Review article

Risks and prevention of severe RS virus infection among children with immunodeficiency and Down's syndrome

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ABSTRACT

By the age of two years, almost all infants are infected with the Respiratory syncytial virus (RSV). One of the main causes of hospitalizations for bronchiolitis and pneumonia at this age is RSV infection. In addition to well-known risks for severe RSV disease, such as prematurity, bronchopulmonary dysplasia and congenital heart disease, immunodeficiencies, chromosomal abnormalities such as Down's syndrome or neuromuscular diseases have also been identified as risks. While the medical needs for RSV prevention in these risk groups are high, clinical evidence to support this is limited. Palivizumab was recently approved in Japan for prophylaxis in children with immunodeficiency or Down's syndrome. A clinical guidance protocol for the prevention of RSV infection using Palivizumab in these risk groups is provided here on the basis of a review of the available literature and on expert opinion. Thus, the present article reviews the published literature related to RSV infections in infants and children with immunodeficiencies or Down's syndrome in order to outline the risks, pathology and physiology of severe RSV disease in these patient groups. The purpose of this article is to facilitate understanding of the medical scientific bases for the clinical guidance.

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Ministry of Health, Labour and Welfare. After examination by the “Review Conference on Unlicensed and Adapted Medicine Highly Necessary for Medical Care”, this application was endorsed and a clinical trial was conducted. In August 2013, two new indications for Palivizumab use in children with immunocompromised conditions and Down’s syndrome were approved.

This article reviews the literature related to RSV infections in immunodeficiencies and Down’s syndrome and outlines risk assessment for severe RSV infections. Based on this review, clinical guidance for prevention of RSV infections through the use of Palivizumab were formulated by expert opinion consensus for the purpose of determining the appropriate use of Palivizumab. Because of the heterogeneous nature and complexity of immunodeficiency disorders, however, these guidelines may not fully cover all of them equally well. Thus, it is necessary to personalize prophylaxis for the prevention of RSV infections based on the individual child’s immunity, risk of exposure to RSV, and anatomical and physiological condition of the respiratory system.

2. Clinical guidance

2.1. Indications

Children with Down’s Syndrome or immunocompromised newborn babies, infants and children under the age of 24 months at the beginning of the RSV season have been recently added to those with an indication for the use of prophylactic Palivizumab. Here, we describe these new indications in the following sections. In addition, respiratory conditions such as underlying respiratory disease and chest deformity, as well as the risk of exposure to RSV (assessed by prevalence in the geographical region or incidence in that particular the hospital, and the presence or absence of siblings), should also be taken into account.

2.1.1. Immunodeficiencies

2.1.1.1. Congenital/acquired immunodeficiencies. For high risk infants and children ≤24 months of age at the beginning of the RSV season having the following congenital or acquired immunodeficiencies, the prevention of severe RSV disease using Palivizumab may be considered as follows:

- Primary immunodeficiencies with predominantly T-cell dysfunctions including, but not limited to, SCID, DiGeorge syndrome, Wiskott–Aldrich syndrome, Ataxia Telangiectasia, etc.
- Acquired T cell dysfunctions such as those caused by HIV infection, use of steroids/immunosuppressive drugs etc.

T-cell dysfunctions include decrease in T-lymphocytes, T-cell functions (such as decreased proliferative responses to PHA) or marked lymphopenia. The following diseases and conditions are not included: auto-inflammatory diseases which do not require medication, abnormality of granulocytes or the complement system, and mild T-cell dysfunction (in the absence of lymphopenia or T-lymhcotyopenia).

For systemic wasting diseases such as HIV infection, general physical conditions should also be considered.

