Rheumatic heart disease is the most serious complication of rheumatic fever. Acute rheumatic fever follows 0.3% of cases of group A beta-hemolytic streptococcal pharyngitis in children. As many as 39% of patients with acute rheumatic fever may develop varying degrees of pancarditis with associated valve insufficiency, heart failure, pericarditis, and even death. With chronic rheumatic heart disease, patients develop valve stenosis with varying degrees of regurgitation, atrial dilation, arrhythmias, and ventricular dysfunction. Chronic rheumatic heart disease remains the leading cause of mitral valve stenosis and valve replacement in adults in the United States.
Acute rheumatic fever and rheumatic heart disease are thought to result from an autoimmune response, but the exact pathogenesis remains unclear. While rheumatic heart disease was the leading cause of death 100 years ago in people aged 5-20 years in the United States, incidence of this disease has decreased in developed countries, and the mortality rate has dropped to just above 0% since the 1960s. Worldwide, rheumatic heart disease remains a major health problem. Chronic rheumatic heart disease is estimated to exist in 5-30 million children and young adults; 90,000 patients die from this disease each year. The mortality rate from this disease remains 1-10%. A comprehensive resource provided by the World Health Organization (WHO) addresses the diagnosis and treatment of this latter population.

Pathophysiology: Rheumatic fever develops in children and adolescents following pharyngitis with group A beta-hemolytic Streptococcus (ie, Streptococcus pyogenes). The organisms attach to the epithelial cells of the upper respiratory tract and produce a battery of enzymes allowing them to damage and invade human tissues. After an incubation period of 2-4 days, the invading organisms elicit an acute inflammatory response with 3-5 days of sore throat, fever, malaise, headache, and an elevated leukocyte count.

In 0.3-3% of cases, infection leads to rheumatic fever several weeks after the sore throat has resolved. Only infections of the pharynx initiate or reactivate rheumatic fever. The organism spreads by direct contact with oral or respiratory secretions, and spread is enhanced by crowded living conditions. Patients remain infected for weeks after symptomatic resolution of pharyngitis and may serve as a reservoir for infecting others. Penicillin treatment shortens the clinical course of streptococcal pharyngitis and, more importantly, prevents the major sequelae.

Group A Streptococcus is a gram-positive coccus that frequently colonizes the skin and oropharynx. This organism may cause suppurative disease, such as pharyngitis, impetigo, cellulitis, myositis, pneumonia, and puerperal sepsis. It also may be associated with nonsuppurative disease, such as rheumatic fever and acute poststreptococcal glomerulonephritis. Group A streptococci elaborate the cytolytic toxins streptolysins S and O. Of these, streptolysin O induces persistently high antibody titers that provide a useful marker of group A streptococcal infection and its nonsuppurative complications. Group A Streptococcus, as identified using the Lancefield classification, has a group A carbohydrate antigen in the cell wall that is composed of a branched polymer of L-rhamnose and N-acetyl-D-glucosamine in a 2:1 ratio.

Group A streptococci may be subserotyped by surface proteins on the cell wall of the organism. The presence of the M protein is the most important virulence factor for group A streptococcal infection in humans. More than 90 M serotypes have been identified, some of which have a long terminal antigenic domain (epitopes) similar to antigens in various components of the human heart. Rheumatogenic strains often are encapsulated mucoid strains rich in M proteins and resistant to phagocytosis. These strains are strongly immunogenic, and anti–M antibodies against the streptococcal infection may cross react with heart tissue. Streptococcal antigens that are structurally similar to those in the heart include hyaluronate in the bacterial capsule, cell wall polysaccharides (similar to glycoproteins in heart valves), and membrane antigens that share epitopes with the sarcolemma and smooth muscle.

Acute rheumatic heart disease often produces a pancarditis characterized by endocarditis, myocarditis, and pericarditis. Endocarditis is manifested as valve insufficiency. The mitral valve is most commonly and severely affected (65-70% of patients), and the aortic valve is second in frequency (25%). The tricuspid valve is deformed in only 10% of patients and almost always is associated with mitral and aortic lesions. The pulmonary valve is rarely affected. Severe valve insufficiency during the acute phase may result in congestive heart failure and even death (1% of patients). Whether myocardial dysfunction during acute rheumatic fever is related primarily to myocarditis or is secondary to congestive heart failure from severe valve insufficiency is not known. Pericarditis, when present, rarely affects cardiac function or results in constrictive pericarditis.

Chronic manifestations due to residual and progressive valve deformity occur in 9-39% of adults with previous rheumatic heart disease. Fusion of the valve apparatus resulting in stenosis or a combination of stenosis and insufficiency develops 2-10 years after an episode of acute rheumatic fever, and recurrent episodes may cause progressive
damage to the valves. Fusion occurs at the level of the valve commissures, cusps, chordal attachments, or any combination of these. Rheumatic heart disease is responsible for 99% of mitral valve stenosis in adults in the United States. Associated atrial fibrillation or left atrial thrombus formation from chronic mitral valve involvement and atrial enlargement may be observed.

**Frequency:**

- **In the US:** At this time, rheumatic fever is uncommon among children in the United States. Incidence of rheumatic fever and rheumatic heart disease has decreased in the United States and other industrialized countries in the past 80 years. Prevalence of rheumatic heart disease in the United States now is less than 0.05 per 1000 population, with rare regional outbreaks reported in Tennessee in the 1960s and in Utah, Ohio, and Pennsylvania in the 1980s. In the early 1900s, incidence was reportedly 5-10 cases per 1000 population. Decreased incidence of rheumatic fever has been attributed to the introduction of penicillin or a change in the virulence of the *Streptococcus*.

- **Internationally:** In contrast to trends in the United States, the incidence of rheumatic fever and rheumatic heart disease has not decreased in developing countries. Retrospective studies reveal developing countries to have the highest figures for cardiac involvement and recurrence rates of rheumatic fever. Estimations worldwide are that 5-30 million children and young adults have chronic rheumatic heart disease, and 90,000 patients die from this disease each year.

