

Infectious Diseases

Lesson 13

ADULT RELEVANT VIRAL ILLNESSES OTHER THAN HIV

Part B – Hantavirus, severe acute respiratory syndrome, influenza, herpes simplex virus, and cytomegalovirus

Bernardino Roca Villanueva

Servicio de Medicina Interna, Hospital General de Castellón
Departamento de Medicina, Universidad Jaime I

broca@uji.es

Objectives, learning
goal and contents

Objectives

To complete the review of the main characteristics of viral infections in the human host

Learning goal

To acquire enough conceptual knowledge to properly manage the patient who presents with the suspicion of a viral infection

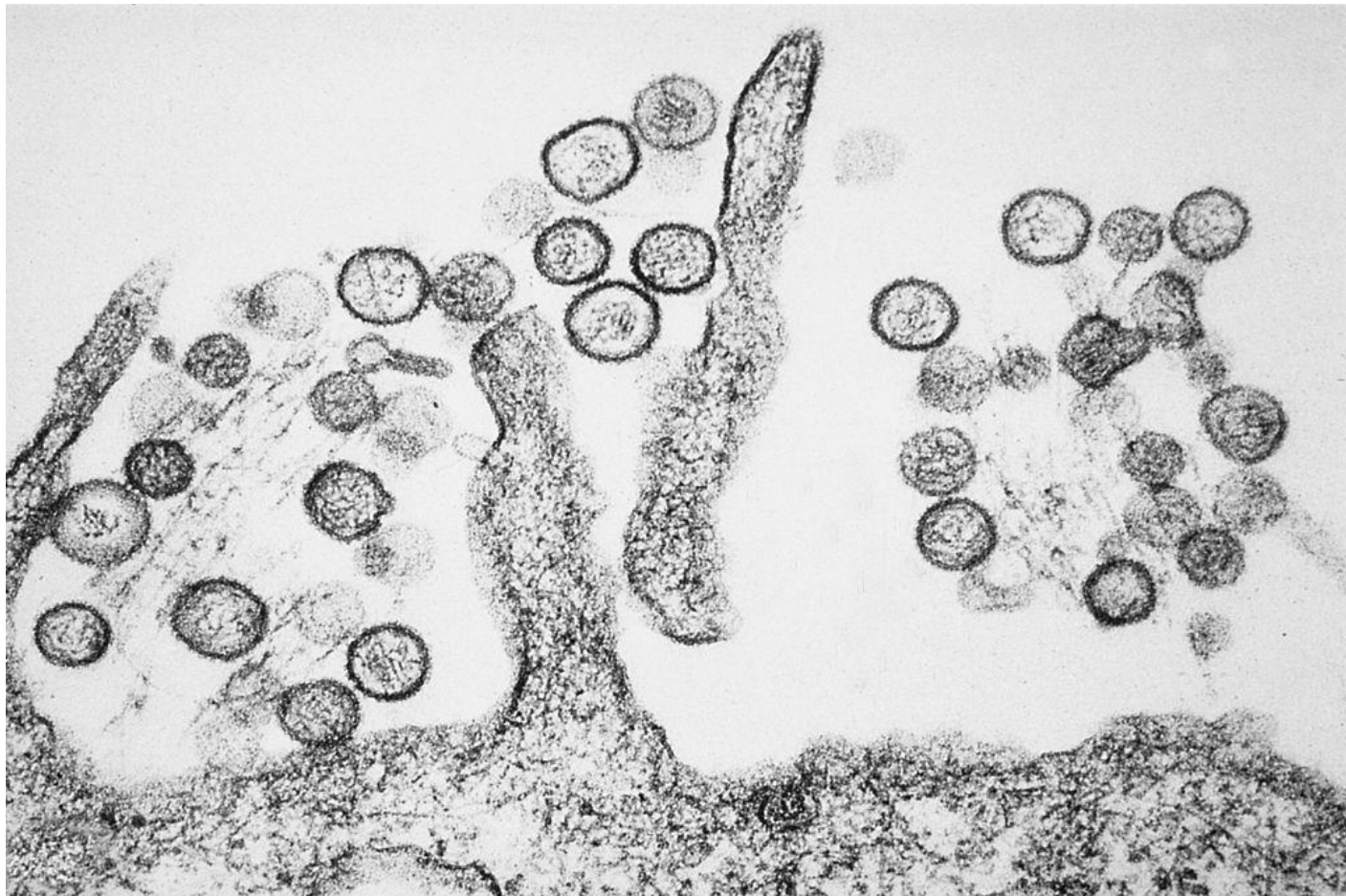
Contents

- [Hantavirus infections](#)
- [Severe acute respiratory syndrome](#)
- [Influenza](#)
- [Herpes simplex virus](#)
- [Cytomegalovirus](#)
- [Key messages](#)
- [Further reading](#)

Hantavirus infections

Virus characteristics

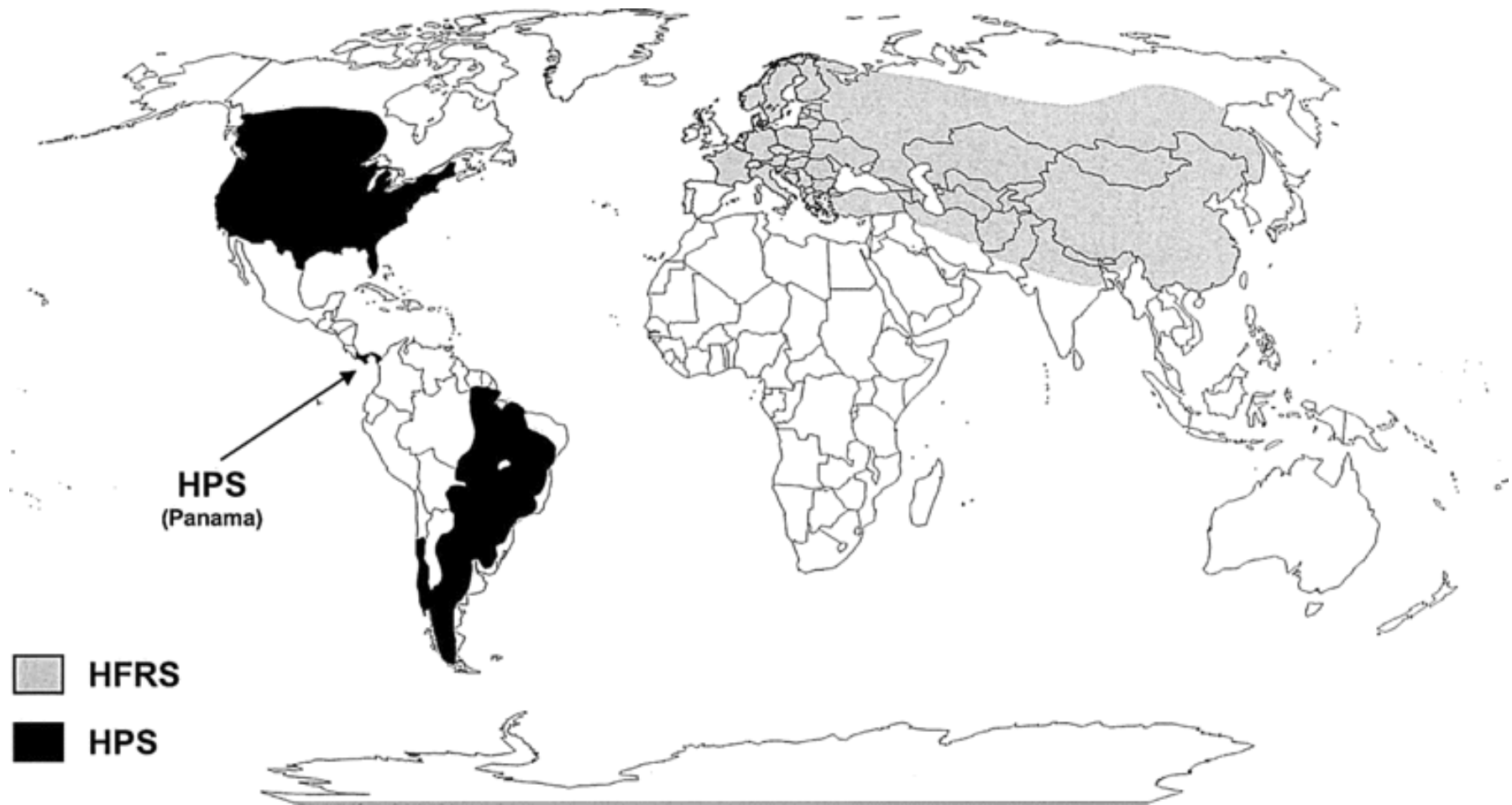
- Hantaviruses was first identified in 1993
- Belong to the Bunyavirus family
- Segmented single-stranded RNA genome
- Nonpathogenic strains



