43 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

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7/13/2022

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Disclosures of Financial Relationships with Relevant Commercial Interests

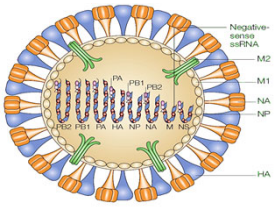
- Commercial Interests: Antimicrobial Therapy Inc, WebMD, Merck

What you need to know for the boards

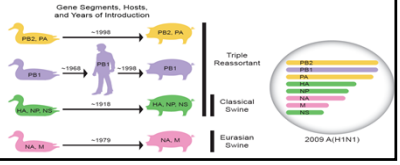
- Minimal virology
- Epidemiology including H7N9
- Diagnosis
- Complications
- Treatment
- Vaccines

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. Cause disease in poultry, and many mammals
- Mutations in neuraminidase and polymerase lead to resistance to NAIs and polymerase inhibitors respectively



Reassortment of genes leads to pandemic shifts
e.g. A/California/7/2009 (H1N1)pdm09, the virus formerly known as swine flu



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

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Groups at Risk for Complications of Influenza

Group	Example/Comment
Children <5 yrs	Highest hospitalization rate children <1 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	Recently added

PREVIEW QUESTION

Question #1

- A 45-year-old international agricultural researcher presents in June in the US with fever, cough, diarrhea, myalgia, sore throat, and dyspnea. He is hypotensive and hypoxemic.
- CBC shows mild leukopenia, chemistry panel and LFT's are normal.
- Three days prior to the onset of his illness he was inspecting poultry operations Jiangsu Province, China.

PREVIEW QUESTION

Question #1 Continued

Assuming the he acquired his severe respiratory illness from the poultry he was inspecting, the most likely diagnosis would be:

A. H1N1 influenza
B. H3N2 influenza
C. Leptospirosis
D. H7N9 influenza
E. Blastomycosis

What makes a human influenza strain

- 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

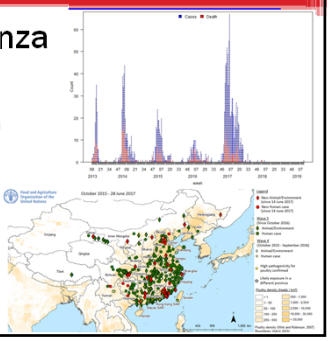
Influenza A viruses infecting humans

- 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 but not humans
- H7N9*: Caused >130 cases of severe disease 2013; >200 in second wave; ongoing
- 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

H7N9 Avian influenza

- > 1500 cases in 5 years
- 22% case fatality
- Avian to human transmission
- Family clusters with human to human documented
- Some oseltamivir resistance
- Exported cases
  - US x 2, Canada, Hong Kong, Taipei
- Largely disappeared after avian vaccine



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Influenza Transmission

- Incubation period: 1-4 days (average: 2 days)
- Serial interval: estimated 3-4 days among household contacts
- 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) may contribute.
- Standard plus droplet precautions recommended
- "Use caution" for aerosol generating procedures
- Monitor and manage ill health care personnel

Question #2

An 18 year old high school student develops chills, fever, cough, myalgia in January. 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 #2 Continued

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

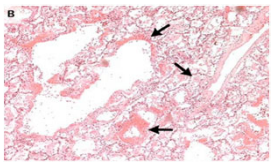
Mild complications of influenza

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

Severe 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

Influenza associated hemorrhagic pneumonitis



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Non-respiratory complications of influenza

Complication	Comment
Neurologic	
Seizures	
Encephalopathy/Necrotizing encephalitis	Viral particles and RNA are rarely found. More common in children but higher mortality in adults
Guillian Barre Syndrome	Up to 10 fold more common with infection than estimated association with vaccine
Musculoskeletal	
Myositis, Rhabdomyolysis	Can be severe and lead to AKI
Cardiac	
Pericarditis	
Myocarditis	
Reyes Syndrome	Acute onset vomiting, altered mental status, seizures. Labs include elevated LFTs, ammonia. Only half of cases associated with ASA before warnings

Question #3

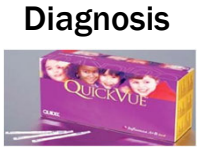
- A 20 year old woman is 18 days out from HSCT in January on and engrafted 3 days ago.
- She develops fever, hypoxemia, bilateral lung infiltrates and is intubated.
- A nasal swab is negative by rapid test for influenza.

