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Chapter

Respiratory Syncytial Virus Infections among Children with Congenital Heart Disease

Maja Daurach and Ina Michel-Behnke

Abstract

Infants and children suffering from congenital heart disease represent a patient cohort particularly at risk for severe RSV infections. Most notably the complication rates in lower respiratory tract infections due to RSV among patients with congenital heart disease are significantly higher compared to other patient collectives. Predisposing factors are altered lung mechanics caused by either increased or decreased pulmonary blood flow, both resulting in a ventilation/perfusion mismatch causing decreased pulmonary compliance and higher airway resistance. Randomized controlled trials have shown that immunoprophylaxis with palivizumab is beneficial for CHD patients. Guidelines from different national societies suggest administration of palivizumab for infants with CHD in young age injected monthly throughout the RSV season, if the CHD is considered hemodynamically significant.

Keywords: congenital heart disease (CHD), respiratory syncytial virus (RSV), palivizumab, immunoprophylaxis, lower respiratory tract infection (LRTI), bronchiolitis

1. Introduction

The burden of respiratory syncytial virus (RSV) infections differs markedly between patients. Clinical symptoms might be mild as in a common cold, while at the other end of the spectrum, children suffer from serious complications and negative impact with chronic respiratory problems that can persist into adulthood [1].

Since the 1980s infants and young children with congenital heart defects (CHD) have been shown to be a particularly vulnerable population developing severe lower respiratory tract infections (LRTIs) caused by RSV. The severity of infections in children with CHD was significantly higher than severity in children without CHD [2].

This chapter will provide an overview of the current state of knowledge regarding RSV infections in children with CHD. In particular, we try to elucidate the mechanisms for the susceptibility of children with congenital heart defects to experience critical illness from RSV LRTI.

2. Mechanisms of susceptibility caused by congenital heart disease

In general pulmonary compliance and airway resistance determine the breathing. The airways of young infants have greater airway resistance due to their smaller diameter. Spontaneous breathing of infants is characterized by a functional residual capacity that is less than the closing capacity, which leads to areas of mechanical collapse of the alveoli. As a result the infant itself is more susceptible to develop ventilation/perfusion mismatch and is at higher risk for respiratory problems just from anatomy and pathophysiology irrespective of congenital heart disease [3].

As cardiac and pulmonary function is closely related, the baseline risk of the young infant is increased by several predisposing factors due to CHD.

Pulmonary sequelae and complications of CHD can be anatomical due to compression of the lung by, e.g., cardiomegaly, subsequently causing atelectases or airway malacia. Surgical or anesthesiologic trauma can result in chylothorax, subglottic stenosis, and laryngeal or phrenic nerve palsy leading to respiratory distress [4].

On the other hand, in particular the altered hemodynamics in CHD contributes to an increased vulnerability of the lung. In this context cardiac defects can be categorized in three main categories: (1) those with left-to-right shunt lesions, (2) those with right-to-left shunt lesions, and (3) those with more complex mixing patterns [5].

2.1 Left-to-right shunt lesions: pulmonary overflow

Typically CHDs with left-to-right shunt are acyanotic. They include atrial septal defects (ASDs), ventricular septal defects (VSDs), patent ductus arteriosus (PDA), atrioventricular septal defects (AVSDs), or double outlet right ventricles (DORV) with normally related great vessels (i.e., with VSD physiology). Very rarely coronary fistula or other extracardiac shunts are detected to cause volume overload of the right heart and the lungs.

When there is unrestricted communication between systemic and pulmonary circulation, the shunt volume is depending on the relative resistance in the two circuits with physiologically lower pulmonary resistance. During the normal transition of an infants' blood circulation in the first months of life, the decrease of pulmonary arteriolar resistance leads to an increase of left-to-right shunt. As a result the pulmonary blood flow is increasing (see **Figure 1**). Subsequently the lung volume and pulmonary artery pressure are elevated, and finally the capillary and left atrial pressures increase. At the end lung edema develops with high lung resistance. Alveolar edema and thus higher lung weight result in reduced lung compliance and therefore a decreased ventilation/perfusion ratio leading to intrapulmonary mismatch and eventually hypoxemia.