Transmission electron micrograph of hantavirus

Epidemiology

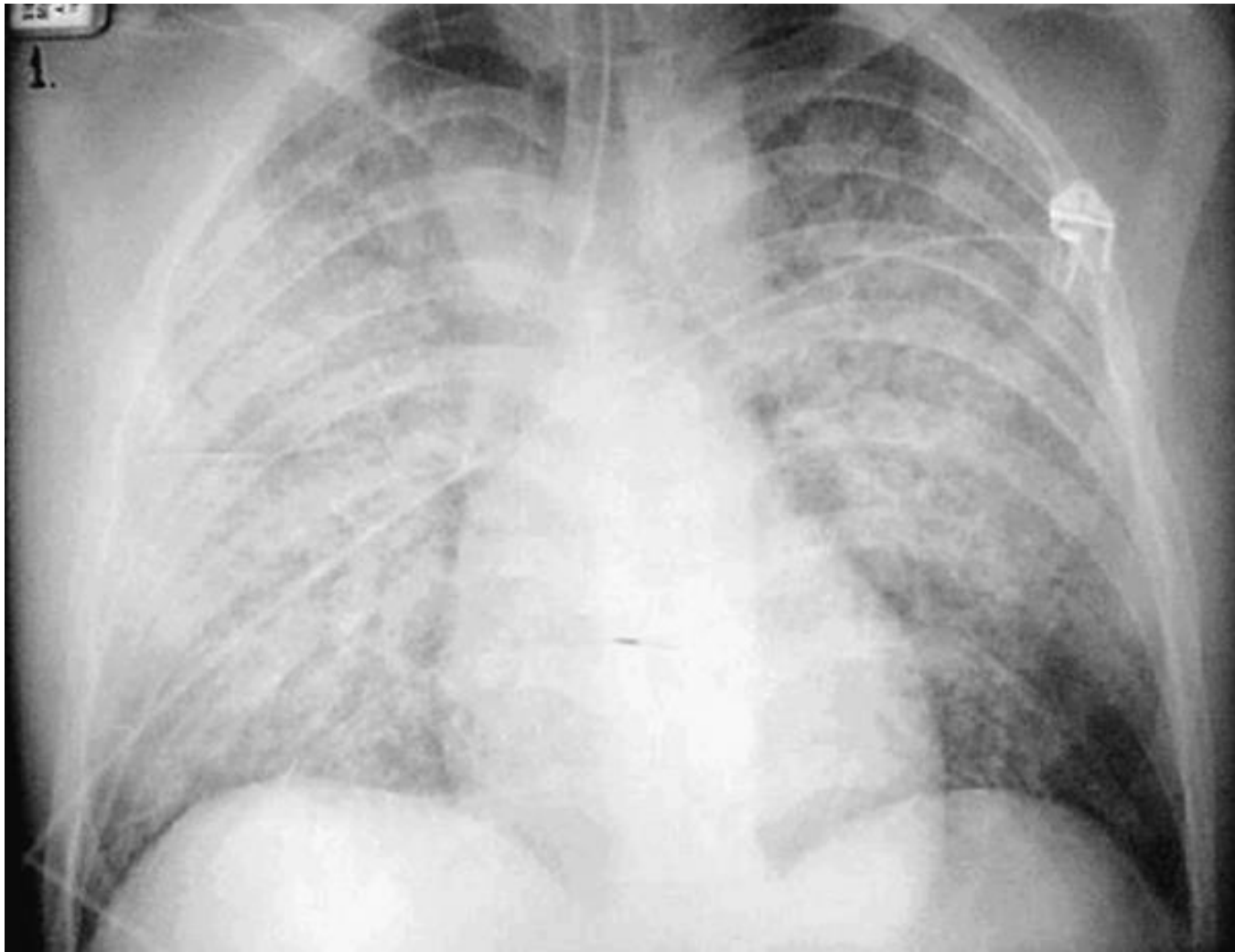
- Hantaviruses are carried by **rodents**, which do not become ill but shed the virus in their saliva and urine
- Humans infected when inhale **aerosols** of these infected fluids
- Several species of mice and rats throughout America, Central Europe, and other regions of the world harbor hantavirus strains
- Most infected people are thought to develop disease, as seropositivity in endemic areas is very low
- Low incidence, but new cases every year
- Incubation 1 to 6 (generally 2 to 4) weeks



Geographic distribution of hantavirus pulmonary syndrome (HPS) and hemorrhagic fever with renal syndrome (HFRS)

Hantavirus pulmonary syndrome

- “Sin nombre” virus strains carried by deer mice, found in America
- Initially **fever, myalgias** and abdominal complaints
- Severe sepsis plus **respiratory symptoms** with **acute respiratory distress syndrome** and disseminated intravascular coagulation
- Little inflammation is seen in autopsies or biopsies of affected lung
- Mortality 20 to 50 %



Acute respiratory distress syndrome due to
hantavirus pulmonary syndrome

Hantavirus hemorrhagic fever with renal syndrome

- Hantaan River, Dobrava-Belgrade, and other strains, carried by several rodents; in Europe, Asia, and Africa
- Known as Korean hemorrhagic fever, epidemic hemorrhagic fever, and nephropathis epidemica
- Redness of cheeks and nose, fever, chills, headaches, sweaty palms, diarrhea, nausea, abdominal and back pain, cough
- Hypotension, tachycardia, hypoxemia and thrombocytopenia
- **Oliguric renal failure** with proteinuria, followed by diuresis of 3 to 6 liters per day

Diagnosis

- Serology, ELISA, etc., is almost always positive in patients at the time of admission, IgM in acute sera and IgG (fourfold rise) is diagnostic
- Immunohistochemistry can identify hantavirus in infected tissue biopsies
- RT-PCR

Therapy and prevention

- If the patient can be supported through the period of hypoxia, shock, etc. recovery can be complete
- Intravenous ribavirin used, but probably not effective
- Prevention: avoid inhalation of aerosolized material contaminated by rodents, and general measures to reduce rodent infestation
- A small risk of human-to-human transmission: universal precautions advised for all those caring for affected patients

Severe acute respiratory syndrome (SARS)

Etiologic agent

- Single-stranded, enveloped, RNA coronavirus (SARS-CoV)
- Similar to influenza and measles viruses
- Other coronaviruses common causes of adult viral upper respiratory infection, symptoms and signs identical to those caused by rhinoviruses
- Does not withstand drying, but may remain infectious in a warmer, moist environment; survives on surfaces and hands for 3 hours

