

# **Myocarditis**

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# Outline

- **Definition**
- **Historical Background**
- **Pathogenesis**
- **Clinical presentation**
- **Etiologies**
- **Diagnostics**
- **Treatment**
- **Prognosis**

# What is Myocarditis?

- Myocarditis is an inflammatory disease of the cardiac muscle
- There are multiple etiologies including viral, bacterial, parasitic, fungal, allergic, eosinophilic, granulomatous, toxic, post-viral immune-mediated response , and infiltrative etc..
- It can be acute, subacute, or chronic, and there may be either focal or diffuse involvement of the myocardium
- It is a histological, not a clinical diagnosis  
the natural history is highly variable

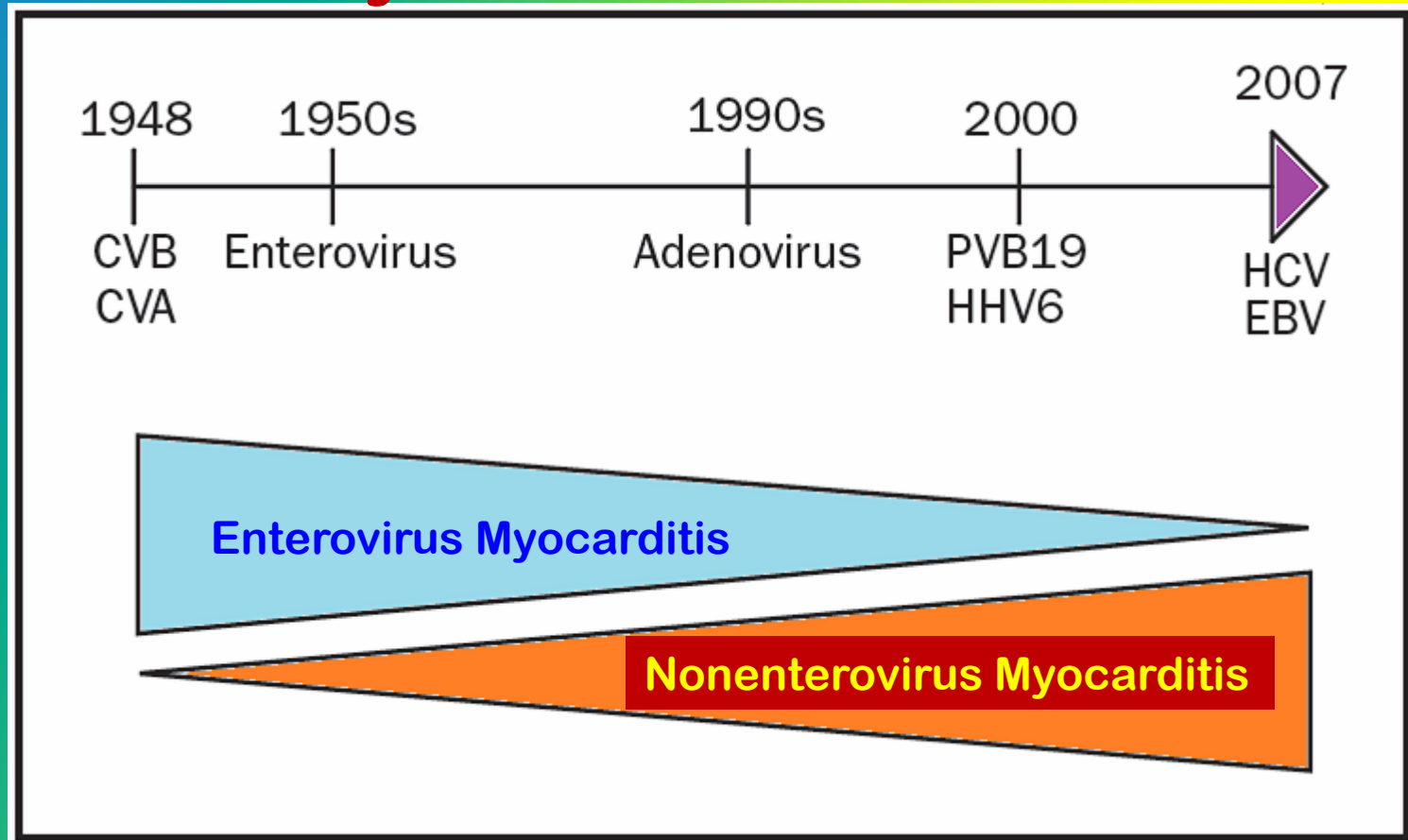
# Dallas criteria

- **Active myocarditis:** the presence of an **inflammatory infiltrate** of the myocardium **with necrosis** and/or degeneration of adjacent myocytes not typical of the ischemic damage
- **Borderline myocarditis:** the presence of an **inflammatory infiltrate** of the myocardium **without necrosis** or degeneration of adjacent myocytes.