2.2 Right-to-left shunt lesions: diminished pulmonary flow

Intracardiac right-to-left shunt leads to cyanosis. The basic pathophysiology of the most frequent cyanotic CHD is the tetralogy of Fallot (TOF) and includes an unrestricted communication between systemic and pulmonary circulation (VSD) and obstruction of the pulmonary outlet (see **Figure 2**). In these patients the main hemodynamic difference is reduced pulmonary blood flow, therefore lower lung volume and hypoplastic airways. The hypoplastic airways are more susceptible to obstruction and lead to higher airway resistance. Ventilation/perfusion ratio is increased in these patients causing dead space ventilation, which aggravates an already preexisting hypoxemia.

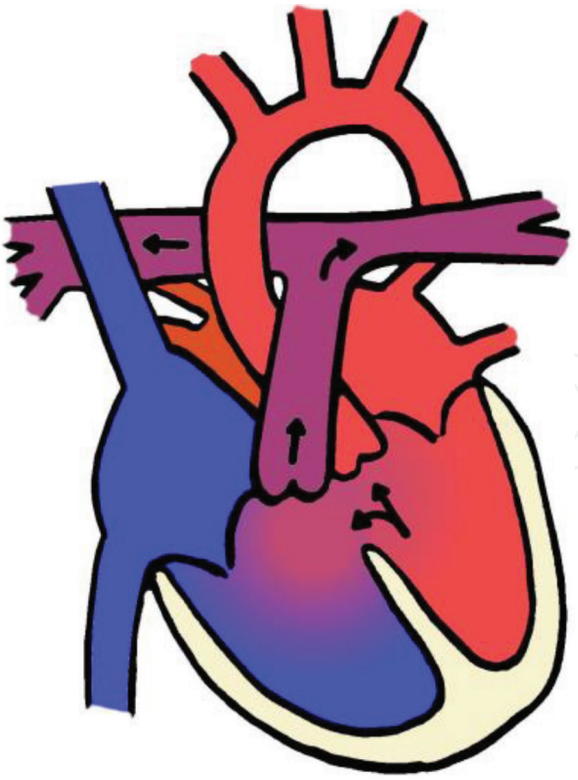

Figure 1.
VSD. Pulmonary overflow due to left-to-right shunt through a ventricular septal defect (VSD).

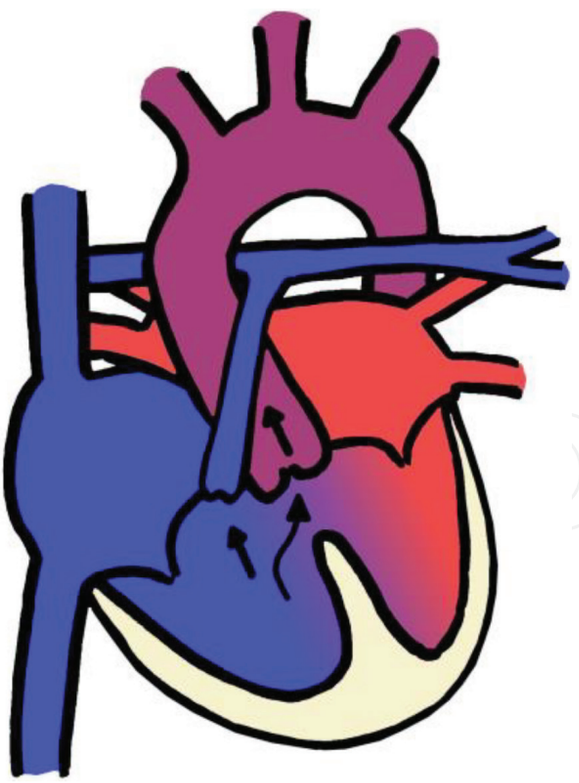

Figure 2.
TOF. Cyanosis due to right-to-left shunt through a VSD when pulmonary stenosis and hypoplastic pulmonary arteries are present in tetralogy of Fallot (TOF).

