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Respiratory syncytial virus: The virus, the disease and the immune response

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Summary RSV is the primary cause of hospitalisation in the first year of life for children in most parts of the world, and nearly 100% of children in the USA are infected with the virus by 2 to 3 years of age. The agent is an enveloped RNA virus with a non-segmented single-stranded negative-sense genome. The viral genome encodes 8 structural and 2 non-structural proteins. Important structural proteins include the fusion (F) protein and the attachment (G) protein which are essential for viral penetration and attachment to the host cells. Both proteins are important in development of immune responses. The virus is estimated to cause 3000 to 4000 deaths annually. Primary infections are as a rule symptomatic. The spectrum of clinical manifestations ranges from mild upper tract illness, infection in middle ear which progresses to acute otitis media, croup, to apnoea in premature infants, pneumonia and bronchiolitis. Premature babies born at 30–35 weeks of gestation, infants with cyanotic congenital heart disease, HIV-infected subjects, and patients on intensive immunosuppressive therapy especially after bone marrow transplant are considered to be at risk for increased mortality and morbidity during RSV infection. The virus does not normally replicate outside of the bronchopulmonary tree and the infection is exquisitely restricted to the respiratory mucosa. However, development of extrapulmonary disease has been observed in certain T and B cell immunodeficiency states. The association of RSV with asthma and reversible reactive airway disease in early childhood has attracted significant attention. Recurrent wheezing for up to 5 to 7 years of age and established airway disease has been observed in a significant number of children with a strong family history of allergy, after primary infection or reinfection with RSV. Immune response to primary infection is relatively small but on reinfection, a significant booster effect with sustained immunologic reactivity is observed in serum and respiratory mucosa. Both CD4+ and CD8+ specific as well as Th1- and Th2-cell specific immune responses have been observed during human infection. In addition, proinflammatory as well as immunoregulatory cytokines and chemokines are induced in the respiratory tract after natural and induced (in vitro) infection. Significant progress has been made in understanding the role of Th1 vs. Th2, IgE, viral induced cytokines and chemokines in the mechanisms of pathogenesis of the disease, development of wheezing and in the prevention and treatment of the infection and its sequelae. Respiratory syncytial virus (RSV) is one of the commonest human viral infections, and virtually every child is infected by the third birthday. Because of its restricted mucosal immunopathology, and frequent association with bronchial hyperreactivity and development of wheezing, RSV has served as an important model to investigate mechanisms of mucosal immune responses and development of mucosal disease following infection. The importance of RSV in bronchopulmonary disease and development of bronchial hyperreactivity has been the focus of several recent symposia [Kimpen JL, Simoes EAF. Am J Respir Crit Care Med 2001; 163:S1–S6]. This brief report will only summarise, based on selected references, the historical landmarks of its discovery and current understanding of the mechanisms of immunity, and their possible role in the pathogenesis of bronchopulmonary disease.

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THE VIRUS

RSV was discovered in 1956, when a group of chimpanzees in a colony outside of Washington, DC (USA) were noted to have developed cold-like illness. Morris and colleagues recovered a cytopathic agent from one of these chimpanzees, who had an upper respiratory tract illness with coryza, runny nose, and malaise. They named this agent “chimpanzee coryza agent” (CCA).2 These investigators examined the entire colony, and nearly 100% of the chimpanzees were found to be infected. An interesting observation was that the human contacts working with the chimpanzees were also infected and exhibited mild upper respiratory tract illness and coryza, somewhat less severe than observed in the chimpanzees. Subsequent studies identified two major isolates of the virus recovered from other patients with upper respiratory tract illnesses. The Long strain, commonly used in laboratory studies, was recovered from the bronchopulmonary washings of a child with bronchopneumonia, and the Schneider strain was recovered from a patient with croup.3,4 On the basis of the cytopathology of this agent in tissue culture with formation of syncytia, and the similarities between the isolates recovered from the monkeys and the Long and the Schneider strains recovered in humans, Chanock and colleagues coined the term “respiratory syncytial virus” to incorporate all available isolates, and provided a classic description of the disease in children.3,4 Shortly thereafter, Beem and colleagues described in detail the epidemiology of RSV infection during community outbreaks.5