# Historical Background

- Recognized as early as 1806 as a persistent inflammatory process of the myocardium following infections, such as diphtheria, that led to progressive cardiac damage and dysfunction
- In 1837, the term *myocarditis* was first introduced to describe inflammation or degeneration of the heart detected by postmortem examination.
- In 1980, Endomyocardial biopsy allowed the sampling of human myocardial tissue during life and consequently enabled antemortem diagnosis of myocarditis.

# Evolution of viral causes of myocarditis over time



CVA = coxsackievirus A; CVB = coxsackievirus B; EBV = Epstein-Barr virus; HCV = hepatitis C virus; HHV6 = human herpesvirus 6; PV-B19 = parvovirus B19.

# Characteristics

- Myocarditis is a complex disease because multiple pathogenetic mechanisms are involved.
- While these mechanisms appear to act in a chronological cascade, they undoubtedly overlap in some cases, rendering diagnosis and treatment difficult.
- Ultimately, dilated cardiomyopathy (DCM) may result.
- A multitude of still-circumstantial evidence points to a major role for viral myocarditis in the etiology of DCM.

# Characteristics

- The common presence of viral genetic material and viral proteins in the myocardium of patients with DCM provides the most compelling evidence, but proof of causality is still lacking.
- Myocarditis is, by definition, an inflammatory disorder, while dilated cardiomyopathy (DCM) is, in most cases, idiopathic.
- However, accumulating data has revealed an important inflammatory component in the pathogenesis of DCM, and there is growing evidence that myocarditis and DCM are closely related.



# PATHOGENESIS

- Both direct viral-induced myocyte damage and post-viral immune inflammatory reactions contribute to myocyte damage and necrosis
- Inflammatory lesions and the necrotic process may persist for months, although the viruses only replicate in the heart for at most two or three weeks after infection
- Evidence from experimental models has incriminated cytokines such as interleukin-1 and TNF, oxygen free radicals and microvascular changes as contributory pathogenic factors

# PATHOGENESIS

Three phases:

Viral Replication



Autoimmune injury



Dilated cardiomyopathy

# PATHOGENESIS

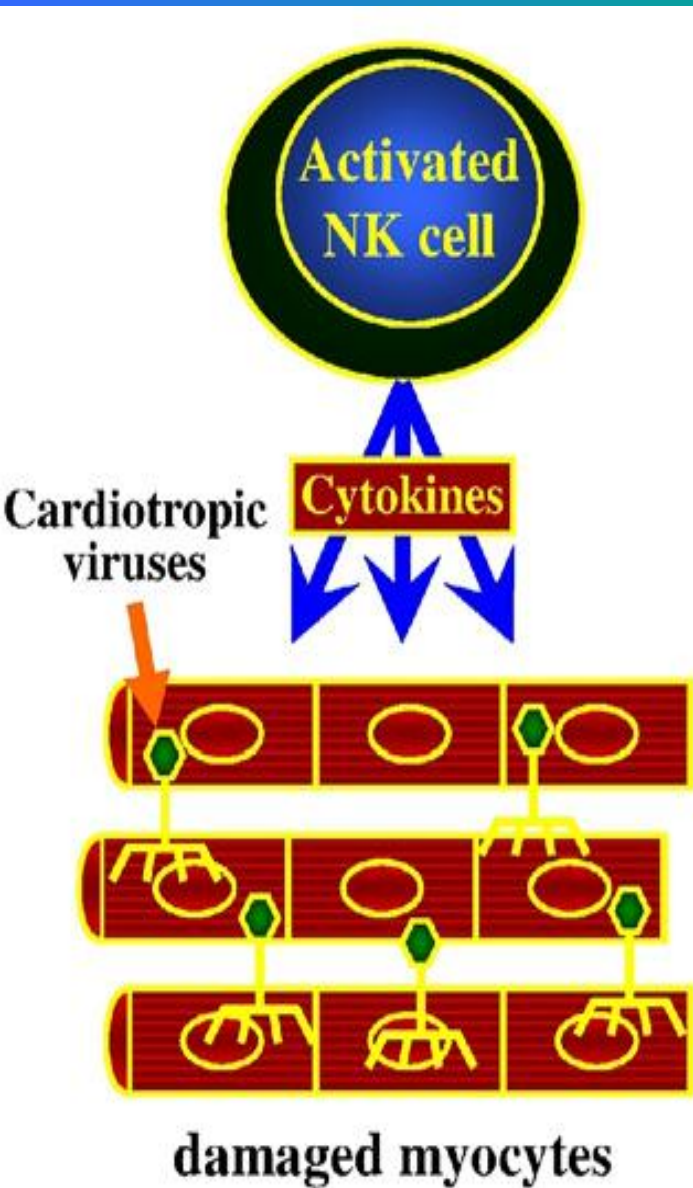
## Phase II: Autoimmunity and injury

- The local release of cytokines, such as interleukin-1, interleukin-2, interleukin-6, tumor necrosis factor (TNF), and nitric oxide may play a role in determining the T-cell reaction and the subsequent degree of autoimmune perpetuation
- These cytokines may also cause reversible depression of myocardial contractility without causing cell death.

