**VIRAL DISEASE**

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Clinical pathology

**Content**
- Respiratory system
- Digestive system
- Systemic with skin eruption
- Systemic with hematopoietic disorder
- Arbovirus and hemorrhagic fever

**Viral structure**
- Nucleocapsid (Naked virus) = Viral genome + Capsid ± Virus-Encoded Enzymes
- Enveloped Virus = Nucleocapsid + Host Membrane with Virus-Encoded Glycoproteins

**Viral infectious cycle**
1. Attachment
2. Penetration
3. Virus uncoating
4. Replication and protein synthesis
5. Assembly
6. Release of virus
Tissue change caused by viral infection

1. Cell necrosis
2. Cell swelling
3. Inclusion body formation
4. Giant cell formation
5. Latent viral infection
6. Oncogenesis

Classification of viral disease

- **Respiratory system**
  - Rhinovirus, Influenza, Respiratory syncytial virus, Adenovirus

- **Digestive system**
  - Viral enteritis, Hepatitis virus (A,B,C,D,E), Mumps virus

- **Systemic with skin eruption**
  - Measles virus, Rubella virus, Varicella zoster virus, Herpes simplex virus 1and 2

- **Systemic with hematopoietic disorder**
  - Cytomegalovirus, EBV, HIV

- **Arbovirus and hemorrhagic fever**
  - Dengue virus 1-4

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**Rhinovirus**

- Picornaviridae family
- Naked, + single strand RNA virus
- Major cause of common cold
- Grow preferentially at 33-34°C (human nasal passage)
- Binding to intercellular adhesion molecule-1 (ICAM-1) receptor on epithelial cells of URI
- Bradykinin from host response → mucous secretion
- Acid labile and completely inactivated at pHs < 3
Rhinovirus

- *Most frequent*: Common cold
- *Occasional*: Exacerbation of chronic bronchitis and asthma
- *Infrequent*: Pneumonia in children

**Clinical feature:**
- Adult: rhinorrhea, nasal congestion, sore throat, cough, fever
- Child: fever

**Common complication:**
- Adult: sinusitis
- Child: otitis media, lower respiratory symptom (bronchopneumonia)

**Lab diagnosis:**
- RT-PCR is standard diagnostic tool for the detection in clinical specimens (more sensitive, faster, and easier to perform than traditional virus isolation)

**Tx & prevention:**
- No specific Tx
- Hand washing & face mask covering

Influenza virus

- Orthomyxoviridae family
- Negative single-stranded RNA
- Classify due to soluble (S) antigen of virion:
  - Subtype A, B, C
- Classify due to glycoprotein envelope:
  - Hemagglutinin (H=1-16)
  - Neuraminidase (N=1-9)
  - Eg. H1N1, H3N2
Influenza virus

**Differences among Influenza A, B, and C Viruses**

<table>
<thead>
<tr>
<th></th>
<th>Influenza A</th>
<th>Influenza B</th>
<th>Influenza C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Host range</strong></td>
<td>Humans, swine, equine, avian, marine mammals</td>
<td>Humans only</td>
<td>Humans and swine</td>
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<tr>
<td><strong>Epidemiology</strong></td>
<td>Antigenic shift and drift</td>
<td>Antigenic drift only; two main lineages cocirculate</td>
<td>Antigenic drift only; multiple variants</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>May cause large pandemics with significant mortality in young persons</td>
<td>Severe disease generally confined to older adults or persons at high risk; pandemic not seen</td>
<td>Mild disease without seasonality</td>
</tr>
</tbody>
</table>

Only three HA and two NA subtypes (i.e. H1–3 and N1–2) have circulated in humans

**Influenza**

- Self limited infection of upper airway, but can extending to lower air way
- Destroy mucociliary function followed by secondary bacterial infection

**Neuraminidase**

- Release of virus from infected cells and spread in respiratory tract
- Target of neuraminidase inhibitors eg. Oseltamivir

**Hemagglutinin**

- Major target of protective antibody
- Continuing genetic and antigenic evolution

