Acute Infections

Lecture 16
Biology 3310/4310
Virology
Spring 2018

You know something’s happening, but you don’t know what it is, do you, Mr. Jones?
—Bob Dylan

Ballad of a Thin Man
General patterns of infection

Acute
- Rhinovirus
- Rotavirus
- Influenza virus

Latent
- Herpes simplex virus

Persistent: asymptomatic
- Lymphocytic choriomeningitis virus
- JC virus

Persistent: pathogenic
- Human immunodeficiency virus
- Human T-lymphotropic virus
- Measles virus SSPE
Acute infections

- Rapid onset of viral reproduction
- Short but possibly severe course of disease
- Production of large numbers of virus particles
- Immune clearance
The course of a typical acute infection

Rapid and self-limiting
Incubation period

- Initial period before *symptoms* of disease are obvious
- Viral genomes are replicating
- Host is responding
- Virus may or may not be transmitted
Incubation periods of some viral infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Incubation period (days)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza virus</td>
<td>1–2</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>1–3</td>
</tr>
<tr>
<td>Ebola virus</td>
<td>2–21</td>
</tr>
<tr>
<td>Acute respiratory disease (adenoviruses)</td>
<td>5–7</td>
</tr>
<tr>
<td>Dengue</td>
<td>5–8</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>5–8</td>
</tr>
<tr>
<td>Coxsackievirus</td>
<td>5–12</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>5–20</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>8–21</td>
</tr>
<tr>
<td>Measles</td>
<td>9–12</td>
</tr>
<tr>
<td>Smallpox</td>
<td>12–14</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>13–17</td>
</tr>
<tr>
<td>Mumps</td>
<td>16–20</td>
</tr>
<tr>
<td>Rubella</td>
<td>17–20</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>30–50</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>15–40</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>50–150</td>
</tr>
<tr>
<td>Rabies</td>
<td>30–100</td>
</tr>
<tr>
<td>Papilloma (warts)</td>
<td>50–150</td>
</tr>
</tbody>
</table>

*Until first appearance of prodromal symptoms.

**Prodrome** - Period of symptoms before those characteristic of disease
Gr *prodromos* = precursor

**Short** - replication at primary site produces symptoms

**Long** - Symptoms beyond primary site
Inapparent acute infections

- Successful infections, no symptoms or disease
- Sufficient virus particles produced to spread in the population
- How do we know?
- Well adapted pathogens
  - >90% of poliovirus infections inapparent
Acute infections are common public health problems

• Serious epidemics affecting millions each year (influenza, norovirus)
• Acute infections are difficult problems: by the time you feel ill, the infection may be over and has spread
Which of the following do acute infections and incubation periods have in common?

A. The virus is not replicating
B. No symptoms are visible
C. Immune defenses are engaged
D. The immune system does not respond
E. All of the above
Viruses that cause acute infections

- Influenza virus
- Poliovirus
- Measles virus
- Norovirus
- West Nile virus
Influenza

- Types: A, B, C
- A, B cause similar disease; C mostly inapparent or mild upper respiratory tract illness
- Only A cause pandemics
- Antigenic variation

Influenza transmission

- Droplets produced by coughing, sneezing, talking
- Direct contact with infected individuals
- Contact with contaminated surface, touch mouth, eyes, nose

α(2,6) human

α(2,3) avian
Uncomplicated influenza

- Incubation period 1-5 days, depending on dose, immune status of host
- Abrupt onset: headache, chills, dry cough
- High fever, myalgias, malaise, anorexia
- Fever peaks within 24 hr, 38° - 40°C
- Fever declines day 2-3, gone by day 6
- As fever declines, respiratory signs intensify
- Cough changes from dry to productive
- Cough, weakness can persist 1-2 weeks
How is influenza diagnosed?

- Influenza-like illness, ILI
- Fever at least 100°F
- Cough OR sore throat
- No other known cause
- Rapid lab tests: poor accuracy
- PCR, viral culture, serology
Seasonal influenza

U.S. WHO/NREVSS Collaborating Laboratories
National Summary, 2004-05 through 2007-08

http://www.cdc.gov/flu/weekly/fluactivitysurv.htm
Influenza statistics, US

- 35-50 million cases (CDC estimate)
- 3,000 - 49,000 deaths (range past 31 yr)

http://www.cdc.gov/flu/weekly/
Complications of influenza

- Primary viral pneumonia
- Secondary bacterial pneumonia
- Myositis - generalized muscle pain
- Cardiac involvement
- Reye syndrome (encephalopathy, liver damage)
Interventions for influenza

- Non-pharmaceutical
- Antiviral drugs
  - Tamiflu (oseltamivir)
  - Relenza (zanamavir)
  - Flumadine (rimantadine)
- Vaccine
Which of the following is characteristic of uncomplicated influenza?

