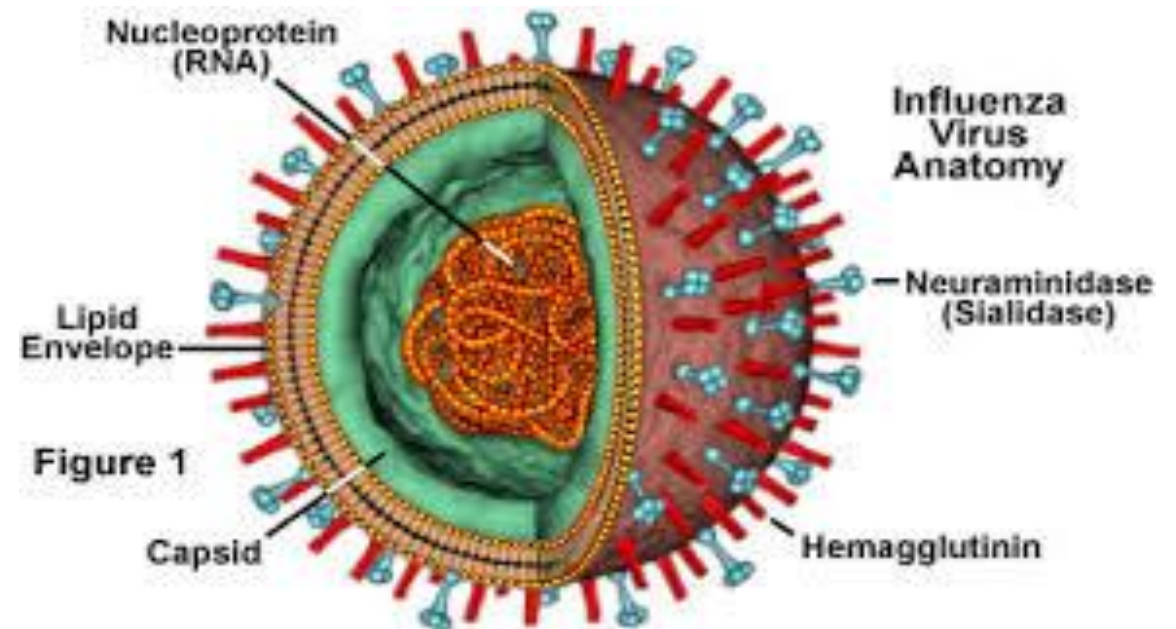


extra-pulmonary complications of influenza infection

Dr.Elmira Mahmoudi



INTRODUCTION

- Severe influenza infection represents a leading cause of global morbidity and mortality. Although influenza is primarily considered a viral infection that results in pathology limited to the respiratory system, clinical reports suggest that influenza infection is frequently associated with a number of clinical syndromes that involve organ systems outside the respiratory tract
- extra-pulmonary manifestations of influenza are likely the result of either unique viral pathogenesis (eg, avian A[H5N1]) or host factors (age, comorbidities, genetic predisposition), or both
- . Most extra-pulmonary complications are associated with the acute phase of the infection and often manifest as the presenting symptoms. Others, particularly the post-infectious central nervous system (CNS) syndromes (eg, Guillain-Barre syndrome [GBS]) and exacerbations of underlying conditions (eg, ischemic heart disease, cerebrovascular disease) may follow infection by weeks to months
- Multiple influenza-associated extra-pulmonary complications can also occur simultaneously in a single patient

Neurologic

Headaches
Dizziness
Encephalopathy
Guillain-Barré
Ageusia
Myalgia
Anosmia
Stroke



Renal

Acute kidney injury
Proteinuria
Hematuria



Hepatic

Elevated aminotransferases
Elevated bilirubin



Gastrointestinal

Diarrhea
Nausea/vomiting
Abdominal pain
Anorexia



Thromboembolism

Deep vein thrombosis
Pulmonary embolism
Catheter-related thrombosis



Cardiac

Takotsubo cardiomyopathy
Myocardial injury/myocarditis
Cardiac arrhythmias
Cardiogenic shock
Myocardial ischemia
Acute cor pulmonale



