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Virology and immunology of the common cold

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SUMMARY

The common cold is a complex infectious syndrome caused by any one of a large number of antigenitically distinct viruses found in four groups. These groups are the myxo- and paramyxoviruses, the adenoviruses, the rhinoviruses and the coronaviruses. The members of the different groups differ in their physical, biochemical, and immunologic characteristics. With currently available methods, it is possible to determine the cause of 60–70% of colds.

The large rhinovirus group is the most important of the known common cold viruses, accounting for approximately 30% of colds. These small RNA viruses have a genome of 7000 nucleotides, which shares considerable homology with poliovirus. The capsid of the rhinovirus is loosely packed, resulting in a relative acid sensitivity compared to the enteroviruses. Although there are at least 89 different antigenic types, all rhinoviruses attach to either one of two cellular receptors. Immunity to rhinovirus is type-specific and associated with neutralizing antibody in nasal secretions and serum. There is a steady acquisition of antibody to the rhinoviruses during childhood and adolescence. The rhinoviruses may be undergoing slow antigenic drift.

The nasal cavity is particularly interesting because of the complexity of its microbial flora. Several families of pathogenic bacteria inhabit the nose on a permanent basis as part of the normal bacterial flora, while on an intermittant, short-term basis are found representatives of several families of viruses (Gwaltney Jr. and Hayden, 1982). The viruses differ from the bacteria in their ability when introduced into the nose to escape clearance by mucociliary cleansing and to initiate infection (Table 1). Thus, for example, a high rate of infection can be achieved when very small doses of rhinovirus are introduced into the nose of volunteers lacking antibody to the challenge virus (Couch et al., 1966). This ability of the respiratory viruses to invade the normal mucous membranes of the upper respiratory tract is a basic feature of their pathogenicity and underlies their importance as a cause of secondary bacterial infection of the sinuses and middle ear. Common cold is a syndrome caused by any one of the more than 100 antigenically

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Table 1. Biologic characteristics of viruses and bacteria in the upper respiratory tract affecting pathogenesis and epidemiology.

	viruses	bacteria
invasion of normal mucous membrane	yes	no*
duration of carriage	short-term** ($\leq$2 weeks)	long-term (weeks-months)

* *Streptococcus pyogenes* is an exception.
** Herpes simplex virus and adenovirus are exceptions.

distinct viruses which intermittantly inhabit the upper respiratory tract. The major respiratory viruses are found in four groups: the myxo- paramyxoviruses, the adenoviruses, the picornaviruses and the coronaviruses (Table 2). Influenza virus is associated with classic influenza, but also is a cause of common cold-like illnesses. The parainfluenza viruses are an important cause of croup and viral

Table 2. The major respiratory viruses and their associated diseases.

myxo- and paramyxovirus groups	
influenza virus (types a and b)	classic epidemic influenza, including viral pneumonia in all ages; colds in all ages; sinusitis and otitis media suspected.
influenza virus (type c)	colds.
parainfluenza virus (types 1–3)	colds in all ages, croup, bronchitis, bronchopneumonia in children, pneumonia (occasional) in adults.
parainfluenza virus (type 4)	colds.
respiratory syncytial virus	bronchiolitis and bronchopneumonia in children, colds in all ages, otitis media suspected.
adenovirus group	
(35 human types)	acute respiratory disease (ARD) in military recruits, pharyngoconjunctival fever in children and young adults, pneumonia in children and occasionnally in adults.
picornavirus group	
enterovirus subgroup	
Coxsackie A (24 types)	type a 21 (Coe virus) – colds and ARD in adults. Others (types 2, 4, 5, 6, 8, 10) herpangina.
ECHO (33 types)	types 8, 11, 20, 22, 24 – colds (importance uncertain)
rhinovirus subgroup	
($>$100 types)	colds in all ages, precipitant of asthma attacks in children and infectious exacerbations in patients with chronic obstructive lung disease, sinusitis suspected.
coronavirus group	
($\geq$types)	colds in all ages, questionable lower respiratory tract disease in children and military recruits.

pneumonia in children and also cause coryzal illness in children and adults. Respiratory syncytial virus is the major cause of bronchiolitis and is also an important cause of childhood pneumonia. As with the others in this group, respiratory syncytial infection in its minor form presents as a typical common cold. The illness associated with adenovirus is called acute respiratory disease ("ARD") in military recruits and pharyngoconjunctival fever in civilians. This illness is characteristically more severe than the average cold although it is usually perceived as a bad cold by the lay public. Pharyngoconjunctival fever and ARD are often associated with severe pharyngitis, which may be purulent, and with malaise, fever, and tracheitis. Also conjunctivitis accompanies approximately one-half of the recognized cases, while conjunctivitis is distinctly unusual in colds due to the other major respiratory viruses.

