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Respiratory Syncytial Virus (RSV) Infections

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Respiratory syncytial virus (RSV) is an enveloped, negative-strand RNA virus of the family *Paramyxoviridae*. Humans are the reservoir of infection although it is unknown as to how the virus is maintained in the population throughout the year.

There is one serotype of RSV, but it may express two major variations in the surface proteins used for host cell surface attachment. As such, there are two antigenic subgroups of RSV, designated A and B, which may have many genetically-distinct strains that will circulate in a community concurrently. Group A is more predominant. Some strains may exhibit variations in virulence, though the clinical and epidemiological significance of certain strains has not been clarified.

The *Paramyxoviridae* family is a large family of pathogenic viruses that includes measles, mumps, human metapneumovirus and an assortment of pathogens that cause respiratory tract infections.

Epidemiology

RSV is one of the most common infections of childhood and an important cause of lower respiratory tract infection (LRTI) in infants and children; almost all children in the United States will have a bout of infection with the virus by their second birthday. In this age cohort, RSV is the most important cause of bronchiolitis and pneumonia; infection can be severe.

RSV causes acute respiratory tract infections in persons of all ages. Most healthy people recover from RSV infection in one to two weeks. The infection is now being recognized as an important cause of respiratory illness in the elderly, the immunocompromised and in people with cardiopulmonary disease.

Risk factors for children include: age younger than six months; male gender; attendance at daycare; and living in a household with young siblings, or with cigarette smokers. For adults, residing in a nursing home or as a hospital inpatient also increases the risk of exposure and serious infection with RSV. Exposure to air pollution and diesel engine fumes have recently been identified as risk factors for developing RSV infection.

The mode of transmission is person-to-person, by direct contact with large expelled droplets, or close contact with surfaces or objects contaminated with secretions. Transmission by small droplets is unlikely. RSV can remain infective for many hours on environmental surfaces and for a half-hour or more on hands. Infection occurs when infectious materials contact the mucous membranes of the eyes and nose. Transmission through the mouth mucosa is less common.

Emission of large droplets is generated by sneezing and coughing. Spreading among household and child care contacts is common, as is re-infection throughout life due to poor lasting immunity against the virus.

Indirect contact transmission through contaminated fomites or environmental surfaces is also very common due to the persistence of the virus in the environment. RSV is sensitive to high and low temperature and to drying conditions. At room temperature it loses infectivity after 48 hours on a porous material and after 24 hours on a hard surface. Heating and freezing does inactivate the virus, as does the application of detergents and chlorine solutions. On hands, RSV remains infectious for about one hour.

There is year-to-year and seasonal variation in RSV activity, though RSV infections typically occur annually in large community epidemics during winter and early spring that often last from four to six months in temperate climates. In tropical climates, RSV outbreaks occur most frequently during the rainy or monsoon season. The timing and severity of outbreaks varies from year to year. Outbreaks in both children and adults have been reported in healthcare settings, most notably in nurseries, bone-marrow transplant centers, intensive care units, and long-term care facilities.

The burden of RSV is considerable due to its ubiquity as a respiratory pathogen infecting humans during the cold season and is a significant cause of morbidity among young children.

Communicability period: the virus is most communicable during acute infection and short term carriage after recovery. However, even after recovery, very young infants and children with weakened immune systems can continue to spread the virus for one to three weeks. The source of the infection is always a symptomatic individual or a short term post-recovery individual. Due to the nature of transmission, the hardiness of the virus in the environment and its infectiousness, RSV is transmitted easily in both community and hospital settings.

Infectious dose: The infectious dose ranges from 160 to 640 viral units through intra-nasal spray.

The incubation period ranges from two to eight days, with four to six days being most common. Viral shedding occurs over a period of three to eight days following infection, though may last as long as three to four weeks in young infants and the immunocompromised.

Pathogenesis

RSV pathogenesis varies considerably among infected individuals, determined by environmental, viral and host factors. Host immunity clearly contributes to RSV pathogenesis; neonates exhibit the most severe infection. More severe RSV infections of the lower respiratory tract have been correlated to premature birth, congenital heart disease, chronic lung disease of prematurity, and T-cell immunodeficiency. Ultimately, whether the immunological response induced by RSV is protective or pathogenic depends on a combination of host factors, with very young age being one of the most important factors.