Pathogenesis

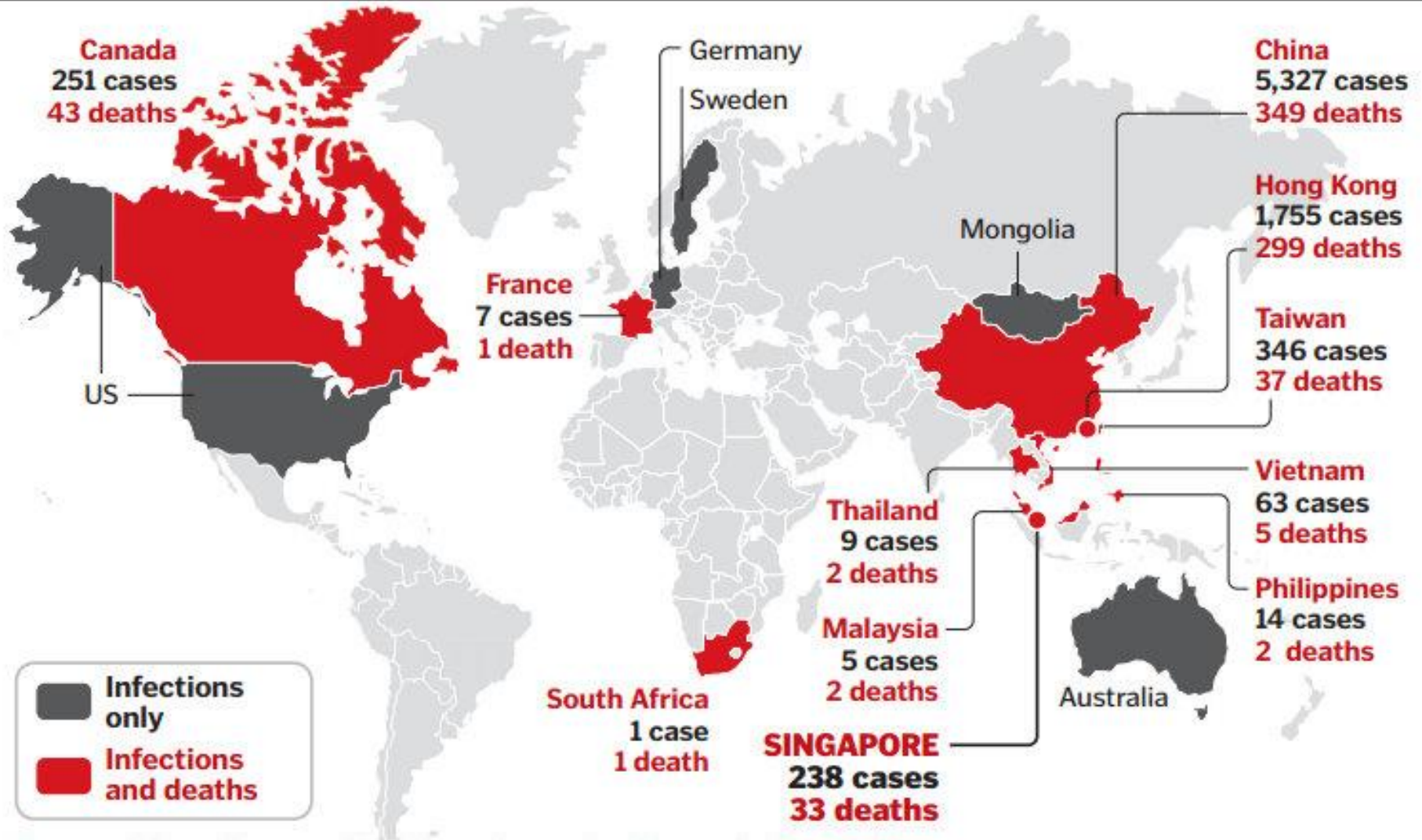
- Patient with SARS coughs → respiratory **droplets** → cells in the respiratory tract of new patient → cytoplasm, where multiplies → released from dead cells or extruded from living cells
- Severe tissue damage thought to be largely a result of the **host's overly vigorous immune response**

Epidemiology

- 2002 to 2003, outbreak in Southeast Asia with spread to 37 countries worldwide
- Spread primarily in closed spaces, including airplanes; family members and hospital personnel affected
- Contact transmission also possible
- Stool and other body products are possible source

SARS 2003: DEADLY VIRUS

774 deaths and 8,096 infections reported from November 2002 to July 2003



Clinical manifestations

- Attacks primarily healthy adults aged 25-70 years
- Incubation 2-14 days
- Severe febrile prodrome with chills and rigors, headache, and myalgias
- Some 3-7 days later severe dry cough, dyspnea and hypoxemia, with 10–20 % of patients requiring mechanical ventilation
- Infectiousness begins at about day 5 and peak at about day 10 of illness

Tests results

- ↓ total leukocyte, lymphocyte, and platelet count
- ↑ creatine phosphokinase (CK), transaminase and lactate dehydrogenase (LDH)
- Renal function usually normal
- Chest X-ray: focal interstitial infiltrates → generalized, patchy, interstitial infiltrates → areas of consolidation
- Autopsy: pulmonary edema, hyaline membranes, desquamation of type 2 pneumocytes and fibroblast proliferation in the interstitium and alveoli



SARS, chest X-ray

Diagnosis

- RT-PCR, rapid and sensitive; in the absence of ongoing SARS transmission, the probability of false positive test is high
- ELISA SARS antibody test available, but titers are generally not observed until the second week of the illness

Treatment, outcome, and prevention

- No specific treatment, meticulous supportive care is all that medical science has to offer
- Overall fatality rate was 9.6 % worldwide; poorer prognosis associated with
 - Older age
 - ↑ serum LDH
 - ↑ peripheral neutrophil count
- Infection control practices including strict respiratory isolation, negative pressure rooms, use of respirator masks (N-95), gowns, gloves, and protective eyewear

