The Turkish Journal of Pediatrics 2024; 66: 161-170
https://doi.org/10.24953/turkjpediatr.2024.4592

Original Article

Effects of palivizumab prophylaxis on respiratory syncytial virus (RSV) infections in Montenegro

Envera Lekic[1], Ljubinka Dragas[1], Drasko Nikcevic[2], Jasmina Lekic[3], Ana Dedic[2], Ljiljana Sulovic[4]

[1]Department of Neonatology, Institute for Children's Diseases, University Clinical Center of Montenegro, Podgorica, Montenegro; [2]Department of Cardiology, Institute for Children's Diseases, University Clinical Center of Montenegro, Podgorica, Montenegro; [3]Faculty of Medicine, University of Belgrade, Belgrade; [4]Department of Pediatrics, Faculty of Medicine University of Pristina, Seat in Mitrovica, Kosovska Mitrovica, Serbia.

ABSTRACT

Background. Respiratory syncytial virus (RSV) is one of the most common pathogens causing severe lower respiratory tract disease in infancy and childhood. In newborns, young infants, and in infants with co-morbidities, the risk of severe infection is increased. Current protection against severe RSV infection is immunoprophylaxis with the monoclonal antibody palivizumab. The study aimed to assess the effects of palivizumab prophylaxis in the Republic of Montenegro in comparison to the pre-prophylaxis period.

Methods. The study was conducted in prospective/retrospective single center format in Montenegro in the Clinical Center of Podgorica, for the period 2009-2019.

Results. A total of 104 high-risk infants in the palivizumab prophylaxis program (2014-2019 RSV seasons) and 168 high-risk children without palivizumab prophylaxis (2009-2013 RSV seasons) were enrolled. A total of 51 children (49.0%) received prophylaxis for prematurity, 33 (31.7%) for bronchopulmonary dysplasia (BPD), 13 (12.5%) for hemodynamically significant heart disease/defect (HSCHD), and 7 (6.8%) for "miscellaneous" indications. In the control group most children had prematurity (101, 60.1%), followed by BPD (59, 35.1%), HSCHD (3, 1.8%), and "miscellaneous" (5, 3.4%) conditions. Readmission to the pediatric intensive care units (PICU) due to RSV infection was significantly lower in prophylaxis group (0.0 vs 16.1%, $p<0.001$). No lethal outcomes were observed in high-risk children with palivizumab prophylaxis compared to 2.4% in the control group.

Conclusions. The introduction of RSV immunoprophylaxis as well as other new protective treatment strategies for high-risk newborns led to significant improvements in infant and childcare in Montenegro. This is the first report on palivizumab prophylaxis in Montenegro, demonstrating the effectiveness and safety of palivizumab use in clinical settings.

Key words: palivizumab, respiratory syncytial virus (RSV), high-risk children, Montenegro.

Respiratory syncytial virus (RSV) is one of the most common pathogens causing severe lower respiratory tract disease in infancy and childhood.[1] In Europe, it is the most frequent cause of lower respiratory tract infections in infants up to 2 years of life. When it comes to hospitalization, most children hospitalized for bronchiolitis are infected by RSV.[2] On the other hand, RSV has proven to be a major cause of death in children in developing countries.[3]

While clinical presentation is usually very mild in adults and older children (rhinitis or coughing), in newborns, young infants, and in infants with specific comorbidities (e.g., prematurity, bronchopulmonary dysplasia/chronic lung disease [BPD/CLD], hemodynamically significant congenital heart disease [HSCHD], airway anomalies, cystic fibrosis, neurological

✉ Envera Lekic
enverarad1@gmail.com

Received 19th Jun 2023, revised 25th Nov 2023, 16th Dec 2023, accepted 21st Feb 2024.

impairments, immunocompromised) the risk of severe RSV infection is increased.[4] During the first two years of life, this high-risk group of children, which is specific in many ways, is characterized by a high sensitivity to respiratory syncytial virus infection. A difficult course and an adverse outcome of the disease can be often expected, which reduces the overall progress of the newborns.

