Medical Virology for 2nd Year M.D. Students

Picornaviruses and Orthomyxoviruses

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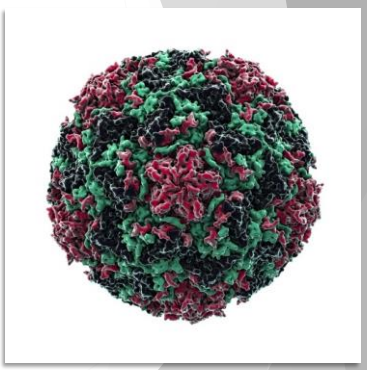
Picornaviridae Family

- Picornaviruses are small, naked and icosahedral viruses which contain a single-stranded, non-segmented RNA genome.
- The genera *Enterovirus*, *Rhinovirus*, and *Hepatovirus* cause a wide variety of clinical syndromes in humans.



Classification of Human Picornaviruses

- Poliovirus (3 serotypes).
- Coxsackieviruses A and B (25 serotypes).
- Echovirus (28 serotypes).
- Human enterovirus (43 serotypes).
- Human rhinoviruses A, B and C (more than 150 serotypes).
- Hepatovirus (Hepatitis A virus, a single serotype).

General Features

- Individuals are infected with enteroviruses by **ingestion of contaminated food or water or via respiratory droplets**.
- Enteroviruses are stable at the low pH of the stomach, replicate in the GI tract, and excreted in the stool (fecal-oral spread).
- After replicating in the oropharynx and intestinal tract lymphoid tissue, enteroviruses can leave the intestine by entering the bloodstream, and thus spread to various target organs. E.g. poliovirus spreads to the central nervous system (CNS).
- Although the great majority of infections are asymptomatic, infection, whether clinical or subclinical, usually results in protective immunity.

General Features

- Enteroviruses are acid-stable (they must survive the acid environment of the stomach). In contrast, rhinoviruses are acid-labile.
- Rhinoviruses, which replicate in the nasal passages, have an optimal temperature for replication that is lower than that of enteroviruses. This permits rhinovirus to replicate efficiently at temperatures several degrees below body temperature.
- All enteroviruses can cause CNS disease. They are the major cause of acute aseptic meningitis.

1. Poliovirus Infections

- For poliovirus, the virus binds to the poliovirus receptor (PVR; CD155).
- The mouth is the portal of entry of the virus, and primary multiplication takes place in the oropharynx or intestine.
- The virus is regularly present in the throat and in the stools before the onset of illness.
- One week after infection, there is little virus in the throat, but virus continues to be excreted in the stools for several weeks even though high antibody levels are present in the blood.

1. Poliovirus Infections

- It is believed that the virus first multiplies in the tonsils, the lymph nodes of the neck, Peyer patches, and the small intestine.
- The CNS may then be invaded by way of the circulating blood.
- Poliovirus can also spread along axons of peripheral nerves to the CNS, where it continues to progress along the fibers of the lower motor neurons to increasingly involve the spinal cord or the brain.
- Poliovirus does not multiply in muscle in vivo. The changes that occur in peripheral nerves and voluntary muscles are secondary to the destruction of nerve cells.

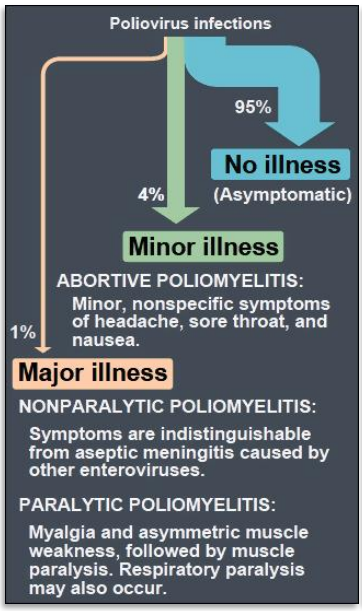
Clinical features of poliovirus infection

- When an individual susceptible to infection is exposed to the virus, the response ranges from inapparent infection without symptoms to a mild febrile illness to severe and permanent paralysis.
- Most infections are subclinical; only about 1% of infections result in clinical illness.
- The incubation period is usually 1-2 weeks, but it may range from 3 to 35 days.

