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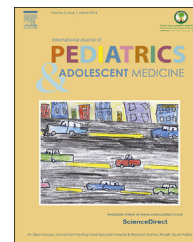


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CLINICAL PRACTICE GUIDELINES

Guidelines for palivizumab prophylaxis in infants and young children at increased risk for respiratory syncytial virus infection in Saudi Arabia



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Abstract Respiratory syncytial virus (RSV) is a leading cause of serious seasonal lower respiratory tract infections (LRTI) in high-risk infants and children, with epidemics occurring annually in Saudi Arabia from October to March.

Premature infants born at less than 29 weeks gestation with chronic lung disease or those with significant congenital heart disease who have RSV infection are more likely to be hospitalized and have increased morbidity and mortality. Palivizumab (Synagis[®], Medimmune) is a humanized monoclonal antibody for the prevention of severe LRTI by RSV in high-risk children. The current use of Palivizumab in Saudi Arabia is not regulated and does not meet approved standards.

This clinical practice policy statement was developed by the Ministry of Health and is supported by the National Immunization Technical Advisory Group (NITAG) in Saudi Arabia. It is based on available national and international data on the use of Palivizumab for the prevention of severe LRTI caused by RSV in high-risk pediatric patients. These guidelines were solicited and endorsed by two Saudi societies: The Neonatology and the Pediatric Infectious Diseases Societies.

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1. Introduction

Respiratory Syncytial Virus (RSV) is a single-stranded, non-segmented RNA negative-sense virus belonging to the Pneumovirinae subfamily of the Paramyxoviridae family. It has two subtypes, A and B, which are distinguished largely by differences in the viral attachment (G) protein and the nuclear (N) protein. During epidemics, either subtype may predominate, or both subtypes may circulate concurrently [1].

RSV is unstable in the environment and is readily inactivated by soap and water. The virus spreads through close contact with infected carriers or contaminated surfaces. Infection occurs when contaminated materials come in contact with the mucous membranes of the eyes, nose or mouth. It can remain infectious on surfaces or fomites for 4–7 h and can survive on unwashed hands [2,3].

The main therapy for RSV in infants is supportive. Palivizumab (Synagis®), a human monoclonal antibody directed against the fusion protein F of RSV (conserved among isolates), is produced by recombinant DNA technology and was licensed for use in RSV prophylaxis in June 1998 by the United States Food and Drug Administration for the reduction of serious lower respiratory tract infection caused by RSV in children at increased risk of severe disease [4–6].

This clinical practice policy statement was developed by the Ministry of Health and supported by the National Immunization Technical Advisory Group (NITAG) in Saudi Arabia based on all available national and recent international data for the use of Palivizumab for the prevention of severe LRTI caused by RSV in high-risk pediatric patients.

The Saudi Pediatrics Infectious Diseases Society (SPIDS) and the Saudi Neonatology Society (SNS) have endorsed these RSV prophylaxis guidelines. These guidelines shall be reviewed and updated every 2 years as needed. The Ministry of Health laboratories will monitor changes in RSV seasons (see Table 1).

2. Purpose of the guidelines

1. Implement national guidelines on RSV immunoprophylaxis to reduce variations across the country and limit Palivizumab to a specific high-risk population on the basis of available evidence, as well as expert opinion.
2. To be a resource for healthcare professionals (HCPs) involved in the management of an RSV Immunoprophylaxis Program.
3. Improve the utilization of resources and enhance cost-effective practices.

3. Epidemiology

RSV is a highly contagious virus that causes serious global outbreaks. The virus results in significant morbidity and mortality in infants during the first year of life, and nearly all infants experience one or more RSV infections by the end of their second year [2]. The disease severity ranges from a mild upper respiratory tract infection (URTI) to a severe lower respiratory tract infections (LRTI). Globally, RSV is estimated to have caused 66,000 to 199,000 pneumonia deaths in children younger than 5 years in 2005. In the United States, the hospitalization rate is 2345 per 100,000 person-years for RSV compared to 151 for influenza, consistent with reports that RSV hospitalizes 1–2% of infants each winter [7,8].

