Mechanisms of Human Disease:
Medical Virology

Goal
To be able to describe:
• transmission
• pathogenesis
• detection
• appropriate vaccine
• anti-viral therapy
  for the most common viral pathogens

Biology of Viruses
• Viruses are tremendously diverse
• Viruses are difficult to combat
• Eliminating disease by vaccination:
  Poliovirus and poliomyelitis
Characteristics of Viruses

- Filterable agents of infectious disease
- Depend on host machinery for their energy production and protein synthesis
- Composed of nucleic acid and protein
- Sensitive to interferon, not antibiotics

Relative sizes of viruses and bacteria

Classification System

- Based on Genetic Information of the Virus
- Each Family Exhibits Similar Morphology and Multiplication Cycle
- Provides a Common Basis for Naming
- Allows for a Common Clinical Approach
Virus Genomes

- **DNA**
  - Single Stranded
  - Double Stranded
  - Circular

- **RNA**
  - (+) or (–) Single Stranded
  - Segmented
  - Double Stranded
  - Segmented

### Genomes of RNA Viruses

**Single Stranded**
- Positive Strand
  - Picornaviruses
  - Noroviruses
  - Togaviruses
  - Flaviviruses
  - Coronaviruses
  - Retroviruses
- Negative Strand

**Double Stranded (Segmented)**
- Rotavirus

**Non-Segmented**
- Pararnyxoviruses
  - Measles
  - Mumps
  - RSV
- Rhinoviruses
- Rabies Virus

**Segmented**
- Orthomyxoviruses
  - Influenza Virus (8 segments)
- Arenaviruses (2 segments)
- Bunyaviruses (3 segments)

### Genomes of DNA Viruses

**Single Stranded**
- Circular
  - Some bacterial viruses
- Linear
  - Polyomaviruses (~5 Kbp)
  - Papillomavirus (~8 Kbp)

**Double Stranded**
- Circular
  - Adenoviruses (~50 Kbp)
  - Herpesviruses (~100 Kbp)
  - Poxvirus (~150 Kbp)
- Linear

Partly Single-Stranded
- Hepatitis B Virus
  (RNA intermediate in replication)
Biology of Viruses

- Viruses are tremendously diverse
- Viruses are difficult to combat
- Eliminating disease by vaccination: Poliovirus and poliomyelitis

The Battle between Virus and Host
A quick review of Host Defenses

Innate Immune Response
Adaptive Immune Response
Innate immune response:
Synthesis of Type I Interferons

Type I Interferons activate New Proteins

Protection by Interferon: The Antiviral State
Interferon leads to degradation of RNA and inhibition of protein synthesis, blocking virus replication.

- Interferon leads to degradation of RNA.
- Inhibition of protein synthesis.
- Blocking virus replication.

**Adaptive Response: Antibodies!**

- IgG
- IgA monomer
- IgA Dimer
  - J chain
  - SC
- IgM monomer
- IgM Pentamer
  - J chain
- IgE
- IgD

**Adaptive Response: Killer T Cells!**

- Host Cell
- Infected Cell
- Surface Antigens
- Attachment
- Cell Lysis
- T-killer Cells
Many viruses have evolved ways to counteract host defenses

**Viral interferon antagonists** block activation or action of type I interferons

Other viral proteins, termed virokines and viroceptors, block host cytokines that promote the adaptive response

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### Genomes of RNA Viruses

**Single Stranded**
- Positive Strand
  - Picornaviruses (nonenveloped)
  - Noroviruses
  - Togaviruses
  - Flaviviruses
  - Coronavirus
  - Retroviruses

- Negative Strand

**Double Stranded (Segmented)**
- Reoviruses
- Orbivirus
- Rotavirus

**Non-Segmented**
- Paramyxoviruses
  - Mumps
  - Mumps
  - RSV
- Rhadoviruses
- Rabies Virus

**Segmented**
- Orthomyxoviruses
  - Influenza Virus (8 segments)
  - Arenaviruses (2 segments)
  - Bunyaviruses (3 segments)

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Case: 39 year old male presents with 3 days of symptoms including generalized, nonthrobbing headache; fever of 38-40°C; sore throat; anorexia; nausea; vomiting; and muscle aches. Two weeks prior, the patient had gone swimming in a lake at a boy scout camp. Over the next 2 weeks, the patient noted severe muscle aches and weakness in his legs, loss of reflexes, which progressed to loose and floppy limbs (flaccid paralysis).
In 1921, the physician made a clinical diagnosis of poliomyelitis.