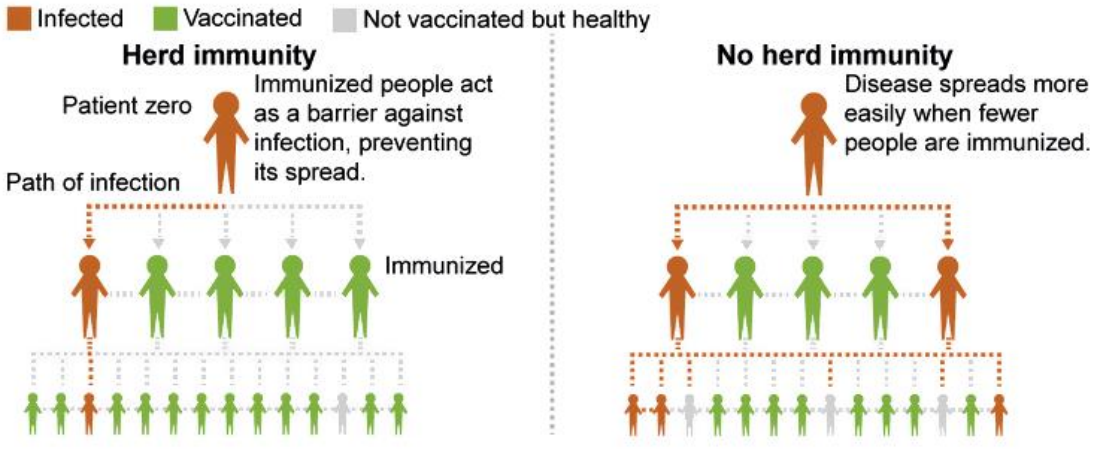
Clinical features of poliovirus infection

- (1) Mild disease is the most common form. The patient has only a minor illness, characterized by fever, malaise, drowsiness, headache, nausea, vomiting, constipation, and sore throat in various combinations. Full recovery occurs in a few days.
- (2) Nonparalytic poliomyelitis (aseptic meningitis) patients have the symptoms of the mild disease plus stiffness and pain in the back and neck.
- The disease lasts 2–10 days, and recovery is rapid and complete. Poliovirus is only one of many viruses that produce aseptic meningitis.
- (3) Paralytic poliomyelitis and progressive postpoliomyelitis muscle atrophy. The predominating complaint is flaccid paralysis resulting from lower motor neuron damage. Respiratory paralysis may occur as well.

Summary of poliovirus infection outcome



Management and Prevention

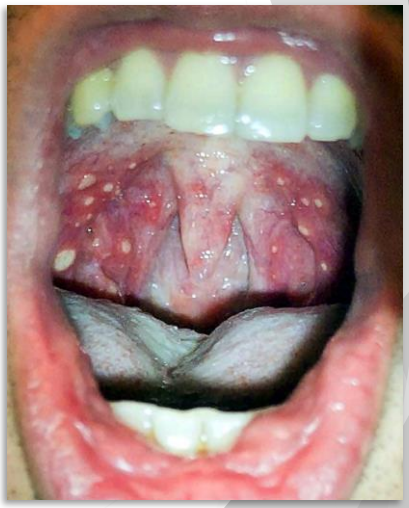


2. Coxsackievirus Infections

- They are divided into two groups: A and B.
- They produce a variety of illnesses in humans, including aseptic meningitis and respiratory and acute febrile illnesses.
- Herpangina (vesicular pharyngitis), hand-foot-and-mouth disease, and acute hemorrhagic conjunctivitis are caused by certain coxsackievirus group A serotypes.
- Pleurodynia (epidemic myalgia; Bornholm disease that presents with fever and stabbing chest pain), myocarditis and pericarditis are caused by some group B coxsackieviruses.

2. Coxsackievirus Infections (Herpangina)

- Herpangina is a febrile illness of relatively sudden onset with complaints of fever and sore throat.
- Characteristic lesions are found on the anterior tonsillar pillars, soft palate, uvula, and tonsils, and on the posterior pharynx.
- The illness, which has a predilection for the young, is usually self-limited and disappears within a few days.



