Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
biologic processes. This article highlighted the integral role that vesicular trafficking plays in lung cell biology as it relates to maintaining efficient respiration through surfactant secretion and reuptake and the maintenance of an intact alveolar–capillary barrier through prevention of mechanical force-induced cell injury. Defects in this trafficking machinery can result in specific respiratory disease.

**See also:** Epithelial Cells: Type II Cells. Leukocytes: Pulmonary Macrophages. Surfactant: Overview; Surfactant Protein A (SP-A); Surfactant Proteins B and C (SP-B and SP-C); Surfactant Protein D (SP-D).

**Further Reading**

Bonifacino JS and Glick BS (2004) The mechanisms of vesicle budding and fusion. *Cell* 116(2): 153–166.

Cohen AW, Hnasko R, Schubert W, and Lisanti MP (2004) Role of caveolae and caveolins in health and disease. *Physiology Review* 84(4): 1341–1379.

Conner SD and Schmid SL (2003) Regulated portals of entry into the cell. *Nature* 422(6927): 37–44.

Dietl P and Haller T (2005) Exocytosis of lung surfactant: from the secretory vesicle to the air–liquid interface. *Annual Review of Physiology* 67: 24.1–24.27.

Janmey PA and Weitz DA (2004) Cellular stress failure in ventilator injured lungs. *American Journal of Respiratory and Critical Care Medicine* 171: 1328–1342.

**VIRUSES OF THE LUNG**

**N G Papadopoulos and C L Skevaki,** University of Athens, Athens, Greece

© 2006 Elsevier Ltd. All rights reserved.

**Abstract**

Respiratory viruses include rhinoviruses and enteroviruses (Picornaviridae), influenza viruses (Orthomyxoviridae), parainfluenza, metapneumoviruses and respiratory syncytial viruses (Paramyxoviridae), coronaviruses (Coronaviridae), and several adenoviruses. With the exception of adenoviruses, all possess an RNA genome. They are usually transmitted by direct hand to hand contact and/or aerosol inhalation, and replicate in both upper and lower airways. Cellular and humoral immunity are both activated in response to respiratory viral infections as well as neural pathways, which contribute to distant inflammatory effects. Respiratory viruses are responsible for a wide variety of clinical syndromes including the common cold, acute otitis media, laryngitis, sinusitis, pneumonia, bronchiolitis, influenza, and exacerbations of asthma and chronic obstructive pulmonary disease. Diagnosis of respiratory viral infections is primarily clinical and is further supported by laboratory techniques such as antigen detection, culture, serology and more recently nucleic acid detection. Preventive strategies are based on avoidance of risk factors and vaccination when indicated. Treatment modalities include over-the-counter and non-specific remedies along with a small number of specific antiviral medications such as the influenza neuraminidase inhibitors.

**Structure and Taxonomy**

Human rhinoviruses (RVs), which probably represent the most abundant pathogenic microorganisms universally, are RNA viruses and belong to the family of Picornaviridae. The Picornaviridae also include the enteroviruses (polio, coxsackie, and echo viruses), which are more closely related to RVs, and the cardio- and aphtho-viruses, which do not infect the respiratory tract. Coxsackie virus A2, 10, 21, 24 and B2, 5 and echovirus type 1, 11, 19, 20, and 22 are the most frequently isolated enteroviral agents in upper respiratory tract infections. More than 100 serotypes of RVs are identified and numbered. They are divided into major (90%) and minor (10%) groups depending on their receptor; major RVs attach to the
intercellular adhesion molecule-1, while low-density lipoprotein receptor is the cellular receptor of minor RVs. RVs consist of a 2 MDa single-stranded positive-sense genomic RNA surrounded by a nonenveloped capsid arranged in an icosahedron, 20–30 nm in diameter (Figure 1). VP1, 2, and 3 structural proteins of the virus are highly variable surface proteins, which interact with antiviral antibodies. VP4 is confined to the interior of the capsid and is closely associated with the viral RNA.

Orthomyxoviridae's major representatives are the influenza viruses (IFVs), which are grouped into three types: A, B, and C. IFVs are negative-stranded segmented RNA viruses. The A and B types are enveloped pleomorphic agents, with spherical and filamentous forms; IFV-C is structurally distinct. IFVs attach to sialic acid receptors on ciliated columnar epithelial cells in the tracheobronchial tree via their hemagglutinin (HA) protein (Figure 2). Following replication, the virion is released by enzymatic action of the neuraminidase (NA) surface protein. The latter, along with the HA protein of the virus, is regularly subjected to small changes, which are capable of producing viral strains causing annual epidemics. This phenomenon is called 'antigenic drift', while 'antigenic shift' is the process by which a sudden major change in the HA or NA proteins of IFV-A occurs due to genetic reassortment. The latter is responsible for influenza pandemics, which have occurred every 10–40 years.