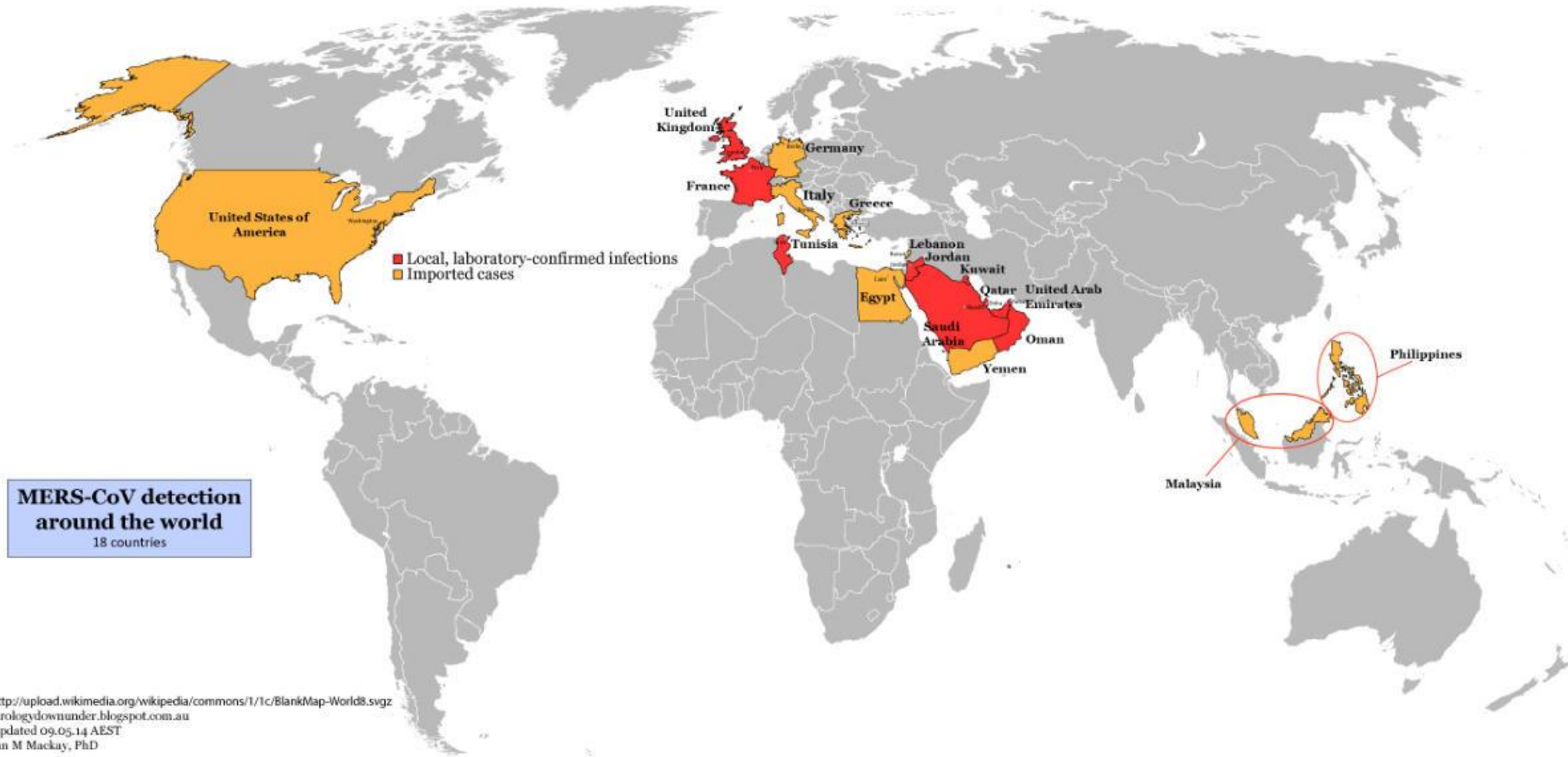


Respirator
masks (N-95)

Middle East respiratory syndrome coronavirus (MERS-CoV) infection

- MERS-CoV a betacoronavirus similar to SARS- CoV, identified in 2012
- Saudi Arabia and other countries, mostly of Middle East
- Some 900 cases reported worldwide so far
- Clinical presentations similar to SARS, but low risk of human-to-human transmission
- Case-fatality ratio around 40 %

Middle East respiratory syndrome coronavirus (MERS-CoV) infection around the world



Influenza

Epidemiology - I

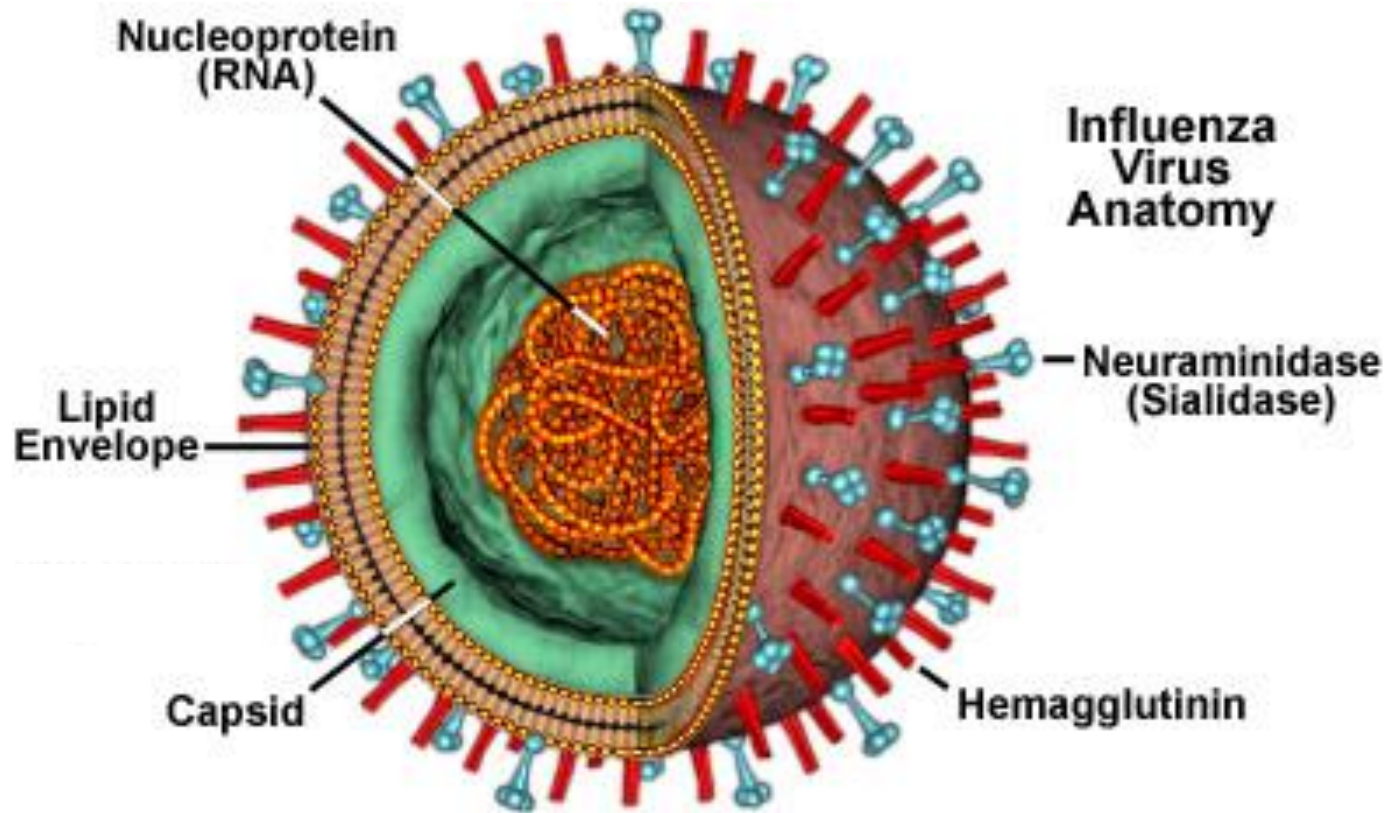
- Influenza A and B virus cause epidemics every 1-3 years
- Influenza A can cause pandemics such as the 1918–1919 one in which at least 20 million people died
- Number of cases ↑ in winter months
- Attack rates highest in the very young
- Greatest morbidity and mortality among elderly people, patients with lung disease or immunocompromised

Epidemiology - II

- Efficiently transmitted by aerosols of respiratory secretions generated by coughing, sneezing, and talking
- Avian strain adapted to human → 1918 pandemic
- H1N1 new strain from reassortment between previously circulating swine influenza viruses and a Eurasian swine strain → 2009 pandemic; most cases in children and younger adults; immunosuppressed and pregnant women particularly affected

Virology - I

- Enveloped RNA virus, 8 genes, 2 of them key:
 - Hemagglutinin (HA), required for binding and infection
 - Neuraminidase (NA), required for virion release
 - Both important for pathogenicity and protective immunogenicity
- Nomenclature: type (A or B)/geographic source/isolate number/year of isolation/HA and NA gene subtypes, example: A/Hong Kong/03/68/H3N2