A. Transmission may occur via respiratory droplets
B. Incubation period is 1-5 days
C. Fever peaks within 24 hr
D. Coughing and weakness can last for 2 weeks
E. All of the above
Poliomyelitis - poliovirus
Poliovirus pathogenesis
Pathogenesis of poliomyelitis

- Humans are only known reservoir
- Spread by fecal-oral transmission
- Peaks during warm months in temperate climates
- Complication: post-polio syndrome
  - 30-40 year interval
  - 25-40%
  - Not an infectious process
Poliomyelitis—United States, 1950-2007

Cases

Inactivated vaccine

Live oral vaccine

Last indigenous case
Measles

- Measles virus, *Paramyxoviridae*
- One of the most contagious human viruses ($R_0 = 15$)
Measles pathogenesis

- One viral serotype, infection confers life-long protection
- Transmitted by inhalation of respiratory secretions
- Period of maximum contagiousness 2-3 days before rash
- Nearly all infected individuals show signs of disease
Uncomplicated measles

- Fever, 38.3°C or above
- Respiratory symptoms: coryza, cough
- Conjunctivitis
- Koplik spots
- Rash from face to extremities
Measles complications

- Acute postinfectious encephalitis (1/1,000)
- Bronchitis, pneumonia, ear infection
- Fatality 1-2/1000 (28% poor nutrition)
- Subacute sclerosing panencephalitis (SSPE)
- Immunosuppression leading to secondary infections (main cause of death in Third World children)
Measles prevention

- US: 3-4 million/yr, 400-500 deaths, 48,000 hospitalizations, 1,000 chronic disability from encephalitis
- Endemic transmission stopped 2000 by vaccine
- MMR: measles, mumps, rubella vaccine
- Wakefield 1998 report lead to decreased MMR immunization, outbreaks in UK, Ireland
- US outbreaks, imported
Measles cases by year, US
114,900 deaths in 2014
From 2000-2014, 17.1 million deaths prevented - measles vaccine one of best buys in public health.
Which of the following is a good reason to get measles vaccine?

A. There is a 1/1000 chance of acute post-infection encephalitis
B. There is a 1-2/1000 chance of death from measles
C. Each infected person spreads measles virus to 15 others
D. Immunosuppression can lead to secondary infections
E. All of the above
In a 24 hour period...

- About 200,000,000 people have gastroenteritis
- The amount of diarrheal water passed equals the volume of water passing over Victoria Falls in 1 minute

65,280,000 liters/min
Norovirus

- **Caliciviridae**
- 
- 
- **(+) strand RNA virus**
- **Cause 50% of all food-borne outbreaks of gastroenteritis (23 million/yr US)**
### Known Causes of Foodborne Illness Outbreaks, U.S., 2006–2010

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Estimated number of illnesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norovirus</td>
<td>5,461,731</td>
</tr>
<tr>
<td><em>Salmonella,</em> nontyphoidal</td>
<td>1,027,561</td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
<td>965,958</td>
</tr>
<tr>
<td><em>Campylobacter</em> spp.</td>
<td>845,024</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>241,148</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
</tr>
</tbody>
</table>
- Fecal-oral spread
- Retain infectivity passing through stomach
- Blunting of villi in proximal jejunum
- Basis for vomiting, diarrhea not known
Enteric bacteria promote human and mouse norovirus infection of B cells
How contagious is norovirus?

Just a very small amount - as few as 18 viral particles - of norovirus on your food or your hands can make you sick.

That means the amount of virus particles that fit on the head of a pin would be enough to infect more than 1,000 people!

SOURCE: Journal of Medical Virology, August, 2008
Clinical and epidemiological features

- Transmission: Fecal–oral; aerosol–vomitus; contact with fomites; food, water, or environmental contamination; foods can be contaminated at the source (oysters, raspberries) or during preparation by food handlers

- Incubation period 10-51 hr

- Symptoms: Sudden onset of vomiting (more common in children), diarrhea (more common in adults), stomach pain

- Duration of illness: 28-60 hr; longer in immunocompromised or with underlying illness

- 30% asymptomatic infections
Clinical and epidemiological features

- Viral shedding peaks 1-3 days after illness onset, may persist for 56 days
- Immunity: short term homologous only; reinfection with other strains may occur, or later in life
Clinical and epidemiological features

- Reservoir: Humans, but evidence for animal reservoir
- Affects all ages
- Year round, peaks in cold weather
- Outbreaks often occur in semi-closed environments (nursing homes, hospitals, cruise ships), military, schools, recreational activities (sports events, camping trips, travel) that favor person-to-person spread
Clinical and epidemiological features

- Treatment: Supportive to prevent dehydration
- Vaccine in development
- Not usually serious, but can be in persons with underlying illness
Real life ‘Airplane!’ Entire flight sickened by norovirus

Wednesday, December 28, 2011

Holiday travel can not only be a hassle but can you get sick -- and in a recent case among Air New Zealand crew members, seriously ill. According to a report last week in Scientific American, recent studies have shown just how easily the cruise ship gastrointestinal bug, norovirus, can be transmitted to travelers on planes.

