PERINATAL PHARMACOLOGY:

INDIVIDUALIZED NEONATAL THERAPY

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CHAPTER 21

GLOBAL (PHARMACOLOGICAL AND NON PHARMACOLOGICAL) PREVENTION OF RSV INFECTION

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There is no cure for birth and death save to enjoy the interval.
G. Santayana

Respiratory syncytial virus infections

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infections in infants in the first two years of life [1, 2, 3]. It is a single-stranded RNA virus of the family Paramyxoviridae (subfamily Pneumovirinae), which includes common respiratory viruses such as those causing measles and mumps. Its name comes from the fact that the F proteins on the surface of the virus cause merging of cell membranes on nearby cells, thus forming syncytia.

RSV infections are seasonal: in temperate climates they generally occur during autumn, winter, and early spring (October-April, with some interannual and interregional variability), in tropical climates infection is most common during the rainy season. The timing and severity of RSV circulation in a given community varies from year to year [4]. RSV is highly infective with low cytophatic and invasive activity and low antigenic variability. Natural infection with RSV induces protective immunity which decreases over time and thus people can be infected multiple times. Sometimes an infant can become symptomatically infected more than once, even within the same season [5]. While it often causes symptoms similar to the common cold in older children and adults, in infants and younger children it can cause bronchiolitis with inflammation in the lungs, wheezing and difficulty in breathing. The probability of severe RSV infection appears to be related to other risk factors: age (< 6 months), prematurity (< 35 weeks of gestation), bronchopulmonary dysplasia (BPD), congenital heart defects (CHD) and immunodeficit. RSV infection

is very common in the first years of life and reinfection is possible. RSV infections are so common that in the United States about two-thirds of children are infected during their first year of life and almost all children will have been infected with the virus by 2-3 years of age. For most children, RSV produces mild infections with only mild symptoms, often indistinguishable from common colds and minor illnesses, but 2-3% will develop severe bronchiolitis, leading to severe respiratory illness requiring hospitalization and 1-2% of these hospitalized children may die. This is more likely to occur in patients that are immunocompromised or infants born prematurely. RSV appears to be the "most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia in children under 1 year of age in the United States" [6].

Children usually develop symptoms about 4-6 days after being exposed to someone with an RSV infection (incubation period). These symptoms initially include just a clear runny nose and decrease in appetite but, as the virus spreads, symptoms may worsen to include coughing, sneezing, vomiting, fever, irritability, tachypnea with retractions and nasal flaring, wheezing and poor feeding. In severe cases, children may have apnea and respiratory failure. Most otherwise healthy infants infected with RSV do not require hospitalization. In most cases, including those who need to be hospitalized, full recovery from illness occurs in about 1 to 2 weeks. In the most severe cases of disease, infants may require supplemental oxygen, suctioning of mucus from the airways or tracheal intubation with mechanical ventilation.

Recurrent wheezing and asthma are more common among individuals who suffered severe RSV infection during the first few months of life than among controls; however it is very difficult to determine whether RSV infection sets up a process that leads to recurrent wheezing or whether those already predisposed to asthma are more likely to become severely ill with RSV [7].

RSV RNA has 10 genes encoding 11 proteins: NS1 and NS2 inhibit type I interferon activity; N is a nucleocapsid protein; M, M2-1 and M2-2 are matrix proteins necessary for viral assembly; SH G and F form the viral coat; L encodes the RNA polymerase; P is a phosphoprotein cofactor for L [8, 9]. In particular G protein is a glycosylated surface protein that functions as the attachment protein and F protein allows entry of the virus into the cell cytoplasm, fusion and formation of syncytia, therefore antibodies against the F protein are neutralizing. The F protein is homologous in both subtypes of RSV, the G protein differs considerably between the two subtypes.

RSV is viable for half an hour or more on hands or for up to 5 hours on countertops, thus direct contact allows transmission very easily. Laboratory diagnosis of RSV infection can be performed with PCR testing for RSV nucleic acids in peripheral blood samples if all other infectious processes have been ruled out or if it is highly suspicious for RSV such as a recent exposure to a known source of RSV infection. RSV infection can be confirmed using several other techniques, such as Direct

Fluorescent Antibody detection and Chromatographic rapid antigen detection. Quantification of viral load can be determined by Plaque Assay, antigen capture enzyme immunoassay (EIA), ELISA and HA, and quantification of antibody levels by HAI and Neutralization assay.