RSV infects the epithelial cells of the lung, targeting type 1 alveolar and non-basilar airway epithelia and possibly alveolar macrophages. Viral replication and cytopathology in the form of giant syncytia in these cells results in sloughing of the epithelia and reduced ciliary function, leading to enhanced cell infiltration by the virus and mucous production by the host.

There is some evidence to suggest that RSV subgroup A is more virulent then subgroup B, although this is controversial.

Clinical Description

The illness is characterized by upper respiratory infections (such as colds) and lower respiratory tract infections (such as bronchiolitis and pneumonia).

When infants and children under the age of four years are first exposed to RSV, 25% to 40% of them will show signs or symptoms of bronchiolitis or pneumonia and 0.5% to 2% will require hospitalization, though infection is rarely fatal. Children hospitalized for RSV infection are most often younger

than six months of age. Up to 20% of children with RSV bronchiolitis are co-infected with another virus that infects the respiratory tract, such as human metapneumovirus or rhinovirus. Most will recover in one to two weeks.

However, the clinical picture can vary:

- In neonates, lethargy, irritability and poor feeding with apneic episodes (brief cessation of breathing) can be more common than a presentation of the typical respiratory tract symptomatology.
- Mild disease in infants and young children may include fever, reduced appetite, runny nose, cough, and wheezing.
- Older children and adults may have a runny nose, sore throat, headache, cough, and suffer general malaise.
- Acute otitis media occurs in up to a third of children and both RSV and assorted bacterial pathogens have been isolated from the middle ears of children suffering from RSV infection.
- Severe disease is characterized by bronchiolitis, pneumonia and lung failure and may necessitate mechanical ventilation.

Risk factors for severity: RSV infection is more likely to be severe and lead to hospitalization in cases with the following risk factors:

- Age: prematurity and old age
- Primary immuno-deficiencies
- Chronic lung and heart conditions: congenital abnormalities of airways, bronchopulmonary dysplasia, cystic fibrosis, congenital heart diseases and severe neuromuscular diseases
- Immuno-suppression: transplant patients and patients on chemotherapy
- Exposure to environmental air pollution

To date, no long-term sequelae of RSV infection have been reported, however there may be an association between an episode of RSV bronchiolitis in early childhood and development of asthma, although this possible relationship remains to be elucidated.

Immuno-prophylaxis with palivizumab decreases the rate of hospitalization due to RSV bronchiolitis in high-risk children. It is administered as an intramuscular injection starting just before RSV season and continued monthly for a total of five doses. It has been shown to decrease the rate of RSV-associated hospitalization; however, it offers no significant decrease in mortality and has not been shown to be cost-effective for use in all at-risk children. Because palivizumab prophylaxis must be initiated before RSV season begins, it is important for physicians to know the timing of RSV season in their area.

Laboratory Tests

Collection of specimens is through nasopharyngeal swabs, washes and aspirates with the latter being the best method of collection.

Enzyme Immunoassays: Enzyme immunoassay techniques that detect viral antigens in nasopharyngeal specimens are available commercially and are generally reliable in infants and young children. Sensitivity of these assays is usually in the 80% - 90% range but may be as low as 53% and generally diminishes as patients age due to decreasing concentrations of RSV shedding. The predictive value of these assays is high during the peak season and decreases when incidence of disease is low.

Immunofluorescence: RSV antigens are directly detected by staining respiratory epithelial cells with FITC (Fluorescein isothiocyanate)-conjugated anti-RSV antibodies (DFA), and examining with fluorescent microscopy. RSV DFA is more sensitive than culture and viability of the virus is not required.

Molecular diagnostic tests: Diagnostic tests using RT-PCR are commercially available and are superior to detecting RSV infection relative to viral isolation and antigen detection methods. However, the tests may lack specificity and can generate false-positives by detecting viral RNA that may persist in the airways for weeks following convalescence and after shedding of detectable infectious virus has ceased. These tests have not been approved by the Food and Drug Administration (FDA) though they have been by the Clinical Laboratory Improvement Amendments (CLIA).

Less common are:

Culture: Viral isolation from nasopharyngeal secretions in cell culture requires one to five days, but the results and their sensitivity can vary among laboratories due to improper methods of collection and transport of specimens. If this method is to be used, it is recommended that specimens be kept cold and protected from the light, stabilized in virus transport media and processed rapidly.