On a recent Air New Zealand flight, a sick passenger passed norovirus along to the crew. "Not only did the crew that cleaned up the mess get sick, but on every successive flight at least one or more crew members got sick with typical symptoms of norovirus," said David Freedman, of the University of Alabama at Birmingham, at a meeting of the American Society of Tropical Medicine and Hygiene held earlier this month.
The happiest place on Earth™?

<table>
<thead>
<tr>
<th>Cruise Line</th>
<th>Cruise Ship</th>
<th>Sailing Dates</th>
<th>Causative Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal Cruises</td>
<td>Crystal Symphony</td>
<td>11/02 - 11/21</td>
<td>Unknown</td>
</tr>
<tr>
<td>Holland America Line</td>
<td>Nieuw Amsterdam</td>
<td>10/18 - 11/07</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Carnival Cruise Lines</td>
<td>Carnival Glory</td>
<td>10/09 - 10/16</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Holland America Line</td>
<td>Zuiderdam</td>
<td>04/20 - 05/08</td>
<td>Unknown</td>
</tr>
<tr>
<td>Celebrity Cruises</td>
<td>Mercury</td>
<td>03/08 - 03/19</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Celebrity Cruises</td>
<td>Mercury</td>
<td>02/26 - 03/08</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Royal Caribbean International</td>
<td>Jewel of the Seas</td>
<td>02/22 - 03/05</td>
<td>Unknown</td>
</tr>
<tr>
<td>Celebrity Cruises</td>
<td>Millennium</td>
<td>02/22 - 03/05</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Holland America Line</td>
<td>Maasdam</td>
<td>02/19 - 03/05</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Celebrity Cruises</td>
<td>Mercury</td>
<td>02/15 - 02/26</td>
<td>Norovirus</td>
</tr>
<tr>
<td>Fred Olsen Cruise Lines</td>
<td>Balmoral</td>
<td>01/05 - 02/04</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cunard Cruise Line</td>
<td>Queen Victoria</td>
<td>01/12 - 01/27</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cunard Cruise Line</td>
<td>Queen Victoria</td>
<td>01/04 - 01/12</td>
<td>Norovirus</td>
</tr>
</tbody>
</table>
Why are noroviruses associated with cruise ships?

- Health officials track illness on cruise ships, so outbreaks are found and reported more quickly on a cruise ship than on land.
- Close living quarters may increase the amount of group contact.
- New passenger arrivals may bring the virus to other passengers and crew.
• *Flaviviridae*, isolated 1937, West Nile district of Uganda

• Absent from Western Hemisphere until 1999

• New York isolate identical to virus from Israeli goose

• Virus infects hundreds of birds, 37 kinds of mosquitoes, 18 other vertebrates
WNV transmission cycle
WNV pathogenesis

- Transmitted to humans by *Culex* mosquito bite
- Incubation period 3-14 days
- 20-30% develop flu-like illness called WNV fever
- 80%: no symptoms
WNV pathogenesis

- 1/150 individuals develop neuroinvasive disease
  - Headache
  - Ocular manifestations
  - Muscle weakness
  - Cognitive impairment
  - Polio-like flaccid paralysis
  - 10% mortality
  - >50% long term neurological sequelae
TLR3
West Nile Virus USA

![Graph showing West Nile Virus cases in the USA from 1999 to 2013. The graph includes data on neuroinvasive disease cases, non-neuroinvasive disease cases, and total cases, with additional data on deaths.](image-url)
West Nile virus disease cases reported to CDC 1999-2016
Average annual incidence of WNV neuroinvasive disease by county 1999-2016

http://www.cdc.gov/westnile/
WNV neuroinvasive disease by age group, 1999-2016

http://www.cdc.gov/westnile/
WNV prevention

- *Culex* species bite evening to morning
- Repellants, screens, clothing
- Human vaccines in development - horse vaccine available

https://www.cdc.gov/chikungunya/pdfs/fs_mosquito_bite_prevention_us.pdf
Viruses and the central nervous system

- Poliovirus, measles virus, West Nile virus invade the CNS
- These viruses are effectively transmitted by shedding elsewhere (gut, respiratory tract) or by mosquitoes (WNV)
- In general viral CNS invasion is a dead end in humans