Paramyxoviridae include parainfluenza viruses (PIVs), the respiratory syncytial viruses (RSVs) as well as the recently identified human metapneumovirus (hMPV). PIVs are grouped into subtypes 1 and 3, which belong to the paramyxovirus genus, and subtypes 2, 4a, and 4b, which belong to the rubella virus genus along with the mumps virus. PIVs are single-stranded negative-sense RNA viruses, 150–200 nm in diameter, with helical nucleocapsids. In contrast to RSVs, PIVs possess both HA and NA proteins, which attach to sialic acid receptors.

RSVs are pleomorphic enveloped viruses, 120–300 nm in diameter, with a nonsegmented negative-sense RNA genome. There are two subtypes: A and B. The viral genome encodes for the glycosylated F (fusion) and G (attachment) proteins among others. The former contributes to the agent's infectivity and virulence, while the latter is involved in virus–cell and cell–cell fusion, and exhibits high variability among different serogroups. MPVs are recently identified paramyxovirus-like pleomorphic agents. They are RNA viruses and two potential subgroups have been distinguished.

Human coronaviruses (CVs) belong to the Coronaviridae and are enveloped, roughly spherical viruses, 100 nm in diameter, with 20 nm-long round surface projections. Their genome consists of a positive RNA strand. Most of the CVs studied so far are closely related to one of two reference strains, OC43 and 229E, which dominate in outbreaks alternately...
from year to year. The former binds to MHC class I molecules, while the latter binds to human aminopeptidase N (CD13). SARS-CoV is another recently identified CV, which differs phylogenetically from all other known human CVs.

Adenoviruses are nonenveloped single-stranded DNA viruses with a genome of 30–38 kbp that encodes 10 structural proteins. They are surrounded by an icosahedral capsid from which a stalk-like structure the fiber, protrudes. Reproduced with permission from Dr N G Papadopoulos.

Adenoviruses are nonenveloped single-stranded DNA viruses with a genome of 30–38 kbp that encodes 10 structural proteins. They are surrounded by a capsid of icosahedral symmetry, from which a stalk-like structure protrudes, called the fiber (Figure 3). The latter interacts with various cellular receptors, such as the MHC class I molecule and the coxsackie-adenovirus receptor. Over 50 serotypes and six subgenera (A–F) have been identified.

Mode of Infection
RVs are transmitted by both, direct hand to surface contact and aerosol inhalation, and more frequently, as with RSVs, through the eye or nose than through the mouth. Nasal epithelium represents the primary site of infection for these viruses. RVs replicate mainly in the nose, although replication takes place in the lower airways as well. IFVs are usually transmitted through inhalation of droplets, which initially attach to the mucous layer covering the tracheobronchial tree and replicate primarily in the lower respiratory tract. Epithelial infection by RVs has a 'patchy' distribution and is not overtly cytotoxic, in contrast to the majority of respiratory viruses, including IFVs, paramyxoviruses, and adenoviruses, which cause extensive inflammation and epithelial shedding.

Respiratory virus infection causes an increase in both vascular permeability mediated by vasoactive amines and glandular secretion under the influence of cholinergic reflexes and neuropeptides. Several cytokines and chemokines have also been implicated in virus-induced inflammation. Inflammatory cells further aggravate events by release of additional mediators.

Humoral immunity is also activated in response to viral infections with production of serotype-specific antibodies. The nature of the response is associated with age, previous infection, and vaccination status of the host. Recovery from respiratory viral illness is usually achieved prior to the detection of specific antibody indicating that cellular and/or non-specific immune responses are primarily responsible for viral eradication. Nevertheless, antibodies are able to provide protection from secondary infections.

Respiratory viruses not only induce a local inflammatory reaction at the level of infected epithelial cells but may also act at a distance through neuronal pathways. All parasympathetic, sympathetic, and nonadrenergic noncholinergic nervous supply of the respiratory tree may be affected by viral infections, suggesting an important neuroimmune interaction, which may contribute to the virus-mediated reactive airway disease (Figure 4).