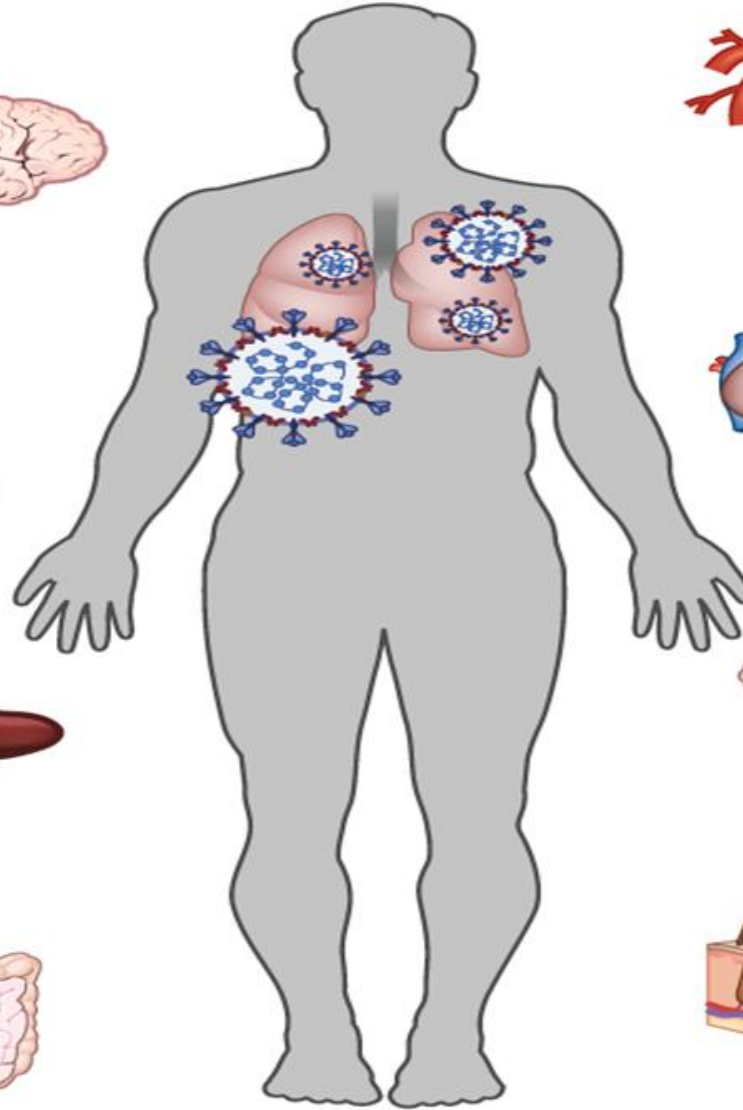
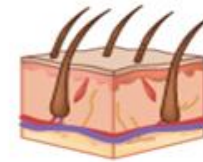
Endocrine

Hyperglycemia
Diabetic ketoacidosis



Dermatological

Petechiae
Livedo reticularis
Erythematous rash
Urticaria
Vesicles
Pernio-like lesions

