MedChem 401 RNA Viruses

These viruses contain a genome composed of RNA

*Remember* plus-sense vs. minus-sense RNA genomes

*Remember* RNA-dependent RNA polymerases (RDRP)

RNA viruses typically have small genomes, probably because RDRP’s are “error-prone”

RNA Viruses

Virus enters by membrane fusion or by receptor-mediated endocytosis

The nucleocapsid uncoats, *usually* in the cytosol where virus replication takes place

*Remember* plus-sense vs. minus sense RNA’s

*Remember* RNA-Dependent RNA Polymerases (RDRP)

*Remember* poly-cystronic viral RNA’s

*Remember* polyproteins and viral protease enzymes
Paramyxoviruses

Paramyxoviruses are enveloped, non-segmented, minus-sense RNA viruses.

Paramyxoviruses infections cause measles, mumps and are the chief cause of hospitalization for community-acquired respiratory disease.

Examples include croup and respiratory syncytial virus (RSV).


Paramyxovirus Development

Transmission of the virus is typically by direct inoculation of eyes and/or nose.

These viruses enter susceptible cells by a membrane fusion mechanisms.

The minus-sense RNA is deposited into the cytoplasm.

Viral RNA synthesis requires a RDRP.
Viral proteins are synthesized in the cytosol using the plus-sense copy of the viral RNA (mRNA)

The nucleocapsids are assembled from capsid proteins and minus-sense genomes in the cytoplasm

Viral glycoproteins are translated as transmembrane proteins and transported to the cell plasma membrane via the ER and Golgi transport pathways

The nucleocapsid buds out through membrane, taking the lipid bilayer and viral envelope proteins

Therapy is primarily supportive
• ribavirin has been used
• pooled immune globulin may attenuate symptoms
Ribavirin

RNA viruses reside at the cusp of an “error catastrophe”

Replication of genomic RNA by RDRP is highly error-prone; this allows the viruses to rapidly adapt to new environments

However, there is a limit to how much variation a genome can accommodate before degradation of genetic information

Ribavirin pushes the mutation rate over the edge resulting in a “genetic meltdown”

Influenza

Influenza is an infectious disease commonly called "the flu".

It is an infection of the respiratory tract caused by the influenza virus.

Symptoms of Influenza
• fever (typically 100°F to 103°F in adults)
• cough, sore throat, runny/stuffy nose
• HA, muscle aches, extreme fatigue

Symptoms usually resolve over 1-2 weeks.

(Note: "Stomach flu" is sometimes used to describe GI illnesses resulting from infection by other organisms)
Influenza

Pneumonia is a serious and potentially life-threatening complication (young, old, immunocompromised).

Annual influenza epidemics are associated with more than 20,000 deaths, and over 100,000 hospitalizations in the US.

During this century, several pandemics have occurred:

- 1918-19 "Spanish flu" A(H1N1)
  - ≈500,000 deaths in the US, 20 million worldwide

- 1957-58 "Asian flu" A(H2N2)
  - ≈70,000 deaths in the US

- 1968-69 "Hong-Kong flu" A(H3N2)
  - ≈34,000 deaths in the US

Influenza Viruses

Influenza viruses belong to the orthomyxovirus family.

These are enveloped, segmented, negative-strand RNA viruses.
Influenza Virus Envelope Glycoproteins

Neuraminidase (NA) is an envelope glycoprotein that may help the virus penetrate mucus to reach epithelial cells.

NA is also critical to virus escape from the infected cell.

There are nine major antigenic NA types.

The virus adsorbs to receptors on the cell surface, mediated by a second envelope glycoprotein, hemagglutinin (HA).

There are 13 major antigenic HA types.

Influenza Virus Development

Virus is taken into the cell by receptor-mediated endocytosis.

Acidification of the endosome releases the nucleocapsid into the cytoplasm.

The nucleocapsid is transported into the nucleus, where mRNA synthesis and replication of viral RNA occurs.

Remember, since this a negative-sense RNA genome, viral RDRP must accompany viral RNA to the nucleus.
Influenza Virus Development

A viral endonuclease (packaged in the nucleocapsid) snips off the 5’ end of a host mRNA.

This is then used as a primer for viral mRNA synthesis by the viral RDRP, which also adds the polyA tail.

Eight primary transcripts are made, one per segment.
Influenza Virus Replication

Two of the capped, polyadenylated RNA segments are spliced in the nucleus yielding two additional mature mRNAs.

The capped, polyadenylated mRNAs are translated in the cytoplasm.

Envelope glycoproteins are moved to the plasma membrane via the ER and Golgi pathways.

Proteins needed for RNA replication and the capsid proteins go to the nucleus.

The capped, polyadenylated plus-sense segments are copied into minus-sense segments in the nucleus.

Influenza Virus Replication

The minus strands are packaged into virions in the nucleus.

The nucleocapsids are transported out of the nucleus and the virus buds through the membrane, taking viral glycoproteins as part of the envelope.

NA probably helps the virus leave the cell by removing sialic acid from cell receptors.
Influenza Virus- Classification

There are three types of influenza viruses: A, B, and C.

**Influenza Type A**

Influenza type A viruses can infect people, birds, pigs, horses, seals, whales, and other animals, but wild birds are the natural hosts for these viruses.

Influenza type A viruses are divided into subtypes based on HA and NA subtypes.

Only some influenza A subtypes (i.e., H1N1, H1N2, and H3N2) are currently in general circulation among people.

Other subtypes are found most commonly in other animal species. (i.e., H5N1 causes severe illness in birds)
Influenza Virus- Classification

**Influenza Type B**

Influenza B viruses are normally found only in humans.

Although influenza type B viruses can cause human epidemics, they have not caused pandemics.

