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Respiratory Syncytial Virus prophylaxis and the " special population"

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ABSTRACT

Bronchiolitis is the most frequent airway infection in the first 2 years of life, and the respiratory syncytial virus (RSV) is the virus more frequent responsible. In selected high-risk groups, RSV may cause severe respiratory disease leading to hospitalisation, need for mechanical ventilation, and even death. These high-risk groups include children with congenital heart disease, infants with neuromuscular impairment, cystic fibrosis, down syndrome, immunodeficiency syndromes and others specific conditions. In these high-risk populations defined in literature as "special population", a 3- to 10-fold increase in the rate of RSV hospitalisation has been observed, justifying RSV specific prophylaxis with Palivizumab, a monoclonal antibody that binds a viral glycoprotein epitope and blocks the link between RSV and target cell. Evidence of safety and efficacy of RSV prophylaxis in these populations is lacking. Given the low incidence of these conditions, randomised clinical trials are not feasible. The purpose of this paper is to give an update from the literature of various conditions at higher risk to develop severe RSV infection, and to offer an overview of the efficacy of Palivizumab in preventing RSV infection in these specific populations.

Keywords: respiratory syncytial virus; special population; palivizumab; down syndrome; congenital heart disease; immunodeficiency.

INTRODUCTION

Bronchiolitis is the most frequent airway infection in the first 2 years of life, and the respiratory syncytial virus (RSV) is the virus more frequently responsible (1). Bronchiolitis causes hospitalization in the first three months, a period in which maternal protective antibodies gradually decline (2).

Numerous evidences demonstrate the deleterious consequences of bronchiolitis (3-5), in particular if those caused by RSV (6, 7). Mortality data are not negligible; most studies of the last 30 years are focused on increased respiratory morbidity as a result of this infection. Children, especially those born preterm, after RSV bronchiolitis might develop bronchospasm and/or severe asthma with a higher frequency than those who did not (8-13). Numerous studies have documented an association between respiratory RSV infection and recurrent wheezing, asthma and allergic sensitization (9).

About 20 years ago, the US Food and Drug Administration approved the use of Palivizumab (PVZ) in children at high risk of severe bronchiolitis, a humanized mouse monoclonal antibody that binds a viral glycoprotein epitope and blocks the link between RSV and target cells (14, 15).

The American Academy of Pediatrics (AAP) has repeatedly updated PVZ recommendations (16, 17), according to risk-benefit balance. The most restrictive indications for the use of the monoclonal antibody are in part related to the high cost of the drug. In Italy, PVZ has been introduced in 2004 and similarly its indications were revised many times, maintaining more flexibility respect to AAP guidelines. Since 2016 AIFA extended the indication of PVZ to children with comorbidities, such as affected by congenital neuromuscular disorders, severe tracheo-bronchial malformations, and primary or secondary immunodeficiency (18, 19). The use of PVZ in premature babies and patients affected by bronchopulmonary dysplasia it is not the topic of the present article, because it will be widely discussed elsewhere. The approach adopted in children worldwide with chronic pulmonary diseases (eg, pulmonary anatomic anomalies, cystic fibrosis), neuromuscular diseases or immunodeficiencies, considered in any case potentially risk classes, is still controversial. It is well known that RSV infections may be severe and even potentially fatal in specific populations of high-risk newborns and infants.

BURDEN OF DISEASE IN SPECIAL POPULATIONS

Prophylaxis with PVZ is also advocated in a limited number of clinical conditions with additional risk factors or on specific underlying diseases that may determine an increased risk for severe RSV disease. Historically, gestational age was the main criteria in order to identify groups and populations for PVZ, reflecting the philosophy that “the more immature, the more at risk of severe RSV infection”. However, there are other situations that have the same or higher risk to develop a

severe RSV infection, and consequentely may need PVZ prophylaxis.

In selected high-risk groups, RSV may cause severe respiratory disease leading to hospitalisation, need for mechanical ventilation, and even death. These high-risk groups include children with congenital heart disease (CHD), infants with neuromuscular impairment, cystic fibrosis, Down syndrome and immunodeficiency syndromes (20- 28).

For these children, bronchiolitis is more severe and the risk is not associated with immaturity of the respiratory tract but rather with the presence of specific anatomical, functional, immune and pathophysiological conditions (29-32). Data obtained by Canadian Registry (CARESS) and the Torino-Verona Italian Registry over the 2002–2014 RSV seasons and demonstrated that infants with neuromuscular disorders (7.88%), airway anomalies (5.95%), bronchopulmonary dysplasia (4.75%) and hemodynamically significant congenital heart disease (4.10%) had the highest risk of hospitalization (29).