Other infant risk factors of importance for severe RSV manifestations are age <6 months during RSV season, multiple births, male gender, siblings in kindergarten and school, passive smoking, close domestic conditions, malnutrition, lack of breastfeeding, and a family history of allergic diseases or asthma.[2]

Currently, there are no anti-RSV drugs available.[5] In September 2023, United States and European Union medical authorities approved a bivalent vaccine for active immunization of pregnant individuals at 32 through 36 weeks gestational age for the prevention of lower respiratory tract disease (LRTD) and severe LRTD caused by RSV in infants from birth through 6 months of age. This vaccine is also approved for active immunization in individuals 60 years of age and older.[6]

The most common immunoprophylaxis available is a monoclonal antibody palivizumab, which has proven to be safe and efficacious against RSV during the epidemic season.[7]

Palivizumab is a humanized monoclonal antibody that binds to the antigenic A site of the F protein on the surface of RSV, which is involved in viral attachment and the process of fusion between the virus and cell membranes, as well as between infected cell membranes, leading to syncytium formation. Palivizumab neutralizes RSV by blocking virus-to-cell and cell-to-cell fusion without any effect on virus attachment or budding.[8] Palivizumab was approved in the USA by the Food and Drug Administration (FDA) for RSV prophylaxis in high-risk children in 1998. In Europe palivizumab was approved by the European Medicines Agency (EMA) in 1999. In the early 2000s use of palivizumab was approved in over 45 countries worldwide.[9]

Although widely used, so far there is no common guideline on the use of palivizumab. Predominately mild course of RSV infections in the majority of patients and the relatively high cost of palivizumab prophylaxis are reasons for which most of the national guidelines weigh cost-effectiveness which results in variability of conclusions and recommendations.

According to Joint Committee of Vaccination and Immunization criteria, RSV prophylaxis in developed countries is required by 0.3%-1.1% of live births.[10]

In the Republic of Montenegro, current national recommendations focus on palivizumab use in following groups: extremely preterm infants (under the 28 weeks of gestational age – 28 wGA), very preterm infants (29-32 6d w GA) with 2 or more risk factors (neurological disease, sibling in day care, etc.), preterm infants suffering from CLD/BPD, as well as infants with HSCDH less than 12 months of age at the beginning of RSV season.[11]

The effectiveness (reduced risk of RSV-related hospitalizations) and safety of palivizumab administration has been confirmed in neonates with prematurity, BPD/CLD and HSCHD in three different prospective, randomized placebo-controlled trials.[12-14] However, it is not uncommon that real-life data differ from data collected in prospective controlled randomized trials. For this reason, prospective observational studies and registries from different countries are warranted to provide valuable information related to palivizumab use in routine clinical practice.

The first RSV prophylaxis season in Montenegro was in the season 2014-2015. So far, there have been no published studies on the use of palivizumab in Montenegro. The study aimed to collect prospective data on palivizumab use, demographic data, data on neonatal hospitalization events, data on the indications

for palivizumab administration, and the frequency of RSV-related readmissions in pediatric intensive care units (PICU) (from 2014 through 2019 RSV seasons). The secondary aim was to compare the results with retrospective data of high-risk children, in the period before prophylaxis was introduced in Montenegro (from 2009 through 2013 RSV seasons), which would fulfill current criteria for palivizumab prophylaxis.

Material and Methods

The study was conducted in a prospective/retrospective single-center format in the Republic of Montenegro, in Clinical Center of Podgorica, which is the only medical institution dealing with potential candidates for palivizumab immunoprophylaxis. The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Clinical Center of Podgorica (protocol code 03/01/4740/1, date of approval 14.05.2021). Informed consent was obtained from all subjects prospectively involved in the study.

The inclusion criterion was any child hospitalized for RSV infection. Data and details on the clinical presentation and course of the disease were obtained from the child's medical chart.

The statistical tests employed were Student t-test, Mann-Whitney U test, repeated measures analysis of variance (ANOVA), for continuous variables, and Fisher's exact test and Pearson chi-square test for nominal variables. A p-value of 0.05 was considered as the limit of significance. All data were examined using SPSS v. 22.0.26

Results

A total of 104 high-risk children in palivizumab prophylaxis program from 2014 through 2019 RSV seasons and 168 high-risk children without palivizumab prophylaxis from 2009 through 2013 RSV seasons were enrolled.

Demographics

Demographic data are shown in Table I. The infants enrolled in both groups were predominantly male (51.9% in the prophylaxis group; 54.2% in the control group). On average, infants had completed 30.7±4.0 wGA in the prophylaxis group and 30.1±2.4 wGA in the control group. Infants in the control group had lower birth weight and were more often twins or triplets in comparison to palivizumab group. Children with BPD who received prophylaxis were more often extremely preterm (≤28 wGA), with lower gestational age and weight average in comparison to the control group with BPD.