**Mortality/Morbidity:** Rheumatic heart disease is the major cause of morbidity from rheumatic fever and the major cause of mitral insufficiency and stenosis in the United States and the world. Variables that correlate with severity of valve disease include the number of previous attacks of rheumatic fever, the length of time between the onset of disease and start of therapy, and sex. (The disease is more severe in females than in males.) Insufficiency from acute rheumatic valve disease resolves in 60-80% of patients who adhere to antibiotic prophylaxis.

**Race:** Native Hawaiian and Maori (both of Polynesian descent) have a higher incidence of rheumatic fever, 13.4 per 100,000 hospitalized children per year, even with antibiotic prophylaxis of streptococcal pharyngitis. Otherwise, race (when controlled for socioeconomic variables) has not been documented to influence disease incidence.

**Sex:** Rheumatic fever occurs in equal numbers in males and females, but the prognosis is worse for females than for males.

**Age:** Rheumatic fever is principally a disease of childhood, with a median age of 10 years, although it also occurs in adults (20% of cases).

**History:** A diagnosis of rheumatic heart disease is made after confirming antecedent rheumatic fever. The modified Jones criteria (revised in 1992) provide guidelines for the diagnosis of rheumatic fever.

- The Jones criteria require the presence of 2 major or 1 major and 2 minor criteria for the diagnosis of rheumatic fever.
  
  - The major diagnostic criteria include carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum.
  
  - The minor diagnostic criteria include fever, arthralgia, prolonged PR interval on the electrocardiogram, elevated acute phase reactants (increased erythrocyte sedimentation rate [ESR]), presence of C-reactive protein, and leukocytosis.

- Additional evidence of previous group A streptococcal pharyngitis is required to diagnose rheumatic fever. One of the following must be present:
Positive throat culture or rapid streptococcal antigen test

Elevated or rising streptococcal antibody titer

History of previous rheumatic fever or rheumatic heart disease

- These criteria are not absolute; the diagnosis of rheumatic fever can be made in a patient with chorea alone if the patient has had documented group A streptococcal pharyngitis.

- After a diagnosis of rheumatic fever is made, symptoms consistent with heart failure, such as difficulty breathing, exercise intolerance, and a rapid heart rate out of proportion to fever, may be indications of carditis and rheumatic heart disease.

**Physical:** Physical findings in a patient with rheumatic heart disease include cardiac and noncardiac manifestations of acute rheumatic fever. Some patients develop cardiac manifestations of chronic rheumatic heart disease.

- Cardiac manifestations of acute rheumatic fever

  - Pancarditis is the most serious and second most common complication of rheumatic fever (50%). In advanced cases, patients may complain of dyspnea, mild-to-moderate chest discomfort, pleuritic chest pain, edema, cough, or orthopnea.

  - On physical examination, carditis is most commonly detected by a new murmur and tachycardia out of proportion to fever. New or changing murmurs are considered necessary for a diagnosis of rheumatic valvulitis.

  - Some cardiologists have proposed that echo-Doppler evidence of mitral insufficiency, particularly in association with aortic insufficiency, may be sufficient for a diagnosis of carditis (even in the absence of accompanying auscultatory findings); however, given the sensitivity of modern Doppler devices, this remains controversial.

  - Other cardiac manifestations include congestive heart failure and pericarditis.

  - Patients in whom the diagnosis of acute rheumatic fever is made should be examined frequently because of the progressive nature of the disease.

- New or changing murmurs: The murmurs of acute rheumatic fever are typically from valve insufficiency. The following murmurs are most commonly observed during acute rheumatic fever:

  - Apical pansystolic murmur is a high-pitched, blowing-quality murmur of mitral regurgitation that radiates to the left axilla. The murmur is unaffected by respiration or position. Intensity varies but is grade 2/6 or greater. The mitral insufficiency is related to dysfunction of the valve, chordae, and papillary muscles.

  - Apical diastolic murmur (also known as a Carey-Coombs murmur) is heard with active carditis and accompanies severe mitral insufficiency. It is related to relative mitral stenosis, as the large volume of regurgitant flow recrosses the mitral valve during ventricular filling. It is heard best with the bell of the stethoscope, while the patient is in the left lateral position and the breath held in expiration. This murmur is low pitched, rumbling, and resembles the roll of a distant drum.

  - Basal diastolic murmur is an early diastolic murmur of aortic regurgitation and is high-pitched, blowing, decrescendo, and heard best along the right upper sternal border after deep expiration while the patient is leaning forward.

- Congestive heart failure

  - Heart failure may develop secondary to severe valve insufficiency or
myocarditis.
  - The physical findings associated with heart failure include tachypnea, orthopnea, jugular venous distention, rales, hepatomegaly, a gallop rhythm, and peripheral swelling and edema.

- Pericarditis
  - A pericardial friction rub indicates that pericarditis is present.
  - Increased cardiac dullness to percussion and muffled heart sounds are consistent with pericardial effusion.
  - A paradoxical pulse (drop in systolic blood pressure with inspiration) with decreased systemic pressure and perfusion and evidence of diastolic indentation of the right ventricle on echocardiogram reflect impending pericardial tamponade. In this clinical emergency, pericardial effusion should be treated by pericardiocentesis.