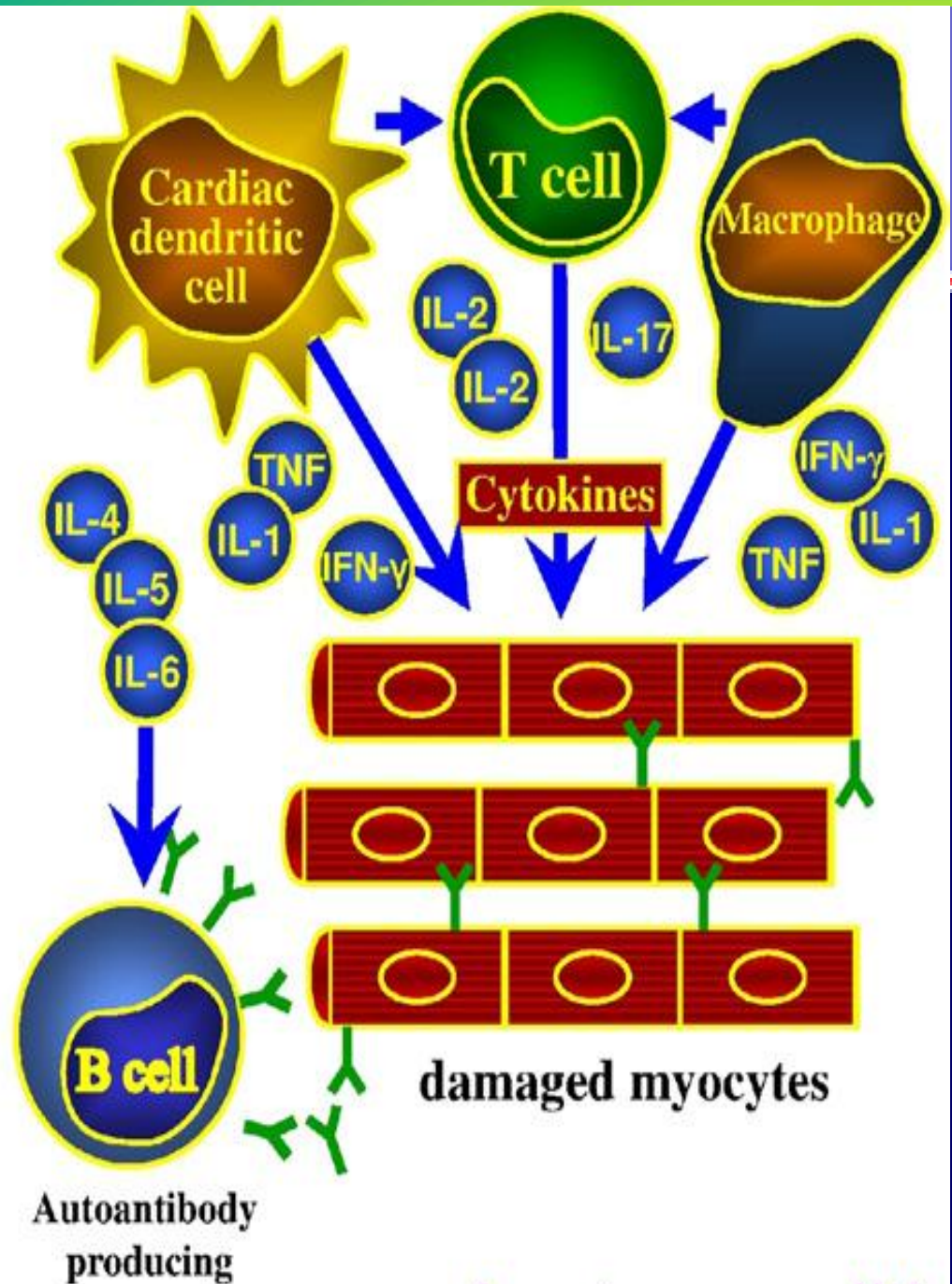
# PATHOGENESIS

## Phase II: Autoimmunity and injury

- Immune-mediated by CD8 lymphocytes and autoantibodies against various myocyte components
- Antigenic mimicry, the cross reactivity of antibodies to both virus and myocardial proteins
- Myocyte injury may be a direct result of CD8 lymphocyte infiltration



