Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

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Disclosures of Financial Relationships with Relevant Commercial Interests

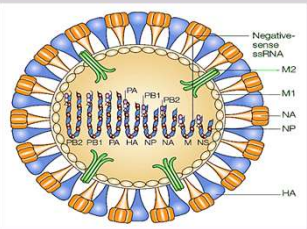
- Antimicrobial Therapy Inc,
- Haleon

What You Need to Know for the Boards

- Minimal virology
- Epidemiology including avian influenza
- Diagnosis
- Complications
- Antivirals
- Vaccines

Influenza Virus

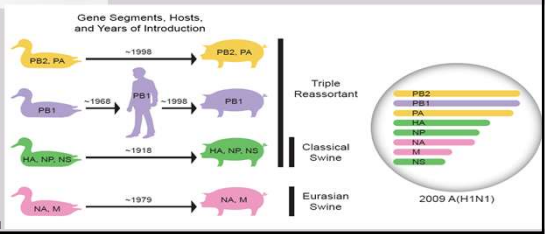
- Orthomyxovirus; 8 gene segments
- Flu A, B and C
- Flu A has 16 HA types, 9 N types
- High error rate leads to point mutations (drift); segment re-assortment leads to shift (pandemics)
- Huge reservoir in wild fowl. Causes disease in birds, poultry, and many mammals



7 Respiratory Viral Infections Including Influenza in Immunocompetent and Immunocompromised Persons
Speaker: Andrew Pavia, MD

Reassortment of genes leads to pandemic shifts

e.g., A/California/7/2009 (H1N1)pdm09, the virus formerly known as swine flu



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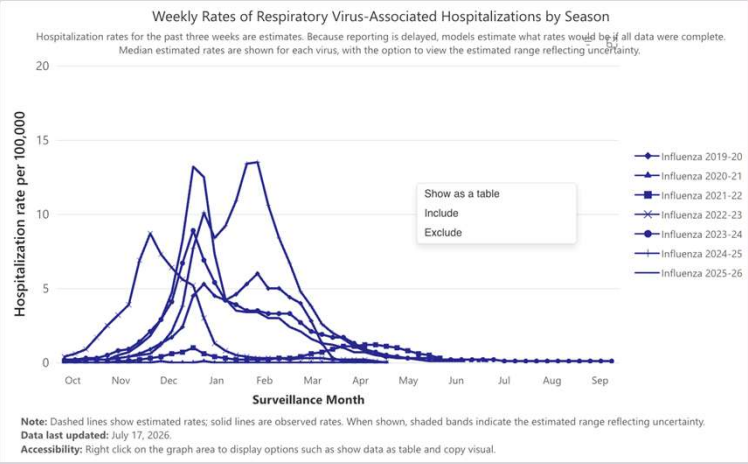

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Groups at Risk for Complications of Influenza

Group	Example/Comment
Children <5 yrs	Highest hospitalization rate children <2 yr
Persons >65 yrs	~~Highest among frail elderly~~
Pregnancy	Highest risk in 3rd trimester **and 2 weeks post partum**
Chronic CVD	~~Hypertension not seen as independent risk~~
Chronic lung	Asthma and/or COPD, cystic fibrosis
Metabolic disorder	Diabetes
Renal, Hematologic	~~Includes sickle cell disease~~
Neurologic	Neuromuscular, neurocognitive, or seizure disorder
Immunosuppression	~~Including HIV, organ transplantation, chemotherapy,~~ hypogamm
Morbid obesity	~~Noted in several studies during H1N1~~
Am. Indian/Alaskan native	May also be increased in other disadvantaged groups

Clinical Findings of Influenza

- Fever, malaise, cough, sore throat, myalgia, chills, eye pain, headache
- Sudden onset is typical
- During an epidemic, fever with cough has high predictive value
- Fever may be absent in the elderly, immunocompromised, very young

Influenza Transmission

- Incubation period: 1-4 days (average: 2 days)
- Shedding:
  - Adults: 1 day before symptoms; 5-7days after illness onset
  - Young children: 1-2 days before illness onset; 10 or more days after symptom onset
  - Immunocompromised or severely immunosuppressed persons: weeks to months
- Large droplets (up to 6 feet) most important.
- Fomite and small droplet (true airborne) likely contribute.
- Standard plus droplet precautions recommended
- "Use caution" for aerosol generating procedures
- Monitor and manage ill health care personnel

https://www.cdc.gov/flu/hcp/infection-control/healthcare-settings.html?CDC_AAref_Val=https://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm

What Makes a "Human Influenza Strain?"