**Influenza Type C**

Influenza type C viruses cause mild, often asymptomatic illness in humans; they do not cause epidemics or pandemics.

Influenza types A and B are responsible for annual epidemics of respiratory illness, and substantial morbidity and mortality.

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The internal antigens (M and NP proteins) represent the type-specific antigens, and determine whether a virus is A, B or C.

The external antigens, hemagglutinin (HA) and neuraminidase (NA), show more variation and determine the subtype and strain.
Influenza Virus- Epidemiology

The Hemagglutinin Protein (HA)
HA is involved in attachment and membrane fusion in the endosome of the infected cell

Antigenic domains on the surface of the protein mutate and the virus can thus avoid a humoral response

The Neuraminidase Protein (NA)
The NA protein is involved in penetration of mucus layer and in facilitating virus release from infected cell

Antibodies to HA and to a lesser extent NA are important in protection

Influenza Virus- Epidemiology

Antigenic Drift
• mutations occur over time that cause a gradual change in the virus (HA/NA) (every 2-3 years)
• "old" antibodies no longer recognize the "new" virus, and provide only partial protection
• constant change enables the virus to evade the immune system, and people remain susceptible throughout life

Antigenic Shift
• an abrupt change in the HA and/or NA proteins, resulting in the sudden emergence of a new subtype
• the population is “naïve” and epidemics/pandemics occur (every 10-15 years)

Influenza A viruses undergo both kinds of changes, while influenza type B viruses change only by antigenic drift
Influenza Vaccine

2002-2003 Vaccine
A/New Caledonia/20/99 (H1N1)
A/Panama/2007/99 (H3N2; an A/Moscow/10/99-like virus)
B/Hong Kong/330/01-like virus strain

2001-2002 Vaccine
A/Moscow/10/99-like (H3N2)
A/New Caledonia/20/99-like (H1N1)
B/Sichuan/379/99-like antigens

2000-2001 Vaccine

1999-2000 Vaccine

Anti-Influenza Drugs

These drugs affect maturation of influenza HA glycoprotein in trans-Golgi network
The progeny virus is poorly infective
Good for oral prophylaxis against influenza A (but not B)
Alternative to vaccine in immunocompromised and the elderly
**Anti-Influenza Drugs**

NA allows the virus to move through mucous secretions so that it can reach the epithelial cells.

NA is also required for viral exit from the cell, and virus spread.

Hemagglutinin sticks to cellular sialic acid.

Neuraminidase degrades cellular sialic acid.

**Neuraminidase Inhibitors - MOA**

Zanamivir (Relenza®) is a potent inhibitor of viral neuraminidase (both types A and B viruses).

Shortens the duration of symptoms by 1-3 days if started early.

The drug must be delivered as an aerosol.

Oseltamivir (Tamiflu®) is a NA inhibitor that can be given orally.
Rhinovirus

Rhinovirus is a naked, non-segmented, plus sense RNA virus. As with poliovirus, rhinovirus must “uncoat” to release the RNA genome into the cytoplasm. Arildone inhibits uncoating. Pleconaril (Picovir®) is a second uncoating inhibitor.

The drugs fit into a hydrophobic pocket (canyon) in the nucleocapsid and prevents uncoating.
Coronaviruses

Coronaviruses are enveloped, non-segmented, plus sense RNA viruses.

The genome (27-31 kbp is 5' capped and 3' polyadenylated.

Virus entry occurs via receptor-mediated endocytosis and membrane fusion.

Replication occurs in the cytosol.

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Coronaviruses

Most coronavirus infections cause a mild, self-limited disease (classical 'cold' or upset stomach).

There may be rare neurological complications.

Severe Acute Respiratory Syndrome (SARS) is a form of viral pneumonia where infection encompasses the lower respiratory tract and can be very severe.

The typical clinical course of SARS involves an improvement in symptoms during the first week, followed by a worsening during the second week of infection. This may be related to patient's immune responses rather than uncontrolled viral replication.

Death may result from progressive respiratory failure due to alveolar damage.
Avian Influenza

The “bird flu” is an infection caused by avian (bird) influenza (flu) viruses.

These viruses occur naturally among birds-
  • Wild birds worldwide carry the viruses in their intestines, but usually do not get sick.
  • The virus is very contagious among birds; however, morbidity and mortality is very high in some domesticated birds, including chickens, ducks, and turkeys.

Avian influenza is caused by a variety of subtypes of influenza A virus.

Avian Influenza

There are 16 different HA subtypes and 9 different NA subtypes of flu A viruses.

All known subtypes of flu A viruses can be found in birds.

When we talk about “bird flu” viruses, we are referring to influenza A subtypes chiefly found in birds; they do not usually infect humans.

The avian influenza A viruses (H5N1, H7N2, H7N7) occur mainly in birds producing severe disease. These strains have spread to humans.

When these viruses infect humans, the “typical” flu symptoms are very severe.
West Nile Virus

West Nile virus (WNV) is a flavivirus, which are enveloped, non-segmented, plus sense RNA viruses.

Flavivirus infections can cause dengue fever, yellow fever, St. Louis encephalitis and Japanese encephalitis.

West Nile virus is transmitted by *Culex* mosquitoes.

Birds serve as the primary reservoir.

Virus isolated from brain tissue of dead crow.
West Nile Virus

Most WNV infections (80%) are asymptomatic.

WNV symptoms are predominantly West Nile Fever -

- fever
- HA
- fatigue
- occasional skin rash on trunk, swollen lymph nodes, eye pain

Severe disease ensues in a small number of patients -

- West Nile Meningitis
- West Nile Encephalitis
- West Nile Poliomyelitis

Treatment is supportive