Like most viral infections, there is no specific medication for RSV infection. Treatment is usually symptomatic and limited to supportive care. In children with wheezing and breathing difficulty, nebulized treatments may be helpful [10, 11]. Other treatments may include supplemental oxygen and intravenous fluids (if enteral intake is insufficient) until the illness runs its course. Children with severe difficulty in breathing and/or apnea need to be placed on ventilation to help them breath via nasal cannula or endotracheal tube. Treatment with antibiotics is not usually helpful, unless the child develops a secondary bacterial infection. An antiviral drug (ribavirin) is licensed for use, but its efficacy is limited. The benefit from adrenaline, bronchodilators and steroids is controversial [12, 13].

Children most at risk of hospitalization and serious complications after an RSV infection include premature infants and infants with chronic pulmonary or cardiac diseases. Fortunately, pharmacological and non-pharmacological prophylaxes are available to prevent RSV infections in these high risk patients.

Non pharmacological prophylaxis

RSV can spread very quickly both in communities and the nosocomial environment. The incubation period is about 4-5 days. People infected with RSV are usually contagious for 8 to 15 days. However, some infants and people with weakened immune systems can be contagious for as long as 4 weeks. RSV is often introduced into the home by school-aged children who are infected with RSV and have a mild upper respiratory tract infection. RSV can be rapidly transmitted to other members of the family, often infecting about 50% of other household members. Infection can result from direct and indirect contact with nasal or oral secretions from infected persons. RSV can be spread when droplets containing the virus are sneezed or coughed into the air by an infected person; if the particles are inhaled or contact someone's nose, mouth, or eye, infection can occur. RSV can survive on surfaces (skin, hands, napkins, etc.) for many hours. Indirect transmission may occur through touching eyes and nose (the main entrance pathways) with infected hands. For these reasons RSV is characterized by widespread and easy diffusion and the most important protection strategy for babies at risk is prevention. Environmental prophylaxis and general hygiene are the easiest, cheapest, most applicable and effective weapons against RSV, also in limiting nosocomial transmission (**Table 21.1**) [14-17].

Whether or not the child is at high risk of having complications from an RSV infection, it is very important to heed simple ways of lessening the chances of

Table 21.1. Environmental prophylaxis to limit RSV diffusion.

Accurate hand washing with water and soap and/or alcoholic gel
Protection from respiratory secretions (covering mouth and nose with adequate masks)
Quick disposal of used handkerchiefs and hand washing after use
Use of masks for health care workers with respiratory symptoms
Avoidance of crowded places during epidemic season
Avoidance of contact with infected people
Air renovation in places where the baby sojourns
Strict avoidance of cigarette smoking in places where the baby sojourns
Accurate disinfection of instruments used for the baby, surfaces and any potentially contaminated object

becoming infected, such as teaching children and care providers to practice frequent hand washing, especially after using the bathroom (including diaper changes) and before eating; frequent washing of toys and other objects that children put in their mouths and all other surfaces; disposing of tissues after wiping or blowing a child's nose; avoiding close contact with other people who are sick; avoiding smoking around babies and in the environment where they sojourn.

Frequent hand washing and wiping of hard surfaces with soap and water or disinfectant may help stop infection and spread of RSV. Also, persons with RSV illness should not share cups or eating utensils with others.

Persons with cold-like symptoms should not interact with high-risk children. In any case, they should cover their mouth and nose when coughing or sneezing and then wash their hands before providing any care. When possible, it is important to limit the time that high-risk children spend in child-care centers or other potentially contagious settings in order to prevent infection and spread of the virus during the RSV season.

Among environmental factors, exposure to cigarette smoking and other pollution agents, schools and nurseries or other crowded places, composition of family with presence of older siblings and poor socio-economic status play a major role.

Several studies have demonstrated that passive smoking increases the risk of RSV infection. In a systematic review of passive smoking and lower respiratory illness in infants and children, Strachan and Cook showed a pooled odds ratio of 1.57 if either parent smoked and an odds ratio of 1.72 if the mother smoked [18]. Stocks and Dezateux reviewed 20 studies of pulmonary function in infants, showing an increase in infection rate in children whose mothers smoked before and during pregnancy [19]. Paternal smoking also has an effect: the prevalence of upper respiratory tract illness increased from 81.6% to 95.2% in infants under 1 year of age in households where only the father smoked.