Influenza A

- Pandemics: severe outbreaks that rapidly progress to involve all parts of the world and are associated with the emergence of a new virus to which the overall population possesses no immunity
- Epidemics: an outbreak of influenza confined to one location, such as a city, town, or country

**Clinical feature:**
- rapid onset of fever, myalgia, headache, weakness, cough
- progressive symptom 3-5 days
- clinical subside 2 weeks

**Complication:** pneumonia, lung hemorrhage, hyaline membrane disease

**Prevention:** Killed viral vaccine

**Epidemics:**

- Influenza
- Influenza B: Pneumonia
- Pneumonia

**Occasional:**

- Influenza A, Pneumonia
- Influenza B: Rhinitis/Pharyngitis

**Infrequent:**

- Influenza
Mechanism of the Cytokine Storm Evoked by Influenza virus

Emergence of Influenza A viruses

Novel reassortant avian-origin influenza A (H7N9) virus (Zoonosis)
• Human-to-human transmission could not be ruled out
• Influenza-like illness → severe lower respiratory tract infect
• Lab diagnosis: Real-time RT PCR from throat-swab specimens
• Tx: Oseltamivir, no vaccine available

Respiratory syncytial virus (RSV)
• Paramyxoviridae family
• Enveloped, negative single-stranded RNA virus
• Transmission
  – by respiratory droplet and secretion
  – Infectivity on the hands is variable from person to person but is usually less than 1 hour
• Inoculation of the conjunctiva or anterior nares
• Incubation period is ~ 4-6 days
Respiratory syncytial virus (RSV)

- **Most frequent**
  - Pneumonia and bronchiolitis in young children
- **Occasional**
  - Common cold in adults
- **Infrequent**
  - Pneumonia in elderly and immunosuppressed patients

**Structure of respiratory syncytial virus**

**Respiratory syncytial virus (RSV)**

- Most common cause of **self-limited lower respiratory tract infection** in young children, e.g., bronchiolitis, pneumonia
- Highest among infants 1-6 months of age

**Histopathology of RSV infection**

- **Upper respiratory tract**
  - Mucosal hyperemia, swelling with predominant infiltration of lymphocytes, monocytes, and plasma cells
  - Mucous overproduction causing obstruction of nasal cavity, sinuses, and eustachian tube
- **Lower respiratory tract**
  - Laryngotracheobronchitis: swelling of vocal cord and abundant mucous secretion causing obstruction of small airway and atelectasis
  - Pneumonia: interstitial infiltration of mainly lymphocytes

**Respiratory syncytial virus (RSV)**

- **Lab diagnosis**: viral isolation, PCR, rapid direct antigen detection tests
- **Tx**:
  - Supportive tx
  - Ribavirin, a synthetic nucleoside, is the only currently approved specific treatment for RSV lower respiratory tract disease in hospitalized infants
- **Prevention**: Strict hygiene, avoid close contact
Adenovirus

• Naked, double-stranded DNA viruses in genus Mastadenovirus, family Adenoviridae
• Cause a broad range of clinical syndromes
• Transmitted by
  – inhalation of aerosolized virus
  – by inoculation of virus into conjunctival sacs
  – fecal-oral route
• Serious opportunistic pathogens in immunocompromised patients who have undergone HSCT or solid organ transplantation

Adenovirus

Most frequent
• Common cold and pharyngitis in children

Occasional
• Outbreaks of acute respiratory disease in military recruits

Infrequent
• Pneumonia in children; lower respiratory tract infection in immunosuppressed patient

Diagnosis
• Not routinely investigated (mild & self limited disease)
• Viral culture
• Antigen-specific assays (IFA: respiratory sample&tissue, ELISA: serotype 40,41 in stool)
• PCR: real-time PCR
• Recovered from nasopharyngeal swabs/aspirates, throat swabs, conjunctival swabs, stool swabs, urine, CSF and tissue

Treatment
• Only symptom-based treatment & supportive therapy
• Currently no approved antiviral agents for the treatment of adenovirus infections