- Common noncardiac (and diagnostic) manifestations of acute rheumatic fever include polyarthritis, chorea, erythema marginatum, and subcutaneous nodules. Other clinical, noncardiac manifestations include abdominal pain, arthralgias, epistaxis, fever, and rheumatic pneumonia.
  - Polyarthritis is the most common symptom and frequently is the earliest manifestation of acute rheumatic fever (70-75%). Characteristically, the arthritis begins in the large joints of the lower extremities (knees and ankles) and migrates to other large joints in the lower or upper extremities (elbows and wrists). Affected joints are painful, swollen, warm, erythematous, and limited in their range of motion. The pain is out of proportion to clinical findings. The arthritis reaches maximum severity in 12-24 hours, persists for 2-6 days (rarely more than 3 wk) at each site, and responds rapidly to aspirin. Aspirin improves symptoms in affected joints and prevents further migration of the arthritis. Polyartthritis is more common and more severe in teenagers and young adults than in younger children.
  - Sydenham chorea occurs in 10-30% of patients with rheumatic fever. Patients present with difficulty writing, involuntary grimacing, purposeless (choreiform) movements of the arms and legs, speech impairment, generalized weakness, and emotional lability. Physical findings include hyperextended joints, hypotonia, diminished deep tendon reflexes, tongue fasciculations (“bag of worms”), and a “milksign” or relapsing grip demonstrated by alternate increases and decreases in tension when the patient grips the examiner’s hand.
  - In the absence of a family history of Huntington chorea, the diagnosis of acute rheumatic fever is almost certain. There is a long latency period (1-6 mo) between streptococcal pharyngitis and the onset of chorea; a history of an antecedent sore throat frequently is not obtained. Patients with chorea often do not demonstrate other Jones criteria. Chorea is slightly more common in females than males. It also is known as rheumatic chorea, Sydenham chorea, chorea minor, and St Vitus dance. Daily handwriting samples can be used as an indicator of progression or resolution of disease. Complete resolution of the symptoms typically occurs with improvement in 1-2 weeks and full recovery in 2-3 months. Cases have been reported, however, in which symptoms wax and wane for several years.
  - Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) may be associated with chorea. Children have been identified in whom group A streptococcal infection appears to have triggered a relapsing-remitting symptom complex characterized by obsessive-compulsive disorder (somatic obsessions and checking, cleaning, and repeating compulsions), and neurologic abnormalities, such as cognitive defects and motoric hyperactivity. The symptoms are prepubertal in onset and may include emotional lability, separation anxiety, and oppositional behaviors. Streptococcal infection has been proposed to trigger the formation of
antibodies that cross-react with the basal ganglia of genetically susceptible hosts in a manner similar to the proposed mechanism for Sydenham chorea, thus causing the symptom complex.

- Erythema marginatum, also known as erythema annullare, is a characteristic rash that occurs in 5-13% of patients with acute rheumatic fever. It begins as 1-3 cm in diameter, pink-to-red nonpruritic macules or papules located on the trunk and proximal limbs but never on the face. The lesions spread outward to form a serpiginous ring with erythematous raised margins and central clearing. The rash may fade and reappear within hours and is exacerbated by heat. Thus, if the lesions are not well visualized, they can be accentuated by the application of warm towels, a hot bath, or the use of tangential lighting. The rash occurs early in the course of the disease and remains long past the resolution of other symptoms. Erythema marginatum also has been reported in association with sepsis, drug reactions, and glomerulonephritis.

- Subcutaneous nodules currently are an infrequent manifestation of rheumatic fever. The frequency has declined over the past several years to 0-8% of patients with rheumatic fever. When present, the nodules appear over the extensor surfaces of the elbows, knees, ankles, knuckles, and on the scalp and spinous processes of the lumbar and thoracic vertebrae where they are attached to the tendon sheath. They are firm, nontender, and free from attachments to the overlying skin and range in size from a few mm to 1-2 cm. They vary in number from one to dozens (mean 3-4). Histologically, they contain areas resembling the Aschoff bodies seen in the heart. Subcutaneous nodules generally occur several weeks into the disease and resolve within a month. They are associated strongly with severe rheumatic carditis, and, in the absence of carditis, the diagnosis of subcutaneous nodules should be questioned.

- Other clinical noncardiac manifestations: Abdominal pain usually occurs at the onset of acute rheumatic fever. This pain resembles abdominal pain from other conditions with acute microvascular mesenteric inflammation and may mimic acute appendicitis. Patients may complain of arthralgias on presentation.

- In the history, it is important to determine if the patient has taken aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) because these may suppress the full manifestations of the disease. Epistaxis may be associated with severe protracted rheumatic carditis. Fevers above 39°C with no characteristic pattern are present initially in almost every case of acute rheumatic fever. Fever may be low-grade in children with mild carditis or absent in patients with pure chorea. It decreases without antipyretic therapy in about 1 week, but low-grade fevers persist for 2-3 weeks. Patients with rheumatic pneumonia present with the same signs as patients with infectious pneumonia. Rheumatic pneumonia should be differentiated from respiratory distress related to congestive heart failure.

- Cardiac manifestations of chronic rheumatic heart disease: Valve deformities, thromboembolism, cardiac hemolytic anemia, and atrial arrhythmias are the most common cardiac manifestations of chronic rheumatic heart disease.

- Valve deformities
  - Mitral stenosis occurs in 25% of patients with chronic rheumatic heart disease and in association with mitral insufficiency in another 40%. Progressive fibrosis, ie, thickening and calcification of the valve, takes place over time, resulting in enlargement of the left atrium and formation of mural thrombi in that chamber. The stenotic valve is funnel-shaped, with a "fish mouth" resemblance. On auscultation, S1 is initially accentuated but becomes reduced as the leaflets thicken. P2 becomes accentuated, and the splitting of S2 decreases as pulmonary hypertension develops. An opening snap of the mitral valve often is heard at the apex, where a diastolic filling murmur also is heard.
Aortic stenosis from chronic rheumatic heart disease typically is associated with aortic insufficiency. The valve commissures and cusps become adherent and fused, and the valve orifice becomes small with a round or triangular shape. On auscultation, $S_2$ may be single because the aortic leaflets are immobile and do not produce an aortic closure sound. The systolic and diastolic murmurs of aortic valve stenosis and insufficiency are heard best at the base of the heart.