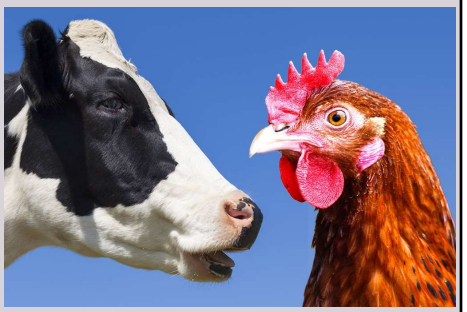
- Use of α2-6-linked receptors. PB2 adaptation
- Despite increasing study, anticipating changes difficult
- Many genes interacting in complex ways determine virulence species specificity and transmissibility (e.g., 1918 H1N1 virus)
- Influenza risk assessment tool (IRAT)
  - https://www.cdc.gov/flu/pandemic-resources/national-strategy/risk-assessment.htm

Influenza A Viruses Infecting Humans

- H1N1*: Emerged in 1918. Re-emerged in 1977
- H2N2: 1956-1977 but replaced by H3N2
- H3N2*: Emerged in 1968 (Hong Kong flu)
- H3N2v*: Assorted swine associated variants
- **H5N1*: Emerged 2003 in Hong Kong. Current strain causing severe outbreak in birds with recent spill over in mammals**
- H7N9: Caused >130 cases of severe disease 2013; >200 in second wave; now rare
- H7N3: Isolated cases in farm workers
- H7N7: H7 viruses associated with conjunctivitis
- H9N2: Sporadic cases associated with poultry
- H10N3: First human case 2021

* Currently causing human disease

H5N1 High Pathogenicity Avian Influenza



HPAI H5N1 Influenza

- Initially identified in goose in Guangdong in 1996
- 18 human cases/6 deaths Hong Kong 1997
- Re-emerged in 2003 with large poultry outbreaks and sporadic human cases – high mortality
- In 2020, reassortment led to emergence of Eurasian clade of HPAI H5N1 Clade 2.3.4.4b
- Large outbreaks among commercial and backyard poultry and wild birds around the world
- ~ 150 million birds culled in US in since 2020

Photo: Mads Claus Rasmussen

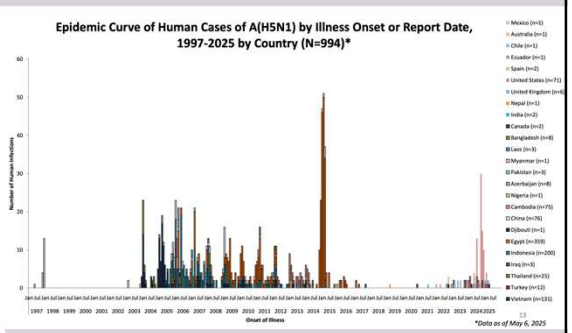
Photo: NBC News

HPAI H5N1 Influenza

- 71 confirmed cases in US, 13 states
- 41 associated with dairy cows
- 24 commercial poultry
- 3 backyard poultry
- 3 unknown exposure

Figure 1. Conjunctivitis with Subconjunctival Hemorrhage in Both Eyes.