When comparing data for children with HSCHD, the control group was on average almost 4 weeks younger and with significantly lower birth weight than the palivizumab receiving group.

A total of 51 children (49.0%) received prophylaxis for prematurity, 33 (31.7%) for BPD, 13 (12.5%) for HSCHD, and 7 (6.8%) for "miscellaneous" indications. At the same time in control group were mostly children with prematurity (60.1%) and BPD (35.1%) ($p<0.001$). The majority of high-risk infants who received prophylaxis in the "miscellaneous" diagnostic group were diagnosed with airway congenital anomalies (3, 2.9%) in prophylaxis group; 4 (2.4%) in the control group. Other conditions in the prophylaxis group were cystic fibrosis (2, 1.9%), immunodeficiency (1, 1.0%), and neuromuscular diseases (1, 1.0%). In addition, 1 infant with HSCHD was also diagnosed with Down syndrome.

The events during hospitalization

Events during the neonatal hospitalization are shown in Table II. Most of the events were less frequent in prophylaxis group (sepsis, intraventricular haemorrhage, periventricular leukomalacia) while the duration of neonatal stay in intensive care unit was similar (64.5±31.7 days in prophylaxis group vs 66.4±23.6 days in control group).

Table I. Demographics.

		Prophylaxis with palivizumab	Control	p value
Sex	male	54 (51.9%)	91 (54.2%)	0.719
	female	50 (48.1%)	77 (45.8%)	
Multiple births – twins		19 (18.3%)	46 (27.4%)	0.020
Multiple births – triplets		1 (1%)	8 (4.8%)	
Gestational age (weeks)		30.7 ± 4.0	30.1 ± 2.4	0.188
Birth weight (g)		1620.8 ± 791.9	1448.8 ± 383.2	0.040*
Prematurity		51 (49.0%)	101 (60.1%)	
Weeks of gestation				
≤28		11 (21.6%)	17 (16.8%)	0.477
29-32		36 (70.6%)	65 (64.4%)	0.442
33-37		4 (7.8%)	19 (18.8%)	0.078
Gestational age (weeks)		30.4 ± 2.0	30.9 ± 2.2	0.348
Birth weight (g)		1452.0 ± 359.6	1515.5 ± 312.9	0.263
BPD		33 (31.7%)	59 (35.1%)	
Weeks of gestation				
≤28		23 (69.7%)	25 (42.4%)	0.012*
29-32		10 (30.3%)	31 (52.5%)	0.040*
33-37		0 (0.0%)	3 (5.1%)	0.550
Gestational age (weeks)		27.8 ± 1.4	29.4 ± 2.1	0.009*
Birth weight (g)		1100.9 ± 207.1	1263.0 ± 359.0	0.007*
HSCHD		13 (12.5%)	4 (2.4%)	
Gestational age (weeks)		37.6±3.6	33.0±0.8	0.026*
Birth weight (g)		3027.7±770.3	1740.0±240.8	0.006*
Miscallaneous		7 (6.7%)	4 (2.4%)	
Gestational age (weeks)		36.0 ± 4.7	34.0 ± 1.8	0.446
Birth weight (g)		2705.7 ± 937.8	2275.0 ± 675.4	0.444

Data are presented as n (%) or mean ± standard deviation. BPD: bronchopulmonary dysplasia; HSCHD: Hemodynamically significant heart disease/def.
* p<0.05; statistically significant

Respiratory support

Respiratory support during neonatal hospitalization was required in more than half of the subjects in both groups (71.2% in the prophylaxis group; 59.5% in control group). Duration of respiratory support averaged 13.5±16.1 days, compared to 9.6±13.1 days in the control group. Continuous positive airway pressure therapy was also more frequent in subjects in the prophylaxis group (58.7%) compared to the control group (35.7%). Oxygen therapy was required in all the subjects in the control group and in 93.3% in prophylaxis group with a duration shorter in the prophylaxis group (41.0±33.4 days) compared to the control group (46.1±19.1 days).

Preterm infants in the control group received significantly less respiratory support (mechanical and non-invasive ventilation), had longer oxygen treatment, and developed more often intraventricular haemorrhage grade 1-2 in comparison to preterm infants that received palivizumab (Supplementary Table I).