Serotype testing (serotyping): Serotyping of acute and convalescent serum specimens may be inaccurate in confirming infection in young infants as sensitivity may be low in this age cohort.

Surveillance

RSV infections are not nationally reportable although participating laboratories in the National Respiratory and Enteric Virus Surveillance System (NREVSS). The NREVSS is a passive, laboratory-based surveillance system that monitors the circulation of RSV and other respiratory and enteric viruses, and voluntarily report the number of RSV tests and the proportion that are positive on a weekly basis to the Centers for Disease Control and Prevention (CDC).

In Louisiana, surveillance of RSV with the purpose of defining the transmission season is done through the Hospital Inpatient Discharge Data system. Positive laboratory tests must be reported by the laboratories.

Case Definition

A case of RSV infection is defined as a respiratory illness that may result in lower respiratory tract infections of variable severity and is confirmed by laboratory isolation of respiratory syncytial virus, or antigen detection from either the respiratory tract or nasopharyngeal secretions.

Investigation

Because of the high prevalence of RSV in the population, investigation of individual cases is impractical and not warranted.

Outbreak Investigation

As in many investigations of droplet-transmitted disease, the goal of an outbreak investigation is not to establish the original causation of the outbreak, as in a foodborne outbreak for example, or to establish the steps in the chain of transmission. The main goal of the investigation is to understand the circumstances that led to the outbreak. Based on this understanding, recommendations for mitigating the spread of the outbreak can be optimized for faster and better results. Therefore, it is important to identify the following factors:

1) Who were the first cases? Where did they come from? Patients, school or daycare children, staff?
2) Who were the initial secondary cases? Where did they occur? In a limited spatial area, are there sporadic cases throughout the facility?
3) What was the spread in space (draw a map of the facility with an approximate path for the outbreak spread; if possible, do a walk-through of the facility) and time (draw an epidemic curve)?
4) What were the factors that may have contributed to the spread or prevention of the outbreak?
    - How early was case finding instituted and how extensive was it?

- Placement of individuals: separate or common rooms? How soon were sick individuals isolated or excluded?
- Individuals with risk factors?
- Cohorting of patients?
- Droplet precautions taken?
- Contact precautions taken?
- Disinfections measures instituted?

With this understanding of the history of the outbreak, discussion on practical control measures becomes significantly more productive.

Prevention

Contact precautions and droplet precautions are indicated. Strict hand hygiene practices are recommended for the duration of RSV-associated illness. A critical aspect of RSV prevention among high-risk infants in the community is the education of parents and other caregivers about the importance of preventive measures that decrease exposure to, and transmission of RSV. Such measures include limiting exposure to potentially contagious settings when possible (e.g., child care centers), and a strict emphasis on hand hygiene.

Hospital Precautions and Control

During nosocomial outbreaks of RSV, there are a variety of measures that may be implemented to reduce the risk of transmission, including:

1. Case finding: laboratory screening of symptomatic patients for RSV infection;
2. Contact and droplet precautions: using gowns, gloves and disposable eye-nose goggles after direct contact with patients and after contact with inanimate objects in the direct vicinity of patients;
3. Cohorting of infected patients and staff;
4. Excluding visitors with current or recent respiratory tract infections; requiring such visitors to wear a simple surgical mask in case of doubt and limiting their visitations;
5. Excluding staff with respiratory tract illness or RSV infection from caring for susceptible individuals;

Controlling health care-associated RSV infections is complicated by the persistent opportunity of transmission through infected patients, staff and visitors. Early identification of RSV-infected patients is important so that appropriate precautions to delimit continual transmission can be instituted immediately.

Cleaning /Disinfection

RSV is quickly inactivated by ether, chloroform, detergents, freezing at -30°C, heating at 55°C and low pH conditions.

Treatment

There is no specific treatment for RSV infection or an existing vaccine. Treatment largely consists of supportive care, which may include hydration, measurement of oxygen saturation, use of supplemental oxygen, mucous suction of the upper airway, and, in serious cases, intubation and mechanical ventilation. Rarely is antiviral therapy, typically in the form of ribavarin, recommended.

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