Clinical Manifestations
Respiratory viruses are related to various distinct as well as non-specific clinical presentations. There is considerable overlap between viruses and clinical presentations; although differences exist, all agents may cause any of several clinical syndromes (Table 1). Among these, the common cold is by far the commonest with an enormous socioeconomic impact. Clinical presentation ranges from asymptomatic to upper respiratory tract (URT) symptoms such as nasal congestion, rhinorrhea and nasopharyngeal irritation, lower respiratory tract symptoms such as cough, to systemic symptoms including general malaise, headache, and sleep impairment depending on the viral culprit and host. The incubation period is 24–48 h and symptoms usually last for 5–7 days. The common cold is a rather benign clinical entity, which may however be complicated by secondary bacterial infections, otitis media, sinusitis, pneumonia, and asthma exacerbations; death may occur in immunocompromised patients.

Viral URT infection often results in impairment of the function of the eustachian tube, which predisposes to the development of acute otitis media. The
latter is one of the commonest infections among children and is very often attributed to viral etiology. Respiratory viruses may also predispose to nasopharyngeal bacterial colonization and alteration of the host’s immune response. Finally, viruses may be responsible for antibiotic treatment failure in cases of concurrent bacterial and viral infections. Likewise, respiratory viruses have been implicated in the development of sinusitis, either directly as an extension of URT infection or as a result of secondary bacterial infection.

Laryngitis and laryngotracheobronchitis-croup have more frequently been associated with the para-influenza virus group. Pneumonia in infants and young children is most commonly attributed to viruses. Disease burden is also significant among the elderly and the immunocompromised. RVs and RSVs are the agents most frequently isolated in viral pneumonias, although age, season, year, and other variations can be considerable. The presence of adenovirus is a risk factor for severe disease in infants. Influenza occurs in yearly winter epidemics and pandemics every 10–40 years resulting in enormous morbidity and mortality, especially among the very young, the elderly, and the immunocompromised.

RSV is also the major pathogen implicated in acute bronchiolitis, which afflicts infants and is responsible for a great number of hospitalizations and deaths in this age group. Host immune response skewed towards type 2 cytokine production seems to play a central role in the pathogenesis of the disease. Bronchiolitis is further associated with recurrent wheezing.

The great majority of acute asthma exacerbations in children and a considerable proportion in adults is preceded by a viral URT infection; such exacerbations may often result in hospitalization. The most frequently isolated offending agent is RV, a fact that reflects the preponderance of the virus among common cold cases. Finally, exacerbations of chronic obstructive pulmonary disease may also have a viral etiology, most commonly due to RVs.

**Diagnosis and Treatment**

The diagnosis of respiratory viral infections relies upon clinical criteria and is further supported by laboratory techniques such as direct viral, nucleic acid or antigen detection, culture, and serology. Direct detection is based on the identification of whole virus or inclusion bodies with electron or light microscopy, respectively. Viral antigens may also be detected by the use of immunofluorescence and enzyme immunoassays but an adequate viral load is required. Viral cultures usually demonstrate the biological effects of an agent, such as the cytopathic effect or hemagglutination, in cultured cells. Culture
methods, however, have drawbacks due to their low sensitivity and extensive time length (days to weeks). Determination of specific viral antibodies in a host’s blood sample and comparison between acute and convalescent phases of respiratory illness is another diagnostic modality, which is mainly used for epidemiological purposes. Serological tests include immunoassays, complement fixation, and passive agglutination assays as well as hemagglutination inhibition. Polymerase chain reaction (PCR)-based techniques are being developed, replacing in several instances other techniques as they are rapid and sensitive, and may also provide an estimation of the number of viral copies present in a given biological sample (real-time PCR).

Control of the transmission of respiratory infections may be partly achieved through adequate hygiene practices and avoidance of congregation and stress. The development of effective vaccines is hampered by the large number of viral serotypes; however, vaccines are available against IFVs, several RSV and PV vaccine candidates are currently under clinical investigation, and oral live attenuated adenovirus vaccines have been successfully used in military recruitment centers in the past. Over-the-counter remedies for the alleviation and reduction of duration of common cold symptoms include vitamin C, zinc, and echinacea, although these agents are only moderately effective. Nasal decongestants, first generation antihistamines, anticholinergic nasal sprays, oral and intranasal β-adrenergic agonists, inhalation of humidified hot air at 42–44°C, non-steroidal anti-inflammatory drugs, and cromones have been proposed for symptomatic relief with moderate results. A combination of specific antivirals with one or more anti-inflammatory drugs may offer the ideal therapeutic approach since it would both inhibit viral replication and block inflammatory events, although cost and compliance are considerable obstacles.