Table II. Neonatal hospitalization events.

Event	Prophylaxis with palivizumab (n=104)	Control (n=168)	p value
Days of neonatal stay (mean±SD)	64.5±31.7	66.4±23.6	0.635
Respiratory support	71.2	59.5	0.052
Duration of respiratory support in days (mean±SD)	13.5±16.1	9.6±13.1	0.022*
Surfactant	50.0	44.6	0.389
Continuous positive airway pressure	58.7	35.7	<0.001*
Oxygen therapy	93.3	100	0.001*
Duration of oxygen therapy in days, median (range)	35.5 (0.0-210.0)	42.0 (21.0-144.0)	0.001*
Proven sepsis	26.9	30.4	0.545
Retinopathy of prematurity	66.3	88.1	<0.001*
Intraventricular haemorrhage	21.2	44.6	<0.001*
Intraventricular haemorrhage grade 1-2	12.5	28.0	
Intraventricular haemorrhage grade 3-4	7.7	14.3	
Hydrocephalus	1.0	2.4	
Periventricular leukomalacia (PVL)	24.3	54.2	<0.001*

Data given as percentages (%) unless indicated otherwise.
* p<0.05; statistically significant

Similar findings were in the group of infants with BPD: children in the control group received significantly less respiratory support (mechanical and non-invasive venilation), while we found no significant difference concerning oxygen treatment, development of sepsis, or neurological complications in comparison to preterm infants that received palivizumab (Supplementary Table II).

The length of stay

When analyzing the data for infants with HSCHD, children who received prophylaxis stayed shorter in the neonatal units (21 vs. 55 days), and needed fewer days of oxygen treatment (10 vs 39 days). There were no such differences in infants with miscellaneous conditions. In both groups, we found no significant differences concerning the development of sepsis, or neurological complications (Supplementary Table III).

A total of 460 injections were administered to 104 high-risk children from 2014 through 2019 RSV seasons. Almost two-thirds of enrolled children 69 (66.3%) received five injections. The average number of injections per child was 4.4 and a median and mode of 5 injections per child.

RSV infection-related events

Children who received prophylaxis had significantly higher body weight (2752 ± 469g) compared to controls (2480 ± 457g) at discharge from the hospital (t=4,720; p<0,001). Also, there was a significant gain in body weight in every high-risk category of children that received immunoprophylaxis depending on the number of doses received (F=297.911; p=0.001) (Table III).

Readmission to the PICU due to RSV infection was significantly lower in the prophylaxis group compared to the control group (0.0 vs 16.1%, p<0.001). No lethal outcomes were observed in high-risk children with palivizumab prophylaxis compared to 2.4% in the control group during the entire study period (immunoprophylaxis - 2014 through 2019 RSV seasons; control - from 2009 through 2013 RSV seasons).

Discussion

Data presented in this paper are prospectively collected results on palivizumab usage and outcomes in 104 children from 2014 through 2019 RSV seasons, and retrospectively collected data on 168 children which would fulfill current criteria for palivizumab prophylaxis in the period before prophylaxis was introduced in Montenegro – from 2009 through 2013 RSV seasons.

Although the sample size of children receiving palivizumab in our study is much smaller compared to other studies (25,003 Canada 2005–2017[4]; 12,729 Germany; 2009–2016[15]; 3200 Russia, 2010–2014[16]; 3780 Poland, 2008–2014[17]; 589 Bosnia and Herzegovina, 2008–2014[18]) we must emphasize that this is the first study on palivizumab use in Montenegro and that only high-risk children were recruited.

In this study, palivizumab was predominately administered for primary indications. The most common indication for palivizumab administration in our study was prematurity (49%), followed by BPD/CLD (31.7%) and HSCHD (12.5%). Similar data are given in other studies although in a study by Heljic et al., there were more children with HSCHD (34.1%) compared to BPD/CLD (13.9%).[18] In data originating from the Canadian CARESS study HSCHD (10.5%) was also more frequent indication for palivizumab compared to BPD/CLD (8.4%).[4] One of the possible reasons for the lower frequency of HSCHD in our study could be the fact that all the infants with HSCHD undergo surgical treatment in institutions out of Montenegro, making the follow-up almost impossible.