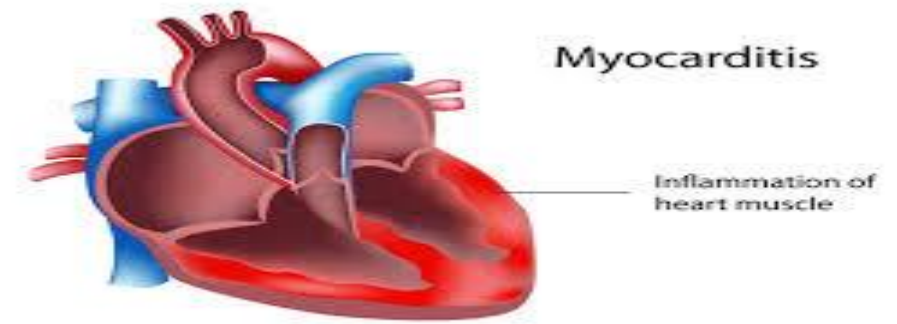


Cardiovascular complications of influenza

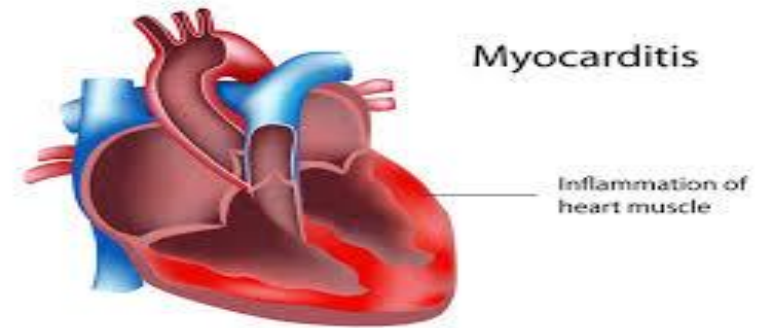
- cardiovascular complications of influenza infection, including exacerbation of heart failure, acute ischemic heart disease, and less often acute myocarditis, are important contributors to morbidity and mortality during influenza infection
- **Myocarditis**
- **Ischemic heart disease**
- **Stroke**



Myocarditis



- Clinically diagnosed myocarditis, based on a combination of symptoms, elevated cardiac enzymes, and echocardiographic finding.
- histopathologic findings, including cellular infiltration and myocyte necrosis
- The severity of influenza-associated myocarditis spans a wide spectrum ranging from asymptomatic to severe disease
- The clinical course of influenza-associated myocarditis is variable, with the majority of patients experiencing an acute onset of symptoms related to cardiac dysfunction, including chest pain, dyspnea, syncope, hypotension, and arrhythmia, between days 4 and 7 following the initial symptoms of viral infection



- cardiac-specific complications have been described in the setting of influenza-associated myocarditis including heart failure, arrhythmias, pericardial effusion, and cardiac tamponade. Congestive heart failure, as diagnosed by regional or global hypokinesis on echo/MRI, is the most common complication
- Other reported complications include :Pericardial effusions, tamponade, life-threatening ventricular arrhythmias, myocardial infarction, recurrent myocarditis , Heart failure independent of myocarditis(right ventricular dysfunction is more common than left ventricular dysfunction), acute respiratory distress syndrome (ARDS)

Ischemic heart disease

- Influenza-associated IHD is posited to be driven by inflammation which is known to have a critical role in the development of acute coronary syndrome. In apolipoprotein E-deficient mice, an animal model of atherosclerosis, animals that were infected with influenza A virus developed subendothelial and smooth muscle inflammatory infiltration with overlying platelets and fibrin strands in atherosclerotic plaques. Additionally, the systemic pro-inflammatory response triggered by influenza infection is accompanied by significant pro-coagulant effects which may also play a role.



Stroke

- Similar to ischemic cardiac complications, the risk of ischemic cerebral vascular accidents (CVA), or strokes, appears to be significantly increased in the days after a respiratory tract infection



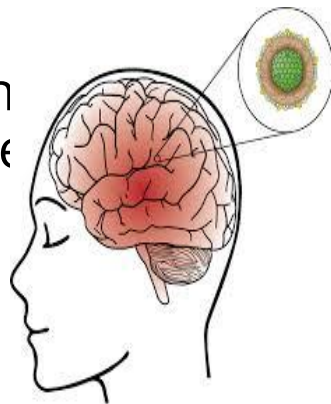
Neurologic complications of influenza

- Influenza infection can lead to a variety of neurologic complications including a number of specific clinical entities grouped together as influenza-associated encephalitis or encephalopathy (IAE), as well as a separate syndrome known as post-influenza encephalitis, GBS, Reye's syndrome, and Parkinsonian symptoms.
- **Influenza-associated encephalitis/encephalopathy**
- **Guillain-Barre syndrome**
- **Other neurologic complications of influenza infection**



