Pathology of Valvular and Neoplastic Heart Disease

I. Normal Valve Morphology
   a. Valve histology
      i. Valves are lined by endothelium on both in-flow and out-flow surfaces
      ii. There is a collagenous core (3 parts – spongiosa, fibrosa, elastosa) with varying density of connective tissue and elastin fibers
   b. Semilunar valves = aortic and pulmonary valves
      i. Have 3 cusps
      ii. Function depends on integrity and movement of cusps and their attachments
   c. Atrioventricular valves = tricuspid and mitral valves
      i. Competency depends on integrity of the valve apparatus
         -annulus, chordae tendinae, papillary muscles, ventricular wall

II. Bicuspid Aortic Valve
   a. Congenital malformation (affects 1-2% of population)
   b. The Aortic valve has 2 cusps (not the usual 3)
      i. Usually the cusps are of unequal size
         -Incomplete embryonic separation results in one larger cusp with a midline raphe
   c. May be asymptomatic
   b. Aortic stenosis may develop
      i. Due to progressive degenerative calcification
      ii. Aortic stenosis manifests at age 50’s and 60’s
   e. There is a predisposition to infective endocarditis
   f. Associated arteriopathy may predispose to aortic dilatation or aortic dissection

III. Valvular Degeneration Caused by Calcification
   a. Valves are subject to high repetitive mechanical stresses which leads to
      i. Cumulative damage to delicate valves
      ii. Deposition of calcium phosphate minerals (dystrophic calcification)
      iii. More recent theory that chronic injury due to hyperlipidemia, hypertension, inflammation may have a role in and may precede the characteristic calcification
         -This process has some similarities to atherosclerosis, but it is not considered to be the same process
   b. Calcific aortic stenosis
      i. If calcification affects structurally normal valves
         -Stenosis usually manifests clinically in age 70’s and 80’s
      ii. If calcification affects bicuspid valves
-Stenosis manifests clinically in 50’s and 60’s (stenosis may manifest at an earlier age since bicuspid valves incur greater mechanical stress than normal tricuspid valves)

vi. Heaped up calcified masses within the aortic cusps protrude through outflow surfaces and prevent the opening of cusps leading to stenosis.

IV. Myxomatous Degeneration of the Mitral Valve
(aka Mitral Valve Prolapse)

a. Affects 3% of U.S. adults (young women most commonly)

b. Pathology
i. One or both mitral valve leaflets are enlarged, redundant, rubbery
   - Floppy valves balloon back (prolapse) into left atrium during systole

ii. Histologically the valve leaflets have deposition of mucoid/myxomatous material

iii. The chordae tendinae are elongated and thinned


V. Infective Endocarditis

a. Destructive inflammation of cardiac valves and endocardium

b. Bacterial infection of a valve is the most common cause

i. Portals of entry of the bacteria (seeding of the bloodstream) include
   -Infection outside the cardiovascular system or
   -Dental or surgical procedures with transient bacteremia or
   -Injection of contaminated material into directly into the bloodstream (ie as seen with intravenous drug abusers) or
   -Occult source

c. Acute infective endocarditis
i. Caused by highly virulent organisms
Staphylococcus aureus

Results in a rapid clinical course with severe destruction of valves

ii. Affected valves are often previously normal
iii. Has up to 50% mortality rate

d. Subacute infective endocarditis

i. Caused by low virulence organisms
   -alpha-hemolytic (viridans) Streptococci

ii. Affects previously deformed valves

iii. Less valvular destruction

iv. Majority of patients recover after appropriate therapy

e. Vegetations are

i. Composed of thrombotic debris, fibrin, inflammatory cells, microorganisms

ii. Large, bulky, friable (leads to embolic phenomena)

iii. Destructive, erosive

f. Risk factors for development of endocarditis include

i. Preexisting valvular disease

ii. Prosthetic valves

iii. Immune deficiency

iv. Diabetes mellitus

v. Intravenous drug abuse

vi. Alcoholism

g. Complications

i. Cardiac
   -Valvular insufficiency (or stenosis)
   -Abscess formation
   -Prosthetic valve dehiscence or paravalvular leak

ii. Embolic complications
   -Brain, kidneys, spleen, lungs
     Physical exam findings suggestive of systemic microemboli:
     -Splinter hemorrhages (are subungual hemorrhages)
     -Roth spots (retinal hemorrhages)
     -Janeway lesions (hemorrhagic nontender lesions on the palms or soles)
     -Osler nodes (subcutaneous nodules on the digit pulp)

h. Diagnosis/Treatment

i. Must have high index of clinical suspicion for patients at risk

ii. Duke Criteria (Diagnostic Criteria for Infective Endocarditis)
   -Identification of new regurgitant murmurs
   -Blood cultures
   -Echocardiogram

iii. Therapy with intravenous antibiotics is paramount
   -Surgical intervention may be necessary
i. **Prophylaxis**

Provide antibiotic prophylaxis for at risk individuals (in particular patients with prosthetic heart valves and those with a prior history of infective endocarditis) undergoing dental, surgical, or other invasive procedures (clear guidelines for prophylaxis have been developed)