2.3 Complex CHD with mixed physiology

In patients with complex CHD, cyanosis and relatively increased pulmonary blood flow may occur at the same time. Examples are hypoplastic left heart

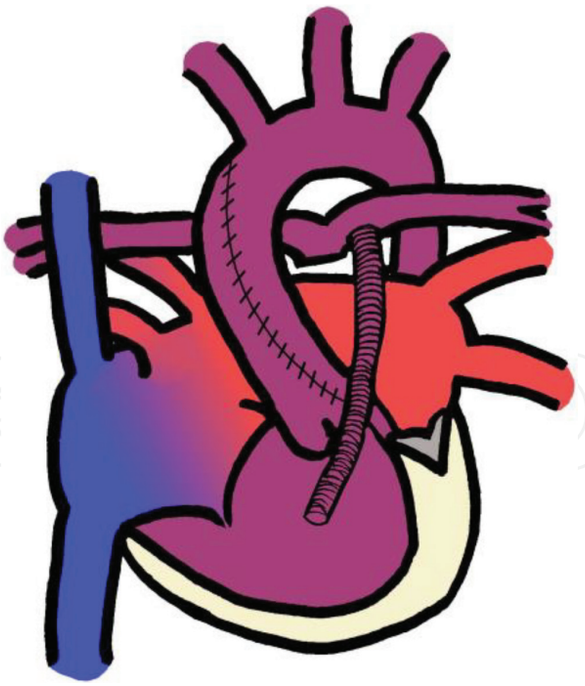

Figure 3.
Norwood-I palliated HLHS. Excessive pulmonary perfusion via Sano shunt leads to relative overflow of the pulmonary arteries, dilated left atrium resulting in higher pulmonary vein pressure causing pulmonary vein congestion.

syndrome (**Figure 3**) or other forms of functionally single ventricle like hypoplastic right heart, tricuspid atresia, or pulmonary atresia. Insertion of systemic to pulmonary shunt as part of the first stage of palliative surgery ideally leads to a balanced pulmonary and systemic perfusion but for the sake of an increased volume load and persisting cyanosis.

These patients are at high risk for ventilation-perfusion mismatch. In addition, impaired ventricular function may contribute to higher pulmonary venous pressures leading to pulmonary venous congestion and subsequently lung edema and higher pulmonary artery pressures [3, 5].

Pulmonary hypertension is known to exacerbate these effects and represents a particular predisposing factor for fatal disease [6].

In the end many complex risk factors are responsible for the susceptibility of young CHD patients. Compromised cardiorespiratory status at baseline, altered pulmonary mechanics, potential cyanosis and/or pulmonary hypertension, and ventilation-perfusion mismatch can increase the negative effects of respiratory disease in this vulnerable patient cohort unable to compensate properly for intercurrent disease. The interplay of the distinct circulation in CHD and the consequences on lung architecture and function contribute to the elevated risk to which these patients are exposed by an RSV infection [5, 7].

3. RSV-related morbidity of children with CHD

RSV accounts for about 20% of all respiratory infections in children below the age of 5 years. Most infections occur in the first 2 years of life. In healthy term infants, hospitalization rates due to RSV LRTI range from 1 to 3%, mainly in the first 6 months of life. Among high-risk populations like preterm infants with or without bronchopulmonary dysplasia (BPD), infants with CHD, Down syndrome, neuromuscular disease, immunosuppressed children, or patients with severe immune deficiency syndromes, hospitalization rates increase up to 10% [8].

As shown in a systematic review as part of the RSV Evidence—A Geographical Archive of Literature (REGAL) series published in 2017 including 38 studies reporting RSV-associated morbidity and mortality, the risk and burden of RSV in CHD still remain serious. RSV hospitalization rates were generally high in young children (<4 years) with CHD varying between 14 and 357/1000 patients. Infants (<2 years) with CHD had a more severe course of RSV infections than patients without CHD. Duration of hospital stay was 4.4–14 days, up to 53% of them requiring intensive care. Case fatality rates of up to 3% were associated with RSV LRTIs in children with CHD. RSV infection in the perioperative period of cardiac surgery and nosocomial infections in ICUs also represent an important cause of morbidity [9].

