formal guidelines or in this consensus document*

Voting results: agree/disagree 8/0; Evidence grade/level: 3, 4^{4,16,36,39-42}

*For example, those with serious CHD, those aged >2 years, older children awaiting heart transplant, patients with haematologic cancers, immunocompromised patients, those with Down syndrome and 22q11.2 deletion syndrome, older children with CLD pulmonary hypertension and hsCHD, and elderly patients with serious CHD.

Question 13. What are the barriers to effective RSV disease prophylaxis in children with CHD, including the delivery of that prophylaxis?

- Barriers to effective RSV immunoprophylaxis in children with CHD include
 - Poor awareness of RSV risks and burden (eg, newly qualified HCPs)
 - Compliance and completion barriers (eg, fears of injections and AEs; failures of HCPs to understand importance of compliance)
 - Data and experience gaps (eg, paucity of trial data)
 - Not considered medically justified or cost-effective
 - Unpredictable RSV seasonality, making it difficult to establish a schedule

Voting results: agree/disagree 7/1; Evidence grade/level: 4^{4,8,34,41,43,53}

Regional variation

- Tropical/subtropical countries: unpredictable RSV seasonality make it difficult to establish when the rainy season will begin and to make an appropriate annual immunoprophylaxis schedule

AE=adverse event; HCP=healthcare professional.

Question 14. What management strategies could be put in place to overcome these barriers to effective prophylaxis of RSV disease in children with CHD?

- Improving awareness of RSV at all levels from the public to HCPs can overcome barriers to effective immunoprophylaxis
 - Establish registries (local, regional, national, and international) and capture more observational data and experiences in at-risk children.
 - Provides a feedback loop on RSV epidemiology and potential effectiveness of immunoprophylaxis
 - Serves as a data bank to support outbreak containment efforts

Voting results: agree/disagree 8/0; Evidence grade/level: 1a, 1a^{43,46,48,49,53,54}

CONCLUSIONS

- There was general consensus among the panel of international experts that RSV immunoprophylaxis should be used in children with hsCHD in the first 12 months of life, including those on medication for left-to-right shunt, with cyanosis (oxygen saturation <85%), with cardiomyopathy or pulmonary hypertension on treatment, and/or on heart transplant waiting lists
- There was divided opinion on the evidence for use of RSV immunoprophylaxis in children >1 year of age, in nosocomial outbreaks or with immune deficiencies, and in those being admitted for cardiac intervention
- Use of RSV immunoprophylaxis was subject to regional variation
 - There is general consensus that RSV immunoprophylaxis should be available more freely in resource-limited countries
 - There is still insufficient evidence to guide its use in subtropical countries and in patients with certain comorbidities
- The opinions of these individual experts may not be a true reflection of regional variation in clinical practice; however, the recommendations presented here can serve as a starting point.

REFERENCES (please see handout and QR code)

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