DIGESTIVE SYSTEM
**Viral enteritis and diarrhea**

- Rotavirus
- Norwalk virus
- Corona virus

**Rotavirus**
- **Reoviridae family**
- double-stranded RNA viral genome
- Most common cause of gastroenteritis in children < 1 year of age
- Transmission by fecal-oral route

**Clinical**:
- fever, vomiting, Abdominal pain, watery nonbloody diarrhea, rhinorrhea

**Pathogenesis**:
- reduce absorption of water and sodium from GI
- Persistent symptom about 1 week

**Treatment**:
- conservative with fluid replacement

**Norwalk virus**
- Caliciviridae family
- a group of nonenveloped, small, round, icosahedral viruses
- (+) ssRNA, nonenveloped virus.
- Noroviruses → previously called Norwalk-like viruses
- Common in childhood
- Clinical, transmission, pathogenesis, clinical course and treatment are similar to Rotavirus
Coronavirus

- Coronaviridae family
- positive sense, single stranded RNA
- Caused by respiratory tract infection and diarrhea
- Self limited disease
- Intermittent epidemiology

Hepatitis virus

- Classified 6 types
  - Hepatitis virus types A, B, C, D, E, G

Hepatitis A virus (HAV)

- Picornaviridae family
- nonenveloped, positive-strand RNA virus
- Transmitted by fecal-oral route (food, water)
- Common cause of acute hepatitis
- Clinical: fever, jaundice, nausea, vomiting
- Complete recovery
- No develop chronic hepatitis and hepatocellular carcinoma
- Lab Diagnosis: HAV-IgM, IgG
Hepatitis B virus (HBV)

- Hepadnaviridae family
- Enveloped DNA virus
- Transmitted
  - by blood transfusion, intravenous drug use, sexual activity, vertical transmission and contact body secretion eg. semen, saliva, breast milk
- Clinical: fever, jaundice, nausea, vomiting

Hepatitis B virus (HBV)

- Cause of:
  - acute hepatitis with resolution
  - chronic hepatitis, cirrhosis and hepatocellular carcinoma
  - fulminant hepatitis with massive liver necrosis
  - result for hepatitis D virus infection
  - carrier

Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course

- Acute (8 months)
- Chronic (Years)
- HBsAg
- HBeAg
- anti-HBs
- Total anti-HBc
- IgM anti-HBc

Weeks after Exposure
Interpretation serology of HBV

Exercise: interpretation of HBV serology

<table>
<thead>
<tr>
<th>Case</th>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>Anti-HBc</th>
<th>Result</th>
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<td>-</td>
<td>มีภูมิต้านทานจากการฉีดวัคซีน</td>
</tr>
</tbody>
</table>

Hepatitis C virus (HCV)

- Flaviviridae family
- positive single-strand, RNA virus
- non-A, non-B hepatitis
- Transmitted by blood transfusion, intravenous drug use, sexual activity, and contact body secretion eg. semen, saliva
- Asymptomatic of acute illness

Hepatitis C virus (HCV)

- Cause of:
  - Persistent infection and chronic hepatitis
  - cirrhosis and hepatocellular carcinoma
- Lab:
Hepatitis D virus (HDV)

- Deltaviridae family
- small single-stranded, circular RNA
- replicate only in the presence of HBsAg
- Infected with HBV:
  - coinfection: expose to serum containing both HBV and HDV
  - superinfection: chronic carrier of HBV with new infection of HDV

Hepatitis E virus (HEV)