2. Coxsackievirus Infections (Hand-foot-and-mouth disease)

- Hand-foot-and-mouth disease is an illness associated with vesicular lesions of the hands, feet, mouth, and, at times, buttocks.
- The main causes of hand-foot-and-mouth disease are A10, A16 and EV71.

3. Echovirus Infections and Human Enteroviruses

- Echoviruses (enteric cytopathogenic human orphan viruses) are associated with the following human infections: Aseptic meningitis, encephalitis, febrile illnesses with or without rash, common colds, and ocular disease.

- Similar clinical syndromes are caused by human enteroviruses. However, certain enteroviruses are associated with specific syndromes. E.g. EV 70 is a main cause of acute hemorrhagic conjunctivitis. EV70 and 71 are associated with severe CNS disease. EV71 is associated with HFM disease.

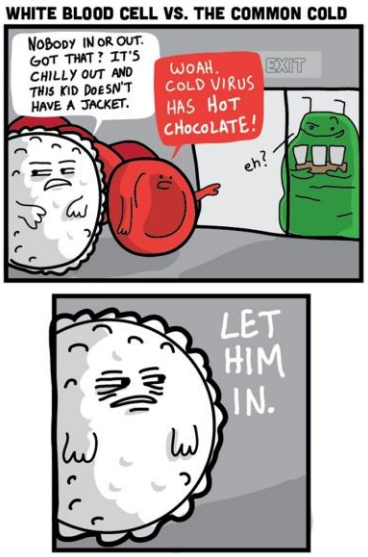
4. Rhinovirus Infections

- Rhinoviruses are the common cold viruses. They are the most commonly recovered agents from people with mild upper respiratory illnesses. They are usually isolated from nasal secretions but may also be found in throat and oral secretions.
- More than 150 types are known that belongs to three species (A, B and C).
- Rhinoviruses use intercellular adhesion molecule-1 (ICAM-1) members of the low-density lipoprotein receptor (LDLR) family as their cellular receptors.

4. Rhinovirus Infections

Viral cause of the common cold

Virus	Estimated annual proportion of cases
Rhinoviruses	30–50%
Coronaviruses	10–15%
Influenza viruses	5–15%
Respiratory syncytial virus	5%
Parainfluenza viruses	5%
Adenoviruses	<5%
Enteroviruses	<5%
Metapneumovirus	Unknown
Unknown	20–30%



4. Rhinovirus Infections

- The incubation period is brief (from 2 to 4 days) and the acute illness usually lasts for 7 days although a non-productive cough may persist for 2–3 weeks.
- The average adult has one or two attacks each year.
- Usual symptoms in adults include sneezing, nasal obstruction, nasal discharge, and sore throat; other symptoms may include headache, mild cough, malaise, and a chilly sensation. There is little or no fever.

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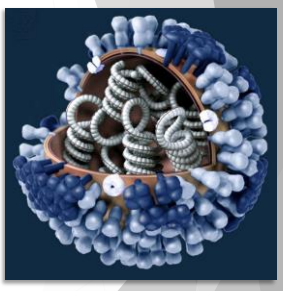
- The average adult has one or two attacks each year.
- Usual symptoms in adults include sneezing, nasal obstruction, nasal discharge, and sore throat; other symptoms may include headache, mild cough, malaise, and a chilly sensation. There is little or no fever. The nasal and nasopharyngeal mucosa become red and swollen.
- There are no distinctive clinical findings that permit an etiologic diagnosis of colds caused by rhinoviruses versus colds caused by other viruses.
- Secondary bacterial infection may produce acute otitis media, sinusitis, bronchitis, or pneumonitis, especially in children. No specific prevention method or treatment is available.

Orthomyxoviridae Family

- Orthomyxoviruses are enveloped viruses containing a segmented, negative-strand RNA genome.
- Viruses in this family infect humans, horses, and pigs, as well as nondomestic water fowl, and are the cause of influenza.
- Orthomyxoviruses are divided into 3 types: influenza A, B, and C.