The agent is a pleomorphic, enveloped, cytoplasmic virus containing single-stranded, negative-sense RNA. The RNA is associated with viral proteins, consisting of a nucleocapsid core that is packaged within a lipid envelope. RSV is classified in the genus Pneumovirus, which belongs to the family Paramyxoviridae. The Paramyxoviridae family also includes two other genera, Paramyxovirus (containing, e.g., parainfluenza virus types 1, 2 and 3 and mumps virus) and Morbillivirus. The genera are differentiated by the diameter of the helix, the number of genes, and the nature of their surface glycoproteins. The surface G glycoprotein of the virus lacks neuraminidase and hemagglutinin. Complementary DNA (cDNA) cloning has identified 10 different viral genes, each coding for a single protein. The sequences of each gene have been described. The characteristics of these genes differentiate RSV from the other members of Paramyxoviridae as reviewed previously.6

Eight of the ten RSV proteins are present in infected cells and in the virions, and therefore are structural proteins. The disulfide-bonded glycoprotein (F, fusion protein) and the large glycoprotein (G, attachment protein) are surface proteins and are the major antigenic determinants of the virus. These proteins induce protective antibodies. The G protein mediates viral attachment. The F protein mediates viral penetration and syncytium formation. The small hydrophobic protein (SH), the matrix protein (M), and the M2 protein are envelope-associated proteins. The nucleoprotein (N), the phosphoprotein (P), and the large nucleoprotein (L) are present in the RSV nucleocapsid. NS1 and NS2 are non-structural proteins; they are found only in infected cells but not in virions.6

RSV displays minimal antigenic heterogeneity. However, two major groups A and B, with antigenic differences on the G, F, N, and P proteins, have now been identified. The G protein is the most variable protein, with only 53% homology in the amino-acid sequences between the proteins of the A and B groups. In contrast, the F and N proteins have a high degree of genetic and antigenic homology between the two groups. Both F and G proteins have several distinct antigenic sites.6 Recent data have shown considerable genetic diversity among groups A and B. The G-protein sequences may differ 20% in different group-A lineages and 9% in different group-B lineages.

The replication of the virus includes the following specific events. The virus attaches the cell through G protein. The viral envelope fuses with the plasma membrane of the host cell through the F protein. After penetration, the nucleocapsid of the virus is released into the cellular cytoplasm, where the replication takes place. The viral RNA serves as a template for messenger RNA. The messenger RNA serves as a template for translation of viral proteins, and complementary RNA serves as a template for transcription of virion RNA. The viral antigens can be detected in 9 hours in cell culture, and the infectious virus in 11 to 13 hours. Human RSV replicates in several animal species, including mice, cotton rats and chimpanzees, and to a smaller extent in guinea pigs and ferrets.6

THE DISEASE

The clinical picture of RSV infection varies according to age. The primary infection at 6 weeks to 2 years of age is usually symptomatic and involves the lower respiratory tract. Asymptomatic primary RSV infection in children is rare. Repeated infections in older children are usually less severe. Respiratory tract infections are frequently associated with expiratory wheezing (variously referred to as bronchiolitis or wheezy bronchiitis, asthma), pneumonia and
acute otitis media. RSV infections in neonates differ from those in older children. Such neonates do not often exhibit wheezing, and apnoea may be the only symptom of infection. The mortality in healthy children is extremely low, but life-threatening infections are common in immunocompromised patients and in patients with cardiac abnormalities. Pneumonia is the most common manifestation in elderly subjects.

Isolated upper respiratory tract infections associated with RSV have been noted, especially in older children and adults during re-exposure. The common symptoms are rhinorrhea, nasal congestion, pharyngitis, and cough. Some studies suggest that common colds induced by RSV may be more prolonged and severe than those induced by other viruses.

Bronchiolitis

The term bronchiolitis has been used as a diagnosis of a specific clinical symptom complex since 1940. The diagnostic criteria vary between different centers in the USA and in other countries. In general, bronchiolitis is a clinical presentation in infants less than 12 months old in whom a first attack of an acute illness, after a brief prodrome of upper respiratory symptoms, is characterised by wheezing, dyspnea, respiratory distress, poor feeding, tachypnea (>50/min), and radiologic evidence of hyperaeration of the lung. Fine crepitation can usually be heard by auscultation of the chest.