Uyeki NEJM 2024



Source CDC

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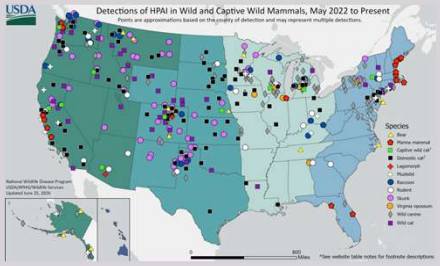
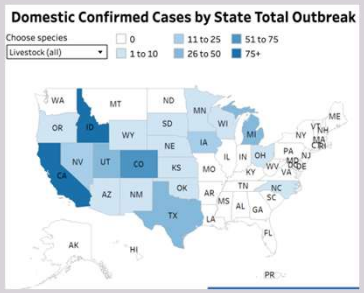
Human and Other Mammalian Cases of H5N1

Other Mammals



Cattle Herds: 1168 cases in 20 states



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https://www.aphis.usda.gov/livestock-poultry-disease/avian/avian-influenza/hpai-detections/mammals

Question #1

An 18-year-old high school student develops chills, fever, cough, myalgia in January 2025. She is prescribed azithromycin, rest and NSAIDS. Fever and cough continue, and she becomes progressively dyspneic and weak. On admission T 39, P 150, RR 24-30, BP 120/50. She has crackles throughout both bases and a gallop. Influenza PCR positive

- WBC =9000/mm3 (60% polys, 30% bands)
- Creatinine 1.9
- BNP and troponin markedly elevated
- CXR shows diffuse bilateral infiltrates and cardiomegaly
- Requires V-A ECMO

Question #1

What is the most likely cause of this influenza complication?

A. Pneumococcal pneumonia
B. Staph aureus pneumonia with purulent pericarditis
C. Influenza cardiomyopathy
D. MIS-C due to recent SARS-CoV-2 infection
E. Viral pericarditis with effusion

Mild Complications of Influenza

Complication	Comment
Otitis media	
Sinusitis	
Parotitis	Newly described
Asthma exacerbation	Antibiotics not indicated
Croup	Young children
Bronchiolitis/Bronchitis	

Severe Cardiopulmonary Complications of Influenza

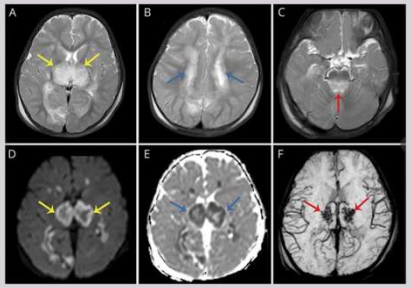
Complication	Comment
Secondary bacterial infection	Strep pneumoniae, GAS, S. aureus. Classically marked worsening after initial improvement. Account for large proportion of pandemic deaths
Exacerbation of underlying illness	COPD, asthma, CHF
Ischemic heart disease	Ecologic association
Viral pneumonia	May be mild or severe hemorrhagic pneumonitis/ARDS
Toxic Shock Syndrome	Staphylococcal TSS most commonly described but GAS also reported
Invasive aspergillosis	Clusters in Belgium and Netherlands. Rare reports worldwide

Non-respiratory Complications of Influenza

Complication	Comment
Neurologic	
Seizures	
Encephalopathy/Encephalitis Acute necrotizing encephalitis	Viral particles and RNA are rarely found. More common in children but higher mortality in adults
Guillain Barre Syndrome	3- to 10-fold more common with infection than estimated association with vaccine
Other	Stroke, ADEM, Reyes Syndrome, cerebellar ataxia, transverse myelitis
Musculoskeletal	
Myositis, Rhabdomyolysis	Can be severe and lead to AKI
Cardiac	
Pericarditis	
Myocarditis	see also Uyeki Ann Intern Med 274:9 Nov 2021

Acute Necrotizing Encephalitis May be Associated with Cytokine Storm and Genetic Predisposition

- No evidence of viral invasion
- Elevated IL-6 and other cytokines in serum and CSF thought to drive pathogenesis
- Strong association with RANBP2 mutations
- No proven therapy; antivirals, pulse steroids and IL-6 inhibitors have been used



Uyeki J Ped Infect Dis Soc 2022; 12:541

Question #2

- A 20-year-old woman is 18 days out from HSCT in January on and engrafted 3 days ago.
- She develops fever, hypoxemia, bilateral lung infiltrates and is intubated.
- A nasal swab is negative by rapid test for influenza.

Question #2

Which of the following is the most appropriate course of action (regardless of other actions you may take)?