In Saudi Arabia, RSV was reported to be the main cause of LRTI in infants in more than one study [1,9–13], accounting for up to 40% of all LRTIs in children aged <1 year and up to 83% in children aged <5 years. Most cases occur from November through March, but infections have been reported in other months in Saudi Arabia [6,11]. Most RSV infections are mild and require minimal hospital stays; however, some children are severely affected, requiring pediatric ICU admission and a longer hospital stay. Risk factors for serious infection with RSV include prematurity; bronchopulmonary dysplasia (BPD); cyanotic congenital heart disease; and immunodeficiency diseases or immunosuppression caused by therapy [12].

Table 1 Summary of studies conducted in Saudi Arabia [14].

| Year | City/province | Hospital | No of samples | Detection test | HRSV positive No. (%) | Type | Ref. |
|------|---------------|--------------------------|---------------|-------------------------|-----------------------|------|----------------------|
| 1993 | Riyadh | KKUH ^a | 127 | IFA ^g | 69 (54) ^k | — | Jamjoom et al |
| 1998 | Riyadh | KFSHRC ^b | 256 | ND | 73(28.5) | — | Al-Hajjar et al [9] |
| 1998 | Riyadh | KKUH | 1429 | ND | 412 (79) | — | Bakir et al [11] |
| 2002 | Riyadh | KKUH | 20 | ND ^h | 8 (40) | — | Kilani |
| 2004 | Mecca-Hajj | KAUH-Jeddah ^c | 500 | IFA | 4 (7.4) | — | Bakhly et al |
| 2005 | Abha | ACH ^d | 51 | ELISA ⁱ /IFA | 20 (40) | — | Al-shehri et al [10] |
| 2005 | Riyadh | KKUH | 4575 | IFA | 884 (19) | — | Sheir and Mona |
| 2006 | Al-Qassim | BMPH ^e | 282 | IFA | 128 (45) | — | Meqdam and Sobaih |

(continued on next page)

Table 1 (continued)

| Year | City/province | Hospital | No of samples | Detection test | HRSV positive No. (%) | Type | Ref. |
|------|---------------|-------------------|---------------|---------------------|-----------------------|----------------|---------------------|
| 2009 | Riyadh | KAMC ^f | 10,617 | IFA | 733 (83) | — | Akhter et al [2] |
| 2009 | Riyadh | KKUH ^a | 200 | RT-PCR ^j | 70 (35) | A(57%)B(42.9%) | Al-majhdi et al [1] |

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^f King Abdulaziz Medical City.

^g Immunofluorescent assay.

^h Not defined.

ⁱ Enzyme linked immunosorbent assay.

^j Reverse transcription polymerase chain reaction.

^k Percentage was calculated on the basis of respiratory samples of confirmed viral origin.

4. Definitions

RSV season in this policy is defined as the period of time during which the prevalence of the infection increases. Although this varies among regions and nations according to seasonality, in Saudi Arabia the onset usually occurs in middle to late October and ends in early to mid-March [6].

Chronic lung disease (CLD) (also known as bronchopulmonary dysplasia) of prematurity was defined as oxygen dependency at 36 weeks corrected gestational age (GA) for babies delivered at less than 32 weeks GA [4].