**acute myocarditis**



**subacute myocarditis**

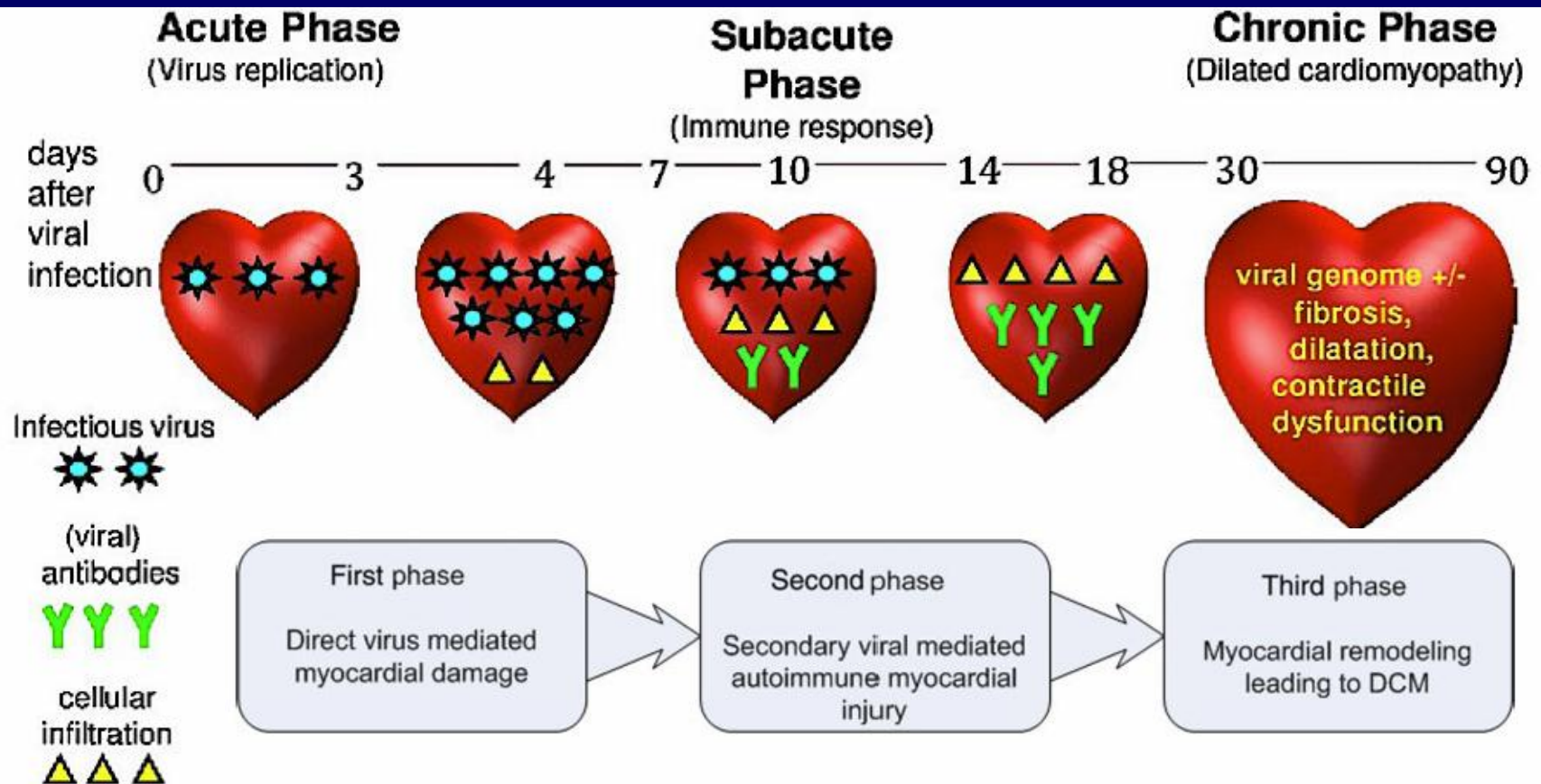
# PATHOGENESIS

## Phase III: Dilated Cardiomyopathy (DCM)

- Viruses may also directly cause myocyte apoptosis.
- During the autoimmune phase, cytokines activate the matrix metalloproteinase, such as gelatinase, collagenases, and elastases.
- In later stages of immune activation, cytokines play a leading role in adverse remodeling and progressive heart failure.
- Cardiomyopathy develops despite the absence of viral proliferation but is correlated with elevated levels of cytokines such as TNF.