Among these specific groups of infants, prophylaxis with PVZ is generally recommended only for those where the benefits of receiving such prophylaxis have been documented in randomised clinical trials.

Arnold was one of the first author that identified in the “special population” a morbidity similar to those with BPD. Patients with cystic fibrosis, recurrent aspiration pneumonitis, pulmonary malformation, neurogenic disorders interfering with pulmonary toilet, tracheoesophageal fistula present no significant differences in duration of hospitalization, intensive care unit (ICU) admission, duration of ICU stay, mechanical ventilation and duration of mechanical ventilation compared to BPD patients, suggesting that prophylactic interventions against RSV should also be considered in these groups (20).

A multicentre study developed by the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) reported a significantly year-to-year variation in the frequency of RSV infection, with a peak during the 1989-1990 winter noted by the majority of centers. The high-risk groups included patients with congenital heart disease, chronic lung disease, immunodeficiency, age less than 6 weeks, gestational age less than 36 weeks, and hypoxia (defined as oxygen saturation less than 90% or arterial oxygen pressure less than 60 mm Hg). In particular, significantly more patients with underlying cardiac disease (3.4%) or lung disease (3.5%) died. Immunocompromised patients had the longest hospital stay, followed by those with underlying cardiac or pulmonary disease, who also required oxygen supplementation for a significantly longer period (33).

In these high-risk populations defined in literature as “special population”, a 3- to 10-fold increase in the rate of RSV hospitalisation has been observed, justifying RSV specific prophylaxis with

PVZ. The main purpose of this paper is to give an updating on congenital heart diseases, lung diseases, cystic fibrosis, neuromuscular diseases, and congenital or acquired immune deficiencies, considered at higher risk to develop severe RSV infection and secondarily an overview of PVZ efficacy in these specific populations.

PREMATURITY AND BRONCHOPULMONARY DYSPLASIA (BPD)

The use of PVZ in premature babies and patients affected by bronchopulmonary dysplasia will be widely discussed elsewhere. However, many studies demonstrated that PVZ reduced significantly the hospitalization due to RSV in children with prematurity or BPD (14, 34-36). It is already known that PVZ reduces need of oxygen, hospital days with a moderate/severe lower respiratory tract illness, and incidence of intensive care unit admission (14).

CONGENITAL HEART DISEASE (CHD)

In children with CHD, lower respiratory tract infections caused by RSV are associated with significant morbidity and mortality (37, 38). Studies indicate that the mortality rate in this population is approximately 3% (39). In particular, the results of a randomized, double-blind, placebo-controlled trial conducted in 1287 children with hemodynamically significant CHD randomly assigned to receive PVZ or placebo, showed a 45% reduction in RSV hospitalizations ($p = 0.003$) for children given prophylaxis with PVZ compared with those treated with placebo (40). Two months following the publication of this study, the AAP revised their policy statement to recommend RSV prophylaxis for children age 24 months or younger who have hemodynamically significant CHD (41).

Infants with symptomatic cardiac disease had a more complicated course of RSV bronchiolitis with longer hospital stay, more frequent intensive care admission, longer intensive care stay and were more likely to receive respiratory support (42). These data are confirmed by MacDonald et al. that also identified pulmonary hypertension as an additional risk factor in these patients, particularly associated with severe RSV illness (38).

A prospective, multicentre, epidemiologic study conducted in 57 hospitals in Spain covering four seasons (2004 –2008), demonstrated that children with hemodynamically significant CHD who received adequate RSV prophylaxis had a 58.2% (95% CI: 37.6–78.33) relative reduction in RSV hospitalization (43).

These results are confirmed by the SINERGY study, a retrospective, multicentre, and epidemiologic study, involving 11 Italian centers. Data collected through hospital database searches of children <2 years old, born between 2007 and 2012 and hospitalized for bronchiolitis, revealed that 27 (77.1 %)

did not receive prophylaxis against RSV and 8 (22.9 %) received prophylaxis (p<0.0001), indicating that passive immunoprophylaxis might prevent hospitalizations for bronchiolitis (44). On the other hand, a Californian study demonstrated that reduction in RSV hospitalization rate for hemodynamically significant CHD patients was <20%, equivalent of seven fewer RSV hospitalizations per year (45).