Thromboembolism occurs as a complication of mitral stenosis. It is more likely to occur when the left atrium is dilated, cardiac output is decreased, and the patient is in atrial fibrillation. The frequency of this complication has decreased with the use of anticoagulation and the development of surgical repair for the valve abnormality.

- Cardiac hemolytic anemia is related to disruption of the red blood cells by a deformed valve. Increased destruction and replacement of platelets also may occur.
- Atrial arrhythmias typically are related to a chronically enlarged left atrium (from a mitral valve abnormality). Successful cardioversion of atrial fibrillation to sinus rhythm is more likely to be successful if the left atrium is not markedly enlarged, the mitral stenosis is mild, and the patient has been in atrial fibrillation for less than 6 months. Patients should be anticoagulated before cardioversion to decrease the risk of systemic embolization.

**Causes:** Rheumatic fever is thought to result from an autoimmune response, but the exact pathogenesis remains unclear. Rheumatic fever only develops in children and adolescents following group A beta-hemolytic streptococcal pharyngitis, and only infections of the pharynx initiate or reactivate rheumatic fever. At least some rheumatogenic strains of group A *Streptococcus* have antigenic domains similar to antigens in components of the human heart. That anti–M antibodies against the streptococci may cross react with heart tissue causing the pancarditis observed in rheumatic fever has been proposed. Streptococcal antigens are structurally similar to those in cardiac myosin and the laminin in heart valves.
Glomerulonephritis

**Lab Studies:**

- **Throat culture:** Throat cultures for group A beta hemolytic *Streptococcus* usually are negative by the time symptoms of rheumatic fever or rheumatic heart disease appear. Attempts should be made to isolate the organism before the initiation of antibiotic therapy to help confirm a diagnosis of streptococcal pharyngitis and to allow typing of the organism if it is isolated successfully.

- **Rapid antigen detection test:** This test allows rapid detection of group A streptococcal antigen and allows the diagnosis of streptococcal pharyngitis and the initiation of antibiotic therapy while the patient is still in the physician's office. Since the rapid antigen detection test has a specificity of greater than 95% but a sensitivity of only 60-90%, a throat culture should be obtained in conjunction with this test.

- **Antistreptococcal antibodies:** The clinical features of rheumatic fever begin at the time antistreptococcal antibody levels are at their peak. Thus, antistreptococcal antibody testing is useful for confirming previous group A streptococcal infection. The elevated level of antistreptococcal antibodies is useful particularly in patients that present with chorea as the only diagnostic criterion. Sensitivity for recent infections can be improved by testing for several antibodies. Antibody titers should be checked at 2-week intervals in order to detect a rising titer.
  
  - The most common extracellular antistreptococcal antibodies tested include antistreptolysin O (ASO), anti–deoxyribonuclease (DNAse) B, antihyaluronidase, antistreptokinase, antistreptococcal esterase, and anti-DNA. Antibody tests for cellular components of group A streptococcal antigens include antistreptococcal polysaccharide, antiteichoic acid antibody, and anti–M protein antibody.

  - In general, the ratio of antibodies to extracellular streptococcal antigens rises during the first month after infection and then plateaus for 3-6 months before returning to normal levels after 6-12 months. When the ASO titer peaks (2-3 wk after the onset of rheumatic fever), the sensitivity of this test is 80-85%. The anti-DNAse B has a slightly higher sensitivity (90%) for detecting rheumatic fever or acute glomerulonephritis. Antihyaluronidase results are frequently abnormal in rheumatic fever patients with a normal level of ASO titer and may rise earlier and persist longer than elevated ASO titers during rheumatic fever.

- **Acute phase reactants:** The C-reactive protein and erythrocyte sedimentation rate are elevated in rheumatic fever due to the inflammatory nature of the disease. Both tests have a high sensitivity but low specificity for rheumatic fever. They may be used to monitor the resolution of inflammation, detect relapse when weaning aspirin, or identify the recurrence of disease.

- **Heart reactive antibodies:** Tropomyosin is elevated in acute rheumatic fever.

- **Rapid detection test for D8/17:** This immunofluorescence technique for identifying the B cell marker D8/17 is positive in 90% of patients with rheumatic fever. It may be useful for identifying patients who are at risk for developing rheumatic fever.

**Imaging Studies:**

- **Chest roentgenogram:** Cardiomegaly, pulmonary congestion, and other findings consistent with heart failure may be seen on chest x-ray. When the patient has fever and respiratory distress, the chest x-ray helps differentiate heart failure from rheumatic pneumonia.

- **Doppler-echocardiogram:** In acute rheumatic heart disease, Doppler-echocardiography identifies and quantitates valve insufficiency and ventricular dysfunction.
  
  - With mild carditis, Doppler evidence of mitral regurgitation may be present during the acute phase of disease but resolves in weeks to months. In contrast, patients with moderate-to-severe carditis have persistent mitral and/or aortic regurgitation.

  - The most important echocardiographic features of mitral regurgitation from acute rheumatic valvulitis are annular dilatation, elongation of the chordae to the anterior leaflet, and a posterolaterally directed mitral regurgitation jet.
During acute rheumatic fever, the left ventricle is frequently dilated in association with a normal or increased fractional shortening. Thus, some cardiologists believe that valve insufficiency (from endocarditis), rather than myocardial dysfunction (from myocarditis), is the dominant cause of heart failure in acute rheumatic fever.

In chronic rheumatic heart disease, echocardiography may be used to track the progression of valve stenosis and may help determine the time for surgical intervention. The leaflets of affected valves become diffusely thickened, with fusion of the commissures and chordae tendineae. Increased echodensity of the mitral valve may signify calcification.

- **Heart catheterization:** In acute rheumatic heart disease, this procedure is not indicated. With chronic disease, heart catheterization has been performed to evaluate mitral and aortic valve disease and to balloon stenotic mitral valves.