Influenza virus

Virology - II

- Antigenic **drift**: change in HA and NA proteins by genetic mutation → variant strains against which humans have less protective antibody
- Antigenic **shift**: influenza A virus acquires a completely different set of antigens due to genome segments reassortment with avian influenza species → humans have no protective antibodies → pandemic

Pathophysiology

- The virus infects the respiratory epithelium, multiplies rapidly, and causes inflammation and necrosis
- Pulmonary function is usually abnormal in most patients

Clinical manifestations - I

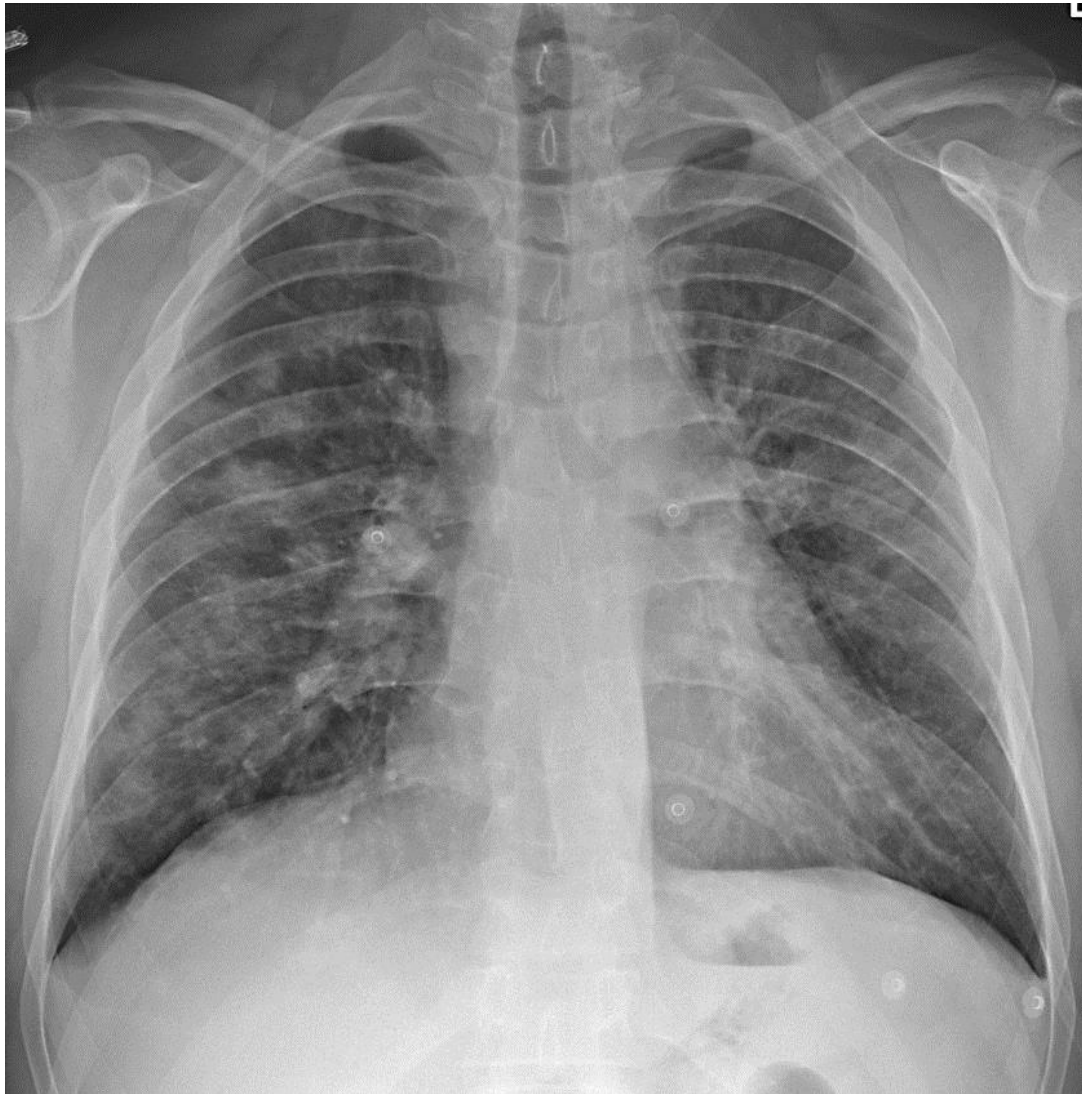
- Abrupt onset of fever, headache, chills and myalgias
- Dry cough, rhinorrhea, cervical adenopathy, nonexudative pharyngitis and diarrhea
- Recovery of most symptoms in 4 to 7 days, but cough and fatigue may persist for several weeks
- May also cause a mild febrile or afebrile upper respiratory disease

Clinical manifestations - II

- 2009 H1N1 common lower respiratory tract disease
- Avian influenza H5N1 generally cause diarrhea and may cause respiratory failure in children
- Lymphopenia is common
- Abnormalities on chest X-ray may occur

Complications

- Viral pneumonia, that can progress to fatal acute respiratory distress syndrome and pulmonary hemorrhage
- Superinfection with ***Staphylococcus aureus***, *Haemophilus influenzae*, or *Staphylococcus pneumoniae*
- Reye syndrome (fatty infiltration of the liver and encephalopathy with lethargy or delirium and coma), related to use of aspirin



Influenza virus
pneumonia

Diagnosis

- Clues to influenza
 - Predominance of the systemic symptoms
 - Epidemic nature of the disease in the community
- Rapid detection tests for A and B types in throat and nasal swabs; sensitivity 60 %, therefore, treatment should not be withheld while awaiting the results
- Culture or RT-PCR

Treatment

- Amantadine and rimantadine inhibit influenza A virus by binding to a membrane protein; resistance to both
- NA inhibitors, **zanamivir** (inhaled) and **oseltamivir** (oral), highly effective in inhibiting both type A and B; most effective soon after onset of infection
- Oseltamivir → neuropsychiatric side effects in children
- Strains of 2009 H1N1 resistant to oseltamivir but generally sensitive to zanamivir

Prevention - I

- Zanamivir and oseltamivir after exposure
- **Inactivated** vaccine against the circulating strains of types A and B influenza virus; decreases both disease severity and infection rate; especially indicated in:
 - Children aged 6 months through 4 years
 - Persons aged 50 years and older
 - Patients with chronic disease
 - Patients with immunodeficiencies
 - Women planning to be pregnant during winter
 - Health care personnel

Prevention - II

- Live attenuated vaccine, administered as a nasal spray
 - Approved for use in patients 2–49 years of age
 - As effective as inactivated vaccine
 - Side effects are generally minor: cough and rhinorrhea
 - Should not be administered to immunocompromised patients
- More effective vaccines still needed

Herpes simplex virus

Epidemiology

- Herpes simplex virus (HSV), ubiquitous, two types:
 - HSV-1 → primarily orolabial lesions
 - HSV-2 → primarily genital lesions
- > 90% of adults worldwide + HSV-1 serology
- Sexual activity correlates with + HSV-2 serology
- Transmission usually person to person, by direct contact with:
 - Infected secretions
 - Mucosal surfaces

Pathophysiology

- HSV enters mucosa or skin → replicates in the epithelium → nerve ending → transported to the nerve ganglion where it establishes a latent lifetime infection
- Trigeminal and sacral ganglia are the most common sites of HSV-1 and HSV-2 latency respectively