# Pathophysiological process of viral myocarditis.



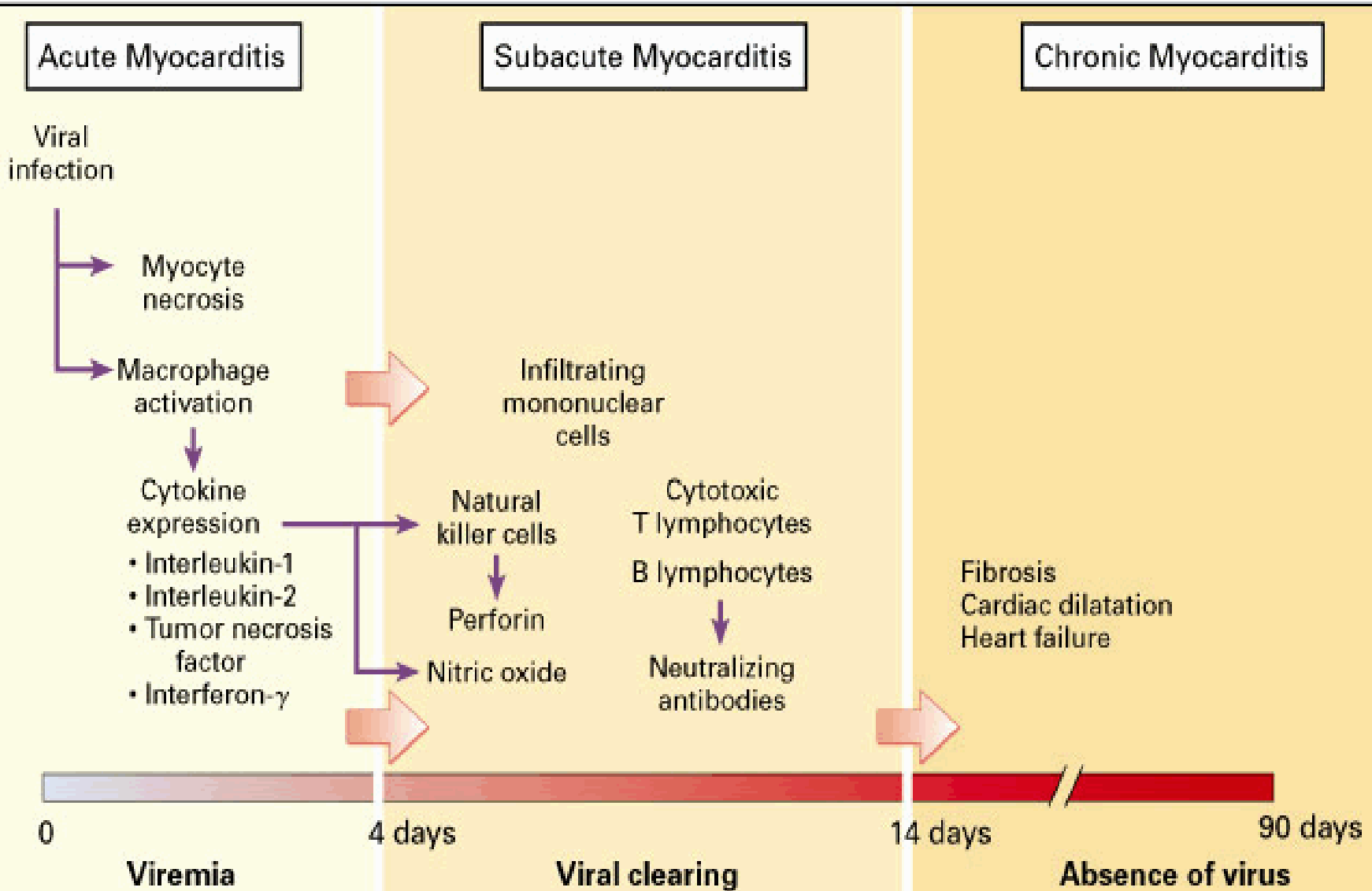
# Mechanisms of Viral and Immune Injury

- There is a stunning array of mechanisms by which cardiotropic viruses can cause congestive heart failure. These include:
  - Myocytolysis by replicating virus in the absence of a specific immune response
  - Cytotoxic T lymphocytes
  - Anti-cardiac antibodies
  - Cytokines also contribute to both recovery from infection and to worsened cellular injury during phase 1, as well as later phases.