The frequency of "miscellaneous" indications (6.8%) was higher compared to Bosnia and Herzegovina (2.2%)[18] and Germany (5%)[15], but lower compared to Canada (17.8%).[4] Since most guidelines on palivizumab use focus on the same three conditions for which palivizumab is most frequently prescribed in Montenegro, the only way to explain the differences in rates for the use of palivizumab in "miscellaneous" indications would be the level of strictness authorities apply in "off label" prescribing, in other words to which degree authorities are willing to accept physicians' assessment in determining priorities.[19,20]

RSV hospitalization rate in our study was 0%, which is lower compared to other studies in which RSVH ranges from 0.7% in Germany[15], over 1.6% in Canada[4] to 8.8% in France.[21] Again, we must mention that rehospitalization data in our study is related to the readmission of high-risk infants with severe RSV infections to the PICU only, both in the group with palivizumab prophylaxis and in the control group without palivizumab administration.

When comparing data to retrospective control demographic characteristics were similar with subjects being predominately male and of similar gestational age, with just a bit lower birth weight in the control group. As for medical conditions/indications for palivizumab use, the most frequent indications in both groups were prematurity and BPD/CLD, followed by HSCHD (49%, 31.7%, and 12.5% in the prophylaxis group vs 60.1%, 35.1% and 1.8% in control group). The number of subjects recruited in the prophylaxis group was approximately 35% smaller compared to the control group, which might be attributed to better health care

Table III. Body weight variation of children according to the number of palivizumab doses received.

Body weight (g)	mean	sd	med	min	max	p-value
First dose	4590.2	2216.7	4220.0	1100.0	10100.0	
Second dose	5343.9	2074.3	5050.0	1700.0	11000.0	
Third dose	5645.8	2107.1	5500.0	1700.0	11000.0	<0.001*
Fourth dose	6213.5	2013.9	6000.0	2350.0	12000.0	
Fifth dose	6727.0	1923.3	6450.0	3600.0	12000.0	

* $p<0.05$; statistically significant

(especially related to the decrease in the number of premature neonates) which has developed over time. On the other hand, the number of available doses in the study period was limited, which could potentially affect the number of subjects recruited in the prophylaxis group.

A significant number of preterm infants exhibit respiratory distress and require substantial respiratory assistance immediately after birth or upon admission to the neonatal intensive care unit (NICU) due to insufficient inspiratory effort, weak intercostal muscles, and compromised diaphragmatic function. These infants face a considerable risk of developing BPD and unfavorable neurodevelopmental outcomes, which are directly influenced by the duration of invasive mechanical ventilation (IMV) and supplemental oxygen. The strong connection between reliance on a ventilator and neurological complications, such as severe intraventricular hemorrhage and periventricular leukomalacia, highlights the severity of their condition. Also, neurodevelopmental problems have been found to be more prevalent when positive pressure support is administered for a period exceeding 60 days, irrespective of whether it is delivered through invasive or non-invasive ventilation (NIV) mode.[22] Preterm infants in the control group received significantly less respiratory support (mechanical and non-invasive ventilation), had longer oxygen treatment, and developed more often intraventricular hemorrhage grade I-II in comparison to preterm infants that received palivizumab. Most of the events during neonatal hospitalization (sepsis, intraventricular hemorrhage) were less frequent in the prophylaxis group, while the duration of neonatal stay in the intensive care unit was similar.

Less frequent events can probably be attributed to better health care provided with more equipment available and improved protocols on neonatal care (e.g. more frequent use of continuous positive airway pressure).

The biggest difference between palivizumab prophylaxis group and the control group was detected in RSV infection-related events. While there were no re-hospitalizations due to RSV and no lethal outcomes in the prophylaxis group, 16.1% of subjects in the control group were readmitted to hospital due to RSV infection, and lethal outcomes occurred in 2.4% subjects.

A prospective, multicenter, longitudinal study performed in Türkiye between 2015 and 2017[23] investigated the frequency and severity of RSV infection in infants of 29 to 35 wGA during two RSV seasons. This study showed that late preterm infants with RSV-associated lower respiratory tract infections needed significantly more hospitalization, PICU admission, and respiratory support. The duration of hospitalization was longer for RSV-positive infants. While strengthening our results, this study also emphasized the need for palivizumab prophylaxis in infants of 29-35 wGA.