VI. **Rheumatic Fever**

a. **Acute** Rheumatic Fever
   i. Acute, immunologically mediated, multisystem inflammatory disease (often involves the heart)
   ii. Occurs few weeks (10 days to 6 weeks) after Group A (beta-hemolytic) streptococcal pharyngitis
   v. Most commonly seen in children 5-15 years old, but certainly can affect adults
   iv. Patients can have repeated “attacks” of acute rheumatic fever with repeat Group A (beta-hemolytic) streptococcal pharyngitis

b. Pathogenesis of Acute Rheumatic Fever
   i. It is though to be a hypersensitivity reaction
      - Immune response to group A *Streptococci* which cross react with host tissues
      - Antibodies directed against M proteins of strep cross-react with self-antigens in the heart
        - CD4+ T cells specific for streptococcal peptides react with cardiac self proteins
        - Produce cytokines which activate macrophages

c. Clinical Manifestations of Acute Rheumatic Fever
   Major Criteria
   - Migratory polyarthritis of large joints
   - Carditis
   - Subcutaneous nodules
   - Erythema marginatum of skin
   - Sydenham chorea
   Minor Criteria
   - Fever
   - Arthralgias
   - Elevated acute-phase reactants

d. **Jones Criteria**
   - Preceeding group A Strep Infection
   - 2 Major Manifestations
   - 1 Major and 2 Minor Manifestations

e. **Acute** rheumatic fever **carditis**
i. Inflammatory response can involve pericardium, myocardium, and/or endocardium (Pancarditis)

ii. One can see Aschoff bodies
   - Represent focal inflammatory lesions of acute rheumatic fever
   - There is collection of lymphocytes, plasma cells, macrophages (the macrophages are called Anitschkow cells)

iii. Pericarditis
   - Fibrinous/serofibrinous pericardial exudates (“bread and butter” pericarditis)
   - Physical exam sign – pericardial friction rub
   - Usually resolves without sequelae

iv. Myocarditis
   - Scattered Aschoff bodies within the interstitium of the myocardium
   - Clinical sequelae – potential arrhythmias, cardiac dilatation, heart failure, functional mitral valve insufficiency

v. Endocarditis
   - Inflammation and foci of fibrinoid necrosis of left-sided > right sided valve cusps
   - Verrucae – Small sterile vegetations on valve cusps (usually along lines of closure)
   - Clinical findings may be a new murmur

f. Chronic rheumatic heart disease
   i. Organization of the acute inflammation (associated with acute rheumatic fever) with resultant fibrosis of valve structures
      - Valve leaflets become thickened, fused
      - The leaflet thickening and fusion can result in a Classic “fish mouth” or “buttonhole” stenosis
      - Chordae tendinae become shortened, thickened, and fused
   ii. The Mitral valve most is commonly involved (alone in 65-75% of cases)
      - Aortic and mitral valve together (25% of cases)
      - Tricuspid valve infrequently affected, pulmonic valve rarely
   iii. Valve replacement may be necessary

VII. Endocarditis of Systemic Lupus Erythematosus (Liebman-Sacks Endocarditis)
   a. Small (1-4mm) sterile vegetations in patients with SLE
      - Most commonly seen on mitral and tricuspid valve undersurfaces
   b. Vegetations are granular
   c. May be associated with marked inflammation and necrosis of valve
      - Could result in valve fibrosis/deformity
      - If severe, valve replacement may be necessary
VIII. Nonbacterial Thrombotic Endocarditis (Marantic Endocarditis)
   a. Characterized by small (1-5mm), sterile vegetations on cardiac valves
   b. Vegetations are composed of fibrin, platelets
   c. Vegetations are non-destructive but loosely attached to valves
      i. Because of loose attachment, main clinical sequelae are due to embolization of the vegetations and resultant infarcts
   d. Most commonly encountered in debilitated patients
      i. Hypothesis—the patients are predisposed to a hypercoagulable state
      ii. Patients with cancer (especially advanced mucin producing pancreatic adenocarcinomas)
      iii. Patients with sepsis, severe burns
      iv. Patients with indwelling intravenous catheters

IX. Neoplastic Heart Disease
   a. Myxoma
      i. Most common primary tumor of the heart in adults
      ii. Benign
      iii. 90% arise in the atria (left: right, 4:1)
      iv. Gross—globular masses, gelatinous appearance, often pedunculated
      v. Microscopic—mucopolysaccharide matrix with scattered cells stellate (myxoma) cells, smooth muscle cells
      vi. Ball-valve obstruction—position dependent movement of pedunculated myxoma into or through AV valves during systole may result in syncope, changing murmur
      vii. Other clinical signs and symptoms
         - Constitutional symptoms (fatigue, malaise)
         - Thought possibly due to elaboration of interleukin-6
         - Sequelea of embolization of tumor fragments
         - Treatment—surgical removal
   b. Rhabdomyoma
      i. Most common pediatric heart neoplasm
      ii. Children present with obstruction of valvular orifice or cardiac chamber
      iii. May spontaneously regress
      iv. Association—Tuberous Sclerosis
   c. Metastatic tumors to heart
      i. Most common lung, breast, melanoma, leukemia, lymphoma
      ii. Consequences
         i. Pericardial effusion, pericardial tamponade, tumor bulk restriction of cardiac filling