Properties of Poliovirus

- Icosahedral capsid enclosing a positive strand RNA
- There are 3 serotypes of poliovirus
- Replicates in cytoplasm, genome acts as mRNA
- Cytolytic virus
- Virus particles resistant to pH 3.0-9.0, mild sewage treatment, temperature
Epidemiology of Poliovirus

<table>
<thead>
<tr>
<th>Reservoir</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission</td>
<td>Fecal-oral, oral-oral possible</td>
</tr>
<tr>
<td>Temporal pattern</td>
<td>Summer-Fall in temperate areas; No seasonal pattern in tropics</td>
</tr>
<tr>
<td>Communicability</td>
<td>Probably 7-10 days before onset; Virus present in stool for 3-6 weeks</td>
</tr>
<tr>
<td>Incubation period</td>
<td>6-20 days, range 3-35 days</td>
</tr>
</tbody>
</table>

Pathogenesis of Poliovirus:

Clinical Outcomes Vary

Human Poliomyelitis

<table>
<thead>
<tr>
<th>Day</th>
<th>Small Intestine:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Invasion Multiplication</td>
</tr>
<tr>
<td>1</td>
<td>Excretion in feces</td>
</tr>
<tr>
<td>2</td>
<td>Bloodstream: Primary Viremia</td>
</tr>
<tr>
<td>3</td>
<td>Viral Multiplication</td>
</tr>
<tr>
<td>4-6</td>
<td>CNS:</td>
</tr>
<tr>
<td>7</td>
<td>Invasion</td>
</tr>
<tr>
<td>8</td>
<td>Multiplication</td>
</tr>
<tr>
<td>9</td>
<td>Intraneural Spread</td>
</tr>
<tr>
<td>10</td>
<td>Paralysis</td>
</tr>
<tr>
<td>11</td>
<td>Paralysis</td>
</tr>
</tbody>
</table>
Poliovirus Infection - Clinical Outcomes

- 90-95%  
  - Inapparent infection without symptoms

- 4-8%  
  - Minor illness without CNS involvement
  - May resemble URI or gastroenteritis
  - Complete recovery

- 1-2%  
  - Nonparalytic with aseptic meningitis

- 0.1-2%  
  - Paralytic poliomyelitis
  - Usually asymmetric, sensory intact
  - May recover some or all function

- Virus in feces

- Viral multiplication in tonsils, cervical nodes, Peyer's patches, mesenteric lymph nodes

- Minor Illness (antibody appears, viremia ceases, viral content diminishes)

- Transient viremia

- Multiplications in various organs

- Major viremia

- Severe Illness

- Central nervous system

- Peripheral nerve ganglia

Poliovirus is primarily an enteric virus which *occasionally* invades the CNS.
Detection of Poliovirus Infection

- Previously:
  - Virus isolation from throat swabs
  - Isolation of virus from multiple fecal samples
  - Serology

- Now: RT-PCR and sequencing
Recognition of Poliomyelitis as an Infectious Disease

- First described by in 1789
- First US outbreak described in 1843
- Epidemics in New York City in 1916

If the poliovirus has been around since the time of the pharaohs, why didn’t we start to experience epidemic poliomyelitis until after the turn of the century?

Effect of the Industrial Revolution on Epidemic Poliomyelitis

- Dramatic changes in sanitation
- Large “naïve” urban populations
Infantile Paralysis: Stay off this street

Iron lungs in Los Angeles County Hospital during polio epidemic in 1950s.

POLIO
An American Story

Winner of Pulitzer Prize in History in 2006
Poliovirus and Poliomyelitis
• Enteric virus, shed for weeks
• Epidemics in “naïve” populations
• Enormous economic and human impact

Prevention of Poliomyelitis
• Salk vaccine - IPV
• Sabin vaccine - OPV
Poliomyelitis – United States
1920-1993

[Graph showing cases by year and vaccine type]

1975-1993 cases are consultant verified

Poliovirus Vaccines

- Seroconversion
  - ≥ 95% after 3 doses of either OPV or IPV

- Protective efficacy
  - Correlates with seroconversion

- Duration of immunity
  - Probably life long after OPV series
  - Longlasting after IPV series

Serum and secretory antibody response to intramuscular inoculation of IPV and to live-attenuated OPV

[Graphs showing antibody response over time for inactivated and live polio vaccines]