  - Postcatheterization precautions include hemorrhage, pain, nausea and vomiting, and arterial or venous obstruction from thrombosis or spasm.

  - Complications may include mitral insufficiency after balloon dilation of the mitral valve, tachyarrhythmias, bradyarrhythmias, and vascular occlusion.

**Other Tests:**

- **Electrocardiogram**

  - Sinus tachycardia most frequently accompanies acute rheumatic heart disease. Alternatively, some children develop sinus bradycardia from increased vagal tone. No correlation exists between bradycardia and the severity of the carditis.

  - First-degree atrioventricular (AV) block (prolongation of the PR interval) is observed in some patients with rheumatic heart disease. This abnormality may be related to localized myocardial inflammation involving the AV node or to vasculitis involving the AV nodal artery. First-degree AV block is a nonspecific finding and should not be used as a criterion for the diagnosis of rheumatic heart disease. Its presence does not correlate with the development of chronic rheumatic heart disease.

  - Second-degree (intermittent) and third-degree (complete) AV block with progression to ventricular standstill have been described. Heart block in the setting of rheumatic fever, however, typically resolves with the rest of the disease process.

  - When acute rheumatic fever is associated with pericarditis, ST segment elevation may be present and is marked most in lead II, III, aVF, and V₄-V₆.

  - Patients with rheumatic heart disease also may develop atrial flutter, multifocal atrial tachycardia, or atrial fibrillation from chronic mitral valve disease and atrial dilatation.

**Histologic Findings:** Pathologic examination of the insufficient valves may show verrucous lesions at the line of closure. Aschoff bodies (perivascular foci of eosinophilic collagen surrounded by lymphocytes, plasma cells, and macrophages) are found in the pericardium, perivascular regions of the myocardium, and endocardium. The Aschoff bodies assume a granulomatous appearance with a central fibrinoid focus and eventually are replaced by nodules of scar tissue. Anitschkow cells are plump macrophages within Aschoff bodies. In the pericardium, fibrinous and serofibrinous exudates may produce an appearance of "bread and butter" pericarditis.

**Medical Care:** Medical therapy is directed toward eliminating the group A streptococcal pharyngitis (if still present), suppressing inflammation from the autoimmune response, and providing supportive treatment for congestive heart failure. Group A streptococcal vaccines are still years away from being available. Oral penicillin V remains the drug of choice for treatment of group A streptococcal pharyngitis. When oral penicillin is not feasible or dependable, a single dose of intramuscular benzathine penicillin G is therapeutic. For patients who are allergic to penicillin, administer erythromycin or a first-generation cephalosporin. Other options include clarithromycin for 10 days, azithromycin for 5 days, or a narrow-spectrum (first-generation) cephalosporin for 10 days. As many as 15% of penicillin-allergic patients also are allergic to cephalosporins. Tetracyclines and
sulfonamides should not be used to treat group A streptococcal pharyngitis.

- For recurrent group A streptococcal pharyngitis, a second 10-day course of the same antibiotic can be repeated. Alternate drugs include narrow-spectrum cephalosporins, amoxicillin-clavulanate, dicloxacillin, erythromycin, or other macrolides.

- In general, antimicrobial therapy is not indicated for pharyngeal carriers of group A *Streptococcus*. Exceptions include the following:
  - Outbreaks of rheumatic fever or poststreptococcal glomerulonephritis
  - Family history of rheumatic fever
  - Outbreaks of group A streptococcal pharyngitis in a closed community
  - When considering tonsillectomy for chronic group A streptococcal carriage
  - Multiple episodes of documented group A streptococcal pharyngitis within a family despite appropriate therapy
  - Following group A streptococcal toxic shock syndrome or necrotizing fasciitis in a household contact

Carriage is difficult to eradicate with conventional penicillin therapy. Thus, oral clindamycin (20 mg/kg/d in 3 divided doses for 10 days) is recommended.

- Treatment of the acute inflammatory manifestations of acute rheumatic fever consists of administering salicylates and steroids. Aspirin in anti-inflammatory doses effectively reduces all manifestations of the disease except chorea, and the response typically is dramatic. In fact, if rapid improvement is not seen after 24-36 hours of therapy, the diagnosis of rheumatic fever should be questioned.
  - Attempts are made to obtain aspirin blood levels at 20-25 mg/dL, but, due to variable GI absorption of the drug, stable levels may be difficult to achieve during the inflammatory phase. Aspirin is maintained at anti-inflammatory doses until the signs and symptoms of acute rheumatic fever are resolved or subsiding (6-8 wk) and the acute phase reactants have returned to normal levels.
  - Anti-inflammatory doses of aspirin may be associated with abnormal liver function tests and GI toxicity, and it may be necessary to adjust the aspirin dosage. When discontinuing therapy, aspirin should be withdrawn gradually over weeks while monitoring the acute phase reactants for evidence of rebound.

- If moderate-to-severe carditis is indicated by cardiomegaly, congestive heart failure, or third-degree heart block, oral prednisone should be added to salicylate therapy. Prednisone should be continued for 2-6 weeks, depending on the severity of the carditis, and tapered during the last week of therapy. Adverse effects can be minimized by discontinuing prednisone therapy after 2-4 weeks and maintaining salicylates for an additional 2-4 weeks. Additional treatment for patients with acute rheumatic fever and congestive heart failure should include digoxin, diuretics, supplemental oxygen, bed rest, and sodium and fluid restriction.

Digoxin should be initiated only after checking electrolyte values and correcting abnormal findings in serum potassium levels. The total loading dose is 20-30 mcg/kg orally with 50% of the dose given initially, followed by 25% of the dose 8 and 16 hours after the initial dose. Maintenance doses typically are 8-10 mcg/kg/d orally in 2 divided doses. For older children and adults, the total loading dose is 1.25-1.5 mg orally, and the maintenance dose is 0.25-0.5 mg/d orally. Therapeutic digoxin levels are present at trough levels of 1.5-2 ng/mL. The diuretics most commonly used in conjunction with digoxin for children with congestive heart failure include furosemide and spironolactone, both at doses of 1-2 mg/kg/dose twice per day.