- Caliciviridae family
- + single-stranded RNA virus
- Transmitted by fecal–oral route
- High mortality rate in pregnant women
- Self limited in most case
- Complete recovery
- No develop chronic hepatitis and hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Hepatitis A Virus</th>
<th>Hepatitis B Virus</th>
<th>Hepatitis C Virus</th>
<th>Hepatitis D Virus</th>
<th>Hepatitis E Virus</th>
<th>Hepatitis G Virus</th>
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<tbody>
<tr>
<td>Transmission</td>
<td>Fecal-oral</td>
<td>Parenteral; close contact</td>
<td>Parenteral; close contact</td>
<td>Parenteral; close contact</td>
<td>Waterborne</td>
<td>Parenteral</td>
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<tr>
<td>Incubation period</td>
<td>2-6 wk</td>
<td>4-26 wk</td>
<td>2-6 wk</td>
<td>4-7 wk</td>
<td>2-8 wk</td>
<td>Unknown</td>
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<tr>
<td>Carrier state</td>
<td>None</td>
<td>0.1-1.0% of blood donors in U.S. and Western world</td>
<td>0.2-1.0% of blood donors in U.S. and Western world</td>
<td>1-10% in drug addicts and hemophiliacs</td>
<td>Unknown</td>
<td>1-2% of blood donors in U.S.</td>
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<tr>
<td>Chronic hepatitis</td>
<td>None</td>
<td>5-10% of acute infections</td>
<td>&gt;50%</td>
<td>&lt;5% coinfection, 80% upon superinfection</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Yes</td>
<td>Yes</td>
<td>No increase above HBV</td>
<td>Unknown, but unlikely</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
**Mumps virus**

- Paramyxoviridae family
- Single-stranded RNA genome
- Transmitted via direct contact, droplet nuclei, or fomites
- Cause of Mumps with self limited disease in 2 weeks
- **Clinical symptoms:**
  - Parotitis → fever, malaise, headache, parotid swelling and pain
  - Epididymo-orchitis

**Pathogenesis**

- Inhalation of respiratory droplet contains virus
  - Dendritic cells at respiratory epithelium capture virus and drainage to lymph nodes
  - Replication in lymph nodes
  - Hematogeneous spread to parotid glands (parotitis), and other organs (CNS, pancreas, testis)

**Histology**

- **Parotitis:** bilateral 2/3 of cases
  - Desquamation of ductal epithelial cells
  - Interstitium edema with lymphocytes, and plasma cells infiltration

- **Orchitis:** developing in 15–30% of cases
  - Testis edema, lymphocytes infiltration, hemorrhage
  - May be infarction → infertility (13%)
**Mumps**

- **complication:**
  - aseptic meningitis (most common)
  - unilateral deafness
  - pancreatitis
- **Lab dx:** detection of viral antigens or RNA or on serology → Mumps IgM Ab
- **Tx & Prevention:** supportive Tx, Live attenuated vaccine

**Measles virus**

- Paramyxoviridae family
- Infected by respiratory droplet
- Measles (rubeola) common in children
- Self limited disease
- Incubation period 10 to 14 days
- Vaccination is highly effective: immunity protect reinfection

**SYSTEMIC WITH SKIN ERUPTION**

**Clinical:**
- conjunctivitis, cough, coryza, fever
- at day 2-3: “Koplik’s spots” at buccal mucosa
- at day 4-5: reddish-brown maculopapular rash, enlarged cervical LN
- 1 week: subside
Pathology

- Multinucleated giant cells with intranuclear and intracytoplasmic inclusion (Warthin-Finkeldey cells) in lymphoid organs and other organs

Rubella virus

- Togavirus family, + single-stranded RNA
- Rubella (German measles)
- Incubation period 14-21 days
- Systemic infection: rash, fever, malaise, coryza, arthritis and arthralgias
- Dx: serology testing (paired acute and convalescent samples collected 10 to 21 days apart)
- Tx: supportive
- Prevention: live attenuated rubella vaccine

Rubella (German measles)

- Exanthem - discrete, pinkish red, fine maculopapular eruption - begins on the face and spreads cephalocaudally

Congenital rubella syndrome

- Infected pregnant woman (first 20th wks)
- Fetal death, premature delivery
- Congenital anomalies
  - Heart defects: PDA, VSD, pulmonary valvular stenosis
  - Eye and ear defects: cataract, glaucoma, deafness
  - CNS defects: microcephaly, mental retardation
Herpes simplex infection

- Herpesviridae family, double-stranded DNA
- Transmitted by direct/sexual contact
- **Diagnosis**: clinically
  - Scrap base of vesicle and a special stain - Giemsa-stained (Tzanck smear)
    - Ballooned epithelial cells with intranuclear inclusions and multinucleated giant
  - Viral cultures take 48 to 96 hours after inoculation