A recent investigation in Austria analyzed data on RSV-related hospitalizations in infants and small children in their first three RSV seasons (November–April). The study was performed retrospectively and included children with CHD born between 2004 and 2008. The study cohort included 602 patients of whom 451 (74.9%) had hemodynamically not significant CHD (HNS-CHD), 102 (16.9%) had acyanotic, and 49 (8.1%) had cyanotic hemodynamically significant CHD (HS-CHD). Pulmonary hypertension was present in 48 of 151 (31.8%) patients with hemodynamically significant CHD. Overall incidence of RSV-related hospitalizations was 9.6%. Hospitalization rates between hemodynamically significant (10.4%) and not significant CHD (7.3%) did not differ significantly. The median duration of hospitalization was 8.5 days, whereas in HS-CHD the length was 14 days compared to 7 days in HNS-CHD. These results demonstrate the more severe course of RSV infections in children with hemodynamically significant disease. The median duration of supplemental oxygen was 1 day (0–38 days). 22.4% of children were treated at the ICU; the median duration of ICU stay was 10 days (2–70 days), and the median duration of mechanical ventilation was 4 days (0–38 days). Children with hemodynamically significant disease and early heart surgery were less often hospitalized compared to those with delayed cardiac surgery [10].

In order to investigate case fatality rates in young children hospitalized because of RSV LRTIs, a systematic review of 34 articles was conducted in 2012. The case fatality rates for RSV-associated bronchiolitis and pneumonia among patient collectives of children, who are at particular high risk, were compared. The subgroups included (1) preterm infants, born before 37 gestational weeks, (2) children with diagnosed bronchopulmonary dysplasia (BPD) within the first 2 years of life, and (3) children with diagnosed CHD within the first 2 years of life. Case fatality rate among preterm infants was 1.2% (0–8.3%, median 0%), among children with BPD 4.1% (0–10.5%, median 7.0%) and among children with CHD 5.2% (2.0–37%, median 5.9%). While case fatality estimates among children not at high risk ranged from 0 to 1.5% (weighted mean 0.2%, median 0.0%), case fatality rates among children at elevated risk of RSV LRTI were significantly higher with the highest case fatality rate for children with diagnosed CHD [11].

All these papers underline the fact that infants and children with CHD especially when hemodynamically significant represent an extremely sensitive patient collective when it comes to RSV disease. Most strikingly they tend to have a more severe course and worse outcome of LRTIs due to RSV.

4. Prevention of RSV

RSV is the most common cause of LRTIs in infants and toddlers and under certain circumstances like in HS-CHD puts the children at elevated risk to develop respiratory or cardiac failure. Therefore, specific infection control measures are necessary to prevent severe RSV infections [12].

Comprehensive hygiene measures are efficacious and cost-effective in preventing the spread of RSV and should always be advocated as a main prophylactic factor. Breast feeding and avoidance of exposure to tobacco and other smoke are further important facts in the prevention of RSV disease [13, 14]. Delayed day-care attendance in high-risk populations may represent a preventive factor from acquiring RSV infections [15].

As mentioned above early surgical correction of CHD remains a prophylactic factor for severe RSV LRTI [10].

Although vaccine candidates have been in clinical evaluation for nearly 50 years, none, to date, have reached licensing. Palivizumab, a humanized monoclonal antibody, is currently the only intervention licensed for the prevention of severe RSV disease [8].

4.1 Palivizumab prophylaxis

In June 1998, palivizumab was licensed by the US Food and Drug Administration (FDA) for prevention of serious LRTI caused by RSV in pediatric patients, who are at increased risk of severe disease including young children suffering from CHD [16]. The efficacy and safety of palivizumab have been evaluated in many multicenter randomized controlled trials as shown in the following data [17–19].

In 2003 a prospective, randomized, double-blind, placebo-controlled multicenter trial including 1287 children with CHD was published. The study was conducted in the RSV seasons 199–2002 (seventy-six centers in the USA, six in Canada, three in Sweden, four in Germany, six in Poland, four in France, and six in the UK). The primary objective was to compare the safety, tolerance, and efficacy of palivizumab with placebo. The secondary objectives were to determine the effect of monthly administered palivizumab on hospitalization outcomes (total hospitalization duration, days with increased oxygen requirement, incidence, and total days of ICU stays and RSV-associated mechanical ventilation), as well as to describe the effect of cardiac bypass on serum palivizumab levels and determine the palivizumab levels before the second and fifth doses.