In the majority of patients, the symptoms and signs resolve within a few days to a week after the onset of illness. In sicker infants, the duration of hospitalisation may last up to 7 days. In the past infants under 6 weeks old and those with underlying illnesses often needed longer hospitalisation.

Although RSV is the most common etiologic agent of bronchiolitis and virtually the only agent that induces epidemics, other respiratory viruses can also induce bronchiolitis. These include parainfluenza type 1 and 3 virus, rhinoviruses, adenoviruses, coronaviruses, and influenza A virus. Adenoviruses can induce very severe bronchiolitis and with high mortality.

Numerous follow-up studies have shown that up to 75% of the patients with RSV bronchiolitis exhibit recurrent wheezing or pulmonary function abnormalities years later. The clinical symptoms gradually decrease and disappear usually during the following 10 years. In some of these patients, the symptoms continue and they are classified as having asthma. A diagnosis of asthma has been established in up to 92% of patients followed prospectively for 5–10 years after bronchiolitis. Even after milder lower respiratory tract RSV disease, increased morbidity was documented through the third and fourth year of life. However, normal pulmonary function was found between the ages of 8 and 12 years. It is not clear whether RSV can induce long-lasting or permanent damage to the small airways and in the growing lung. It is possible that development of bronchiolitis during primary infection may be restricted to subjects already genetically and anatomically at risk for pulmonary hyperreactivity. This possibility is strongly supported by the findings that pre-existing diminished lung function measured very early in life (before any respiratory illness) was found to be a risk factor for recurrent wheezing.

Infection in newborns, adults and the elderly

Although RSV infection is rare in the first 4 weeks of life, epidemics in neonates have been described. RSV infection has been observed in 20–30% of babies studied in a neonatal unit and in 35% of those hospitalised for 6 days or longer. In this study, 61% of the babies had respiratory illness, and of these, approximately half had upper respiratory tract infection, the other half had pneumonia. When pneumonia during the first month of life was studied, RSV was found to make up 55% of all isolates.

It is now well-documented that RSV infection occurs commonly in adults as well as children. In a family study, 17% of the adults living with infected children also became infected. In adults, RSV infection can be asymptomatic or can induce mild to moderate upper respiratory tract symptoms. In healthy adults, the infection is rarely severe or fatal. The symptoms include fever for 1 to 4 days, nasal congestion, rhinorrhea, sore throat, ear pain, and cough lasting 10 days or longer. The average duration of virus shedding is 5 days. Based on clinical features, RSV infection cannot be differentiated from other agents associated with cold-like symptoms. Adults who are immunocompromised, institutionalised, or aged, or who have some underlying illness (especially chronic pulmonary disease) are at risk of severe RSV pneumonia. The occurrence of pneumonia in long-term care facilities varies from 5% to 67%, with mortality rates ranging from 0 to 53%. The chest radiograph usually reveals patchy changes, diffuse consolidation or interstitial infiltrates. During outbreaks, RSV must be included in the differential diagnosis of fever with evidence of pulmonary infiltrates in immunocompromised adults.

Disease in high-risk children

Children at increased risk from RSV infection include
young infants with prematurity, bronchopulmonary dysplasia, congenital heart disease, congenital or acquired immunodeficiency, subjects with hematologic malignancies, patients with bone-marrow or organ transplants, and cystic fibrosis. As mentioned earlier, premature infants are more likely to have apnoeic spells, atelectasis/infiltrates, and hyperinflation as seen on the chest radiograph, and may require oxygen therapy and mechanical ventilation. Consequently, these patients need longer hospitalisation. Some studies suggest that intubation increases the risk for fatal illness. RSV infection is a major reason for re-hospitalisation of children with bronchopulmonary dysplasia. In these patients, a large number of siblings, parental smoking and recent need for home oxygen therapy are major risk factors.6