In patients with moderate-to-severe mitral valve regurgitation, enalapril therapy was associated with significant reduction in left ventricular diameter and mitral regurgitation volume.

- Surgery is indicated to decrease valve insufficiency when heart failure persists or worsens during the acute phase after aggressive medical therapy. Mitral valve repair (posterior collar annuloplasty, commissurotomy, cusp level chordal shortening, cusp thinning, cleft suture, and cusp excision or plication) has also been shown to be feasible in children with chronic rheumatic mitral valve disease.
Preventive and prophylactic therapy is indicated after rheumatic fever and rheumatic heart disease to prevent further damage to valves. The initial course of antibiotics given to eradicate the streptococcal infection also serves as the first course of prophylaxis. An injection of 0.6-1.2 million units of benzathine penicillin G intramuscularly every 4 weeks is the recommended regimen for secondary prevention for most patients in the United States. The same dosage should be given for 3 weeks in areas where rheumatic fever is endemic, in patients with residual carditis, and in high-risk patients.

- While oral penicillin prophylaxis also is effective, data from the World Health Organization suggest that the recurrence risk for group A streptococcal pharyngitis is lower when penicillin is administered parentally.

- The duration of antibiotic prophylaxis is controversial. Antibiotic prophylaxis should be continued indefinitely for patients at high risk (eg, health care workers, teachers, daycare workers) for recurrent group A streptococcal infection. Ideally, prophylaxis should be continued indefinitely because recurrent group A streptococcal infection and rheumatic fever are possible at any age. The American Heart Association, however, currently recommends that rheumatic fever patients without carditis receive prophylactic antibiotics for 5 years, or until aged 21 years, whichever is longer.

- Patients with rheumatic fever and carditis but no valve disease should receive prophylactic antibiotics for 10 years or well into adulthood, whichever is longer. Finally, patients with rheumatic fever and carditis and valve disease should receive antibiotics at least 10 years or until aged 40 years. Patients with rheumatic heart disease require antibiotic prophylaxis before certain surgical and dental procedures to prevent bacterial endocarditis. Patients who have had rheumatic fever without valve disease do not need prophylaxis for prevention of endocarditis. Penicillin should not be used for prophylaxis of endocarditis in patients who are receiving secondary rheumatic fever prophylaxis because of relative resistance to penicillin. The recommended alternative for these patients is erythromycin.

**Surgical Care:** When heart failure persists or worsens after aggressive medical therapy for acute rheumatic heart disease, surgery to decrease valve insufficiency may be life-saving.

- Forty percent of patients with acute rheumatic fever subsequently develop mitral stenosis as adults.

- In patients with critical stenosis, mitral valvulotomy, percutaneous balloon valvuoplasty, or mitral valve replacement may be indicated.

- Due to high rates of recurrent symptoms after annuloplasty or other repair procedures, valve replacement appears to be the preferred surgical option.

**Diet:** The diet should be nutritious and without restrictions except in the patient with congestive heart failure, whose fluid and sodium intake should be restricted. Potassium supplementation may be necessary because of the mineralocorticoid effect of corticosteroid and the diuretics (if used).

**Activity:** Initially, patients should be placed on bed rest followed by a period of indoor activity before being permitted to return to school. Full activity should not be allowed until the acute phase reactants have returned to normal levels.

Medical therapy is directed at eliminating the group A streptococcal pharyngitis (if still present), suppressing inflammation from the autoimmune response, and providing supportive treatment for congestive heart failure. The treatment and prevention of group A streptococcal pharyngitis outlined here is based on the current recommendations of the Committee on Infectious Disease (American Academy of Pediatrics). See the eMedicine article [Pharyngitis](https://www.emedicine.com/medicine/topic753.htm).

Penicillin V is the drug of choice for treatment of group A streptococcal pharyngitis. Ampicillin or amoxicillin may be used instead of penicillin V but have no microbiologic advantage. Tetracyclines and sulfonamides should not be used to treat group A streptococcal pharyngitis. For recurrent group A streptococcal pharyngitis, a second 10-day course of the same antibiotic can be repeated. Alternate drugs include narrow-spectrum cephalosporins, amoxicillin-clavulanate, dicloxacillin, erythromycin, or other macrolides for 10 d. As many as 15% of patients allergic to penicillin also are allergic to cephalosporins.

**Drug Category:** **Antibiotics** -- Antibiotics are used for the initial treatment of group A streptococcal pharyngitis to prevent the first attack of rheumatic fever (primary prophylaxis), for recurrent streptococcal
pharyngitis, and for continuous therapy to prevent recurrent rheumatic fever and rheumatic heart disease (secondary prophylaxis).