A. Do not initiate anti-influenza therapy due to result of rapid test. The timing suggests idiopathic pulmonary syndrome (engraftment)
B. Initiate anti-influenza therapy empirically and send tracheal aspirate or BAL for influenza PCR
C. Send IgG and IgM for influenza
D. Send RSV EIA and initiate empiric IV ribavirin

Diagnosis

Diagnosis of Influenza

- Performance of all tests depends on prevalence of virus in community and specimen quality
- Clinical diagnosis: up to 80% PPV during peak (pre-Covid)
- Rapid influenza detection tests have low-moderate sensitivity 10-70%; reasonably specific
- Positive antigen test in peak season high PPV; negative test should not be used for decisions
- PCR/NAAT recommended by IDSA Guidelines, rapid platforms NAAT expanding. When flu is circulating, test for both SARS-COV-2 and flu
- Serology has no role

Influenza in Transplant Pearls

- Typical flu symptoms less common
- Virus may not be present in nasopharynx in patients with influenza pneumonia – lower tract specimens should also be tested.
- Spread on transplant units can be explosive - High mortality
- Prolonged shedding is common
- Resistance may develop on therapy especially in HSCT patients

Question #3

- A 32-year-old nurse is 34 weeks pregnant during influenza season. She develops influenza symptoms and is seen at an instacare where a rapid test is positive, and she is given azithromycin.
- 72 hours after the onset she presents to the ED with fever, tachypnea, hypoxemia and decreased urine output.
- CXR shows bilateral hazy infiltrates. She is hospitalized.

Which of the following is correct?

A. She should get supportive care only since she has had symptoms for >48 hours
B. Oseltamivir is relatively contraindicated in pregnancy
C. Zanamivir is clearly preferred because of low systemic absorption
D. Baloxavir is the recommended therapy
E. Oseltamivir should be started as soon as possible

ACIP and IDSA Guidelines for Antiviral Use 2025

- Antiviral treatment is recommended for patients with confirmed or suspected influenza as soon as possible:
  - Who are hospitalized regardless of duration of symptoms
  - Have severe, complicated or progressive illness regardless of duration of symptoms
  - Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications
  - Consider for otherwise healthy outpatients within 48 hrs of symptom onset

https://www.cdc.gov/flu/professionals/antivirals/index.htm
Uyeki. IDSA Guidelines Clin Infect Dis 2019;68(6):895

ACIP Guidelines for Antiviral Use 2026

- Recommended medications for outpatients:
  - Oseltamivir, baloxavir, inhaled zanamivir
- Recommended medications for inpatients:
  - Oseltamivir. IV peramivir if unable to get any enteral therapy at all

https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

CDC Antiviral Treatment Recommendations

- Empiric antiviral therapy should be offered to pregnant women and women up to 2 weeks postpartum
- Treatment duration
  - NAIs: 5 days
  - Baloxavir: single dose
- Initiating treatment within 2 days of symptoms results in improved outcomes
  - Substantial reduction in morbidity and mortality in hospitalized patients up to 5 days after sx

https://www.cdc.gov/flu/professionals/antivirals/avrec_ob.htm

Baloxavir

- Cap-dependent polymerase inhibitor
- Non inferior to oseltamivir in two phase 3 studies
- Superior for influenza B in patients with risk factors
- Shorter duration of shedding
- Resistance mutations emerge on treatment in 10-20%

Hayden NEJM 2018; 379:913-923
Ison Lancet Infect Dis 2020:Jun 8;S1473-309
Uehara JID 2019; 221:346

Antiviral Prophylaxis

- Chemoprophylaxis should not replace vaccination
- Oseltamivir, zanamivir, baloxavir 70-90% effective in trials
- **PEP is recommended to control influenza outbreaks in nursing homes**
- Prophylaxis may increase selection of resistant viruses
- PEP can be considered for high-risk persons with unprotected close contact with patient with flu
- Post exposure prophylaxis should not be given after 48 hours from exposure
- Post exposure prophylaxis for otherwise healthy persons is generally discouraged; prompt empiric therapy is preferable

Vaccines

ACIP Recommendations for Influenza Vaccination 2024-25

- Routine influenza vaccination is recommended for all persons aged 6 months and older.
- All vaccines are now trivalent!!! (TIIV = Trivalent inactivated influenza vaccine) H1N1, H3N2, B Victoria
- Enhanced vaccines recommended for those >65
  - High dose inactivated, adjuvanted, recombinant
- Consider HD or adjuvanted for solid organ recipients

https://www.cdc.gov/flu/season/faq-flu-season-2024-2025.htm

Vaccine Pearls (Cont.)