# Stages of Viral Myocardium Infection

*New England Journal of Medicine 343:1391 2000*



# Pathophysiology

- Myocarditis generally results in a decrease in myocardial function, with concomitant enlargement of the heart and an increase in the end-diastolic volume caused by increased preload.
- Normally, the heart compensates for dilation with an increase in contractility (Starling law), but because of inflammation and muscle damage, a heart affected with myocarditis is unable to respond to the increase in volume.
- In addition, inflammatory mediators, such as cytokines and adhesion molecules, as well as apoptotic mechanisms are activated.

# Pathophysiology

- The progressive increase in left ventricular end-diastolic volume increases left atrial, pulmonary venous, and arterial pressures, resulting in increasing hydrostatic forces.
- These increased forces lead to both pulmonary edema and congestive heart failure.
- Without treatment, this process may progress to end-stage cardiac failure and death.

# Viral Causes

Infesting organisms include the following:

- **Coxsackievirus** types A and B, especially type B, are the most common viral causes of myocarditis.
- Adenovirus (types 2 and 5 most common)
- Cytomegalovirus
- Echovirus
- Epstein-Barr virus
- Hepatitis C virus
- Herpes Simplex virus
- Human immunodeficiency virus
- Influenza and parainfluenza viruses
- Measles virus
- Mumps, associated with endocardial fibroelastosis (EFE)
- Parvovirus B19
- Poliomyelitis virus
- Rubella virus
- Varicella -Zoster virus

# Coxsackieviruses

- Coxsackie B viruses are estimated to be responsible for at least 50% of the cases of infection-caused heart diseases.
- For reasons yet unknown, the cardiac disease caused by this virus mainly occurs in middle-aged men, with onset occurring, on average, around age 42 years.
- The cardiac disease becomes apparent about two weeks after exposure to the virus.

# Clinical Presentation

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- Clinical presentation varies considerably.
- In mild forms, there are few or no symptoms.
- In severe cases, patients may present with acute cardiac decompensation and progress to death.

# Clinical Presentation

- Most cases of acute myocarditis are clinically silent
- 60% of patients had antecedent flulike symptoms
- Large number identified by heart failure symptoms
- 35% of patients with myocarditis and HF have chest pain
- May mimic an acute MI with ventricular dysfunction, ischemic chest pain, ECG evidence of injury or Q waves

# Clinical Presentation

- May present with syncope, palpitation with AV block or ventricular arrhythmia
- May cause sudden death
  - myocarditis found at autopsy in 20% of Air Force recruits with sudden death\*
- May present with systemic or pulmonary thromboembolic disease



# Clinical Manifestations

A variety of cardiac symptoms can be induced by myocarditis

- Chest pain may occur, usually due to concomitant pericarditis
- Excessive fatigue or decreased exercise ability may be the initial sign of myocardial dysfunction
- Since both ventricles are generally involved, patients develop biventricular failure
- Patients present with signs of right ventricular failure such as hepatomegaly, and peripheral edema
- If there is predominant left ventricular involvement, the patient may present with the symptoms of pulmonary congestion: dyspnea, orthopnea, rales, and, in severe cases, acute pulmonary edema

**Heart failure:** This is the most common presenting picture in all ages.

**Chest pain:** Although rare in young children, this may be the initial presentation for older children, adolescents, and adults.

Chest pain may be due to myocardial ischemia or concurrent pericarditis.

# Arrhythmia:

Patients can present with any type of dysrhythmia, including ;

- Atrioventricular conduction disturbances.
- Sinus tachycardia is typical and the rate is faster than expected for the degree of fever present, which is typically low-grade.
- Junctional tachycardia is also seen and can be difficult to control medically.

# Physical Findings

- Signs of diminished cardiac output, such as tachycardia, weak pulse, cool extremities, decreased capillary refill, and pale or mottled skin may be present.
- Heart sounds may be muffled, especially in the presence of pericarditis.
- Hepatomegaly may be present in younger children.
- Rales may be heard in older children.
- Jugular venous distention and edema of the lower extremities may be present.

# Physical Findings

- In addition to the signs of fluid overload, the physical examination often reveals direct evidence of cardiac dysfunction in symptomatic patients
- S3 and S4 gallops are important signs of impaired ventricular function
- If the right or left ventricular dilatation is severe, auscultation may reveal murmurs of functional mitral or tricuspid insufficiency
- A pericardial friction rub and effusion may become evident in patients with myopericarditis

# Adolescents

- Presentation may be similar to that of younger children but with a more prominent decrease in exercise tolerance, lack of energy, malaise, chest pain, low-grade fever, arrhythmia, and cough.
- End-organ damage and low cardiac output may be present.