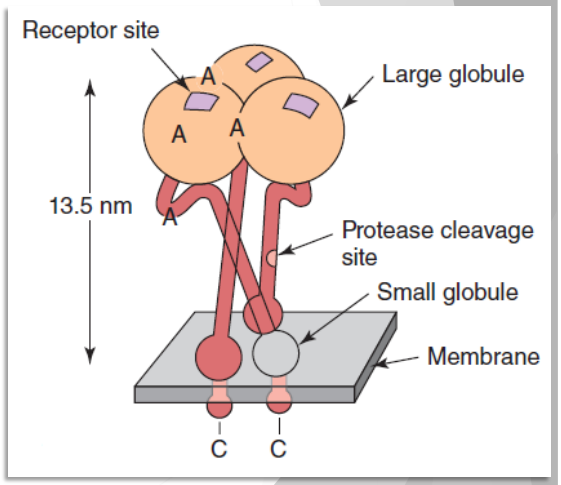


Orthomyxovirus Structure

- The single-stranded, negative-sense RNA genomes of influenza A and B viruses occur as eight separate segments; influenza C viruses contain seven segments of RNA, lacking a neuraminidase gene.
- Influenza virus particles contain nine different structural proteins. The nucleoprotein (NP) associates with the viral RNA to form a ribonucleoprotein (RNP) structure that assumes a helical configuration and forms the viral nucleocapsid. Three large proteins (PB1, PB2, and PA) are bound to the viral RNP and are responsible for RNA transcription and replication (polymerase basic and acidic proteins).
- The matrix (M1) protein, which forms a shell underneath the viral lipid envelope, is important in particle morphogenesis and is a major component of the virion (~40% of viral protein).

Influenza HA Structure & Function

- The HA protein of influenza virus binds virus particles to susceptible cells and is the major antigen against which neutralizing antibodies are directed.
- The HA protein is cleaved into two subunits, HA1 and HA2.
- The HA spike on the virus particle is a trimer composed of three intertwined HA1 and HA2 dimers.

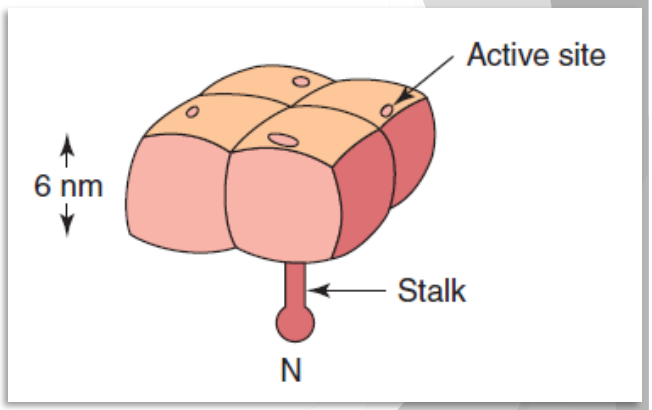


Influenza HA Structure & Function

- The cleavage of HA is necessary for the virus particle to be infectious and is mediated by cellular proteases.
- Influenza viruses remain confined to the RT because the proteases that cleave HA are common only at those sites.
- More virulent viruses that have adapted to use a more ubiquitous enzyme, (e.g. plasmin) to cleave HA and promote widespread infection of cells.

Influenza NA Structure & Function

- The spike on the virus particle is a tetramer composed of four identical monomers.
- The NA functions at the end of the viral replication cycle. It is a sialidase enzyme that removes sialic acid from glycoconjugates.