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Penicillin VK (Beepen-VK, Betapen-VK, Pen-Vee K) -- DOC for treatment of group A streptococcal pharyngitis. Inhibits the biosynthesis of cell wall mucopeptide. Bactericidal against sensitive organisms when adequate concentrations are reached, and most effective during the stage of active multiplication. Inadequate concentrations may produce only bacteriostatic effects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>500 mg PO bid/tid for 10 d</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Children: 250 mg (400,000 U) PO bid/tid for 10 d Adolescents: Administer as in adults</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity</td>
</tr>
<tr>
<td>Interactions</td>
<td>Probenecid may increase effectiveness by decreasing clearance; tetracyclines are bacteriostatic, causing a decrease in the effectiveness of penicillins when administered concurrently</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Caution in renal impairment; administer 1 h ac or 2 h pc</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Penicillin, benzathine (Bicillin L-A) and procaine (Wycillin) -- Used when oral administration of penicillin is not feasible or dependable. Discomfort of IM injection may be minimized if the penicillin G is brought to room temperature before injection or if a combination of benzathine penicillin G and procaine penicillin G (Bicillin CR) is used. Initial course of antibiotics given to eradicate the streptococcal infection also serves as the first course of prophylaxis. Benzathine penicillin G IM q4wk is recommended for secondary prevention for most United States patients. The same dosage should be used q3wk in areas where rheumatic fever is endemic, in patients with residual carditis, and in patients with high risk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>1.2 million U of benzathine penicillin G or a combination of 900,000 U of benzathine penicillin G with 300,000 U of procaine penicillin G single dose IM to eradicate streptococcal infection; for secondary prevention of rheumatic fever, administer the above dose q3wk (high-risk areas or patients) or q4wk (most areas in United States)</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>&lt;27 kg: 600,000 U of benzathine penicillin G single dose IM to eradicate the streptococcal infection; for secondary prevention of rheumatic fever, administer the above dose q3wk (high-risk areas or patients) or q4wk (most areas in United States) &gt;27 kg: Administer as in adults</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity</td>
</tr>
<tr>
<td>Interactions</td>
<td>Increases risk of bleeding when administered concurrently with warfarin; ethacrynic acid, aspirin, indomethacin, and furosemide may compete with penicillin G for renal tubular secretion increasing penicillin serum concentrations</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Never use IV route to administer penicillin G procaine; perform cultures after treatment to confirm streptococcal eradication</td>
</tr>
</tbody>
</table>

| Drug Name | Erythromycin estolate (Ilosone) or ethyl succinate (E.E.S, EryPed) -- Used to treat patients allergic to penicillin. Inhibits bacterial growth, possibly by blocking dissociation of peptidyl tRNA from ribosomes causing |
RNA-dependent protein synthesis to arrest.

<table>
<thead>
<tr>
<th>Adult Dose</th>
<th>1 g/d PO divided bid/qid for 10 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Dose</td>
<td>20-40 mg/kg/d PO divided bid/qid for 10 d</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; hepatic impairment</td>
</tr>
<tr>
<td>Interactions</td>
<td>Coadministration may increase toxicity of theophylline, digoxin, carbamazepine, and cyclosporine; may potentiate anticoagulant effects of warfarin; coadministration with lovastatin and simvastatin, increases risk of rhabdomyolysis</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Caution in liver disease; estolate formulation may cause cholestatic jaundice; GI adverse effects are common (give doses pc); discontinue use if nausea, vomiting, malaise, abdominal colic, or fever occur</td>
</tr>
</tbody>
</table>

Drug Category: **Anti-inflammatory agents** -- The manifestations of acute rheumatic fever (including carditis) typically respond rapidly to therapy with anti-inflammatory agents. Aspirin, in anti-inflammatory doses, is the drug of choice. Prednisone is added when there is evidence of worsening carditis and heart failure.

**Drug Name**

Aspirin (Anacin, Ascriptin, Bayer Aspirin) -- Also called acetylsalicylic acid. Inhibits prostaglandin synthesis, which prevents formation of platelet-aggregating thromboxane A2. Start immediately after the diagnosis of rheumatic fever has been made. Initiation of therapy may mask manifestations of the disease.

**Adult Dose**

4-8 g/d PO in 4-6 divided doses; maintain salicylate serum levels in a 20-25 mcg/dL range until all symptoms resolve and the acute phase reactants return to normal values

**Pediatric Dose**

80-100 mg/kg/d PO in 4-6 divided doses; maintain salicylate serum levels in a 20-25 mcg/dL range until all symptoms resolve and the acute phase reactants return to normal values

**Contraindications**

Documented hypersensitivity; liver damage, hypoprothrombinemia, vitamin K deficiency, bleeding disorders, asthma; because of association of aspirin with Reye syndrome, do not use in children (<16 y) with flu

**Interactions**

Effects may decrease with antacids and urinary alkalinizers; corticosteroids decrease salicylate serum levels; additive hypoprothrombinemic effects and increased bleeding time may occur with coadministration of anticoagulants; may antagonize uricosuric effects of probenecid and increase toxicity of phenytoin and valproic acid; doses >2 g/d may potentiate glucose lowering effect of sulfonylurea drugs

**Pregnancy**

C - Safety for use during pregnancy has not been established.

**Precautions**

Pregnancy category D in third trimester; risk of salicylate intoxication and poisoning; watch for hyperventilation with prolonged expiratory phase with respiratory alkalosis and metabolic acidosis; risk of tinnitus, hepatic dysfunction, GI discomfort, and ulceration; taken during pregnancy increases the risk of pulmonary hypertension in the neonate

**Drug Name**

Prednisone (Deltasone, Orasone) -- May decrease inflammation by reversing increased capillary permeability and suppressing PMN activity.

If moderate to severe carditis is indicated by cardiomegaly, congestive heart failure, or third-degree heart block, 2 mg/kg/d PO should be used in addition to, or in lieu of, salicylate therapy. Prednisone should be continued for 2-4 wk, depending on the severity of the
Angiotensin-converting enzyme (ACE) inhibitors -- These agents are competitive inhibitors of ACE. They reduce angiotensin II levels and thus decrease aldosterone secretion.

**Drug Name**
Enalapril (Vasotec) -- Indicated for chronic aortic and/or mitral regurgitation. Prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, resulting in increased plasma renin levels and a reduction in aldosterone secretion. Helps control blood pressure and proteinuria. Decreases pulmonary-to-systemic flow ratio in the catheterization laboratory and increases systemic blood flow in patients with relatively low pulmonary vascular resistance. Has favorable clinical effect when administered over a long period. Helps prevent potassium loss in distal tubules. Body conserves potassium; thus, less oral potassium supplementation needed. Goal is to decrease afterload to left ventricle (by reducing systemic blood pressure and by peripheral vasodilatation).