# Diagnostics: Expanded Criteria for Diagnosis of Myocarditis

- **Category I: Clinical Symptoms**

- Clinical heart failure
- Fever
- Viral prodrome
- Fatigue
- Dyspnea on exertion
- Chest pain
- Palpitations
- Pre-syncope or syncope

## **Category II: Evidence of Cardiac Structural or Functional Perturbation in the absence of Regional Coronary Ischemia**

- **Echocardiography evidence**
  - ✓ Regional wall motion abnormalities
  - ✓ Cardiac dilation
  - ✓ Regional cardiac hypertrophy
- **Troponin release**
  - ✓ High sensitivity ( $>0.1$  ng/mL)
- **Positive indium In 111 antimyosin scintigraphy and**
- **Normal coronary angiography or**
- **Absence of reversible ischemia by coronary distribution on perfusion scan**



## **Category III: Cardiac Magnetic Resonance Imaging**

- **Increased myocardial T2 signal on inversion recovery sequence**
- **Delayed contrast enhancement after gadolinium-DTPA infusion**

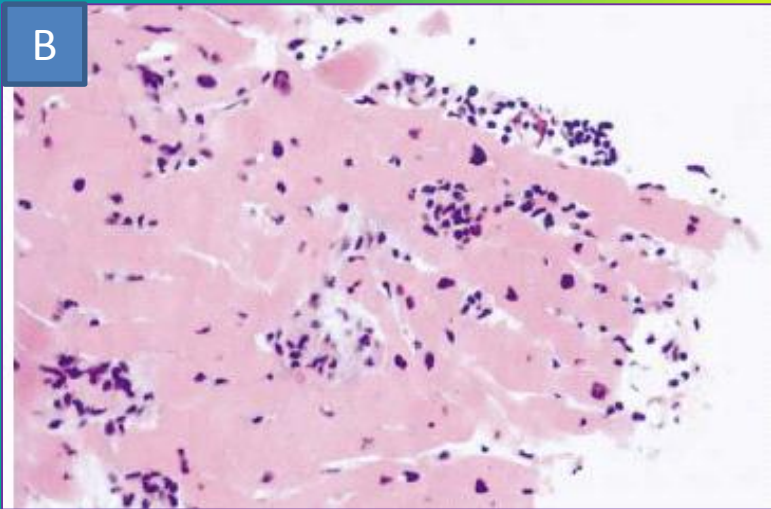
# Category IV: Myocardial biopsy – Pathologic or Molecular Analysis

- Myocarditis can be classified into:
- **Active myocarditis** - Characterized by abundant inflammatory cells and myocardial necrosis.
- **Borderline myocarditis** - Characterized by an inflammatory response that is too sparse for this type to be labeled as active myocarditis; degeneration of myocytes is not demonstrated with light microscopy
- Presence of viral genome of polymerase chain reaction or in situ hybridization
  - ✓ 80-100% specificity when performed from myocardial biopsy