2.1.1.2. Hematological malignancies, solid tumors, bone marrow deficiencies, hematopoietic stem cell transplantation and organ transplants. In patients with these diseases and conditions, some reports of fatal cases of severe RSV infection have appeared. For infants and children ≤24 months of age at the beginning of the RSV season having the following conditions and diseases, the prevention of severe RSV disease using Palivizumab may be considered:

- Allogeneic hematopoietic stem cell transplantation (HSCT)
- Autologous HSCT before hematological recovery
- Recipients of and candidates for chemotherapy causing significant bone marrow suppression
- Bone marrow failure accompanied by immunosuppression, such as in aplastic anemia
- Organ transplants. There have been reports of severe RSV infections in solid organ transplant (SOT) recipients. For infants and children ≤24 months of age at the beginning of the RSV season receiving solid organ transplants, the prevention of severe RSV disease using Palivizumab may be considered:
- Both recipients of and candidates for HSCT or SOT with significant organ dysfunction or immunosuppression are included in the above criteria. These patients are considered at high risk of severe RSV infection even though they are hospitalized.

2.1.1.3. Use of immunosuppressive medications for kidney diseases, rheumatic/inflammatory diseases. For infants and children ≤24 months of age at the beginning of the RSV season having either (1) or (2) below, the prevention of severe RSV disease using Palivizumab may be considered:

1. Use of corticosteroids, immunosuppressants, or biologics for the following diseases:
   - Rheumatic diseases (juvenile idiopathic arthritis, systemic lupus erythematosus and juvenile dermatomyositis etc.), auto-inflammatory syndrome, inflammatory bowel disease, so on.
   - Nephrotic syndrome, chronic glomerulonephritis, etc.
2. Children who have the following kidney diseases, regardless of medications:
   - Congenital nephrotic syndrome
   - Chronic peritoneal dialysis, hemodialysis

#1: Including high-dose corticosteroid therapy (>0.5 mg/kg prednisolone every other day for approximately four weeks or longer, excluding local treatments of inhalation, topical use or joint injection), immunosuppressants (azathioprine, methotrexate, mizoribine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, everolimus, rapamycin, etc), and biologics (including cytokine inhibitors).

#2: Pharmacokinetics and effectiveness of Palivizumab may differ in individual cases.

Optimal doses and intervals between them should be decided individually.

#3: The drug may be lost through urine. No effectiveness data for Palivizumab in this group is available. The risks of exposure to, and severe disease from RSV, should be carefully assessed when administering Palivizumab.

2.1.2. Down’s syndrome

Down’s syndrome itself has been shown to be a risk factor for severe RSV infection, even in the absence of congenital heart disease. For infants and children with Down’s syndrome ≤24 months of age at the beginning of the RSV season, the prevention of severe RSV disease using Palivizumab may be considered when the patient suffered any of following past or present complications, or has abnormal laboratory test results:

- Anatomical, physiological or functional abnormalities of the respiratory system: Airway obstruction and/or associated apnea due to marked megalolossia, glossophtosis, respiratory tract malacia, or other airway abnormalities, pulmonary hypertension, pulmonary hypoplasia/dysplasia, or emphysematous lung,

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• Previous severe respiratory diseases or viral infections: History of hospitalizations due to viral infections/respiratory infections
• Abnormal laboratory tests of immunological function: Low lymphocyte or T-lymphocyte counts*

* Although the normal values vary depending on the months of age, one suggestion would be 2000/mm² or lower and 1000/mm² or lower for lymphocyte counts and T-lymphocytes, respectively.

2.2. Precautions

(1) If patients have a tendency to bleed due to thrombocytopenia (such as because of Wiskott–Aldrich syndrome and myeloablation) or other coagulopathy, or they are receiving anticoagulants and/or antiplatelet drugs, bleeding resulting from an intramuscular injection of Palivizumab may be serious. It is recommended that Palivizumab be carefully given to such patients, for example, with application of pressure to the injection site for an appropriate length of time to ensure hemostasis.

(2) Effectiveness of Palivizumab in treating RSV infection has not been established.

(3) The latest package insert and the published guidelines for prematurity and congenital heart diseases should also be referred to.