**Adult Dose**
2.5 mg PO bid initially; therapeutic range within 2.5-20 mg/d in 2 divided doses; not to exceed 40 mg/d

**Pediatric Dose**
0.1 mg/kg PO bid/qid; not to exceed 40 mg/d Alternatively, 5-10 mcg/kg IV qid, infuse slowly over 5 min

**Contraindications**
Documented hypersensitivity

**Interactions**
NSAIDs may reduce hypotensive effects of enalapril; ACE inhibitors may increase digoxin, lithium, and allopurinol levels; rifampin decreases enalapril levels; probenecid may increase enalapril levels; the hypotensive effects of ACE inhibitors may be enhanced when given concurrently with diuretics

**Pregnancy**
C - Safety for use during pregnancy has not been established.

**Precautions**
Pregnancy category D in second and third trimesters; caution in renal impairment, valvular stenosis, or severe congestive heart failure
Further Outpatient Care:

- Patients usually show significant improvement after initiation of anti-inflammatory therapy. They should not be allowed to resume full activities, however, until all clinical symptoms have abated and laboratory values have returned to normal levels.

- The importance of prophylaxis against recurrent streptococcal pharyngitis and rheumatic fever should be emphasized with each patient. Each recurrent episode of rheumatic carditis produces further valve damage and increases the likelihood that valve replacement will be required. Patients should remain on antibiotic prophylaxis at least until their early twenties. Many physicians believe that lifelong prophylaxis is appropriate.

- Patients should be examined regularly to detect signs of mitral stenosis, pulmonary hypertension, arrhythmias, and congestive heart failure.

Deterrence/Prevention:

- Primary prevention of rheumatic fever consists of diagnosis and treatment of group A beta-hemolytic streptococcal pharyngitis.

Complications:

- Potential complications include heart failure from valve insufficiency (acute rheumatic carditis) or stenosis (chronic rheumatic carditis). Associated cardiac complications include atrial arrhythmias, pulmonary edema, recurrent pulmonary emboli, infective endocarditis, intracardiac thrombus formation, and systemic emboli.

Prognosis:

- Manifestations of acute rheumatic fever resolve over a period of 12 weeks in 80% of patients and may extend as long as 15 weeks in the remaining patients.

- Rheumatic fever was the leading cause of death in people aged 5-20 years in the United States 100 years ago. At that time, the mortality rate was 8-30% from carditis and valvulitis but decreased to a 1-year mortality rate of 4% by the 1930s.

- Following the development of antibiotics, the mortality rate decreased to almost 0% by the 1960s in the United States; however, it has remained 1-10% in developing countries. The development of penicillin also has affected the likelihood of developing chronic valvular disease after an episode of acute rheumatic fever. Before penicillin, 60-70% of patients developed valve disease as compared to 9-39% of patients since penicillin was developed.

- In patients who develop murmurs from valve insufficiency from acute rheumatic fever, numerous factors, including the severity of the initial carditis, the presence or absence of recurrences, and the amount of time since the episode of rheumatic fever, affect the likelihood that valve abnormalities and the murmur will disappear. The type of treatment and the promptness with which treatment is initiated does not affect the likelihood of disappearance of the murmur. In general, the incidence of residual rheumatic heart disease at 10 years is 34% in patients without recurrences but 66% in patients with recurrent rheumatic fever. Disappearance of the murmur, when it occurs, happens within 5 years in 50% of patients. Thus, significant numbers of patients experience resolution of valve abnormalities even 5-10 years after their episode of rheumatic fever. The importance of preventing recurrences of rheumatic fever is evident.

Patient Education:

- Emphasize the importance of prophylaxis against recurrent streptococcal pharyngitis and rheumatic fever with each patient.

- For excellent patient education resources, visit eMedicine's Heart Center. Also, see eMedicine's patient education article Mitral Valve Prolapse.
Medical/Legal Pitfalls:

- The incidence of rheumatic heart disease, the facilities available for identifying and treating the illness, and the caring physicians training and experience with this disorder all vary widely with geographic location. Further, scientific understanding of rheumatic heart remains incomplete. For these reasons, it is difficult to recommend a fixed set of medical-legal guidelines which will apply for all situations.


• Sampaio RO, Grinberg M, Leite JJ, et al: Effect of enalapril on left ventricular diameters and exercise capacity in asymptomatic or mildly symptomatic patients with regurgitation secondary to mitral valve prolapse or rheumatic heart disease. Am J Cardiol 2005 Jul 1; 96(1): 117-21[Medline].
• WHO: Rheumatic Fever and Rheumatic Heart Disease. WHO technical report series 2004; 923:[Full Text].

NOTE:

Medicine is a constantly changing science and not all therapies are clearly established. New research changes drug and treatment therapies daily. The authors, editors, and publisher of this journal have used their best efforts to provide information that is up-to-date and accurate and is generally accepted within medical standards at the time of publication. However, as medical science is constantly changing and human error is always possible, the authors, editors, and publisher or any other party involved with the publication of this article do not warrant the information in this article is accurate or complete, nor are they responsible for omissions or errors in the article or for the results of using this information. The reader should confirm the information in this article from other sources prior to use. In particular, all drug doses, indications, and contraindications should be confirmed in the package insert. FULL DISCLAIMER.

Rheumatic Heart Disease excerpt
Privacy Policy Changes

Important Announcement:

WebMD, Inc. ("WebMD Health"), a leader in online health information services to the medical professional community has acquired eMedicine. This acquisition was completed January 18, 2006. As we become more fully integrated, eMedicine users are now eligible to utilize the services available to physicians through WebMD Health's professional portals, including Medscape.com, theheart.org and Medsite.com. Your eMedicine account information will now be accessible to WebMD Health where it will be maintained in accordance with the WebMD Professional Services Privacy Policy. **Click here** to view the WebMD Professional Services Privacy Policy.

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