Question #3 Continued

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
- Rapid influenza detection tests have low-moderate sensitivity 10-70% (less for H1N1); 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 expanding. When flu is circulating, test for both SARS-COV-2 and flu
- Serology useless for clinical diagnosis

Influenza in transplant pearls

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

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Question #4

- 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.

Question #4 continued

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. Oseltamivir should be started as soon as possible

ACIP and IDSA Guidelines for Antiviral Use 2022

- Antiviral treatment is recommended for patients with confirmed or suspected influenza as soon as possible for:
  - 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

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

ACIP Guidelines for Antiviral Use 2022 (con't.)

- Recommended medications for outpatients:
  - Oseltamivir, baloxavir, inhaled zanamivir and IV peramivir
- Recommended medications for inpatients:
  - Oseltamivir

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
- Pregnancy should not be considered a contraindication to therapy.
- 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

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%
- ? Testable

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

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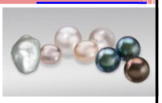
Antiviral Prophylaxis

- Chemoprophylaxis should not replace vaccination
- Oseltamivir, zanamivir, baloxavir 70-90% effective in trials
- Prophylaxis may increase selection of resistant viruses
- PEP is recommended to control influenza outbreaks in nursing homes
- 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

Influenza antiviral pearls



- Antivirals not effective after 48 hours in outpatients with uncomplicated flu but show benefit out to 5 daysin hospitalized patients
- Double dose oseltamivir not more effective
- Resistance to oseltamivir occurs most often through a specific point mutation H275Y in H1N1 viruses (functionally same as H274Y in N2).

Vaccines

ACIP Recommendations for Influenza vaccination 2021-2022

- Routine influenza vaccination is recommended for all persons aged 6 months and older.
- "During the COVID-19 pandemic, reducing the overall burden of respiratory illnesses is important to protect vulnerable populations at risk for severe illness, the healthcare system, and other critical infrastructure."
- All vacines now quadrivalent (QIIV = Quadrivalent inactivated influenza vaccine) H1N1, H3N2, B Yamagata, B Victoria

Vaccine pearls

- Efficacy varies by year and group
- Generally 50-70%; lower in elderly, children < 2, renal disease, immunosuppressive therapy and transplant pts.
- In HIV, response related to CD4 count
- Major mismatch occurs at least every 10 years
- Egg adaptation may lower efficacy

Vaccine pearls (con't.)

- Enhanced vaccines recommended for those >65
  - High dose inactivated, adjuvanted, recombinant
- 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

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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.

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

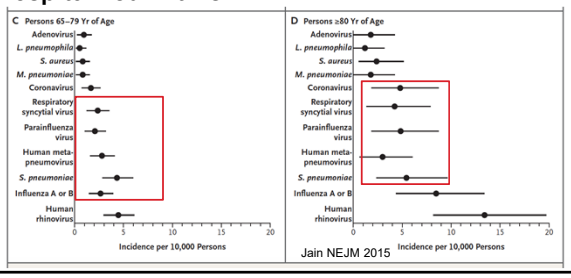
Other important respiratory viruses Adenovirus, RSV, hMPV, parainfluenza, coronaviruses, hantaviruses (and more)

Photograph by Adam Clark

What you may be tested on

- Focus on lower respiratory tract disease in compromised hosts, *including* the elderly
- RSV, adenoviruses, hMPV are fair game
- Parainfluenza viruses possibly
- Coronaviruses including MERS (possible) and SARS-1 (unlikely) possibly SARS-CoV-2
- Hantavirus pulmonary syndrome is a popular zebra