Clinicians have long been aware that RSV infection may be particularly severe, long lasting, and sometimes fatal in children with congenital immunodeficiency diseases, especially those with both T- and B-cell defects. Animal studies have suggested that T-cell mediated cellular immunity is responsible for terminating RSV infection. No reports are available of possible increased severity of RSV disease in children with isolated hypogammaglobulinemia. Increased morbidity and mortality have, however, been documented in children undergoing chemotherapy. Severe RSV infection has been reported in children who underwent liver transplantation. The risk factors appeared to be acquisition of infection soon after transplantation and pre-existing lung disease.10 Recently, RSV infection has been studied in human immunodeficiency virus (HIV)-infected children who experienced pneumonia and prolonged viral carriage. Up to 25% of such children may develop fatal illness.10,11

Congenital heart disease is another well-established risk factor for severe RSV infection. Cardiac function is not depressed in patients with normal hearts who have RSV infection. Infants with heart disease and RSV infection often need more treatment in the intensive care unit and more ventilator therapy than those without congenital heart disease. The mortality in infants with heart disease has been estimated to be about 37%. Even higher mortality (73%) has been reported in patients with pulmonary hypertension.6,10,11

Mortality and morbidity

The mortality associated with primary RSV infection in otherwise healthy children is estimated to be 0.005% to 0.020%.6 In hospitalised children, mortality rates are estimated to range from 1% to 3%.3 However, considerably higher mortality rates have been observed in children with cardiopulmonary abnormalities and in immunosuppressed subjects.

Due to the ubiquitous nature of RSV infection, even a low mortality rate may have marked impact on the total mortality of young children. The temporal patterns of respiratory viral isolations from ten laboratories in the USA with that of deaths of children has suggested that RSV isolations were clearly associated with the respiratory deaths of children 1 to 11 months old and with influenza in children 24 to 59 months of age.

A significant correlation has been shown to exist between the occurrence of sudden infants death syndrome (SIDS) and RSV infections.12,13 RSV has been demonstrated in the lungs of up to 25% of infants who died from SIDS.13 Prolonged apnoea, which is a major sign of newborn RSV infection, may explain some of these deaths. At present, however, the role of RSV in SIDS is not fully understood.

Community-acquired respiratory viruses are important causes of potentially serious acute respiratory illnesses in hospitalised bone-marrow transplant (BMT) recipients. Approximately one-third of such patients are infected with one of these viruses, although multiple viruses have been isolated continuously during these winter study periods.10 The morbidity and mortality associated with these infections were substantial. More than half (58%) of these infections may be complicated by pneumonia, with an associated mortality of over 50%. In immunocompromised patients with RSV infection, the pneumonias are almost exclusively viral in origin and may be associated with a mortality of 100% if not treated promptly. Many of the pneumonias in patients infected with other viruses, such as influenza virus, appeared to be either self-limited or appeared to have a substantial bacterial component, as judged by their favourable response to antibacterial therapy. However, fatal viral pneumonias occur as well. It is noteworthy that only a few infections due to parainfluenza virus and adenovirus are observed during these winter seasons and that their potential to cause fatal viral pneumonia has not been appreciated.10,11 In BMT recipients with an acute respiratory illness, community-acquired respiratory viruses must be considered seriously. Other recent studies have also suggested extremely high morbidity and mortality with RSV infection in patients with leukemia and hematologic malignancies.10

IMMUNE RESPONSE AND IMMUNOPATHOGENESIS OF DISEASE

RSV infection is followed by the development of both serum and mucosal IgM, IgA and IgG antibodies
Table 1
Proposed mechanisms of immunopathology during RSV induced bronchopulmonary disease

- Neuropeptides and increased expression of specific receptors (substance P and NK1)
- Prostaglandins–leukotrienes, and other cellular metabolites
- Activation of mast cells, eosinophils
- IgE
- Shift to or persistence of Th2 cellular responses
- Development of proinflammatory or immunoregulatory cytokines
  - IL-4, IL-13, RANTES, IL-2, MIP-1α, MCP-1
  - IFN-γ, IL-6, IL-8, TNF-α

RSV infection induces IgM response in 5 to 10 days, depending on the age of the patient. Lower IgM responses have been observed in patients less than 6 months old. IgM antibodies persist, usually, for 1 to 3 months. However in a few studies, IgM antibodies against RSV were found to remain detectable for at least 1 year.6