Children aged less than 24 months, who had documented hemodynamically significant CHD, not yet corrected or partially corrected, were included. Patients were randomly assigned 1:1 to receive either 5 monthly (every 30 days) intramuscular injections of 15 mg/kg body weight palivizumab or placebo. Children were followed for 150 days for hospitalization and occurrence of adverse events. Monthly prophylaxis with palivizumab was associated with a 45% relative reduction in RSV hospitalization rate (9.7% in the placebo group, 5.3% in the palivizumab group). The length of total hospital stays was reduced by 56% (129 days in the placebo group vs. 57.4 days in the palivizumab group), days with increased oxygen requirement were reduced by 73% (101.5 days placebo vs. 27.9 days palivizumab), days at ICU were reduced by 78%, and days on mechanical ventilation showed a 41% reduction.

Regarding safety and tolerability, the incidence of adverse events in the palivizumab and placebo group was similar. None of the children had drug-related severe adverse events.

The effect of cardiopulmonary bypass on serum palivizumab levels showed a notable decrease (58%) of antibody titers making early restart of palivizumab injections necessary [17].

Another paper documenting the effects of palivizumab in subjects with CHD was published in 2008. During the RSV seasons 2000–2004, data from 19,548 subjects who received immunoprophylaxis with palivizumab were collected prospectively in the palivizumab outcomes registry. One thousand five hundred subjects with CHD (7.7% of the entire cohort) were enrolled. Seventy-one percent had acyanotic CHD. About 1.9% of patients prophylactically treated with palivizumab

were hospitalized because of RSV infections, compared to 1.2% of patients included in the registry without CHD, which are low hospitalization rates compared to hospitalization rates before immunoprophylaxis [18].

A further study evaluated the impact of palivizumab prophylaxis on RSV hospitalizations among children with hemodynamically significant CHD by comparing the outcome before and after palivizumab prophylaxis. The American Academy of Pediatrics (AAP) revised the bronchiolitis policy statement and recommended the use of palivizumab in children younger than 24 months old with hemodynamically significant CHD in 2003. California statewide hospital discharge data from years 2000 to 2002 (pre-AAP policy revision) were compared to those from years 2004 to 2006 (post-AAP policy revision). Overall RSV hospitalization rate was 71 per 10,000 children younger than 2 years. 3.0% were children with CHD and 0.50% hemodynamically significant CHD. HS-CHD patients accounted for 0.56% of RSV hospitalizations in 2000–2002, compared to 0.46% RSV hospitalizations in 2004–2006, which means a 19% reduction in RSV hospitalizations among HS-CHD patients after 2003 [19].

4.2 Recommendations for the use of palivizumab in RSV prevention

As shown in many trials, RSV infections still represent increased complication rates in high-risk populations like infants and young children with CHD [2, 10, 11, 20]. There is consensus that palivizumab currently is the only licensed immunoprophylaxis that can and should be offered [21–33].

In this subsection the guidelines and recommendations for palivizumab use in children with CHD in the German-speaking countries will be compared to the guidelines of the USA, the UK, and Canada [21–30].

Table 1 summarizes the most important points of the latest recommendations.

There are substantial differences particularly regarding the age groups of children with CHD, who shall or may receive immunoprophylaxis. All national committees agree on the fact that only children with hemodynamically significant CHD shall get palivizumab. Therefore, if the CHD is considered not hemodynamically significant, i.e., without indication for corrective surgery, intervention or cardiac medication, for example, small atrial septal defects (ASDs), small ventricular septal defects (VSDs), patent ductus arteriosus (PDA), mild aortic or pulmonary stenosis, or mild coarctation, there is no indication for palivizumab. After corrective surgery or intervention is performed, there is no need of palivizumab anymore as the risk is no longer elevated, unless the patients require further cardiac medication or there are other risk factors for severe RSV disease. In this case, the administration of palivizumab after cardiopulmonary bypass shall be given as soon as the patient is stable.

The definition for hemodynamically significant CHD is not consistent throughout the national recommendations.

All of them have in common that cyanotic CHD is considered significant, as well as the presence of pulmonary hypertension. While the recommendations in the USA suggest prophylaxis for moderate and severe pulmonary hypertension (PH), in Switzerland palivizumab shall just be offered for children with severe PH [25, 28].