HSV-1

- >90% of primary infections are subclinical
- Fever blister or cold sores at facial skin, e.g. lip, nose, gingivostomatitis

HSV-2

- Genital pathogen
- Neonatal herpes

Recurrent herpes simplex infection

- Triggers include fever, sunlight, local trauma, menses, emotional stress
- Once virus reaches the dermal-epidermal junction, there are two possible outcomes: subclinical shedding or recurrence defined clinically by a skin blister and ulceration

Herpes simplex virus

- **Pathology**:
  - Pink to purple, glassy intranuclear inclusion (Cowdry type A)
  - Mononucleated or multinucleated cells
**Pathogenesis**

Initial infection in skin or mucous membrane

- travel along sensory nerve ending and retrograde axonal flow to neuron in dorsal root ganglia (latent infection)
- reactivate of latent infected neuron (e.g. stress, fever, UV)
- newly replicated virus is transported anterograde to a site at or near portal of entry into body causing localized vesicles

**Neonatal herpes infection**

- Infected fetus by contact vaginal secretion contains viruses
- **Clinical features**
  - mucocutaneous vesicles
  - virus spread to other organs e.g. brain, liver, lung
- High mortality rate

**Varicella zoster virus (VZV)**

- Herpesviridae family, double-stranded DNA
- Cause of chickenpox, herpes zoster (shingles)
- Incubation period ranges from 10-20 days
- Transmitted by inhalation of airborne respiratory droplets from an infected host or direct contact
- **Tx:** Acyclovir
- **Prevention:** Live vaccine
**Varicella zoster virus (VZV)**

- Primary acute infection of VZV: “chickenpox”
- Reactivation of latent VZV: “shingles or herpes zoster” distributes to sensory nerves

**Pathogenesis**

Primary infection (chickenpox)

- VZV spread from mucosal and epidermal lesions to local sensory nerves
- VZV remains latent in dorsal ganglion cells of sensory nerves
- Reactivation of VZV results in syndrome of herpes zoster (shingles)

**Varicella zoster virus (VZV)**

- Gross:
  - chickenpox: diffuse, scattered vesicles
  - shingles: vesicles distribution along the peripheral nerve (dermatome)
- Histology:
  - Intranuclear inclusion of infected cells (multinucleated cells)

**Intranuclear inclusion of VZV**

Cytopathologic changes, including fusion of epithelial cells, which produces multinucleate cells with molding of nuclei to one another (long arrow in B), and eosinophilic haloed nuclear inclusions (short arrow in B).
Coxsackie Virus

- Picornaviridae family, enterovirus genus
- **Type A**
  - Causes herpangina and hand-foot-and-mouth disease
- **Type B**
  - Causes Pluerodynia
- **Both**
  - Causes meningitis, myocarditis and pericarditis, also can cause juvenile diabetes

Hand-foot-and-mouth disease

**Prodome** - low-grade fever, malaise, sore mouth, anorexia

1-2 days later, rash appears

- Oral lesions - shallow, yellow ulcers surrounded by red halos
- Cutaneous lesions - begin as erythematous macules then evolve to small, thick-walled, grey vesicles on an erythematous base

**Treatment:** Supportive

Hand, Foot, and Mouth Disease

- Coxsackie Virus A, B & Enterovirus 71
- Causes painful red blisters on:
  - Throat
  - Tongue
  - Gums
  - Cheeks
  - Palms of hands
  - Soles of Feet

SYSTEMIC WITH HEMATOPOIETIC DISORDER
Cytomegalovirus (CMV)

- Herpesviridae family
- Linear, double-stranded DNA
- Produce a variety of disease depend on age, immune status
- Cause of asymptomatic in healthy person or severe systemic infection in neonates and immunocompromised host (opportunistic infection)

Cytomegalovirus (CMV)

- Transmitted by:
  - Intrauterine transmission
  - Perinatal transmission
  - Breast milk
  - Respiratory droplets
  - Semen and vaginal fluid
  - Blood transfusion
  - Organs transplantation

Cytomegalovirus (CMV)

- Clinical feature depends on infected organs
- Organ involvement: eyes, salivary glands, kidney, liver, pancreas, brain, etc.