The coronaviruses are the most recently recognized of the respiratory viruses. Because these viruses grow poorly in cell culture, it has been difficult to do epidemiologic studies. Coronavirus infections have been associated with the common cold syndrome in children and adults. They may also cause infection of the lower respiratory tract, but this is less certain. Coronavirus infections appear to be most prevalent in the mid-winter period while the other major common cold viruses, the rhinoviruses, are found most frequently in the fall and spring.

At the present time, it is possible to determine the cause of approximately 60% of common colds (Table 3). The rhinoviruses account for approximately one-third of the total. The other viruses as a group are associated with another third of colds and one-third cannot be diagnosed by currently available methods and are presumably due to, as yet, undiscovered viruses. It is thought by many that the percentage of colds due to the coronaviruses may be larger than has been found to date ($\simeq 10\%$) and that with better techniques for diagnosis, coronavirus infec-

Table 3. Etiologies of the common cold.

agent	number of antigenic types	approximate percentage of cases
rhinovirus	89 numbered (plus 20 more awaiting enumeration)	30
coronavirus	≥3	≥10
respiratory syncytial virus	1	10–15
influenza virus	3	
adenovirus	33	
other viruses (enterovirus, varicella, rubeola)		5
presumed undiscovered viruses		30–40
*streptococcus pyogenes**		5

* Streptococcal pharyngitis is not always clinically distinct from viral pharyngitis.

tions will be shown to account for a significant proportion of the undiagnosed cases.

Because the viruses in the different families vary in their physical and biochemical characteristics, it is not possible to review them all in the time allotted. Since the rhinoviruses are the most important of the known common cold viruses, they will be considered in more detail. Rhinovirus grows best in human embryonic lung fibroblasts where the cytopathic effect is characterized by rounding and detachment of the cells. Electron microscopic examination of the cytoplasm of rhinovirus infected cells shows characteristic crystalline structures composed of a lattice work of the virus particle (Figure 1). Because the individual rhinovirus particle is similar in size to a cellular ribosome, it is not possible to identify an individual virion in an infected cell unless it is located in a crystal. This presents a problem in identifying rhinovirus by electron microscopy in clinical specimens such as nasal biopsies and the exfoliated ciliated epithelial cells found in nasal mucus. Turner and co-workers (1982) have shown that ciliated epithelial cells are not seen by light microscopy in nasal secretions from well persons, but do appear in the secretions from persons with experimental rhinovirus colds. They also showed by immunoperoxidase staining the presence of rhinovirus antigen in the cytoplasm of such cells, thus establishing a direct relationship between viral in-

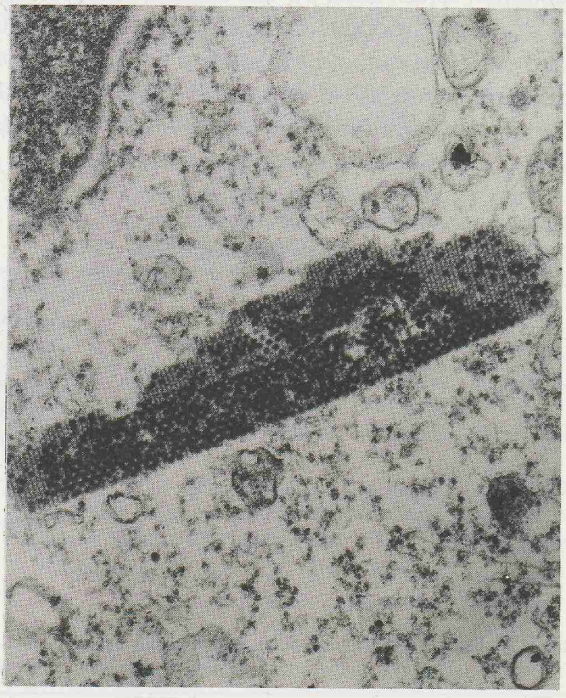

Figure 1.
Rhinovirus crystal in the cytoplasm of a HeLa Cell.

Table 4. Physical and biochemical characteristics of rhinovirus.

27–28 nm
single stranded RNA genome (7209 nucleotides long; 45–62% homology with polio virus)
codes for 240,000 MW polyprotein
4 polypeptides in capsid (loosely packed)
89 numbered antigenic types
2 receptor families (85% share a common receptor)

fection and the cell damage. Although these virus-containing cells are present in the nasal secretions of rhinovirus infected persons, they are not present in large numbers. The histologic examination of nasal biopsies from volunteers with rhinovirus colds has not shown discernible damage to the epithelium (in press). However, the results of studies to determine where rhinovirus grows in the upper respiratory tract have shown that most virus is produced in the nose and nasopharynx rather than in the oropharynx or mouth (Gwaltney Jr., 1980).