Incidence of pathogens in older adults hospitalized with CAP



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	Consolidated, 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
- Consider testing in hospitalized elderly

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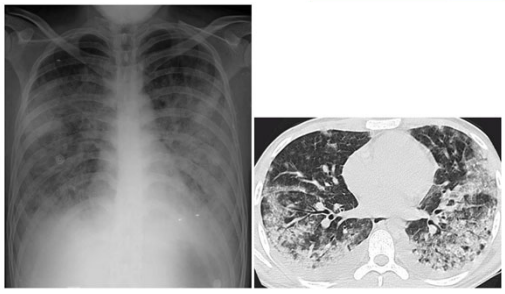
Respiratory Viruses in HSC Transplant Patients

Virus	Mortality for pneumonia	Treatment	Comment
RSV	7-33%	IVIG, ribavirin	LRI associated with severe outcomes
Influenza	25-28%	Oseltamivir, zanamivir, peramivir	Antiviral resistance may develop
Parainfluenza	35-37%	IVIG?	
Adenovirus	30-50%	Cidofovir	May disseminate
hMPV	33-40%	IVIG?	27-41% progress from URI to LRI
Coronavirus (non-SARS)	?	?	Progression to LRI less common
Rhinovirus	<5	?	Severity unclear

Falsey, Walsh. Clin Microbiol Rev 2000;13: 371
Nichols. Blood 2001;98:573
Englund. Ann Intern Med 2006;144:344
Reynaud. Curr Opinion Infect Dis 2011:333
Boeckh. Br J Haematol. 2008; 143: 455
Larosa. Clin Infect Dis 2001;32:871
Ison. Clin Infect Dis 2003;36:1139

Case

- A 20 year old soldier undergoing advanced infantry training presents in March with several days of fever, cough, chest pain, tachypnea, hypoxia and conjunctivitis with this CXR.
- No travel, hiking, animal exposures
- WBC 3.0, platelets 160, CRP 2.5, AST 75



Korean J Radiol 17(6), Nov/Dec 2016

Question #5

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

Question #5

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

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D. Hantavirus pulmonary syndrome
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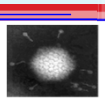
Adenovirus



- DS DNA; 7 species, >50 serotypes
- Associated with URI, pharyngitis, pneumonia, conjunctivitis, hemorrhagic cystitis; hepatitis, disseminated disease in compromised hosts
- Adenovirus 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

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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

Question #7

- A 75 yo 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 #7 Continued

The recommended strategy, pending more lab results, regarding isolation should be:

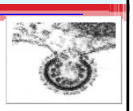
A. Put him in a regular two bedded room with standard precautions
B. Put him in a single room with standard precautions
C. Put him in a single room with contact/droplet precautions
D. Put him in an airborne isolation room with airborne isolation

Question #8

- 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 elderly and immunocompromised
- Transmitted by large droplet and contact; Late fall to spring (usually December- April)
- As common as influenza among hospitalized persons > 65

Falsey NEJM 2005, Widmer 2012

RSV

- Long incubation period 2-8 days
- Diagnosis by antigen detection, PCR
- No indications for palivizumab (Synagis)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

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Human Metapneumovirus

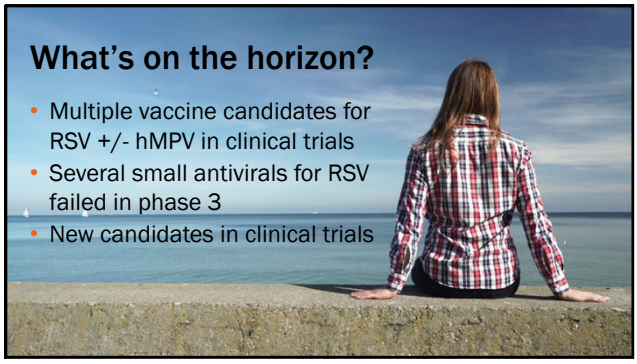
- "Discovered' in the last decades
- Nonsegmented, single stranded, negative sense RNA virus: Paramyxoviridae family, Pneumovirinae subfamily
- Causes URI, bronchiolitis, pneumonia similar to RSV
- Winter/Spring in temperate climates
- In younger adults, URI common with sore throat, hoarseness, wheezing, 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