- All influenza vaccines can be given to those with egg allergy.
- For those with anaphylaxis to egg, consultation with allergist no longer recommended.
- Anaphylaxis to flu vaccine is still a contraindication

Egg Allergy

- Persons with a history of egg allergy who have experienced only hives after exposure to egg should receive flu vaccine. Any licensed and recommended flu vaccine (i.e., any form of IIV or RIV) that is otherwise appropriate for the recipient's age and health status may be used.
- Persons who report having had reactions to egg involving symptoms other than hives... or who required epinephrine or another emergency medical intervention, may similarly receive any licensed and recommended flu vaccine (i.e., any form of IIV or RIV) that is otherwise appropriate for the recipient's age and health status. **If a vaccine other than ccIIV4 or RIV4 is used**, the selected vaccine should be administered in an inpatient or outpatient medical setting (including but not necessarily limited to hospitals, clinics, health departments, and physician offices).
- A previous severe allergic reaction to flu vaccine, regardless of the component suspected of being responsible for the reaction, is a contraindication to future receipt of the vaccine.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

CDC https://www.cdc.gov/flu/prevent/egg-allergies.htm

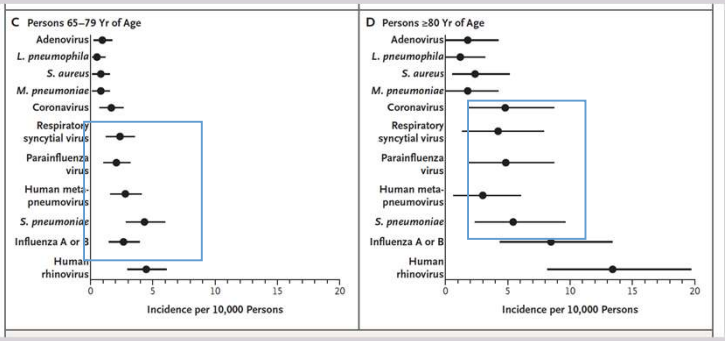
Other Important Respiratory Viruses Adenovirus, RSV, hMPV, Parainfluenza, Coronaviruses, Hantaviruses (and More)

What You May Be Tested On

- Focus on lower respiratory tract disease in compromised hosts, *including* older adults
- RSV, adenoviruses, hMPV are fair game
- Parainfluenza viruses possibly
- Coronaviruses including MERS (possible) and SARS-CoV-2 (separate talk)
- Hantavirus pulmonary syndrome is a popular zebra

Photo: ©Andrew Pavia

Incidence of Pathogens in Older Adults Hospitalized With CAP



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Jain NEJM 2015

Findings which may Suggest Viral vs. Bacterial CAP: Beware the Overlap!

Characteristic	Viral	Bacterial
Onset	Gradual	Sudden
Season	Winter, associated with viral outbreaks	Slightly less seasonal
Host	Older age, more cardiac and pulmonary disease	Any age
Exam	Wheezing	Consolidation
CBC	Leukopenia	Leukocytosis
Procalcitonin	< 0.1	>0.5
CRP	Lower	Higher
CXR (big overlap)	Interstitial, multilobar	Consolidation, effusion

Diagnosis of Respiratory Viruses in Adults

- Generally, shed less virus than children
- Sensitivity depends on test and specimen. Flocked swab and swabbing nose and throat may be better
- Virus may be present in lower respiratory tract (TA/BAL) but not upper in patients with pneumonia
- PCR most sensitive. FDA cleared multiplex platforms available
- Testing is critical in immunocompromised and transplant patients with respiratory symptoms
- Testing makes sense in hospitalized elderly

Question #4

- A 77-year-old man with COPD, history of MI is admitted in January with progressive dyspnea, cough, tachypnea, low grade fever. ROS is positive for rhinitis.
- He has been spending time with young grandchild who has bronchiolitis.
- Rapid Covid test negative. CXR shows bilateral perihilar infiltrates but no consolidation or effusion

Question #4

What should the recommended strategy be, pending more lab results, regarding isolation?