Also, the children that received palivizumab prophylaxis had shown significant weight gain that was proportional to the number of doses received and neurological outcome. This positive effect of palivizumab was also recognized in the study of Orgun et al.[24] where RSV prophylaxis had positive effects on weight percentiles in infants with HSCHD. No RSV reinfection or re-hospitalization led to better and faster pulmonary function recovery, which, in combination with adequate nutrition, healthcare, and family support is a guarantee of healthy infant growth and development.

Similar results were seen in a study performed by Tavsu et al.[25], where palivizumab prophylaxis in preterm infants led to a significant reduction of RSV-related hospitalization and lower respiratory tract infections in the first and second year after prophylaxis compared to infants that had not received palivizumab prophylaxis. The Palivizumab group had shown higher bodyweight that had not reached statistical significance, and there were no significant changes in neurodevelopment between the experimental and the control group. The authors themselves recognized that this was

probably caused by inclusion criteria (preterm infants with no significant comorbidities).

Apart from being effective, palivizumab administration has also proven to be safe in our study which is similar to the results of previously published studies.[13,16,22] The use of palivizumab has also proven to be safe even in patients who are treated with palivizumab in 2 subsequent RSV seasons.[21] In our study there were no adverse effects (AE) reported which might be the result of a small sample size. The other potential reason might be the voluntary reporting of AE and serious AE by the participating physicians, unlike active surveillance ran by trained research nurses in CARESS.[26]

Limitations

Although we have provided valuable information, since data on palivizumab use in Montenegro have not been published before, there are several limitations of this study. In Montenegro, there is no electronic database on palivizumab use. For this reason, the accuracy and completeness of the primary data collected by the attending physician might limit the quality of our primary dataset. On the other hand, detection of RSV in patients hospitalized for respiratory tract infection is not mandatory during palivizumab prophylaxis in Montenegro. This fact might have resulted in underreporting of RSV-related hospitalizations. Due to the limited amount of palivizumab available during the study period the sample size was small. The sample size was also affected by recruitment of high-risk children only, who were hospitalized in the PICU.

This study report on palivizumab administered to 104 children from 2014 through 2019 RSV seasons is, best to our knowledge, the first report on palivizumab use in high-risk children in Montenegro. With the mentioned limitations kept in mind, this study demonstrates the effectiveness and safety of palivizumab prophylaxis in clinical settings and increases the pool of valuable information related to palivizumab use in routine clinical practice.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjpediatr.2024.4592

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Clinical Center of Podgorica (protocol code 03/01/4740/1, date of approval 14.05.2021).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: EL, LD, LS; data collection: EL, DN; analysis and interpretation of results: EL, JL, AD, LS; draft manuscript preparation: EL, JL, AD, LS. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory syncytial virus--a comprehensive review. Clin Rev Allergy Immunol 2013; 45: 331-379. https://doi.org/10.1007/s12016-013-8368-9
2. Liese J, Forster L. S2k-Leitlinie zur Prophylaxe von schweren Erkrankungen durch Respiratory Syncytial Virus (RSV) bei Risikokindern (German guideline on severe RSV infection prophylaxis in children at risk). Update 2017/2018.

3. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010; 375: 1545-1555. https://doi.org/10.1016/S0140-6736(10)60206-1

4. Mitchell I, Li A, Bjornson CL, Lanctot KL, Paes BA; CARESS Investigators. Respiratory syncytial virus immunoprophylaxis with palivizumab: 12-year observational study of usage and outcomes in Canada. Am J Perinatol 2022; 39: 1668-1677. https://doi.org/10.1055/s-0041-1725146

5. Higgins D, Trujillo C, Keech C. Advances in RSV vaccine research and development - A global agenda. Vaccine 2016; 34: 2870-2875. https://doi.org/10.1016/j.vaccine.2016.03.109

6. Verwey C, Dangor Z, Madhi SA. Approaches to the prevention and treatment of respiratory syncytial virus infection in children: rationale and progress to date. Paediatr Drugs 2024; 26: 101-112. https://doi.org/10.1007/s40272-023-00606-6

7. Resch B. Product review on the monoclonal antibody palivizumab for prevention of respiratory syncytial virus infection. Hum Vaccin Immunother 2017; 13: 2138-2149. https://doi.org/10.1080/21645515.2017.1337614

8. Huang K, Incognito L, Cheng X, Ulbrandt ND, Wu H. Respiratory syncytial virus-neutralizing monoclonal antibodies motavizumab and palivizumab inhibit fusion. J Virol 2010; 84: 8132-8140. https://doi.org/10.1128/JVI.02699-09