Current Antimicrobial Therapy

Unfortunately, there are only a limited number of antiviral agents available against respiratory viruses due to the frequent mutations resulting in the constant emergence of new and often resistant strains. Specific antiviral chemotherapy exists against IFVs in the form of the classical adamantanes (amantadine and rimantadine) as well as the new NA inhibitors, zanamivir (intranasal formulation) and oseltamivir. The former were only effective against IFV A, had significant adverse effects, and often resulted in the development of resistant strains, in contrast to the latter which are active against both A and B IFVs, possess minimal adverse effects, and are currently indicated for both prophylactic and therapeutic purposes. Palivizumab is a monoclonal antibody against RSV, which may be administered prophylactically to infants at high risk for severe bronchiolitis; ribavirin is an antiviral agent currently less frequently used.

The most effective compound against a variety of respiratory viruses and the resulting common cold is interferon alpha-2b, administered intranasally, before or shortly after exposure. However, due to its high cost, dosage frequency (six times daily), and side effects (mainly nasal irritation and bleeding) clinical application has been abandoned.

Several other agents have been assessed for activity against rhinoviruses. Pleconaril is an oral agent, which binds to VP1, a capsid protein of Picornaviruses, and thus inhibits capsid function, viral attachment to cellular receptors, and viral uncoating. Ag7088 (rupintrivir) is a well-tolerated irreversible inhibitor of Picornavirus 3C protease. Reported adverse effects were usually restricted to blood-tinged mucus and nasal passage irritation. Both compounds are currently under clinical trials.

See also: Antiviral Agents. Asthma: Acute Exacerbations. Bronchiectasis. Bronchiolitis. Chronic Obstructive Pulmonary Disease: Acute Exacerbations. Laryngitis and Pharyngitis. Panbronchiolitis. Pediatric Pulmonary Diseases. Pneumonia: Viral. Signs of Respiratory Disease: Breathing Patterns; Clubbing and Hypertrophic Osteoarthropathy; General Examination; Lung Sounds. Symptoms of Respiratory Disease: Cough and Other Symptoms. Upper Respiratory Tract Infection.

Further Reading

Johnston SL and Papadopoulos NG (eds.) (2003) Respiratory Infections in Asthma and Allergy. New York: Dekker.
McCracken GH (2000) Etiology and treatment of pneumonia. Pediatric Infectious Diseases Journal 19: 373–377.
Mossad SB (1998) Treatment of the common cold. British Medical Journal 317: 33–36.
Myint SH (1994) Human coronaviruses: a brief review. Reviews in Medical Virology 4: 35–46.
Papadopoulos NG and Johnston SL (1999) The acute exacerbation of asthma: Pathogenesis. In: Holgate ST, Boulos HA, and Fabbri LM (eds.) Difficult Asthma, pp. 183–204. London: Martin Dunitz.
Papadopoulos NG and Johnston SL (2001) Viral infections of the nose and lung. In Wallaert B and Chanez P (eds.) The Nose and Lung Diseases, pp. 79–100. European Respiratory Monographs.
Papadopoulos NG and Johnston SL (2003) Rhinoviruses. In Zuckerman AJ, Banatvala JE, Griffiths P, Pattison JR and Schoub B (eds.) Principles and Practice of Clinical Virology, 5th edn. Chichester: John Wiley & Sons.
Papadopoulos NG, Xatzipsalti M, and Johnston SL. The common cold. In: Torres, Ewig, Mandell, and Woodhead (eds.) Respiratory Infections. London: Arnold (in press).
Phelan PD, Landau LI, and Olinsky A (1994) Respiratory Illness in Children, 4th edn. Oxford: Blackwell Scientific Publications.
Rabella N, Rodriguez P, Labeaga R, et al. (1999) Conventional respiratory viruses recovered from immunocompromised patients: clinical considerations. Clinical Infectious Diseases 28: 1043–1048.
Stein RT, Sherrill D, Morgan WJ, et al. (1999) Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 354: 541–545.
Turner R (1997) Epidemiology, pathogenesis, and treatment of the common cold. Annals of Allergy, Asthma and Immunology 78: 531–539; quiz 9–40.