5. Policy statement [4,15–20]

1. RSV clinics shall dispense RSV prophylaxis from the middle of October until the middle of March.
2. Palivizumab prophylaxis shall be administered to all infants born before 29 weeks gestation who are younger than 12 months at the start of the RSV season.
3. Palivizumab prophylaxis must not be administered to healthy infants born at 29 weeks gestation or more who are free of CLD, as they experience a lower RSV hospitalization rate than preterm infants born at <29 weeks gestation.
4. Prophylaxis must be given in the first year of life for preterm infants with BPD.
5. Infants with certain hemodynamically significant heart diseases (a cyanotic heart disease under medical support and moderate to severe pulmonary hypertension) should also be given RSV prophylaxis.
6. Children with immunocompromised conditions, cystic fibrosis, pulmonary abnormalities or neuromuscular disease should not routinely be offered Palivizumab because of limited and inconclusive data. However, prophylaxis may be considered for children younger than 24 months of age with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways, infants who are on home oxygen, who have had a prolonged hospitalization for severe pulmonary disease or who are severely immunocompromised.
7. Palivizumab should be administered up to a maximum of 5 monthly doses (15 mg/kg per dose administered intramuscularly once every 30 days) during the RSV season to infants who qualify for prophylaxis in the first year of life. A child with a history of a severe allergic reaction following a dose of Palivizumab should not receive additional doses.
8. Qualified infants born during the RSV season must receive fewer doses according to their month of birth. For example, infants born in January would receive their last dose in March.
9. Palivizumab prophylaxis should not be administered in the second year of life except for children who require supplemental oxygen at 36 weeks corrected gestational age who also continue to require medical intervention (supplemental oxygen, chronic corticosteroid treatment, or diuretic therapy) in the six months prior to the second season.
10. Monthly prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization.
11. Palivizumab prophylaxis is not recommended for the prevention of health care-associated RSV disease.
12. Injection Palivizumab should be stored in a refrigerator at 2 °C–8 °C.
13. To reduce the risk for RSV and other viral infections, all infants, especially preterm infants, should be offered breast milk. The parents should be instructed to avoid smoke exposure, attendance at large group childcare during the first winter season and contact with ill people.
14. It is recommended that household members should be immunized against influenza and practice good hand and cough hygiene.
15. Palivizumab is not approved or recommended for the treatment of RSV disease.
16. Palivizumab does not interfere with routine childhood immunizations.

6. Procedure

6.1. Preparation of palivizumab (synagis) [5].

1. Obtain Palivizumab Injection from the refrigerator and dilute the powder using water for injection.

2. Use 1 ml of water for injection of a 100 mg vial of Palivizumab, and 0.6 ml for a 50 mg vial, for a final concentration of 100 mg/ml.
3. Slowly add the water along the inside wall of the vial to minimize foaming. Tilt the vial slightly and gently rotate the vial for 30 s. DO NOT SHAKE THE VIAL.
4. Leave the Palivizumab solution at room temperature for a minimum of 20 min until the solution clarifies.
5. Because the Palivizumab does not contain any preservatives, it must be administered within 3 h of preparation.

6.2. Administration of palivizumab [5].

1. Verify the patient identity and data.
2. Calculate the dose to be administered according to the weight. The dose should be 15 mg/kg.
3. For example:

$$\text{Weight} \times \frac{15\text{mg}}{100\text{mg}} = \text{ml to be administered}$$
4. Obtain the required amount of injection and administer intramuscularly in the anterolateral aspect of the thigh using standard aseptic technique. The gluteal muscle is not preferred as an injection site because of the risk of sciatic nerve damage.
5. Administer the injection volumes over 1 ml as a divided dose.
6. Palivizumab is contraindicated in patients with hypersensitivity to the active substance or other humanized monoclonal antibodies.
7. Keep all equipment needed for the treatment of severe hypersensitivity reactions ready before the administration of prophylaxis.
8. Do not reconstitute Palivizumab with any other diluents or medicinal components.
9. Educate the mother regarding adverse effects such as fever, nervousness and diarrhea, which are common post-administration of prophylaxis. All side effects should be reported to the Saudi Food and Drug Authority.
10. Document the patient details and the date of administration in the RSV log book and card.

It should be noted that Palivizumab does not interfere with the immune response to other live or inactivated vaccines and the childhood immunization schedule should be followed for all children, regardless of Palivizumab use. Furthermore, more effort should be made to monitor data for the seasonality of RSV circulation and disease burden in various regions of Saudi Arabia and to fully investigate the burden of RSV among Saudi children.

Conflicts of interest

No conflicts of interest are reported.

Ethical approval

None.

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