Influenza-associated encephalitis/encephalopathy

- Influenza-associated encephalopathy or encephalitis (IAE) is a rapidly progressive encephalopathy primarily characterized by an impaired level of consciousness developing within a few days of influenza infection.
- A number of distinct clinical syndromes have been described, category of IAE including acute necrotizing encephalopathy (ANE), acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), and mild encephalitis/encephalopathy with reversible splenial lesion (MERS).
- The pathogenesis of influenza-associated encephalopathy and encephalitis in adults remains undefined. Demonstration of viral RNA, as detected by rRT-PCR, in brain tissue and CSF suggests direct viral invasion of the CNS .Patients with IAE more frequently experience concurrent hepatic and renal function dysfunction, which suggest a component of metabolic encephalopathy coexisting with severe influenza illness rather than as a direct effect of the virus itself



Guillain-Barre syndrome

- Guillain-Barre syndrome is an acute immune-mediated polyneuropathy characterized by progressive ascending symmetric muscle weakness and accompanied by absent deep tendon reflexes. Most cases of GBS are thought to represent an autoimmune response triggered by an infectious agent with onset of symptoms within 2-6 weeks of the initial infection, most commonly with *Campylobacter jejuni*, *Mycoplasma pneumoniae*, or Epstein-Barr virus. However, 60%-70% of cases of GBS in Western countries do not have a clear etiology identified, although influenza has been proposed as an additional causative agent
- In contrast to other infectious agents, the majority of patients with influenza-associated GBS developed neurologic symptoms within 1 week of the onset of influenza-like illness.





- Closely related to GBS are the neuro-inflammatory demyelinating diseases, acute disseminated encephalomyelitis (ADEM) which affects both the brain and spine and transverse myelitis which affects the spine. Both conditions can occur as post-infectious complications and influenza have been implicated as an etiologic agent.
- presented with focal myasthenia and paresthesia, areflexia or hypotonia, urinary retention.

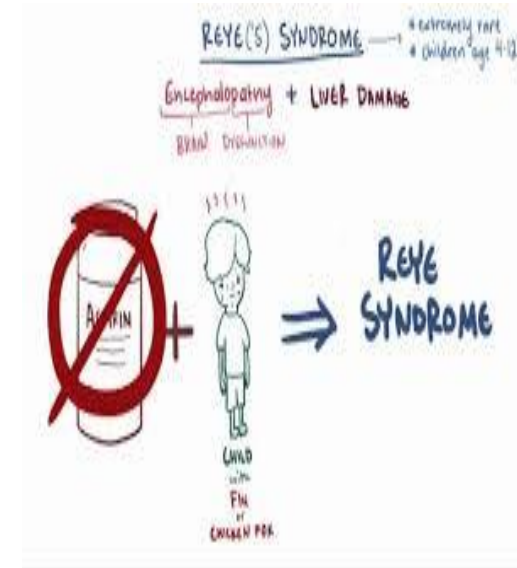
Other neurologic complications of influenza infection

- Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness with nighttime disturbance and can be associated with cataplexy, the sudden loss of muscle tone triggered by strong emotions. It is caused by loss of neurons in the hypothalamus that secrete hypocretin, neuropeptides involved in regulation of arousal and wakefulness. By week 4 following infection, viral antigens could be detected in the lateral hypothalamus along with loss of up to half of the hypocretin-secreting neurons in some brains, suggesting direct viral invasion as a potential mechanism. However, the relationship between influenza infection and the development of narcolepsy in humans remains unclear.



Other neurologic complications of influenza infection

- Reye's syndrome, a rapidly progressive disease characterized by encephalopathy and fatty infiltration of the liver, has been associated with viral infections including influenza treated with acetylsalicylic acid. Although this was predominantly seen in children, adult cases were reported in the 1970s and 1980s. Since the recognition of the role of acetylsalicylic acid in Reye's syndrome, there has been a steep decline in the incidence of reported cases due to the avoidance of aspirin in the treatment of viral infections.
- Encephalitis lethargica (EL) is a neuropsychiatric disorder characterized by sleep disturbances, lethargy and symptoms of basal ganglia dysfunction, or post-encephalitic Parkinsonism, which includes movement disturbances, abnormal gait, increased muscle tone, and tremor. The relationship between encephalitis lethargica, Parkinson disease, and influenza infection remains unclear.