RSV, hMPV in older adults

- RSV, hMPV, Parainfluenza viruses are common as cause of CAP 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 may be important

What's on the horizon?

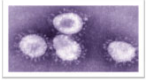


- Multiple vaccine candidates for RSV +/- hMPV in clinical trials
- Several small antivirals for RSV failed in phase 3
- New candidates in clinical trials

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 but to date, 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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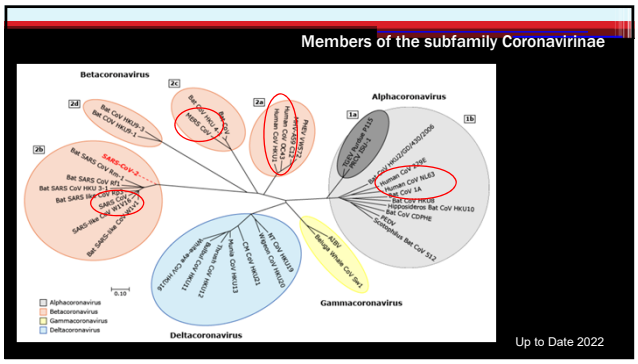
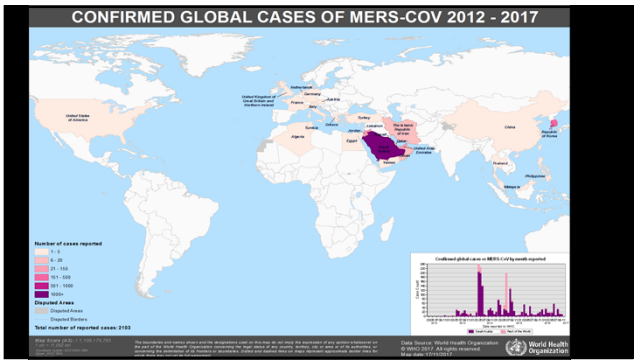




Question #9

- A 35 yo 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 abd pain.
- History: Recently camped in cabins at Yosemite National Park which has had rodent infestations issues.
- Has parakeet, dogs, cat had kittens recently, owns a hot tub. 2 kids in daycare have URI.

Question #9 (con't.)

- 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 #9 (con't)

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

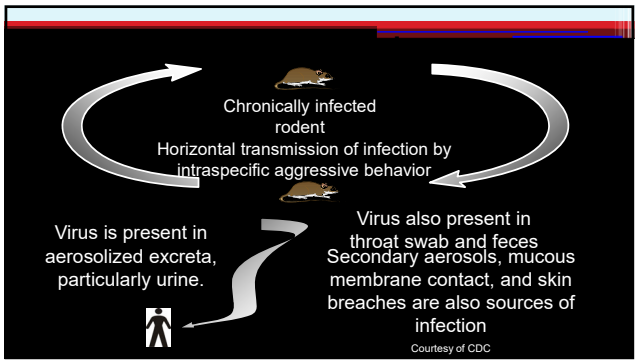
A. Adenovirus
B. Influenza
C. Anthrax
D. Coxiella burnetii
E. Sin Nombre virus (Hantavirus Pulmonary Syndrome)

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.
  - Previously unrecognized viruses cause HPS, Sin Nombre virus, Black Creek Canal, New York virus
  - Prior to the HPS outbreak, the only known hantaviruses were those that caused HFRS

43 - Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients

Speaker: Andrew T. Pavia, MD



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 an 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

Good Luck on the Exam!

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