Pharmacological prophylaxis

As the virus is ubiquitous, avoidance of infection is not possible. An early vaccination soon after birth would be the best choice, but immune response of the infant would be altered by the incomplete maturation of the immune system and by the presence of high level concentration of maternal IgG against several viral proteic fractions. A vaccine trial in the 1960s using a formalin-inactivated vaccine (FI-RSV) increased disease severity in children who had been vaccinated [20]. Experimental vaccines against RSV (viral subunits) in children with BPD or cystic fibrosis have shown to be safe and well tolerated but with poor immunogenic activity. Other vaccines with attenuated viruses appear not to be safe for infants or have demonstrated poor efficacy. An intranasal inactivated RSV vaccine is one of the innovative interesting RSV vaccines under development. Some of the most promising candidates are based on temperature-sensitive mutants that target genetic mutations to reduce virulence [21, 22]. There is much active investigation ongoing in the development of a new vaccine, but at present none is available.

The only effective available pharmacological protection is passive immunoprophylaxis with administration of antibodies against RSV [23]. This prophylactic medication (not a vaccine) should be available for infants at high risk, such as preterm birth (under 35 weeks' gestation) infants and infants with CHD or BPD. A medication with concentrated immunoglobulins against RSV (RSV-IVIG) was licensed in 1996 to prevent RSV infections in high risk patients and was available as a monthly intravenous infusion to provide children with antibodies against RSV and some other respiratory viruses and provide protection against infection. A newer medication, palivizumab, is a monoclonal antibody directed against the RSV surface fusion protein, which is the molecule that makes possible viral penetration into airway cells and therefore determines the disease. It is available as an intramuscular injection, it is not a blood product and will not interfere with the child's immunizations (children cannot receive the measles, mumps, and rubella [MMR] or chickenpox vaccine until 9 months after ending their RSV-IVIG infusions). These antibodies guarantee only temporary protection and so they must be administered by monthly injections during autumn and winter, beginning just prior to the RSV epidemic season and continuing for five months. There is possibly a need for a universal guideline but there are many obstacles. The high cost of this drug limits its use in many parts of the world. Therefore indications and recommendations for RSV prophylaxis may vary in different countries. The American Academy of Pediatrics (AAP) has produced guidelines for palivizumab prophylaxis in babies at risk (**Table 21.2**) [24]. The Italian Society of Neonatology (SIN) recommends pharmacological prophylaxis against RSV in specific at-risk babies (**Table 21.3**), according to other international scientific committees [25, 26]. SIN recommends starting palivizumab administration one month before the beginning of the RSV epidemic season (September-October) and to continue it until the end of the season (April-May) with maximum 5-6 administrations. The recommended dosage is 15 mg/kg intramuscular. The first dose should be administered before the RSV epidemic season

Table 21.2. Infants and children for whom palivizumab prophylaxis may be considered (American Academy of Pediatrics [AAP] 2009 guidelines [24], modified).

Infants and children	Condition
GA ≤ 28	whenever RSV season occurs during the first 12 months of life
29 ≤ GA < 32	age < 6 months at the start of RSV season
32 ≤ GA < 35	• age < 3 months at the start of the RSV season or • born during the RSV season if they have at least one of the following 2 risk factors: 1. the infant attends child daycare 2. the infant has a sibling younger than 5 years of age at home
GA < 35	• congenital abnormalities of the airway or • neuromuscular disease that compromises handling of respiratory secretions
age < 2 years	• cyanotic or complicated congenital heart disease or • treated for chronic lung disease within 6 months of the start of the RSV season

GA: gestational age (weeks).

to guarantee adequate protection. Subsequent doses should be administered every 28 ± 2 days until the end of the epidemic season. Intramuscular administration is able to determine immunoglobulin serum concentrations similar to intravenous administration but with significant advantages (less invasiveness, hospitalization not required) and fewer collateral effects.

Preterm babies are more susceptible to RSV infection because of the immaturity of their immune systems, altered pulmonary development and reduced respiratory function. In fact, placental transfer of maternal IgG to the fetus and pulmonary development with an increase in alveolar number and airway diameter which take place in the last trimester of gestation. Therefore, a preterm delivery predisposes to reduce defenses against infections, bronchial hyperreactivity and poor respiratory performances.

Late preterm babies are a borderline category whose protection with palivizumab prophylaxis is practiced only in specific conditions which differ from country to country following different guidelines (see risk factors in **Tables 21.2** and **21.3**). In particular, AAP 2009 guidelines may appear to be insufficient and expose a large number of babies to the risk of RSV, therefore a multicentric data collection is needed to measure the incidence of hospitalization for RSV infection of infants born > 33 weeks of gestational age, with particular regard to the last part of the RSV epidemic season.