Musculoskeletal complications of influenza

- While myalgias are a common complaint among individuals with many viral infections, the development of rhabdomyolysis represents a less common but more serious complication. In cases of virus-associated rhabdomyolysis, influenza is identified as the most common etiology.
- As myalgias are a common symptom in viral illness, the diagnosis of rhabdomyolysis relies on evidence of muscle necrosis
- Rhabdomyolysis can lead to renal failure by tubular obstruction from excess myoglobin, direct tubular injury, or vasoconstriction of renal blood vessels.
- Early recognition of this influenza-associated complication is necessary to institute aggressive therapy for myositis-related complications including rhabdomyolysis and/or compartment syndrome



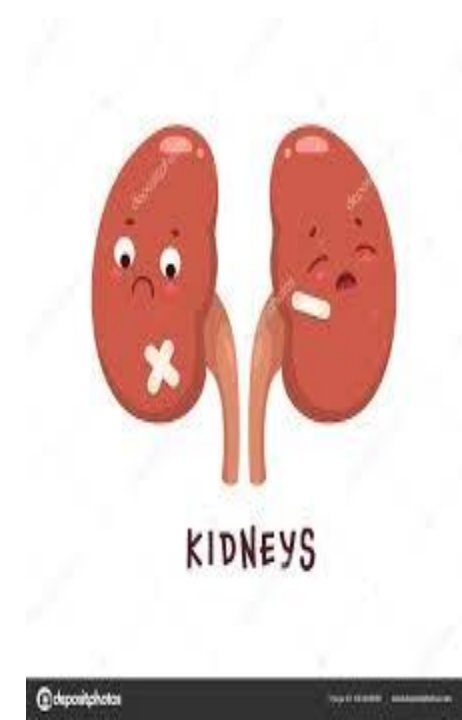
Ocular manifestations of influenza infection

- Influenza-associated ocular disease can result from direct conjunctival invasion by influenza virus and presents most commonly as a conjunctivitis although retinopathy, uveal effusion syndrome, and optic neuritis have also been reported.
- Both the uveal effusion syndrome and the optic neuritis responded to treatment with corticosteroids.
- oseltamivir may have efficacy against influenza-associated conjunctivitis.



Renal complications of influenza

- Influenza infection can also affect renal function through a number of complications including acute kidney injury (AKI), acute glomerulonephritis, minimal change disease, and acute tubulointerstitial nephritis (ATN).
- Risk factors for the development of AKI include obesity, presence of chronic kidney disease prior to illness, older age, and increased severity of illness at admission as determined by various scoring systems including the Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA).
- The underlying pathogenic mechanism of renal injury in influenza infection is likely multifactorial. Aside from rhabdomyolysis-mediated kidney injury, possible mechanisms include decreased renal perfusion secondary to hypovolemia or the vasodilatory state of sepsis frequently associated with severe influenza infection, potentially leading to an acute tubular necrosis (ATN).
- Direct viral injury to the kidneys is another postulated mechanism of disease, but there is limited evidence to support this.