A. Put him in a regular two bedded room with standard precautions
B. Put him in a single room with standard precautions
C. Put him in a single room with contact/droplet precautions
D. Put him in an airborne isolation room with airborne isolation

Question #5

Multiplex PCR of his nasal swab shows RSV

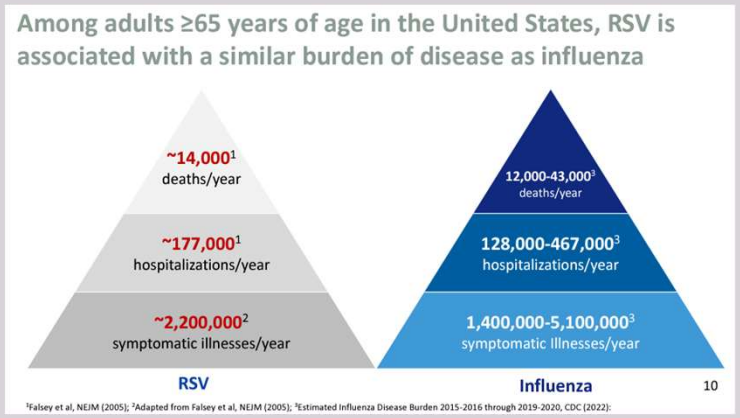
Which of the following is correct?

A. RSV is an incidental finding which might cause URI symptoms
B. RSV likely accounts for infiltrate. He should be immediately started on palivizumab (Synagis) and ribavirin
C. RSV likely accounts for infiltrate. Supportive care is appropriate
D. He has high risk CAP and should be started on vancomycin and piperacillin tazobactam

RSV

- Most common cause of LRTI in children
- Common cause of URI with rhinitis in adults.
- AE-COPD, worsened CHF, asthma exacerbation and pneumonia in adults
- Transmitted by large droplet and contact; Late fall to spring (usually December- April)
- Similar rates of hospitalization to influenza among those> 65

Falsey NEJM 2005, Widmer 2012
Brance Clin Infect Dis 2022



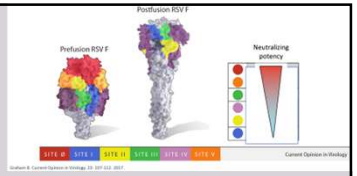
Havers F, ACIP meeting June 23, 2022

Risk Factors for RSV Hospitalization Among Adults

- Age
- CHF
- CAD
- COPD
- Diabetes mellitus
- Immune compromise, especially hematopoietic stem cell transplant and solid organ transplant
- Asthma
- Morbid obesity

Anderson et al, Diagn Microbiol Infect Dis (2016): https://doi.org/10.1016/j.diagmicrobio.2016.02.025
Prasad et al, Clin Infect Dis (2020): https://doi.org/10.1093/cid/ciaa730
Kujawski et al, Plos One (2022): https://doi.org/10.1371/journal.pone.0264890
Branche et al, Clin Infect Dis (2022): https://doi.org/10.1093/cid/ciab595

RSV Prevention!



- Three licensed vaccines for those
  - Protein >80% effective at preventing severe RSV
  - Target pre-fusion F protein
    - GSK adjuvanted single dose
    - Pfizer un-adjuvanted single dose
    - Moderna mRNA single dose
- Pfizer licensed for pregnant women to protect infant ~ 70% effective
- ACIP recommends adults ≥75 or ≥55 with risk factors

RSV

- Long incubation period 2-8 days
- No indications for palivizumab (Synagis) or nirsevimab in adults
- Inhaled ribavirin controversial
  - Limited efficacy, high cost, occupational risk
- Case series suggest benefit aerosolized RBV +/- IVIG in HSCT patient with LRTI; no good data in SOT.
- Oral ribavirin appears equally effective, much less expensive

Question #6

- A 35-year-old man is admitted to the ICU in July with fever, conjunctivitis, respiratory failure, hypotension.
- Symptoms have been present for 48 hours.
- History: He recently completed a 3-day adventure race with fresh water exposure.
- Has parakeet, dogs, cat had kittens recently, owns a hot tub. 2 kids in daycare have URI and conjunctivitis.