Clinical presentation of HSV-1 infections

- Primary infection:
 - Often subclinical and many people never suffer reactivation
 - Others gingivostomatitis (especially small children)
 - Usually ulcerative and exudative, and may involve extensive areas of the lips, oral cavity, pharynx, and perioral skin
 - Healing after several days to 2 weeks, usually without scarring
- Secondary episodes:
 - Less severe, “fever blisters” (vesicular and ulcerative lesions)
 - At the vermilion border of the lips, or surrounding areas
 - Triggers: sunlight exposure, stress, and viral infections



Herpes simplex virus type 1 primary infection



Herpes simplex virus type 1 primary infection



Herpes simplex virus type 1 secondary infection

Clinical presentation of HSV-2 infections

- In both women and men, HSV-2 causes genital herpes
- Vesicular, pustular, or ulcerative lesions, involving the penis in men and vagina and cervix in women
- Pain, itching, dysuria, and vaginal or urethral discharge
- Symptoms of primary infection tend to be more severe in women
- Primary infection can be associated with mild systemic symptoms such as fever and aseptic meningitis
- Temporary bladder or bowel dysfunction



Herpes simplex virus type 2 secondary infection



Herpes simplex virus type 2
secondary infection

Other clinical manifestations of HSV infection

- Both HSV-1 and HSV-2 can also affect many other sites in the body where they have been inoculated
- “Whitlow”, HSV infection of the finger, from inoculation into abraded skin; person-to-person or autoinoculation in health care workers; often mistaken for bacterial infections
- “Herpes gladiatorum”, HSV infection acquired by wrestlers, in whom the virus is inoculated into breaks in the skin during wrestling competition



Whitlow



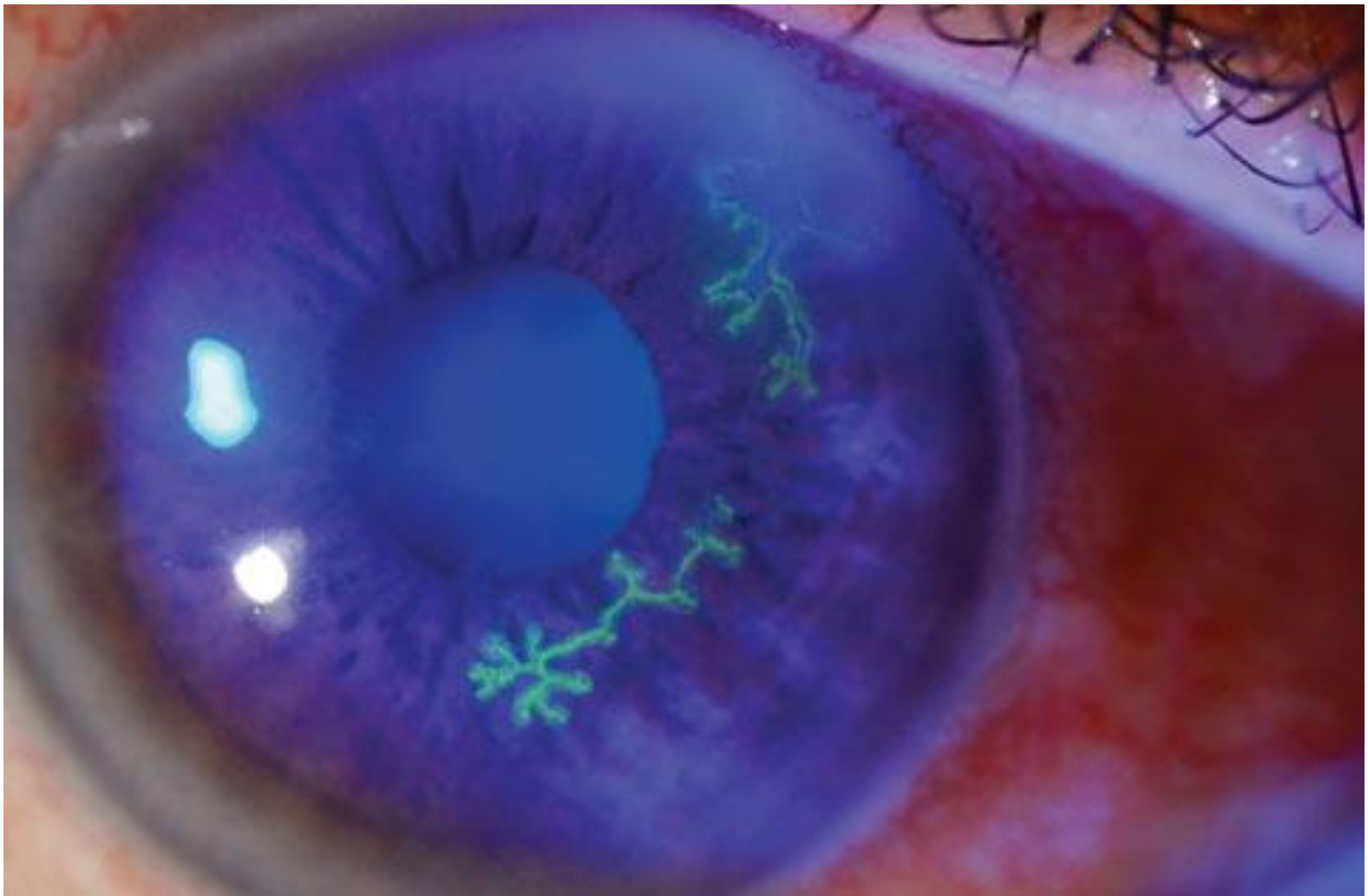
Whitlow



Herpes gladiatorum

Complications: keratitis

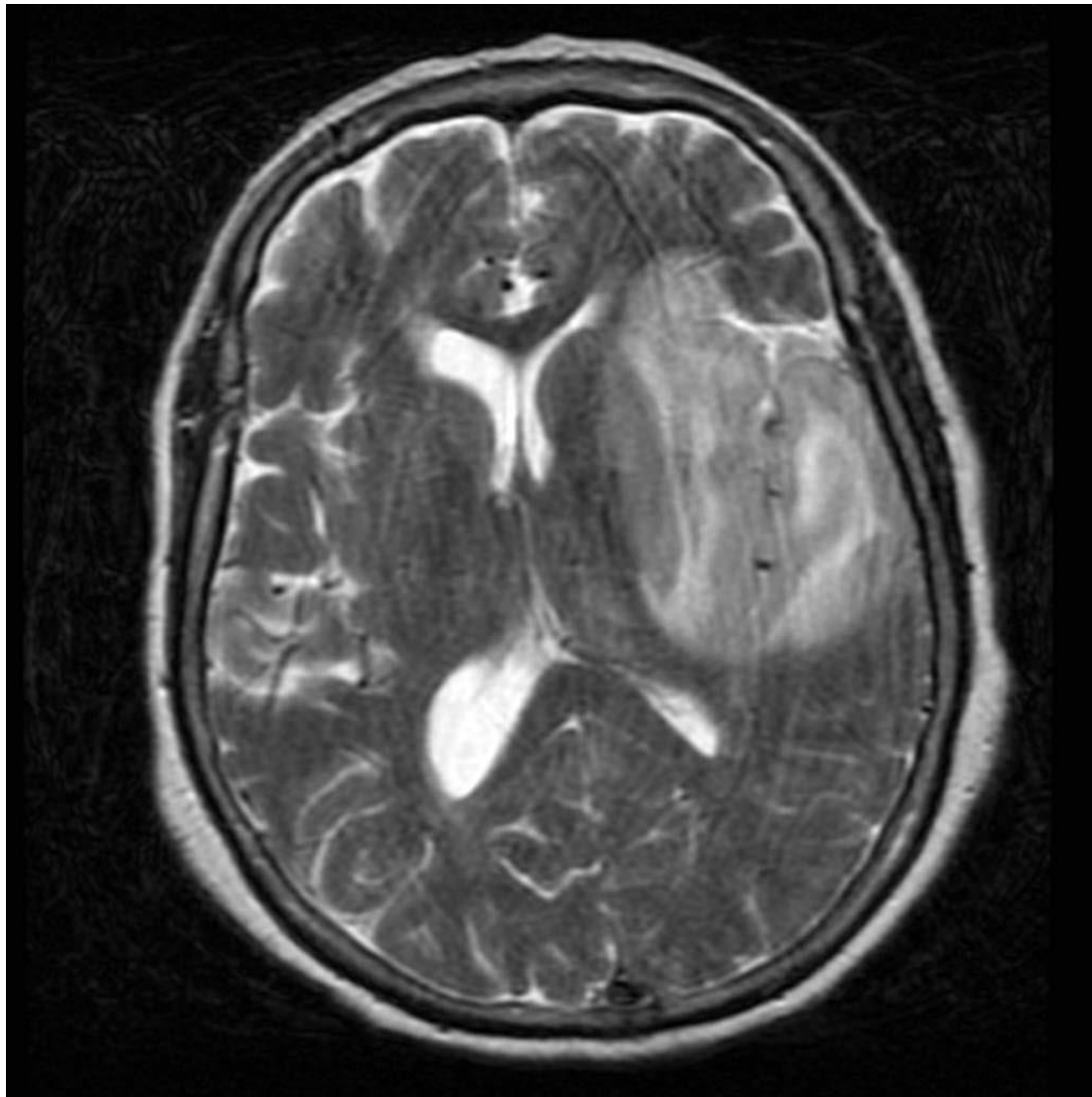
- More commonly due to HSV-1
- Recurrences
- One of the most common causes of blindness in developed countries
- Tearing, pain, erythema, and conjunctival swelling
- Dendritic corneal lesions are easily visualized by fluorescein staining
- Involvement of deeper structures or corneal scarring can lead to blindness