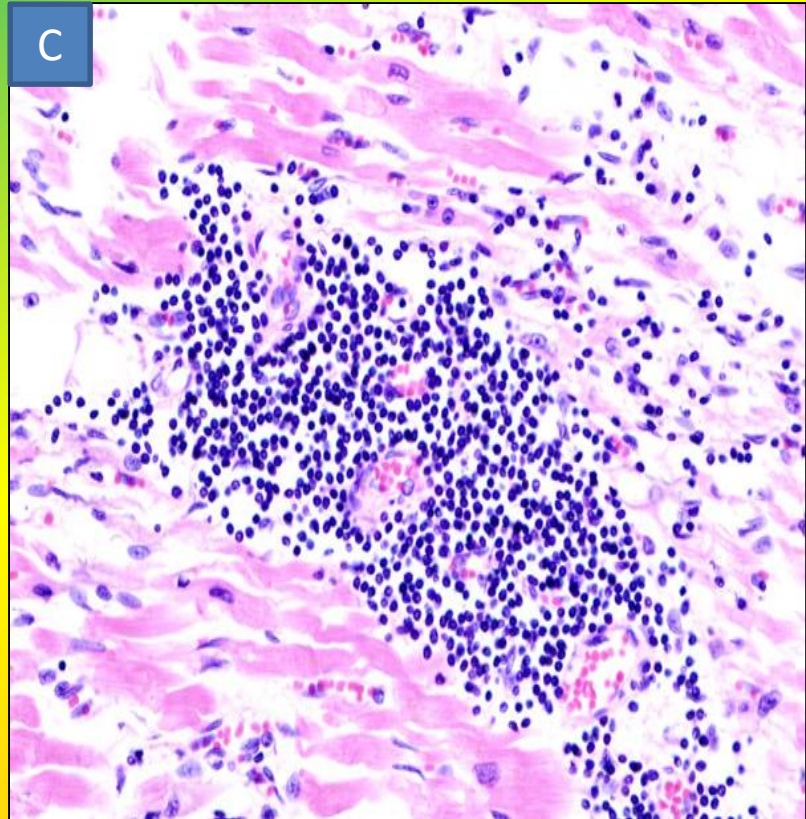
A



B



C



## Endomyocardial biopsy

A: Normal Myocardium

B: Borderline Myocarditis

C: Typical and diffuse myocarditis in each histologic section

# Lab Diagnosis

- **Complete blood count with differential**
  - Acute anemia of any origin may cause heart failure, and chronic anemia exacerbates heart failure; both respond to blood transfusion.
  - The presence of lymphocytosis or neutropenia supports diagnosis of a viral infection.
- **Blood culture:** It is important to rule out any bacterial infection
- **Viral culture:** Nasopharyngeal and rectal swabs may help identify etiology.
- **Viral Serology:** A 4-fold increase in a specific titer from the acute to convalescent phase is strong evidence of infection.
- **Molecular Tests:**
  - In situ hybridization
  - Polymerase chain reaction (PCR)

# Enzyme biomarkers

- Elevated secondary to myocardial damage from inflammatory cell infiltrates, cytokine activation and virus-mediated cell death
- More useful when high sensitivity thresholds are used
- Troponin T threshold of  $>0.1\text{mg/mL}$  increases sensitivity from 34% to 53% and a specificity of 94%
- Cardiac biomarkers i.e. creatine kinase and troponin T and I (elevated in around 40%) are routinely measured
- CKMB is not useful due to low predictive value.
- ESR found to have low sensitivity and specificity.

# Management of myocarditis

- Management is dictated by clinical signs and symptoms.
- Conventional heart failure therapy is currently the only accepted therapy for myocarditis including ACE inhibitors, angiotensin receptor blocking agents, diuretics,  $\beta$ -blockers or amiodarone.



# **Diet and Lifestyle**

- **Restrict salt intake to 2-3g of sodium per day**
- **Exercise especially during the acute phase of Coxsackie virus B3 murine myocarditis enhances viral replication rate, enhances immune mechanisms and increases inflammatory lesions and necrosis. Resumption of physical activity can take place within 2 months of the acute disease.**

# Treatments/Therapeutic Approaches

- **Supportive Therapy**
- **Immunosuppression**
- **Interferon**
- **Intravenous Immune Globulin**
- **Immune Adsorption Therapy**
- **Hemodynamic Support**



# Prognosis

- **Poor Prognostic**

- Dilated cardiomyopathy with positive enteroviral genome
- Viral genome persistence on myocardial biopsy
- Excessive apoptosis
  - Myocardial expression of Fas ligand or tumor necrosis factor receptor 1 showed minimal recovery

- **Good prognosis**

- Echo evidence of small left atrial and LV size was predictive of recovery in one small study

# Epidemiology

- No racial predilection exists.
- No sex predilection exists in humans, but there is some indication in laboratory animals that the disease may be more aggressive in males than in females.
- Certain strains of female mice had a reduced inflammatory process when treated with estradiol.
- In other studies, testosterone appeared to increase cytolytic activity of T lymphocytes in male mice.
- No age predilection exists.
- Younger patients, especially newborns and infants, and immunocompromised patients may be more susceptible to myocarditis.

# **Mortality/Morbidity**

- **With suspected coxsackievirus B, the mortality rate is higher in newborns (75%) than in older infants and children (10-25%).**
- **Complete recovery of ventricular function has been reported in as many as 50% of patients.**
- **Some patients develop chronic myocarditis (ongoing or resolving) and/or dilated cardiomyopathy and may eventually require cardiac transplantation.**

# PREVENTION

- As a result of the widespread use of vaccination in developed countries, myocarditis secondary to measles, rubella, mumps, poliomyelitis, and influenza is now rare
- Similarly, the elimination of trichinosis by meat inspection has eliminated this infection
- It is possible that vaccines against other cardiotropic viruses may prevent viral myocarditis

# Other Rare Causes of Heart Infection

## Bacterial Causes

- **Diphtheria** - Myocarditis
- **Psittacosis** (*Chlamydia psittaci*) - Endocarditis
- **Q fever** (*Coxiella burnetii*) - Pericarditis, myocarditis, and endocarditis. Endocarditis is frequently associated with purpuric rash, renal insufficiency, stroke, and heart failure.
- **Typhus** (*Rickettsia spp*) - Myocarditis

## Parasitic Causes

- **Chagas' Disease** (*Trypanosoma cruzi*) - Myocarditis
- **Trichinosis** (*Trichinella spiralis*) - Myocarditis
- **Amebiasis** (*Entameba histolytica*) - Pericarditis
- **Trypanosomiasis** (*Trypanosoma brucei rhodesiense* or *T b gambiense*) - Myocarditis

**The End**