Important new information has recently become available on the biochemistry of rhinovirus (Table 4). These small RNA viruses are members of the picornavirus family. The viral genome is 7209 nucleotides, and sequencing of some rhinovirus types has now been completed (Colonno et al., 1984). Some of the types studied have shown 45–62% homology with poliovirus. The capsid of the rhinovirus is loosely packed compared to the capsid of the enteroviruses, which explains the relative acid sensitivity of rhinoviruses and the acid resistance of the enteroviruses. Also, although there are at least 89 different antigenic types of rhinovirus, all these viruses attach to either one of two cellular receptors with the majority (85%) sharing a common receptor (Abraham and Colonno, 1984).

As with their physical and biochemical properties, the different respiratory viruses differ in their immunological characteristics, making it impossible to review the various groups in detail. As a general principle, it has been observed that infection with those virus groups which contain only a single or a few antigenic types such as respiratory syncytial virus, the parainfluenza viruses, and coronaviruses, tend to be associated with poor immunity following infection; thus, resulting in recurrent infections throughout life. On the other hand, infection with the groups containing multiple antigenic types such as the rhinoviruses, adenoviruses and enterovirus tend to give more long lasting immunity, although reinfection with these viruses does occur. Another general principle is that resistance to infection with the non-enveloped viruses, such as the rhinoviruses, appears to be primarily associated with humoral immunity, while with the enveloped viruses, such as the myxo- and paramyxoviruses, both cellular and humoral immunity have been proposed as being important in natural resistance to infection (Foy and Grayston, 1982).

Serum neutralizing antibody titers rise in 35 to 80% of persons with rhinovirus

cold (Gwaltney Jr., 1982). IgA, IgG, and early in infection, IgM fractions of immunoglobulin are associated with neutralizing activity. Titers of serum antibody of ≥ 8 have been associated with protection from infection under natural conditions. Nasal secretory antibody also appears following rhinovirus infection and is thought to have a primary role in protection. The ratio of nasal to serum neutralizing antibody has been reported as being higher (1/2) following a recent infection than when measured at a later date (1/16). While specific immunity appears to be important in prevention of infection, it is not thought to be of primary importance in recovery from illness, where other mechanisms such as interferon may have a major role.

A study of the prevalence of antibody to a representative group of rhinovirus serotypes has shown that there is a steady acquisition of antibody during childhood and adolescence, reflecting the repeated occurrence of rhinovirus colds during this period. The peak in rhinovirus prevalence is in young adulthood, presumably reflecting the exposure of parents to the young children in their home. Antibody prevalence declines somewhat in later years, a time when the incidence of colds is reduced, probably as a result of less exposure to children in the home. Finally, there is a suggestion that the antigenicity of the rhinoviruses may be undergoing a gradual modification. If it is true that these viruses are showing a slow rate of antigenic drift, this will add another complexity to the understanding of their immunology.

This has been a brief review of the virology and immunology of the common cold with an emphasis on rhinovirus. The common cold is one of the more complex of the infectious syndromes. Although considerable progress has been made in understanding colds since the discovery of the major cold viruses in the 1950's, a complete elucidation of the etiology of colds remains to be accomplished. Enough is known to realize that an understanding of colds can only be achieved through approaching each of the different groups of viruses as causing distinctive and specific infections. Work on the rhinovirus has proceeded farthest, but even with this virus, much remains to be learned. Progress on the biochemistry of rhinovirus has moved more rapidly than work on its immunology and pathogenicity, but progress on the latter is being made.

ZUSAMMENFASSUNG

Die klassische "Erkältung" ist ein komplexes infektiöses Syndrom, das durch eines einer Großzahl von Viren mit verschiedenen Antigenen verursacht wird. Diese Viren werden in vier Gruppen eingeteilt: Myxo/Paramyxoviren, Adenoviren, Rhinoviren und Coronaviren. Die Angehörigen dieser Gruppen unterscheiden sich in ihren physikalischen, biochemischen und immunologischen Eigenschaften. Mit den derzeitigen Kulturmethoden ist es möglich, 60–70% der klassischen Erkältungskrankheiten virologisch zu diagnotizieren.

Die große Rhinovirengrupe ist die wichtigste unter den uns bekannten Erkältungsviren und ist verantwortlich für etwa 30% der Erkrankungen. Diese kleine RNS-Viren haben ein Genom von 7000 Nukleotiden, das starke Homologie mit dem Poliovirus zeigt. Das Kapsid des Rhinovirus ist lose gepackt und macht daher dieses Virus, im Vergleich mit den Enteroviren, relativ säureempfindlich. Obwohl es mindestens 89 Antigentypen gibt, binden alle Rhinoviren an einen von zwei Zellrezeptoren. Immunität gegen Rhinoviren ist typenspezifisch und zeigt sich als neutralisierender Antikörper in Nasenschleim und Serum. Antikörpertiter gegen die Rhinoviren steigen in der Kindheit und Adoleszenz stetig an. Rhinoviren sind anscheinend einer langsamen Antigenverschiebung unterworfen.

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