Dendritic corneal lesions visualized by fluorescein staining, herpetic keratitis

Complications: encephalitis

- Annually 1 in 250,000 to 500,000 population
- Preponderance of HSV-1
- Concurrent skin lesions are usually not present
- May be the result of primary infection, but most frequently is a reactivation
- Fever, altered mentation, focal neurologic signs, personality changes, bizarre behavior, and seizures
- Typically affects the temporal lobe unilaterally
- Fulminant variant with frank hemorrhagic necrosis of the affected areas of the brain, > 15% mortality



Herpetic
encephalitis

Other complications

- Widespread cutaneous dissemination (eczema herpeticum) in people with eczema
- Visceral dissemination, rare in the normal host, for example herpetic tracheobronchitis → pneumonitis, in debilitated, intubated hospitalized patients

Diagnosis

- Clinical generally, however, the typical vesicle on an erythematous base is not always present
- Culture of vesicle fluid is highly sensitive and specific
- Direct staining for HSV antigens can also be used
- Tzanck test: giant cells in stained lesion scrapings, quick, but low specificity and sensitivity
- HSV encephalitis:
 - CSF PCR highly sensitive and specific
 - MRI and electroencephalogram: temporal abnormalities

Treatment

- Oral and genital: acyclovir, famciclovir, or valacyclovir
 - Effective for first episodes of all types
 - May reduce duration of symptoms in recurrent episodes, especially in HSV-2, but results are not dramatic
 - Suppressive if frequent and severe recurrent genital herpes
- HSV encephalitis: intravenous acyclovir for at least 14 days
- Disseminated infection, particularly in the immunosuppressed, usually high-dose intravenous acyclovir

Cytomegalovirus

Epidemiology

- A common infection worldwide
- In developed countries, more than 50 % of children are infected by puberty
- Young children are a major source of infection for adults
- Person-to-person spread, by contact with any human body substance: blood, urine, saliva, breast milk, etc.
- Also spread by sexual contact and by blood transfusion and organ donation

Pathophysiology and clinical manifestations

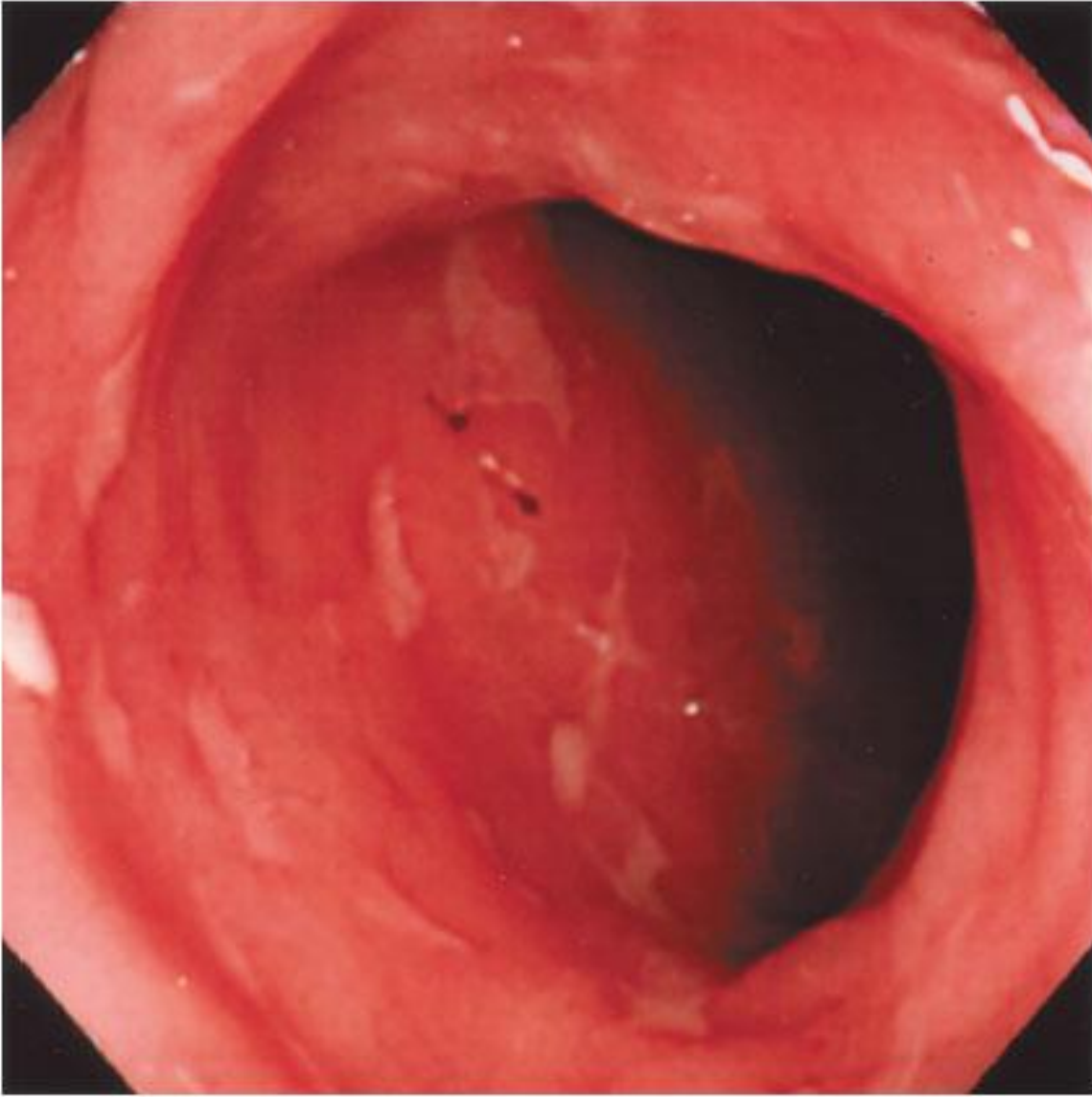
- Most human infections are subclinical, but primary infection in the normal host occasionally results in a mononucleosis syndrome
- Causes 10 to 20% of mononucleosis cases
- The major cause of heterophil-negative mononucleosis
- Difficult to distinguish from Epstein-Barr virus-associated mononucleosis, but
 - Tends to occur in slightly older adults
 - Pharyngitis and cervical adenopathy are less common