The latest American Academy of Pediatrics (AAP) recommendations suggest prophylaxis for children, who are born within 12 months of onset of the RSV season and suffer from hemodynamically significant heart disease. Consultation with a cardiologist for decisions about prophylaxis is recommended for patients with cyanotic heart disease. Children with acyanotic HS-CHD, who are receiving medication to control congestive heart failure and will require cardiac surgical procedures, and infants with moderate to severe pulmonary hypertension, as well as children younger than 2 years who undergo cardiac transplantation during the RSV season may be considered for palivizumab prophylaxis [25].

Country	Age	Type of cardiac disease
Austria	<24 m	HS-CHD • Cyanotic or acyanotic • Pulmonary hypertension Myocarditis, dilatative cardiomyopathy, congestive heart failure
	>24 m	High-risk constellation
Germany	<6 m	"Shall" HS-CHD (requires surgery or intervention) • Cyanotic • Pulmonary hypertension • Pulmonary venous congestion Congestive heart failure, requires medication
	6–12 m	"Can"
Switzerland	<12 m	HS-CHD • Cyanotic • Pulmonary hypertension • No surgery before RSV season Congestive heart failure
USA	<12 m	HS-CHD • Cyanotic or acyanotic • Pulmonary hypertension Cardiomyopathy requiring medication for congestive heart failure post-heart transplantation
	12–24 m	
Canada	<12 m	HS-CHD • Cyanotic or acyanotic • Requiring corrective surgery • On cardiac medication
	12–24 m	Ongoing HS-CHD case-by-case
UK	<12 m	HS-CHD Plus significant co-morbidities

Table 1.
Recommendations of different national committees on palivizumab prophylaxis in children with CHD.

The dosage of palivizumab is 15 mg/kg body weight in all recommendations. Prophylaxis shall be provided in the RSV season, which in the northern hemisphere is November until March, with slight differences in some US areas. Five monthly doses of the antibody shall be administered to provide antibody levels for 6 months.

Another important factor is to improve compliance by parental education. A large study from the Canadian registry of palivizumab found out that adherence to the monthly injection regimen was significantly associated with a lower incidence of RSV infections [34].

4.3 Pharmacoeconomics

Due to the high costs of palivizumab, which exceed the costs of RSV-related hospitalizations, the cost-effectiveness of the product is considered controversial [19].

A cost-utility trial performed in Spain published in 2017 estimated the cost-effectiveness of immunoprophylaxis with palivizumab versus placebo among

children with CHD. It concluded not only costs of hospitalization but also the impact of delayed cardiac surgery and the complications of performed surgery despite infections. The sequelae of asthma and allergic sensitization were put into calculation as well as indirect costs like parental absence from work. The model demonstrated that palivizumab prophylaxis results in more quality-adjusted life years (QALY) than placebo in children with CHD. Palivizumab prophylaxis was shown to be a cost-effective health-care intervention according to the commonly accepted standards of cost-effectiveness in Spain [35].

A nationwide cost-utility study based on epidemiological data over 16 RSV seasons performed in Austria compared the costs per QALY years in high-risk populations. Overall these long-term epidemiological data suggest that palivizumab is cost-effective in the prevention of RSV diseases in all groups. The results showed lowest costs per QALY years in patients with CHD (8484€) compared to 26,212€ in preterms and 24,654€ in BPD patients [36].

Data on cost-effectiveness still remains controversial but considering the limited treatment strategies for severe RSV infections and possible severe consequences in this especially vulnerable patient cohort may actually justify the costs of this only licensed immunoprophylaxis.

5. Conclusion

LRTIs caused by RSV among children with CHD put patients under high risk of developing respiratory or congestive heart failure. Regarding the increased fatality rates of RSV infections among infants and young children with CHD, immunoprophylaxis with palivizumab may be justified in this patient collective. Used properly (starting in time with regular repetitions throughout the RSV season) palivizumab leads to a significant decrease in RSV-related hospitalization rates, as well as ICU days, days on mechanical ventilation, and days on supplemental oxygen. Unless a vaccine against RSV is found, immunoprophylaxis with palivizumab remains the only way to reduce the burden of RSV disease among this high-risk patient collective at the moment.

Conflict of interest

None.

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