2.3. Importance of basic infection control

It is important to employ strict infection control measures even when using Palivizumab. It is particularly important to educate guardians, since their cooperation is essential in managing high-risk children. It is also important to provide instructions not only for RSV infection, but also for other pathogens causing respiratory tract infections. In addition, guardians should understand that adhering to the administration schedule is critical to maximize the effectiveness.

3. Comments

3.1. Congenital/acquired immunodeficiency diseases

Recent medical advances have improved the lives of immunocompromised patients, but as a result, the chance of exposure to and infection by RSV among these high risk patients has increased. Severe RSV infections in immunodeficiency disorders such as SCID have long been recognized, at least since the 1980s [2,4,5]. Hall et al. examined the immunological status of 608 infants under the age of five who were hospitalized with an RSV infection over a ten year period [2]. 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). The frequency of nosocomial infections, as well as the rates of infection in the lower respiratory tract, admissions to the ICU and mortality was compared with immunologically normal children. Nosocomial infections accounted for 25 cases including one with primary immunodeficiency. Lower respiratory tract infections developed in all patients with immunodeficiency syndromes and in those receiving chemotherapy, with high rates of 80% and 60% admission to the ICU and 40% and 15% mortality in the syndrome and chemotherapy groups, respectively. Moreover than half of the patients who received steroids developed LRTI (12 of 22), but with no cases of mortality and two requiring ICU admission (9%).

More recently, a population-based cohort study of RSV infections in Denmark identified congenital immunodeficiency as a significant risk factor, among others including Down’s syndrome [3].

In general, cellular immune functions are considered important in controlling virus infection. RSV-specific CD8+ and CD4+ T cells can be found in adult peripheral blood, which suggests a persistently important role for cellular immunity against RSV [6–9]. Mbawuike reported that infants possessing CTL activity against RSV during their first year of life were less likely to have LRTI in their second year [10], indicating the importance of CTL activity.

Human Immunodeficiency Virus (HIV) infects CD4+ T cells and causes immunodeficiencies. In recent years, comprehensive measures to prevent mother-to-child transmission (MCT) have been widely and successfully implemented in Japan, and the frequency of new occurrences of MCT is fortunately as low as only one every few years. Nevertheless, according to reports from Africa, where MTC is still a significant public health problem, there is a higher rate of lower respiratory tract infection and mortality in children infected with HIV compared to those uninfected [11].

Overall, the available literature indicates the importance of cellular immunity to control RSV infection. Nonetheless, the humoral response is also important for controlling RSV infection, as immunoglobulin is effective in preventing severe RSV infections. However, there is insufficient available information to be included in this guidance.

3.2. Malignant tumors, hematopoietic stem cell transplants, and organ transplants

Severe RSV infections have been widely reported in those with hematological malignancy and HSCT. Generally, younger patients, lymphocytopenia and neutropenia, infection prior to or early after transplantation, high doses of steroids, and failure to treat with ribavirin have all been reported as risks for severe RSV infection [12–15]. Allogeneic HSCT recipients are considered to be at particularly high risk of severe infection and suffer high mortality rates [13,16,17]. In addition, there have been reports of severe RSV infection in malignant diseases without HSCT [13,18,19], indicating that underlying diseases and bone marrow suppression due to anticancer treatments are also risks for severe RSV infections. On the other hand, there have also been reports that the frequency of RSV infection and severity is not high, and that deaths are rare in these patient groups [20,21].

Severe RSV infections have also been reported in solid organ transplant patients. From reports of a high frequency of severe infection of 50–80% [22,23], there are also reports that it is only around 20% [24,25]. There are also reports of mortality [23,25]. According to a survey at organ transplant centers in the United States, of those facilities that responded, nearly half reported that they took some form of measure to prevent RSV infection [26]. In that study, it was also reported that 27% (17/62) of institutions had seen RSV LRTI infection during the previous season and that of those who received Palivizumab 4% required hospitalization (4 of 109), whereas of those who did not it was 11% (22 of 195) (p = 0.03).