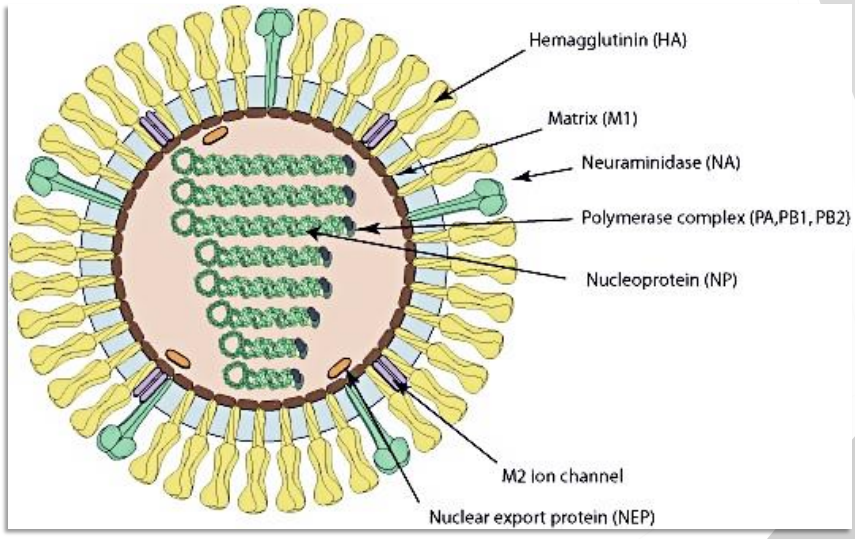


Influenza NA Structure & Function

- NA facilitates release of virus particles from infected cell surfaces during the budding process and helps prevent self-aggregation of virions by removing sialic acid residues from viral glycoproteins.

- It is possible that NA helps the virus negotiate through the mucin layer in the respiratory tract to reach the target epithelial cells.

Orthomyxovirus Structure

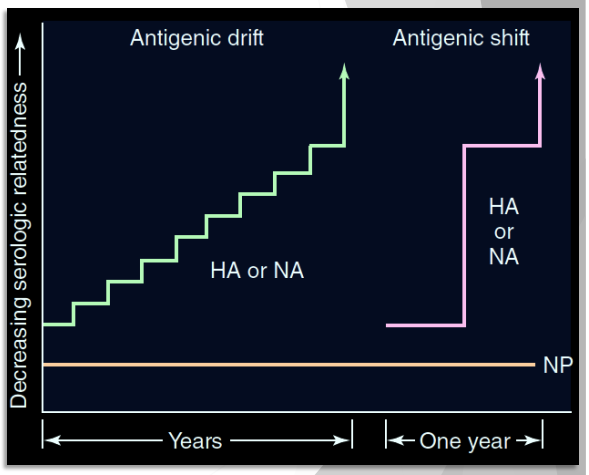


Classification and Nomenclature

- The standard nomenclature system for influenza virus isolates includes the following information: type, host of origin, geographic origin, strain number, and year of isolation.
- Antigenic descriptions of the HA and the NA are given in parentheses for type A. The host of origin is not indicated for human isolates, such as A/Hong Kong/03/68(H3N2), but it is indicated for others, such as A/swine/Iowa/15/30(H1N1).
- So far, 15 subtypes of HA (H1–H15) and nine subtypes of NA (N1–N9), in many different combinations, have been recovered from birds, animals, or humans. Four HA (H1–H3, H5) and two NA (N1, N2) subtypes have been recovered from humans.

Genetic Variability

- The two surface antigens of influenza undergo antigenic variation independent of each other.
- Minor antigenic changes are termed antigenic drift; major antigenic changes in HA or NA, called antigenic shift, result in the appearance of a new subtype.
- Antigenic drift is caused by the accumulation of point mutations in the gene, resulting in amino acid changes in the protein.



Genetic Variability

- Antigenic shift reflects drastic changes in the sequence of a viral surface protein, changes too extreme to be explained by mutation.
- The segmented genomes of influenza viruses re-assort readily in doubly infected cells.
- The mechanism for shift is genetic re-assortment between human and animal influenza viruses.
- **Influenza B and C viruses do NOT exhibit antigenic shift because few related viruses exist in animals.**

Clinical Features of Influenza Infection

- Influenza attacks mainly the upper respiratory tract.
- It poses a serious risk for elderly adults, very young children, and people with underlying medical conditions such as lung, kidney, or heart problems, diabetes, or cancer.
- Symptoms of classic influenza usually appear abruptly and include chills, headache, and dry cough followed closely by high fever, generalized muscular aches, malaise, and anorexia.

Clinical Features of Influenza Infection

- The fever usually lasts 3–5 days, as do the systemic symptoms.
- Respiratory symptoms typically last another 3–4 days. The cough and weakness may persist for 2–4 weeks after major symptoms subside. Mild or asymptomatic infections may occur.
- These symptoms may be induced by any strain of influenza A or B. In contrast**, influenza C rarely causes the influenza syndrome, causing instead a common cold illness**. Coryza and cough may last for several weeks.