From the numerous observational studies reported in literature there are not yet univocal interpretations and results are still conflicting, mainly because of their limited significance due to the poor number of enrolled CHD patients (19, 46-47).

Nevertheless, updated AAP guidelines, published in 2014, limited the PVZ prophylaxis to children with CHD who at the start of RSV season were <12 months of age (48). Thus the cost-benefit ratio of PVZ prophylaxis for children with CHD continues to be a much debated issue. Walpert et al. compared hospital discharge data of patients with CHD affected by RSV infection, before and after 2014 AAP guidelines, and observed no difference in terms of length of stay, ICU admission rate, in-hospital mortality, or direct costs for children 13–24 months old and no variations on deaths in 13–24 month olds, regardless changes of guidelines (49).

The efficacy of a monthly protocol in selected patients with hemodynamically significant CHD under 1 year of age in subtropical areas were tested in a multicentre study, comparing the pre-PVZ and post-PVZ periods. The efficacy of this protocol was more prominent in patients with cyanotic hemodynamically significant CHD. The annual respiratory syncytial virus-associated hospitalization rates also decreased significantly from the pre-PVZ to the PVZ period (from 4.8% to 2.0%; p=.038), ascertaining the efficacy of PVZ also in hemodynamically significant CHD (50).

NEUROMUSCOLAR DISODERS AND MALFORMATION SYNDROMES

Children with congenital neuromuscular diseases might have low functional residual capacity and ineffective coughing due to less thoracic muscular support, scoliosis due to decreased muscle support, decreased glottal closing ability, decreased spontaneous movement with reduction of normal ventilation redistribution, and high prevalence of gastroesophageal reflux and swallowing dysfunction, which leads to aspiration (51, 52).

In the PICNIC study was observed that severe RSV disease in neurogenic disorders is associated with significantly higher rates of intensive care unit admission and mechanical ventilation when compared to children with a history of bronchopulmonary dysplasia (20).

A German prospective multicentre RSV database, confirmed these data, identifying neuromuscular disease as an independent risk factor for ICU admission (OR 4.94, 95% CI 2.69–8.94) and mechanical ventilation (OR 3.85, 95% CI 1.28–10.22) (52).

An Austrian study, involving 863 premature infants (29–32 weeks) hospitalised for RSV infection, observed that neurological disease doubled the risk for re-hospitalisation (OR 2.157, 95% CI 0.770–5.247) (47).

A cohort study aimed at determining the risk factors for death in children with severe RSV infection, requiring ICU admission, revealed that 4.4% of 406 patients, included over an 8-years time period, died from RSV-related disease (53). All children who died becuase of RSV infection had pre-existing medical conditions. In particular, neuromuscular disease was present in 15% of them.

Furthermore, neuromuscular diseases are often associated with a number of malformation syndromes or sequences (e.g. Pierre-Robin, CHARGE, Jeune syndrome, craniofacial dysostosis associated and airway anomalies such as severe laryngo-tracheomalacia and oro-labial clefts etc.) with impairment of breathing, sucking and swallowing that associated with the long-term respiratory morbidity from RSV bronchiolitis may justify the use of prophylaxis (32, 52, 54-58).

CONGENITAL DIAPHRAGMATIC HERNIA (CDH) AND OTHER SEVERE RESPIRATORY DISEASES

The results of a Delphi process involving 48 experts in Spain showed a uniform concordance on the off-label indications of palivizumab in clinical practice in infants with severe respiratory diseases. In particular, the clinical scenario of “congenital malformations of the lung and tracheobronchial tree” showed the highest percentage of agreement (59).

Consensus was reached in 56% of the statements regarding appropriateness of palivizumab use in children with the following disorders: severe respiratory involvement due to neuromuscular disease, congenital or acquired immunodeficiency, storage disease, cystic fibrosis, diseases involving impaired ciliary clearance, esophageal atresia and/or tracheoesophageal fistula with the need for surgery, diaphragmatic hernia, bronchopulmonary malformations, severe tracheomalacia, lung transplantation (either recipients or patients in the waiting list for lung transplant), oxygen-dependency for severe interstitial lung disease and severe pulmonary hypertension.