RSV-specific IgG antibody response can be detected in most patients; it reaches maximum values in 20 to 30 days after the onset of symptoms. Again, lower responses in young infants have been reported. IgG responses occur mainly in IgG1 and IgG3 subclasses, indicating the antigenic nature of the protein moieties of the F and G proteins of RSV. One year after the primary infection occurs, RSV-specific IgG levels appear to decline to low levels. After re-infection, a booster effect is noted, with high titers of IgG detectable within 5 to 7 days.14

The serum IgA response occurs several days later than IgM and IgG responses.15 Interestingly, IgA can be found free and cell-bound in nasopharyngeal secretions of patients with RSV infections. Free anti-RSV IgA appears within 2 to 5 days after infection, and peak titers are obtained between 8 and 13 days. The nasopharyngeal IgA response is greater in children older than 6 months. A mucosal immune response to RSV has also been demonstrated by RSV-induced antibody response in vitro in tonsillar lymphocytes.16 Furthermore, nasal secretions contain free RSV-specific IgE and cell-bound IgE during RSV infection.14

Several studies have demonstrated specific antibody responses to major RSV structural proteins. Antibody responses to the F protein of RSV are often cross-reactive with both RSV strains tested, whereas antibody responses to the G protein are subgroup specific. Similar findings were reported for group-specific antibody responses to primary and secondary RSV infections. These observations suggest that primary and secondary infection with group-A viruses can induce cross-reactive neutralising antibody responses to group-B viruses. RSV infection induces specific cell-mediated immune responses, including lymphocyte transformation, cytotoxic T-cell responses, and antibody-dependent cellular cytotoxicity responses.1

A number of mechanisms have been proposed to explain the association of RSV infection with increased bronchial reactivity and wheezing (Table 1). These include anatomic restrictions of the neonatal bronchial tree, and tissue damage produced by the infection itself as a result of direct cytopathology of the mucosa. During the course of acute infection, there is sloughing of the respiratory epithelium with exposure and activation of irritant receptors, which induce neurogenic stimulation of bronchial smooth muscle and development of bronchial spasm. There is loss of inhibitory mediators and cholinergic neural activity as observed during parainfluenza and influenza virus infections. Recent in vitro studies have demonstrated that RSV significantly augments the proinflammatory effects of substance P by upregulating the expression and density of its specific receptor NK1 on target cells. Substance P is a neuropeptide which has been shown to exhibit significant bronchoconstrictor effects in experimental animal studies.17 Because of the anatomy of airway in the neonate, these neurogenic factors may be more important in the induction of bronchial hyperreactivity in early infancy and childhood than later in life.17

There is good evidence from both clinical studies and experimental models with RSV, that early respiratory infections may contribute to early systemic sensitisation to other antigens or allergens in a genetically prone or atopic child (Table 2). Such children may start building up homocytotropic immune responses to environmental allergens very early on in life.18,19

Antibody-mediated immune responses are to a large extent protective. IgG, IgA and IgM do not seem to contribute to the development of disease. In fact, they seem to be important in protection. High levels of maternal antibody are indeed protective against disease. However, the magnitude of such immune response in the early years is low. It has been observed that the primary immune responses against RSV are relatively ineffective,
Table 2
Characteristics of cellular immune reactivity in children and adults relative to atopic susceptibility

| Susceptibility             | Response                                      |
|----------------------------|----------------------------------------------|
| **Adults**                 |                                              |
| Atopic                     | Th₂ response to common inhalant allergens    |
| Non-atopic                 | Low levels of Th₁ response                  |
| **Children**               |                                              |
| Cord blood                 | Low levels of Th₁ response to food and inhalant allergens (evidence of in utero sensitization) |
| Atopic early childhood     | Boosted Th2                                   |
| Non-atopic early childhood | Deviated Th1                                  |

but when such children get reinfected, they develop significant boosting, particularly for the IgG and IgA responses.6

It is important to recognise that virtually all children who get infected with RSV develop virus-specific IgE homocytotropic antibody in the respiratory tract. Such IgE activity is predominantly cell-bound to the mucosal epithelial of the respiratory tract.20 In general, there is not much free IgE detectable in respiratory excretions, unless children are wheezing or they have bronchiolitis or pneumonia. It seems that most children produce IgE to RSV early in life, but it is the amount, the persistence and the duration of this response which is critical in determining which patients are going to develop bronchiolitis and wheezing. It has been observed that persistent virus-specific IgE response in respiratory mucosa is an important element in the development of immunopathology for both RSV and parainfluenza viruses.20