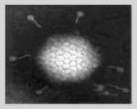
Question #6

2 days later he is in ICU on high levels of support.

What would you suspect?

A. Pneumococcal pneumonia
B. Borrelia hermsii with capillary leak and ARDS
C. Adenovirus
D. Hantavirus pulmonary syndrome
E. MRSA pneumonia
F. Group A streptococcus with TSS

Adenovirus

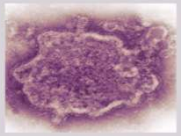


- DS DNA; 7 species, >50 serotypes
- Associated with URI, pharyngitis, conjunctivitis, otitis, pneumonia, myocarditis, hemorrhagic cystitis; hepatitis, disseminated disease in compromised hosts
- Adenovirus species F type 40/41 associated with gastroenteritis; unclear association with pediatric liver failure
- Outbreaks of pneumonia in day care, closed settings, stressed populations e.g., military barracks
- No real seasonality

Adenovirus in Transplant Patients

- More common with Campath (alemtuzumab)
- URI progresses to LRI in about half, with high mortality
- May disseminate and cause severe hepatitis, encephalitis
- May cause hemorrhagic cystitis, tubulointerstitial nephritis
- May lead to loss of graft in SOT patients; HLH
- Diagnosis by PCR of **respiratory secretions, blood**, pathology of organ biopsy
- Cidofovir, Brincidofovir have been used for Rx

Human Metapneumovirus



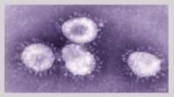
- "Discovered' in the last decades
- Non-segmented, single stranded, negative sense RNA virus: Paramyxoviridae family, Pneumovirinae subfamily
- Causes URI, bronchiolitis, pneumonia similar to RSV
- Winter/Spring in temperate climates
- In younger adults, URI common with sore throat, hoarseness, wheezing, asthma exacerbation, AE-COPD, and CAP
- More severe in elderly, more wheezing; ECF outbreaks
- Mortality among HSC transplant similar to RSV

Falsey J Ped Inf Dis 2008
Walter Inf Dis Clin North America 2017

Parainfluenza Virus

- Paramyxovirus with 4 subtypes 1-4
- Spring and fall seasonality
- Causes URI, bronchiolitis, croup, pneumonia in children. Parainfluenza 3 more severe.
- Causes URI, cough illness and viral pneumonia in adults
- May cause severe disease in transplant patients and all respiratory viruses be associated with COP (formerly known as BOOP)

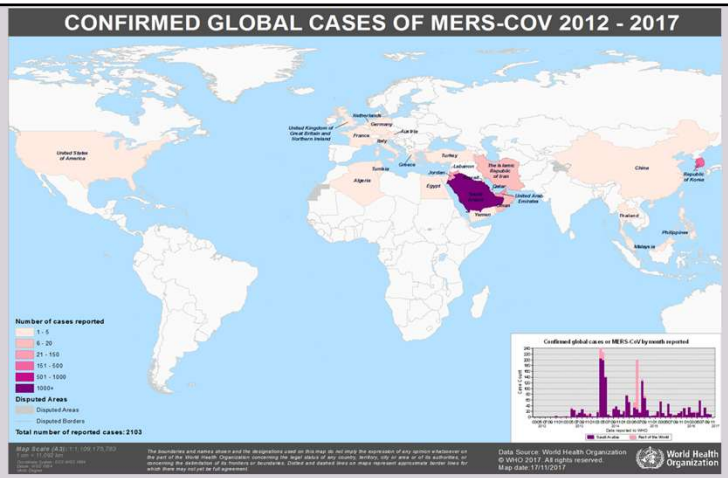
Other Human Coronaviruses



- HuCoV 229e, HuCoV OC43
  - "Older" associated predominantly with URI
- HuCoV HKU1, HuCoV NL63
  - Recently described using molecular techniques. Associated with URI and some pediatric and adult pneumonia
- May be detected on newer multiplex platforms (Luminex, FilmArray). Do not cross react with SARS-CoV-2
- Can cause severe disease in HSCT population