9. Simoes EA, Groothuis JR. Respiratory syncytial virus prophylaxis-the story so far. Respir Med 2002; 96(Suppl B): S15-S24. https://doi.org/10.1016/s0954-6111(02)90066-1

10. UK Health Security Agency. Respiratory syncytial virus: the green book, chapter 27a. 2015. Available at: https://www.gov.uk/government/publications/respiratory-syncytial-virus-the-green-book-chapter-27a

11. European Foundation for the Care of Newborn Infants (EFCNI). Position paper: Respiratory syncytial virus (RSV) in preterm and ill infants. 2021. Available at: https://www.efcni.org/wp-content/uploads/2023/04/EFCNI_Positionpaper_RSV_EN_web.pdf

12. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med 2013; 368: 1791-1799. https://doi.org/10.1056/NEJMoa1211917

13. The IMpact-RSV Study Group. Palivizumab; a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998; 102: 531-537. https://doi.org/10.1542/peds.102.3.531

14. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003; 143: 532-540. https://doi.org/10.1067/s0022-3476(03)00454-2

15. Simon A, Gehrmann S, Wagenpfeil G, Wagenpfeil S. Use of palivizumab in Germany - Report from the German Synagis™ Registry 2009 - 2016. Klin Padiatr 2018; 230: 263-269. https://doi.org/10.1055/a-0595-7771

16. Baranov AA, Ivanov DO, Aliamovskaia GA, et al. Palivizumab: four seasons in Russia. Vestn Ross Akad Med Nauk 2014; (7-8): 54-68. https://doi.org/10.15690/vramn.v69i7-8.1110

17. Borecka R, Lauterbach R. Compliance with the RSV immunoprophylaxis dosing schedule in the Polish registry for palivizumab (2008-2014). Dev Period Med 2018; 22: 308-314. https://doi.org/10.34763/devperiodmed.20182204.308314

18. Heljic S, Maksic H, Begic H, et al. Palivizumab prophylaxis of RSV infections in Bosnia and Herzegovina. J Pediatr Neonat Individual Med 2016; 5: e050129. https://doi.org/10.7363/050129

19. Robinson JL, Le Saux N; Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Preventing hospitalizations for respiratory syncytial virus infection. Paediatr Child Health 2015; 20: 321-333. https://doi.org/10.1093/pch/20.6.321

20. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics 2014; 134: 415-420. https://doi.org/10.1542/peds.2014-1665

21. Lacaze-Masmonteil T, Rozé JC, Fauroux B; French Pediatricians' Group of Sunagis Patients' Name-Based Programs. Incidence of respiratory syncytial virus-related hospitalizations in high-risk children: follow-up of a national cohort of infants treated with Palivizumab as RSV prophylaxis. Pediatr Pulmonol 2002; 34: 181-188. https://doi.org/10.1002/ppul.10175

22. Shi Y, Muniraman H, Biniwale M, Ramanathan R. A Review on non-invasive respiratory support for management of respiratory distress in extremely preterm infants. Front Pediatr 2020; 8: 270. https://doi.org/10.3389/fped.2020.00270

23. Ozkan H, Celebi S, Koksal N, et al. Risk factors for respiratory syncytial virus infections in moderate/late premature infants in Turkey: a prospective multicenter epidemiological study. Am J Perinatol 2021; 38: 1540-1546. https://doi.org/10.1055/s-0040-1713928

24. Orgun A, Çetin İİ, Gürsu HA. Does prophylaxis against respiratory syncytial virus infection affect the weight percentiles of infants with hemodynamically significant congenital heart disease? Journal of Behçet Uz Children's Hospital 2021; 11: 174-180. https://doi.org/10.5222/buchd.2021.60320

25. Tavsu I, Gursoy T, Dirman S, Erbil N, Ovali F. Palivizumab prophylaxis: does it have any influence on the growth and development of the infants? Am J Perinatol 2014; 31: 667-672. https://doi.org/10.1055/s-0033-1356485

26. Chen JJ, Chan P, Paes B, et al. Serious adverse events in the Canadian Registry of Children Receiving Palivizumab (CARESS) for respiratory syncytial virus prevention. PLoS One 2015; 10: e0134711. https://doi.org/10.1371/journal.pone.0134711