Pathophysiology and clinical manifestations

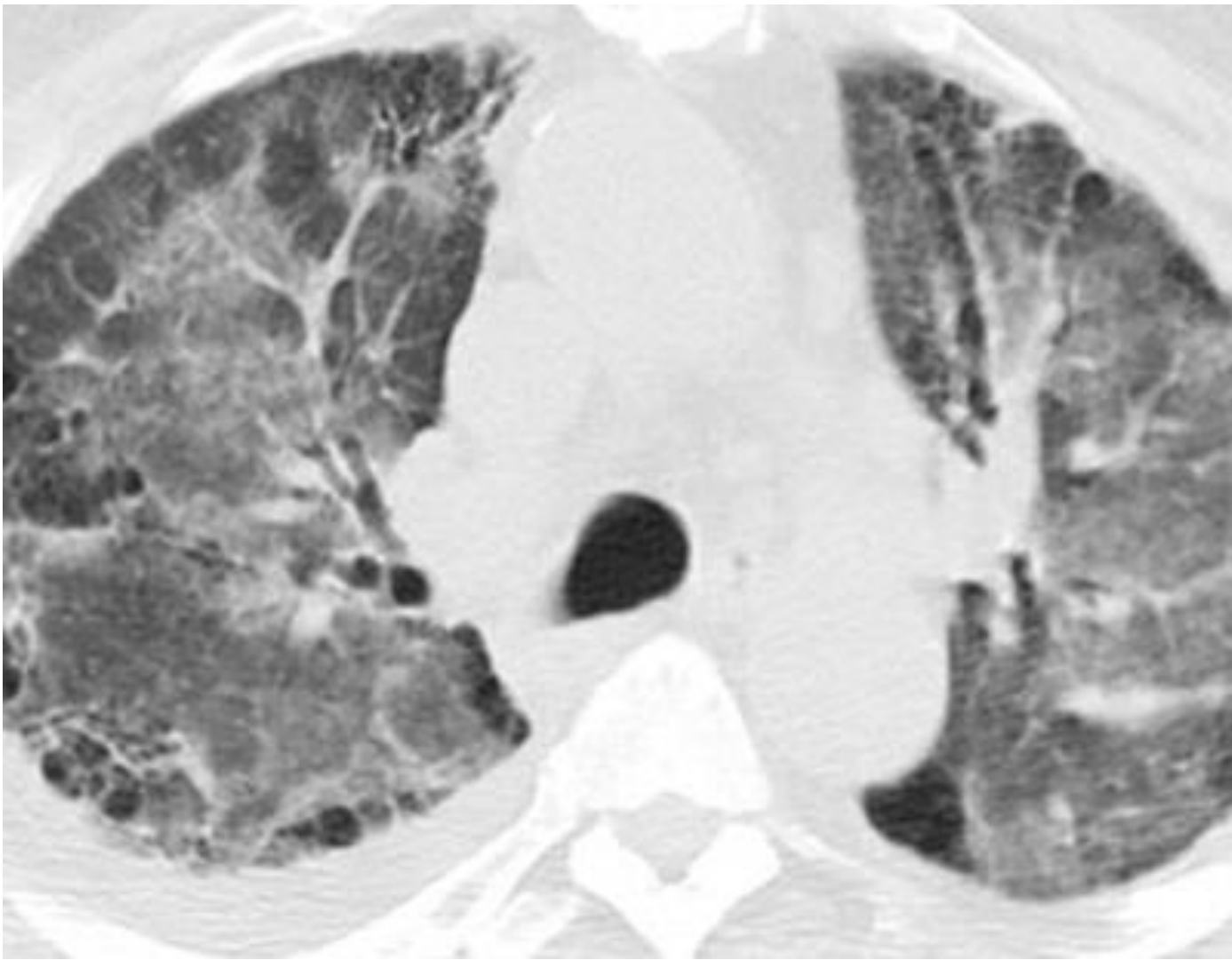
- Fever may last on average > 3 weeks
- Mild liver enzyme abnormalities are common, although severe hepatitis and jaundice are rare
- Rash is present in about 30 % of patients, and ampicillin provocation of rash has been noted
- **Complications** in the normal host: include hepatitis, pneumonitis, and Guillain-Barré syndrome
- Some cases present with **remitting** and **relapsing** fever and malaise for months

Presentation in the immunocompromised host

- Severe disease in any of multiple organs, causing:
 - Retinitis
 - Hepatitis
 - Pneumonitis
 - Gastric and esophageal ulcers and colitis
 - Meningoencephalitis
 - Polyradiculopathy
- Significant association with Guillain-Barré syndrome



Cytomegalovirus
colitis



Cytomegalovirus pneumonitis
in a transplant recipient patient

Presentation in the new born

- Primary infection of pregnant woman → congenital disease in ½ of cases
- Risk is highest early in pregnancy
- Disease in the neonate:
 - Jaundice, petechiae, and visceral involvement
 - Microcephaly, chorioretinitis, and cerebral calcifications
 - Lethargy, seizures and mental retardation
 - Immediate perinatal death

Other clinical consequences

- Perinatal infection: no severe manifestations, but subtle defects in cognitive development and deafness
- Moreover, cytomegalovirus infection...
 - ...may incite an inflammatory response in endothelial cells
 - ...has been associated with a higher incidence of cardiovascular disease and pathology

Diagnosis

- Culture and other tests not useful for diagnosing acute infection in the normal host, as the virus may persist in body fluids for a long time
- The most reliable test: **↑ x4 in virus IgG titer**
- Detection of IgM antibody is also strong evidence for acute infection, although IgM can occasionally be seen in normal hosts during virus reactivation
- Quantitative PCR of viral DNA, in immunocompromised host

Treatment and prevention

- Antivirals almost never required in the normal host
- Corticosteroids may be used for complications
- Ganciclovir, valganciclovir, foscarnet or cidofovir primarily used in the immunocompromised patient
- Rising resistance to ganciclovir and foscarnet, a serious problem in transplant patients and others who may require prolonged or repeated therapy
- A vaccine may become available soon

Key messages

To remember...

- Hantavirus infection and the severe acute respiratory syndrome are rare diseases that occasionally provoke outbreaks of life-threatening conditions
- Influenza is a common disease with great impact on morbidity in the general populations and on mortality in debilitated patients
- Herpes simplex virus is the cause of a generally benign but recurrent oral and genital infection
- Cytomegalovirus generally provokes an asymptomatic infection in the general population but severe diseases in the immunocompromised patients

Further reading

Used references

- Southwick F. Infectious disease. A clinical short course. 3rd Edition. New York: McGraw-Hill, 2014. Chapter 14.
- Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill, 2012. Chapters 179, 182, 186, 187 and 196.

Preparing the exam

- Southwick F. Infectious disease. A clinical short course. 3rd Edition. New York: McGraw-Hill, 2014. Chapter 14.
- These slides.