Reciprocal polio antibody titers:
- Serum IgG
- Serum IgA
- Serum IgM
- Nasal and duodenal IgA
- Nasal IgA
Oral Poliovirus Vaccine

- Safe and effective even in newborn children
- Heat stable
- Simple oral administration
- Elicits powerful mucosal immunity

OPV Poliovirus Vaccine

Adverse Effects

- Paralytic poliomyelitis
- More likely in immunodeficient persons
- No procedure available for identifying persons at risk of paralytic disease
- Death from paralytic disease

Paralytic Poliomyelitis – United States

1964-1992
**Ratio of Number of Cases of VAPP to Doses of OPV Distributed – United States, 1980-91***

<table>
<thead>
<tr>
<th></th>
<th>Recipient</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Overall (all doses)</td>
<td>1:6.9 million</td>
<td>1:6.9 million</td>
</tr>
<tr>
<td>First dose</td>
<td>1:1.6 million</td>
<td>1:2.1 million</td>
</tr>
<tr>
<td>Subsequent dose</td>
<td>1:32.8 million</td>
<td>1:15.2 million</td>
</tr>
</tbody>
</table>

* From 1980 through 1991, 243 million doses of OPV were distributed and 98 total cases of VAPP were reported. Overall risk of VAPP was 1:2.5 million doses.

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**Summary of Evolution of Type 3 Poliovirus from a Primary Vaccinee**

Vaccinate with OPV at Day 0, collect feces daily, select for “wild type” polioviruses

<table>
<thead>
<tr>
<th>Day</th>
<th>2</th>
<th>11</th>
<th>42</th>
<th>52</th>
<th>73</th>
</tr>
</thead>
</table>

Types of “wild type” viruses recovered: revertants, other point mutants, and recombinant viruses
Potential Problems with OPV

- **VAPP**
  - Vaccinee and household contacts are at risk (1:1,600,000 first doses)

- **Shedding of revertant viruses**
  - Revertants in fecal material may contaminate local water supply

2004 Recommendation of the American Academy of Pediatrics

**3 Dose Regimen for Poliovirus Vaccination**
- First vaccination, IPV
- First boost, IPV
- Second boost, IPV

This vaccination regimen is designed to eliminate VAPP in the United States
Since humans are the only natural host for poliovirus, elimination of poliomyelitis by vaccination is theoretically possible.

Progress Toward Elimination of Poliovirus
W.H.O. 1961-2001

Determining the Effectiveness of Polio vaccination efforts

- Report all cases of Acute Flacid Paralysis (AFP)
- Confirm virus by culture, serotype and sequence assays
Determining the Effectiveness of Polio vaccination efforts

- Last case of polio type 2 - 1999
- Switch from OPV to IPV patch?

A dissolving microneedle patch on a finger
A better way to administer IPV??

Poliovirus and Poliomyelitis

- Pathogenesis of Poliovirus: clinical outcomes vary
- Prevention of Poliomyelitis: OPV, IPV and VAPP
### Seven Question Approach to Medical Virology

1. What virus is associated with the disease?

<table>
<thead>
<tr>
<th>Virus</th>
<th>Disease</th>
</tr>
</thead>
</table>

### Seven Question Approach

2. How is the virus transmitted?

- Respiratory
- Fecal-oral
- Transcutaneous
- Sexual
- Mother to fetus
- Zoonoses

### Seven Question Approach

3. How is the viral infection detected?

- Detection of viral sequences - RT-PCR or PCR
- Serology - acute IgM, convalescent IgG
- Detection of viral antigens - ELISA or IFA
- Virus isolation - culture, look for CPE
### Seven Question Approach

#### 4. What is the mechanism/pathogenesis of disease?
- Viremia?
- Target organ?
- Lytic infection?
- Immunopathology?

#### 5. Are there any anti-viral therapies for this viral infection?
- Acyclovir
- Ganciclovir
- Amantadine
- RT-inhibitors
- Protease inhibitors

#### 6. Are there any vaccines that protect against infections with this virus?
- Live-attenuated virus
- Killed virus
- Subunit vaccines
Seven Question Approach

7. Are there any long term consequences associated with infection of this virus?
   - Immunity
   - Persistent infection
   - Latent infection/recurrence
   - No long-term immunity/re-infection possible

Test your knowledge by taking the 7 question quiz:

- Loyola wired
- LUMEN
- MHD
- Educational resources
- Virus 7 question approach quizzes

Pick your favorite!