World Killer: Influenza **Twitter/Instagram: @emboardbombs**

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Objectives: Briefly review the epidemiology and virology of the influenza virus, discuss clinical presentation, diagnosis, treatment of influenza in the outpatient and inpatient setting, discuss the complications.

Epidemiology

Perhaps no greater virus exists in the history of humanity than influenza.
From the Italian language "Influence", meaning the cause of the illness was influenced by astrology.
Whatever the name, its been around as far as medicine itself. Hippocrates described it over 2,000 years ago. It is responsible for many epidemics, most notably the killing of millions of Native Americans upon the arrival of the Europeans, as well as the infamous Spanish 1918 flu epidemic, which is regarded as the worst pandemic in human history, even worse than the Black Death.

During the Spanish flu epidemic, **it is roughly estimated that *at least* 50 million people died**. It is said to have killed nearly as many people as the Black Death (which we do not have records of). The craziest part of all this is that WW1 ended in November 1918 and is regarded as one of the worst conflicts in human history with an estimated 20 million deaths over 4 years. The influenza A virus killed over twice that amount in less than 4 months. Imagine living in a time when approximately *70 million* people died… within 5 years.

Influenza outbreaks:

-Rate among general public: 10-20% attack rate (up to 50% in pandemics).
-An average of 500,000 die worldwide each year due to influenza-associated illness.

Influenza A or B are responsible for the usual outbreaks that occur annually.
Who is most at risk of dying from the flu?

> Adults >65 or children <4, residents of nursing homes/chronic care facilities, pregnant women, anyone with comorbid illnesses (common sense stuff like lung and heart disease, diabetes, liver and kidney disease, etc), even obese individuals.

Incubation period after exposure: ~1-4 days. It's a quick turnaround and patients become symptomatic in about 1-2 days.

Clinical Presentation

- **Abrupt** onset of headaches, myalgias, malaise, and **fever**. On board exams, for a patient to have influenza, they *must* have a fever. If not, it's not influenza.
- In patients >60, fever (LR 3.8), malaise (LR 2.6), or chills (LR 2.6) are the strongest indicators.
- The triad of fever, cough, and acute onset (LR 5.4). In contrast, sneezing is less likely to be associated with influenza.
- In summary, fever and chills, cough, and nasal congestion all put together add up to a diagnosis of about 80-90% which is pretty good. Also, in the board question it is usually mentioned that it is during a **winter month**.

Diagnosis

- Clinical as noted above. Laboratory studies are NOT helpful and in low risk patients you should not get them unless suspicious of secondary infection.
- **Rapid Antigen test** ("Flu swab"): <30 minute results. Very specific, but *poorly sensitive* (98% spec, 55% sens). If positive, the patient has the flu, but if negative than they still very well could.
- **Molecular assay**: RT-PCR. The most sensitive and specific test for influenza. It takes several hours to perform and is not cheap. It also differentiates the type of influenza strains present.

Who should you test?

- In general, any undifferentiated "sick-looking" patient with upper respiratory symptomatology and is being admitted.
- All immunocompromised patients, those pregnant, high-risk children <10 with acute febrile illness

Supportive management

- Hydration along with Tylenol alternating with Ibuprofen every 4 hours is the best regiment for influenza. This is not really high yield testable stuff (more like common sense). There is some hesitation in prescribing nearly around the clock ibuprofen in higher risk patients, but this should be weighed case by case.

Pharmacologic treatment:

-Zanamivir, Oseltamivir (Tamiflu), Peramivir: all neuraminidase inhibitors. They block viral exit from infected cells. All are active against both A and B.

Benefits: shorten duration of flu-like illness to 1-2 days in *most* patients. *For maximum benefit, the drug must be initiated within 48 hours of symptom onset.* There have been mixed results on whether or not these drugs reduce hospitalizations, flu-related mortality, or complications. Right now, many say that they do *not*.
Adverse effects: severe nausea and vomiting (more than the flu ironically).
Who gets it: any age really. CDC and APA are fine with birth through adulthood. FDA states >2 weeks old.

-Amantadine and Rimantadine: adamantanes- only active against influenza A. Due to increased resistance found in isolated strains, these should not be used unless special circumstances and in consultation with critical care specialists (i.e. patient is being admitted and extremely sick).

Complications

THIS is where a lot of test questions come from. Who gets even *sicker* from influenza?

-The elderly are most commonly affected and tested on boards. Also, young children, pregnant patients, and those with comorbidities (especially respiratory ones).

Secondary infections are marked by another pathogen (e.g. bacterial) establishing an infection after the body's immune system has become weakened after fighting the flu.

Pneumonia: the most common cause of pneumonia overall in the elderly is influenza. The most common cause of pneumonia post-influenza is *S. aureus*. This is a *critical*, commonly tested fact on tests that you must remember.

Classic vignette: grandfather picks up sick children from school and 1-2 days later grandfather gets a high fever and myalgias. Initially he feels better but 4-5 days later now has a worsening cough with sputum production.

What is the most likely causative pathogen of the patient's current presentation? **S. aureus** (patient was ill, recovered, then relapsed).
What is the next step in management? **Chest x-ray**
What is the likely disposition for this patient? **Admission.** Post-influenza complications have a high mortality rate, especially in the elderly.

Meningitis/Encephalitis: nothing too special here, but there is always a risk of viral or bacterial (less common) infection in the CNS. If Encephalitis, HSV is the most common in elderly after influenza.
These patients will obviously need admission to the hospital and often require intensive management.

Bonus material- (For those who want to understand the microbiology behind the clinical presentation)

Virology

Influenza A virus: structure and classification is based on the hemagglutinins and neuraminidases on the surface. The influenza family has a segmented, RNA genome.

Hemagglutinin: surface glycoprotein that binds to respiratory epithelial cells and allows viral entry.
Neuraminidase: allows viral liberation with release of new viral particles.

The ability of the virus to change these surface receptors due to accumulation of genetic mutations is called **antigenic drift**. Each time they are changed means that our antibodies cannot bind directly to them and therefore we do not recognize the infection (this is why we can get the flu repeatedly each year and never be immune for life).

Due to its segmented genome (it is not linear and connected like our DNA), the virus has a remarkable ability to basically mix up its DNA order, much like a card dealer shuffling cards. This practice of *reassortment* is defined as **antigenic shift**. It only occurs when 2 or more influenza strains invade a host cell at the same time. They combine to form a brand new virus that has strong potential to perform a pandemic.

How to tell the difference between drift and shift? **"A new influenza strain? Oh Shift!"** Antigenic shift is more serious.

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