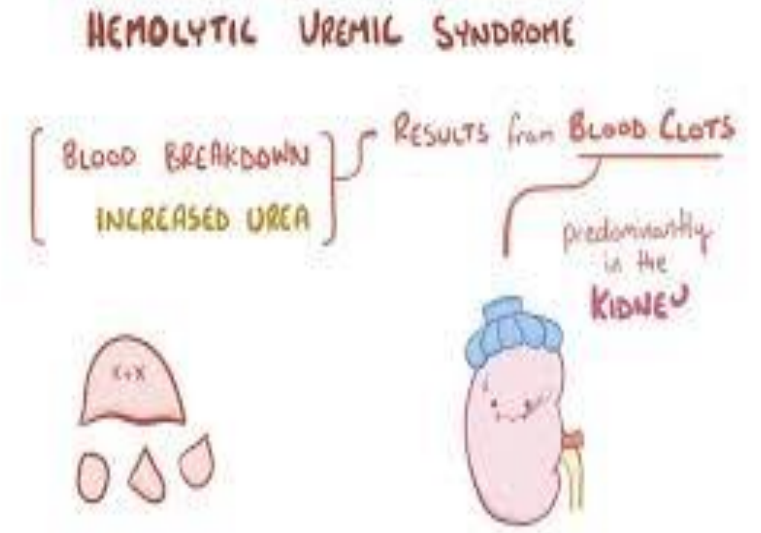
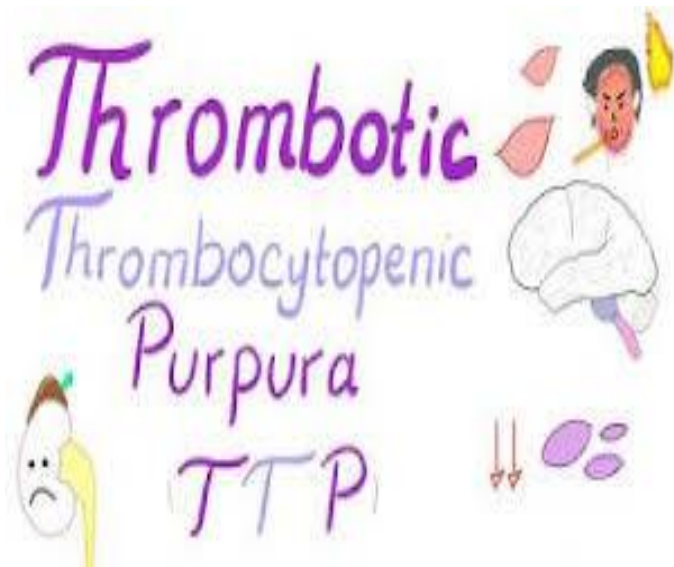
Hepatic complications of influenza

- Hepatic complications of influenza are rarely reported, yet recent reports suggest that liver injury occurs in the setting of influenza infection
- hepatitis may develop as the result of collateral damage during a systemic immune response against a non-hepatotropic viral infection or in response to drugs that are administered during treatment.
- Liver injury due to influenza infection, possibly secondary to systemic inflammation mediated by viral infection, appears to be present in a percentage of cases suggesting that liver enzymes should be monitored closely.



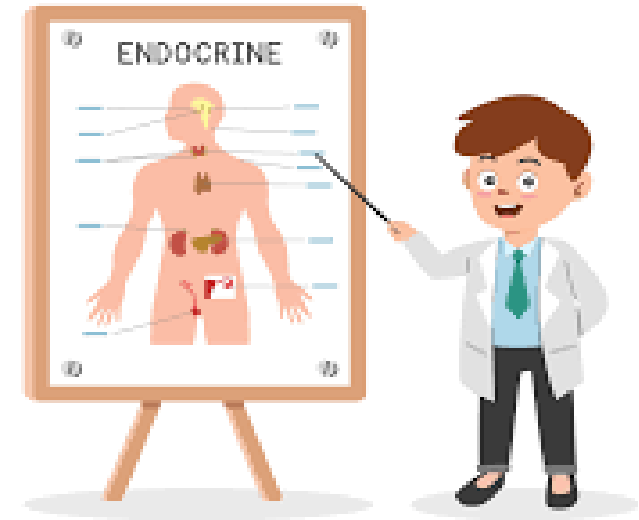
Hematologic complications of influenza

- Influenza infection is associated with a variety of hematologic complications including thromboembolic disease, thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), and hemophagocytic syndrome (HPS).



Endocrine complications of influenza

- infectious diseases are frequently the trigger for diabetic complications including diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar non-ketotic coma (HHNK).



CONCLUSIONS

- Influenza-specific prevention with vaccines has been shown to reduce the risk of some of these complications
- early antiviral therapy appears to reduce the risk and/or severity of certain complications
- Early recognition of the extra-pulmonary manifestations of influenza infection is critical to the initiation of therapeutic interventions and organ-specific supportive care.

THANK YOU