Infants who survive to a congenital diaphragmatic hernia (CDH) have 24–40% risk of recurrent respiratory tract infections, independently associated with duration and assistance during their neonatal course, which may impact ipsilateral lung growth (60, 61). Also in these patients RSV infection should be presented with a more severe course, because of residual, obstructive airway disease. Since 1997, Muratore et al. have instituted routine prophylaxis for all CDH patients aged <2 years and 36% required treatment for respiratory distress without admission to intensive care (62). In an 8-year review of 21 survivors with severe CDH, 40% (2/5) suffered a recurrence of CDH

following RSV infection (63).

The North American chILDRN study, which included children under the age of 2 years with childhood interstitial lung disease (chILD), confirmed by lung biopsy, reported a mortality rate of 30%, with 50% of patients experiencing ongoing morbidity (64). These children with severe chILD often receive high dose of corticosteroids. They may be at high risk of hospitalization for bronchiolitis, including that due to RSV infection, but the very low prevalence of chILD, estimated at one case/million, prevents from being performed a randomized controlled trial to demonstrate the cost-efficiency of PVZ prophylaxis. In a retrospective study, conducted in France in 24 children with chILD and on corticosteroid treatment, during their first two RSV seasons, a higher rate of RSV-related hospitalization and a longer hospitalization compared to the general population were observed (65). Thus, eventhough the effectiveness of PVZ prophylaxis in this population remains to be demonstrated, these patients are at high risk of hospitalization for RSV-bronchiolitis. Prophylaxis with PVZ is the main strategy for the "prevention" of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.

Children with cystic fibrosis (CF) are prone to recurrent lung inflammation, bacterial colonisation and subsequent chronic airway disease, so that they are considered at high-risk for RSV infection. Respiratory viruses have been implicated in pulmonary exacerbations that may lead to irreversible pulmonary damage (66), causing a more rapid onset of wheezing and bacterial superinfections.

It is unclear if PVZ can prevent respiratory syncytial virus hospitalisations and intensive care unit admissions in children with cystic fibrosis. A systematic review of literature evaluated the efficacy of PVZ compared with placebo. Only one randomised controlled trial (186 infants) was identified, comparing five monthly doses of PVZ to placebo in infants up to two years old with cystic fibrosis. A systematic review of literature evaluated the efficacy of PVZ compared with placebo. Only one randomised controlled trial (186 infants) was identified, comparing five monthly doses of PVZ to placebo in infants up to two years old with cystic fibrosis. However, the results are inconclusive. The overall incidence of adverse events was similar in both groups. Six months after treatment, the authors reported no clinically meaningful differences in outcomes (67). The data support the need of additional randomised studies to establish the safety and efficacy of PVZ in children with cystic fibrosis.

In a study conducted in Denmark, children with CF aged <2 years have a 4.3-fold increased risk of hospitalization and a 1.3-fold longer duration of hospital stay than healthy children (68).

Actually, there is limited evidence to support the use of PVZ in CF patients. Kua et al. reviewing a total of 10 studies involving 3891 patients with CF (69), reporting that PVZ prophylaxis had a positive impact on the rate of RSV hospitalization.

In an 8-year retrospective study of 75 CF patients aged <18 months, 35 received prophylaxis and showed a trend for shorter hospital stay for respiratory illness with fewer RSV infections (70). These evidences suggest that PVZ may have a potential role in reducing RSV hospitalization in children aged less than 2 years with CF. However, additional research is warranted to better understand the efficacy and safety of prophylactic PVZ in infants with CF. Furthermore, it is already known a close correlation between RSV and Pseudomonas aeruginosa. The proliferation and epithelial adhesion of the latter pathogen is facilitated by the concomitant presence of RSV (70). The preliminary results of a recent study suggest a trend towards less RSV-related hospitalizations in children with CF treated with PVZ, however the study involved few patients and results are to be considered as exploratory (71). Significant differences in length of overall stay was demonstrated in CF patients with respiratory-related illness and RSV, suggesting a lower illness severity in the PVZ group versus not prophylaxes group. This data were collected retrospectively in CF infants aged <2 years in Alberta, Canada, from 2000 to 2017. In RSV hospitalized subjects, those that underwent PVZ prophylaxis experienced shorter length of overall stay ($p=0.048$). At the same time, also patients with respiratory-related illness prophylaxes with PVZ showed shorter overall intensive care unit ($p=0.003$) and hospital length of overall stay ($p=0.04$) (72).