MERS Coronavirus

- Discovered April 2012
- > 600 cases in or with contact with Gulf area, predominantly Saudi Arabia
- Transmission documented in health care settings and families, super spreaders suspected in Korea
- Mortality 56% with small number of asymptomatic
- Closest relative is a bat virus
- Camels play important role



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Question #7

- A 25-year-old man is admitted to the ICU in July with fever, respiratory failure, hypotension.
- 5 days PTA he complained of having the "flu;" fever, malaise, myalgia, mild abdominal pain.
- History: He works as a lineman in northern Arizona. He remembers electrical boxes with rodent infestations.
- Has parakeet, dogs, cat had kittens recently, owns a hot tub. No one in family is ill.

Question #7

- Labs: Hct 52; WBC 6.0 (20% bands, 45% polys, 2+ atypical lymphs), platelets 90K,
- AST 105, PT 18, PTT 25
- CXR: Rapidly progressing bilateral infiltrates leading to white out

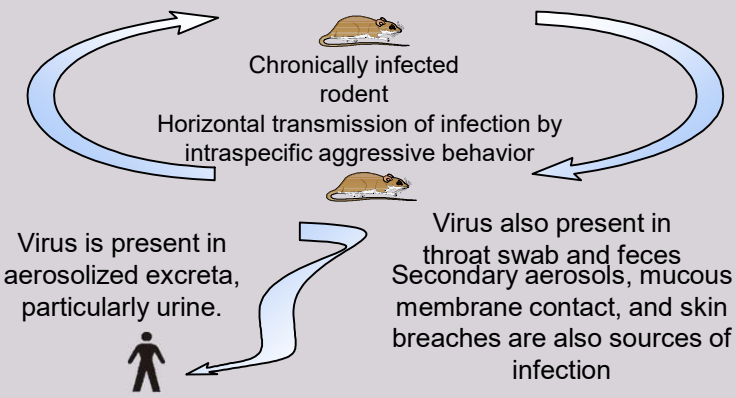
Question #7

Which of the following is the most likely cause of his illness?

A. Adenovirus
B. Influenza
C. Anthrax
D. Coxiella burnetii
E. Sin Nombre virus (Hantavirus Pulmonary Syndrome)

Hantavirus Pulmonary Syndrome (HPS)

- First described in a 1993 outbreak in the 4 Corners
- Outbreak in 2012 Yosemite. Endemic cases of HPS in much of US, Chile, Argentina .
- Caused by specific North American and Latin American hantaviruses – member of Bunyaviridae family.
  - In North America, HPS caused by Sin Nombre virus, Black Creek Canal, New York virus and others
  - Several viruses in Chile and Argentina; Andes virus best known and only new world Hantavirus with documented human to human transmission



Stages of Hantavirus Pulmonary Syndrome (HPS)

- Incubation (4-30 days)
- Febrile phase
  - Fever, myalgia, malaise occasionally N, V, abd pain
- Cardiopulmonary phase
- Diuretic phase
- Convalescent phase

HPS-Cardiopulmonary Phase

- Acute onset of cough and dyspnea
- Presentation and rapid progression of shock and pulmonary edema (4-24h non-productive cough and tachypnea (shortness of breath)
- Hypovolemia due to progressive leakage of high protein fluid from blood to lung interstitium and alveoli, decreased cardiac function

HPS-Cardiopulmonary Phase

- Hypotension and oliguria
- Critical clues:
  - **Thrombocytopenia (98%)**
  - **Hemoconcentration**
  - **Left shift with atypical lymphs**
  - **Elevated PT, abnormal LFTs**

Respiratory Viruses: Take Home

- RSV, hMPV, Parainfluenza viruses are common causes of CAP and exacerbation of underlying cardiopulmonary disease in elderly
- COPD and heart disease are risk factors
- Exposure to children probably a risk factor
- Nosocomial transmission has been documented in hospitals and ECF
- Testing and use of appropriate precautions
- HPS has distinct epidemiologic risks and recognizable lab abnormalities

7 Respiratory Viral Infections Including Influenza in Immunocompetent and Immunocompromised Persons

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