Palivizumab prophylaxis is very expensive and requires an adequate organization of health services with monthly admissions during the RSV season, but familial compliance is usually very good if preceded by adequate counseling, administration is easy and fast and adverse events are rare and mild. Therefore it can be defined as a safe and well tolerated drug.

Table 21.3. Italian Society of Neonatology (SIN) indications for pharmacological prophylaxis with palivizumab (adapted from references 25 and 26).

Palivizumab prophylaxis is highly recommended for:

1. infants born with gestational age ≤ 32 weeks and postnatal age < 1 year at the beginning of the RSV season;
2. infants with BPD or CLD (requiring oxygen and/or other therapy in the last 6 months) and postnatal age < 2 years at the beginning of the RSV season;
3. infants with congenital heart disease (hemodynamically significant or on pharmacological treatment or associated with a mild degree pulmonary hypertension or cyanosis) and postnatal age < 2 years at the beginning of the RSV season (with exclusion of infants with congenital heart defects not requiring pharmacological therapy or already treated with definitive surgical correction not requiring the support of pharmacological treatment);
4. infants born with gestational age between 33 and 35 weeks and postnatal age < 1 year at the beginning of the RSV season, if there are also two other risk factors such as:
   a. discharge from the hospital after birth during the RSV season,
   b. low birth weight (< 2,500 g or < 10th percentile),
   c. exposure to passive smoking,
   d. no maternal breastfeeding,
   e. positive familiar history for atopy,
   f. exposure to high grade air pollution,
   g. birth from multiple pregnancy,
   h. older siblings at home,
   i. attendance at daycare services,
   j. concomitant serious diseases (cystic fibrosis, chest wall malformations, neuromuscular disorders, immunodeficits, hematologic diseases, neoplastic diseases, etc.),
   k. living in places with very difficult access to health resources (hospitals, emergency care, etc.).

In addition:

- if the infant is in the high risk categories, during the RSV season, the first palivizumab administration is recommended 48/72 h before discharge;
- if an infant undergoing palivizumab prophylaxis is hospitalized for RSV infection, the prophylactic schedule must be continued;
- for an isolated case or a nosocomial epidemic palivizumab prophylaxis is not justified, but accurate hygienic measures are required.

Conclusions

RSV can be transmitted by direct and indirect contact with nasal or oral secretions from infected persons. Environmental prophylaxis and general hygiene are the easiest, cheapest, most applicable and most effective weapons against RSV, also in limiting nosocomial transmission. Therefore it is very important to focus on simple ways to lessen the chances of infection, such as teaching children and care providers to practice frequent hand washing, frequent washing of toys and other objects that children put in their mouths and all other surfaces and disposal of tissues after wiping

or blowing a child's nose, avoiding close contact with other people who are sick, avoiding smoking around babies and in the environment where they sojourn.

A prophylactic medication is available for infants at high risk, such as preterm babies and babies with CHD or BPD. Palivizumab is a monoclonal antibody that reduces the incidence of severe RSV illness and hospitalizations due to RSV infection [27-30]. It is administrated by monthly intramuscular injections during the RSV season, which generally lasts from October through April with wide variability in different countries and geographic areas. It is very important to protect infants at risk to prevent severe life-threatening bronchiolitis and subsequent susceptibility to airway hyperreactivity and wheezing. The drug can help prevent development of serious RSV disease, but it cannot help cure or treat children already suffering from serious RSV disease. Researchers are working to develop RSV vaccines, but none is available at present.

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The origin of this book lies on the awareness that we have to do more for identifying unmet needs and improving a tailor-made treatment for each newborn.

After a large introduction on developmental pharmacology, this book analyses in detail new advances on antibiotics (aminoglycosides), antifungals, antivirals (CMV, RSV, HIV), analgosedatives, steroids, caffeine, and cardiovascular drugs. An updated pharmacologic treatment of respiratory diseases (respiratory distress syndrome, meconium aspiration syndrome, chronic lung disease, persistent pulmonary hypertension) is presented, as well as for persistent patent ductus arteriosus and retinopathy of prematurity. Finally, neuroprotection is considered, with special emphasis on antioxidants and melatonin.

A special part is devoted to drug-induced renal toxicity and liver toxicity and complete the volume, also quoting the so-called '-omics' sciences such as genomics and metabolomics.

The topics are covered by international experts in the field and the subtle red line that links all the chapters together is the perspective of individualized treatments to reach our ultimate goal: the right therapy for each newborn without any side effects.

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