DOWN SYNDROME

Down Syndrome (DS) itself has been shown to be a risk factor for severe RSV infection, even in the absence of congenital heart disease. This was confirmed by a cohort studies conducted in the Netherlands, demonstrating that the incidence of RSV-related hospitalizations is of approximately 10% (about 3– 4 times higher than in the normal population) in all DS subjects, with and/or without congenital heart disease (73). Several mechanisms responsible for severe RSV bronchiolitis in this population may be considered. DS patients are known to have small thyme and some degree of cellular immunodeficiency caused by thymic insufficiency, which may also be related to susceptibility to severe respiratory viral infections. In DS, anatomical, physiological or functional abnormalities of the respiratory system, should be taken into account when assessing the risk of severe RSV infections. This data are confirmed by a prospective observational registry conducted in Germany, including 249 children below 25 months of age with DS, receiving PVZ prophylaxis between 2009–2016 seasons. The RSV-related hospitalization rate in patients with DS was 1.20%, and the hospitalization rate in patients without DS was 0.71%, revealing important differences between patients with and without DS concerning the main indication for PVZ use and additional risk factors (74).

This finding suggests that specific prophylactic measures are warranted in these children during

their first two years of life (73, 75-76).

IMMUNODEFICIENCY

CD4-and CD8-specific as well as Th1- and Th2-cell specific immune responses, which are responsible for viral clearance and resolution of the RSV infection, are pivotal against RSV. Immunodeficiency predispose to greater and more prolonged viral loads. Patients at greater risk are those with immunodeficiency affecting the T lymphocyte response, while a decrease in effectiveness of the B-mediated antibody immune response is not as severe (77, 78).

In particular, both primary or secondary immunodeficiency (such as bone marrow or solid organ transplant recipients, severe combined immunodeficiency (SCID), Di George or Wiskott-Aldrich syndromes, neonatal HIV, etc.) demonstrate a marked inability to clear the virus, to prevent its replication, leading to pulmonary damage (29).

Hall et collaborators examined retrospectively the immunological status of 608 infants <5 years of life, hospitalized with an RSV infection over a ten year period. They identified 47 patients with immunologic abnormalities, including those receiving chemotherapy (20 cases) or steroids (22 cases) and those with primary immunodeficiency syndrome (5 cases). Immunodeficiency syndromes and patients receiving chemotherapy have higher rates of lower respiratory tract infections, 80% and 60% admission to the ICU, respectively, and 40% and 15% mortality in the two groups, compared to immunologically normal children (79).

In a ten-year retrospective cohort study of immunocompromised patients presenting with RSV disease documented at University Hospitals of Lausanne and Geneva was observed a higher burden of RSV disease in immunocompromised adults compared to children, more specifically among patients with solid tumors, leukaemia/lymphoma or those requiring chronic immunosuppression for connective tissue disease or vasculitis. In particular, 47.8% of children presented with lower respiratory tract infection and were more likely to be admitted to hospital compared to adults (75% vs 62.9%, p= 0.090), conversely inpatients admitted to the intensive care unit (17/19) or those who died (11/11) were mainly adults (80).

Although the evidence for RSV prophylaxis in the immunodeficiency disorders exists, the number of patients in individual studies is relatively small which currently precludes the use of routine passive immunisation (78, 81).

INFANTS UNDERGOING BONE MARROW TRANSPLANTATION

Hematopoietic cell transplant (HCT) may be a risk factor for morbidity and mortality from respiratory viral infection, and in particulare for RSV infection. Fisher et al observed among 1560

HCT recipients, that 16.6% were hospitalized at least once for respiratory viral infection within 1 year after their transplant. The median age of these patients was lower than that without a respiratory viral infection (4.8 vs 7.1 years; P < .001). 48% required some respiratory support, and 14% suffered significant pulmonary sequelae. This study demonstrated that in this multicenter cohort study respiratory viral infection requiring hospitalization is relatively common in pediatric HCT recipients and contribute to significant morbidity and death (82).

At moment, is not yet recommended the prophylaxis with PVZ in this group of patients, because the cost-efficacy ratio is still debated. In a retrospective, multicenter, cohort study of 1522 pediatric HCT recipients with RSV infection, 3% of patients were diagnosed with RSV, among them 19.1% were admitted to the pediatric intensive care unit, 12.8% received invasive mechanical ventilation, and 1 died. Rowan and collaborators observed in a multicenter cohort, that RSV was not common in children following HCT. However, the few children infected with RSV required critical care (83).

HCT recipients with RSV infection, during conditioning for transplant were at higher risk for invasive mechanical ventilation. In these settings, RSV infections usually occur during regular community outbreaks of bronchiolitis and sporadic cases presenting beyond the traditional autumn–winter season.