In the last decade there has been considerable interest in examining the role of cell-mediated immune responses in the mechanism of immunopathology in the respiratory tract. Both CD4+ and CD8+ cells and Th₁ and Th₂ types of CD4+ cells have been implicated in the development of disease especially during RSV, rhinovirus and influenza virus infections.1,18,19

In addition to IgE antibodies and their interaction with mast cells and the subsequent release of inflammatory mediators, the interaction between RSV and the respiratory epithelium also results in the release of several other mediators. These proteins are very important in mobilising other cells to the site of disease. Studies conducted by our group during the past decade have demonstrated the release of leukotrienes, eosinophil degranulation byproducts and epithelial cell-derived cytokines and chemokines during the course of RSV infection in *in vitro* and/or *in vivo* settings.20−23 There is a wide spectrum of cytokines, chemokines and arachidonic acid metabolites, which are generated during the course of RSV infection. Many of these products are critical in recruiting cells to the site of disease. Furthermore, during the course of infection, there is induction of several cell-adhesion molecules and homing ligands (CD11B, ICAM-1, E-selectin) necessary for inflammatory and immune cells to be mobilised to the site of disease, to rollover, bind, and stick to the virus-infected tissues. They also induce expression of antigen-presenting molecules like HLA class I and II. Thus, there is a complex array of events set in motion by RSV infection of respiratory epithelium, which mobilise inflammatory and possibly immunoregulatory cells to the site of disease in the mucosal epithelium.24

Considering the large number of mechanisms proposed as explanations for the disease caused by the virus it is important to attempt to separate the primary cause and the subsequent effects of specific cell–virus interactions in mucosal tissues. Is RSV disease a true consequence of all these different pathogenic mechanisms proposed, or are they set in motion as a result of the activation of different immunoregulatory pathways during the replication of the virus in the mucosa? Studies to date have identified a number of other viral- or host-induced events during RSV-associated clinical disease. Clearly, all these events cannot be the cause of the disease seen after infection with RSV. In order to provide a unifying base to the multiplicity of phenomena observed, it has been proposed that RSV infection may trigger the activation of a “master switch” of genetic control, regulating the expression of one or more cellular functions identified above.

Previous studies in molecular biology have described in detail the role of transcription factors in activating certain genes or groups of genes. There are a number of nuclear factors, which mobilise gene activation processes and activate many cellular functions. RSV has been shown to induce activation of several such transcription factors. Recently Garafalo et al. and others have shown that RSV activates the gene promoters...
for NF-IL-6 and NF-κB. Such transcription factors regulate the synthesis of a variety of cytokines and chemokines and other important immunomodulating proteins. These include TNF-α, IL-1β, IL-2, IL-6, GM-CSF, and G-CSF; adhesion molecules ICAM-1, VCAM-1 and E-selectin; and chemokines, IL-8, MIP-1α, MCP-1, and eotaxin. These molecules are important in initiating the inflammatory cascade and in mobilising cells to the site of disease.\(^\text{24,25}\)

It appears that RSV, during the course of replication at the level of the cell, initiates activation of certain transcription processes which may have a profound effect on expression of many mediators of immunoregulation and inflammation. Other viruses such as influenza, rhinoviruses and adenoviruses have been shown to induce a similar activity. Recent studies suggest that the ultimate expression of allergy involves a multiplicity of genetic and environmental factors. Failure to switch off expected Th2 phenotype may be a key factor in eventual development of allergic sensitisation. A number of other environmental factors in early infancy and childhood may also determine the outcome of allergic sensitisation by shifting cellular immune response towards immunologic hyperactivity (Table 3).

It is thus proposed that a balance between the expression of different pro-inflammatory cytokines and chemokines, and the development of Th\(_1\) vs Th\(_2\) or CD\(_4\) vs CD\(_8\) cellular response following RSV infection may ultimately determine the degree of pathology or the level of protection against bronchopulmonary disease.

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