Direct ophthalmoscope:
Arcuate zone of retinitis with hemorrhages and optic disk swelling

Cytomegalovirus (CMV)

- Congenital CMV infection
  - 90% asymptomatic
  - 10% symptomatic eg. Hemolytic anemia, jaundice, thrombocytopenia, pneumonia, hepatosplenomegaly, retinitis, brain damage, mental retard or dead
Histology of CMV

- Large purple intranuclear inclusion surrounded by clear halo called “owl’s eye” appearance and smaller basophilic intracytoplasmic inclusion

Epstein-Barr Virus (EBV)

- Herpesviridae family, double-stranded DNA
- Cause of heterophile-positive infectious mononucleosis
- Self-limiting illness of children & young
- Transmitted by contact saliva
- EBV associated with hairy leukoplakia, Burkitt lymphoma and nasopharyngeal carcinoma

Clinical of infectious mononucleosis:
- fever
- generalized lymphadenopathy
- hepatosplenomegaly
- sore throat (patch on tonsil)
- may be CNS lesion
- may be hepatitis, pneumonia

Pathogenesis

EBV replicates in B-lymphocytes in tonsil
B-lymphocytes disseminates in circulation
Atypical T lymphocytes in blood circulation
Role of EBV in the genesis of this tumor remains uncertain.

Epstein-Barr Virus (EBV)

- Diagnosis:
  - Lymphocytosis + atypical lymphocytes >10%
  - Elevated liver enzymes
  - Heterophile antibodies - specific
  - Specific EBV antibody titers and PCR

Human Immunodeficiency Virus (HIV)

- Retroviridae family
- single-stranded, enveloped RNA viruses
- HIV 1, HIV 2
- lead to acquired immunodeficiency syndrome (AIDS)
Human Immunodeficiency Virus (HIV)

- Primarily infects in helper T cells (CD4+ T cells), macrophages, and dendritic cells
- HIV infection leads to low levels of CD4+ T cells by 3 main mechanisms
  - Direct viral killing of infected CD4+ T cells
  - Increased rates of apoptosis in infected CD4+ T cells
  - Killing of infected CD4+ T cells by CD8 cytotoxic lymphocytes that recognize infected cells
- ↓CD4+ T cell Cell-mediated immunity (CMI) is lost, and the body becomes susceptible to opportunistic infections

HIV infection 4 stages

- Incubation period
  - asymptomatic, 2-4 weeks after infection
- Acute infection
  - rapid viral replication
  - fever, rash, myalgia, malaise, lymphadenopathy
  - pharyngitis (sore throat)
- Latency stage
  - few or no symptoms, duration 2 weeks - 20 years
- AIDS
  - symptoms of various opportunistic infections
  - Candida, Pneumocystis jirovecii, TB, CMV, MAC

The replication cycle of HIV

Typical course of an untreated HIV-infected individual
**Arbovirus**

- Arbovirus is a term used to refer to a group of viruses that are transmitted by arthropod vectors.
- The word *arbovirus* is an acronym (ARthropod-BOrne viruses)

**Japanese encephalitis virus**

- Flaviviridae family
- Japanese Encephalitis
- transmitted by *Culex tritaeniorhynchnus*
- Animal host: pig
- **Clinical**: confusion, seizure, coma
- **Pathology**: mononuclear cells around vessels, necrosis of neuron and brain tissue
- **Prevention**: inactivated vaccine

**Dengue virus**

- Flaviviridae family
- Dengue virus 1-4
- transmitted via bite of mosquitoes eg. *Aedes aegypti, Aedes albopictus*
- Symptoms of dengue include:
  - high fever, headache
  - rash
  - nausea and vomiting
  - myalgia
  - leukopenia (neutropenia), thrombocytopenia
Dengue virus

• Infection with one serotype provides lifelong immunity to that particular serotype but not to the other three
• Secondary infections predispose to DHF
• **Lab diagnosis:** IgM ELISA, paired serology during recovery, antigen-detection ELISA, RT-PCR during acute phase
• **Tx:** supportive