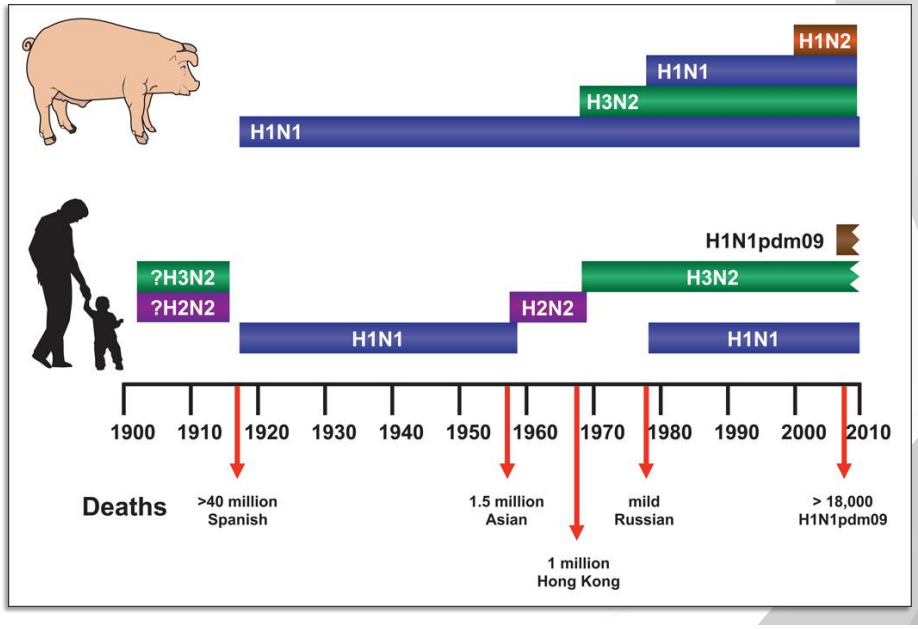
Clinical Features of Influenza Infection

- Serious complications usually occur only in elderly adults and debilitated individuals, especially those with underlying chronic disease.
- Pneumonia complicating influenza infections can be viral, secondary bacterial, or a combination of the two.
- This is attributed to loss of ciliary clearance, dysfunction of phagocytic cells, and provision of a rich bacterial growth medium by the alveolar exudate. Bacterial pathogens are most often *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *H. influenzae*.

Epidemiology

- Influenza viruses occur worldwide and cause annual outbreaks of variable intensity. It is estimated that annual epidemics of seasonal influenza cause 3–5 million cases of severe illness and 250,000–500,000 deaths worldwide.
- The incidence of influenza peaks during the **winter**.
- Influenza outbreaks occur in waves, the experience in any given year will reflect the interplay between extent of antigenic drift of the predominant virus and waning immunity in the population.
- The period between epidemic waves of influenza A tends to be 2–3 years.
- Every 10–40 years, when a new subtype of influenza A appears, a pandemic results.

Epidemiology



Dx, Rx and Prevention

- Definitive diagnosis cannot be made on clinical grounds **except in an epidemic situation**.
- Rapid diagnosis can be made by the demonstration of viral antigens in respiratory tract secretions.
- **PCR provides definitive diagnosis of flu**.
- First-generation antiviral agents effective against influenza A include two related drugs, **amantadine and rimantadine**. Both drugs stop viral un-coating by inhibition of the viral M2 membrane protein. These agents reduce both the duration and the severity of flu symptoms, but only if given early in infection.
- Second-generation antiviral agents effective against influenza A and B include zanamivir and oseltamivir. They inhibit viral neuraminidase.

Dx, Rx and Prevention

- Inactivated viral vaccines are the primary means of prevention of influenza.
- Existing vaccines are continually being rendered obsolete as the viruses undergo antigenic drift and shift.
- Although transmission of influenza virus occurs primarily by aerosol spread, hand transmission also is potentially important.
- Studies have shown that **hand washing** with soap and water or the use of alcohol-based hand rubs is highly effective at reducing the amount of virus on human hands.

THANK YOU