3.3. Use of steroids/immunosuppressive drugs, and kidney and rheumatic diseases

In adult patients with rheumatoid and autoimmune diseases, cases of severe RSV infections including fatality have been reported [27,28]. Furthermore, in some reports, exacerbation of the underlying diseases [29], and rejection of the transplanted kidney [1] or even death [24] have been reported.

3.4. Down’s syndrome

Chromosomal abnormality and congenital malformations are regarded as risks for severe RSV infections in infants [3,30], for
which it is speculated that immunologic abnormalities and anatomic abnormalities in the lungs and airways are responsible. Pulmonary hypertension is a common complication accompanying congenital heart disease in about half of Down’s syndrome patients. On the other hand, Down’s syndrome itself without congenital heart disease is also a risk factor for severe RSV infections [31,32]. Bronchomalacia and tracheomalacia is frequently seen in persons with Down’s syndrome [33,34], as well as lung hypoplasia and emphysematous changes [34]. There are also reported cases of aspiration pneumonia and obliterating bronchiolitis associated with RSV infections [32,34,35]. In addition to the aforementioned anatomical and histological abnormalities, Down’s syndrome patients are known to have small thymi. A measure of the release of new T-cells from the thymus, the amount of T-cell receptor excision circles (TRECs), is low in Down’s syndrome [36], and the peripheral blood naïve CD4+ T cell count, as well as the overall T-cell count, and the B-cell count, are all decreased [37], which may also be related to susceptibility to severe respiratory viral infections. Thus, in Down’s syndrome, these anatomical and histological abnormalities, as well as quantitative and qualitative abnormalities in immunological parameters, should be taken into account when assessing the risk of severe RSV infections.

3.5. Other considerations

There are various factors complicating immunodeficiencies and Down’s syndrome that can aggravate RSV infections. Of these, there are some important conditions in common, such as a decline in the number and function of T-lymphocytes, including marked lymphopenia, mentioned specifically above for congenital and acquired immunodeficiency and others. Steroids, tacrolimus, biological preparations and other such treatments cause functional impairment. A numerical decline is seen in recipients of chemotherapy and HSCT. Severe bone marrow aplasia such as in aplastic anemia is included in these conditions. The number of lymphocytes, T-cells and PHA responsiveness are examples of parameters useful for the evaluation of cell-mediated immunity and T-cell-related functions at bedside. However, abnormalities may not always be detected through such tests in all diseases, such as those involving STAT mutations, so caution is necessary [38]. In addition, immunodeficiencies in which T-cell dysfunction is not important (e.g. autoinflammatory diseases, polymorph abnormalities, complement abnormalities, slight T-cell immunodeficiency) were omitted from the list of indications for Palivizumab use, but as research progresses and risks for aggravated RSV infection are clarified, it will be necessary to review these current guidance again.

In general, in the early recovery stages after transplantation and chemotherapy, when the level of immunosuppression and myelo-suppression is still high, it may be thought that the risk of RSV exposure is low during hospitalization. On the other hand, if RSV does happen to be transmitted to patients in such an advanced immunocompromised state, the risk of severe disease even to the point of death is considerable. In addition, most RSV infections in adults present with mild or even no symptoms, so the risk of infection from an adult during times when it is prevalent cannot be completely prevented. That is why a section on preventing RSV infection during hospitalization was included in this guidance above. Therefore, it is important to be thorough in taking basic measures to prevent infection, considering the risk of infection, regional prevalence of RSV and the conditions and numbers or visitors, and to formulate a prevention plan.

At the present time, while the prevention of RSV using Palivizumab in those with immunodeficiencies and Down’s syndrome has been approved in Japan before anywhere else in the world, there is currently insufficient evidence of efficacy and safety of its use. Thus, the importance of collecting information on Palivizumab use and reporting our experience with this antibody in our country to the international community cannot be overemphasized.

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