Otherwise, recent evidence also supports immunomodulatory effects of RSV infections among lung transplant recipients, in whom a significant association between the development of chronic lung allograft dysfunction and RSV infections has recently been reported (84-86).

Early diagnosis and intervention may be the best approach to improve outcomes; however, these data should help inform interventional studies specific to each viral pathogen, also in order to identify markers to prevent which patients with RSV upper respiratory tract infection develop a fatal pneumonia and might benefit from an earlier intervention. Furthermore, timing of antiviral administration is strongly associated with clinical outcomes.

OTHER CONDITIONS

The efficacy of RSV prophylaxis in infants with pre-existing medical illness such as chromosomal and genetic disorders, those with hydrocephalus and cerebral palsy, chronic aspiration and chronic lung disease and ventilator dependency >2 years of age, are not yet well studied, and for this reason not firmly supported by national guidelines. Otherwise, there are many clinical conditions for which the decision of prophylaxis should be entrusted to the specialists:

– genetic malformation or disease with compromised respiratory and swallow functions,

– tracheotomy,

– serious syndrome or malformation (e.g., Pierre Robin, CHARGE, Jeune syndrome).

The recommendation of PVZ prophylaxis should be evaluated case by case in the single patient and should be documented by the specialists.

CONCLUSIONS

Many infants have an increased risk for severe RSV disease related either to their prematurity, or to an underlying clinical disorder, or both. The hospitalisation rates, the need for ICU admission or for mechanical ventilation in hospitalised patients and mortality are the commonly used indicators of RSV related severity. These indicators are helpful but may not reflect the true burden of disease severity, as well as its related long-term consequences. PVZ is associated with a significant decrease in the hospitalisation rate due to RSV infection in high-risk infants. However, cases of hospitalization for RSV occurring in infants after prophylaxis, described as treatment failure, have been reported. In these cases, the absence of long-lasting protection against RSV during the season in PVZ-treated infants has been attributed to uncertainties about the pharmacokinetic and pharmacodynamic features of the drug, lack of compliance or inappropriate dosing schedules in specific subgroups of patients (87-90).

Effective treatment strategies and prevention of RSV infection is the best option to decrease the burden of disease and its considerable impact on social health, especially in high-risk groups. Preventative strategies rely not only on passive prophylaxis, but also on strict hygiene measures, cohorting and avoiding possible contact with siblings or daycare attendance. Furthermore, in particular in “special population” methodologically valid scientific documentation supporting safety and efficacy of anti-RSV prophylaxis with PVZ is still lacking, and the benefits of PVZ have been assessed only in selected subgroups through studies of high methodological quality. The number of patients in individual studies is relatively small which currently precludes the use of routine passive immunisation. Probably other “special” populations exist, but the low incidence of the desease and small number of patients limit the possibility to perform randomized controlled trials.

In conclusion, prophylaxis with PVZ is actually recommended to a specific group of patients, according to national guidelines, but additional studies will be useful to identify other diseases at risk for severe RSV infection that could benefit from prophylaxis.

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Conflicts of interest

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Table 1. Palivizumab and special populations in Italy.

Special populations	Italian recommandations	Evidences of Palivizumab efficacy
Congenital heart disease	Hemodinamically significant* congenital heart disease (age < 1 year) **defined as:* *- Heart failure requiring medical therapy* *- Cyanosis with SatO2 <90%* *- Pulmonary hypertension*	Reduction in hospitalization Reduction of length hospitalization Reduction of need of respiratory support Reduction of intensive care unit admission (40, 42, 43) Conflicting results (49)
Neuromuscolar disorders	Neuromuscolar disease or ineffective cough (age < 1 year)	Reduction of intensive care unit admission and mechanical ventilation (20, 52)
Malformation syndromes	Congenital severe tracheobronchial malformations (age < 1 year)	More trials needed
Immunodeficiencies	Confirmed primary or secondary immunodeficiency (age < 2 years)	More trials needed
Down syndrome	Not specified	Reduction in hospitalization (74)
Other severe lung diseases	Not specified	Reduction in hospitalization in ILD patients Reduction of length hospitalization in ILD patients (64, 65) Conflicting results in CF and CDH patients (62, 63, 68-72)
Transplantations	After heart transplantation	More trials needed

CDH: Congenital diaphragmatic hernia
CF: Cystic fibrosis
ILD: interstitial lung disease