

Corso di Laurea Magistrale in Medicina e Chirurgia

Università degli Studi di Napoli Federico II

Corso Integrato di Immunologia Clinica e Allergologia, Malattie Cutanee e Veneree e Chirurgia Plastica

Acute Rheumatic Fever

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Definitions

- **Acute Rheumatic Fever** results from the body's autoimmune response to a throat infection caused by *Streptococcus pyogenes* (Group A *Streptococcus* bacteria)
- **Rheumatic Heart Disease** refers to the long-term cardiac damage caused by a single episode or multiple recurrent episodes of ARF. RHD remains a significant worldwide cause of morbidity and mortality, particularly in resource-poor settings
- Improved living conditions and widespread treatment of superficial *S. pyogenes* infections have caused these diseases to become rare in wealthy areas

Epidemiology

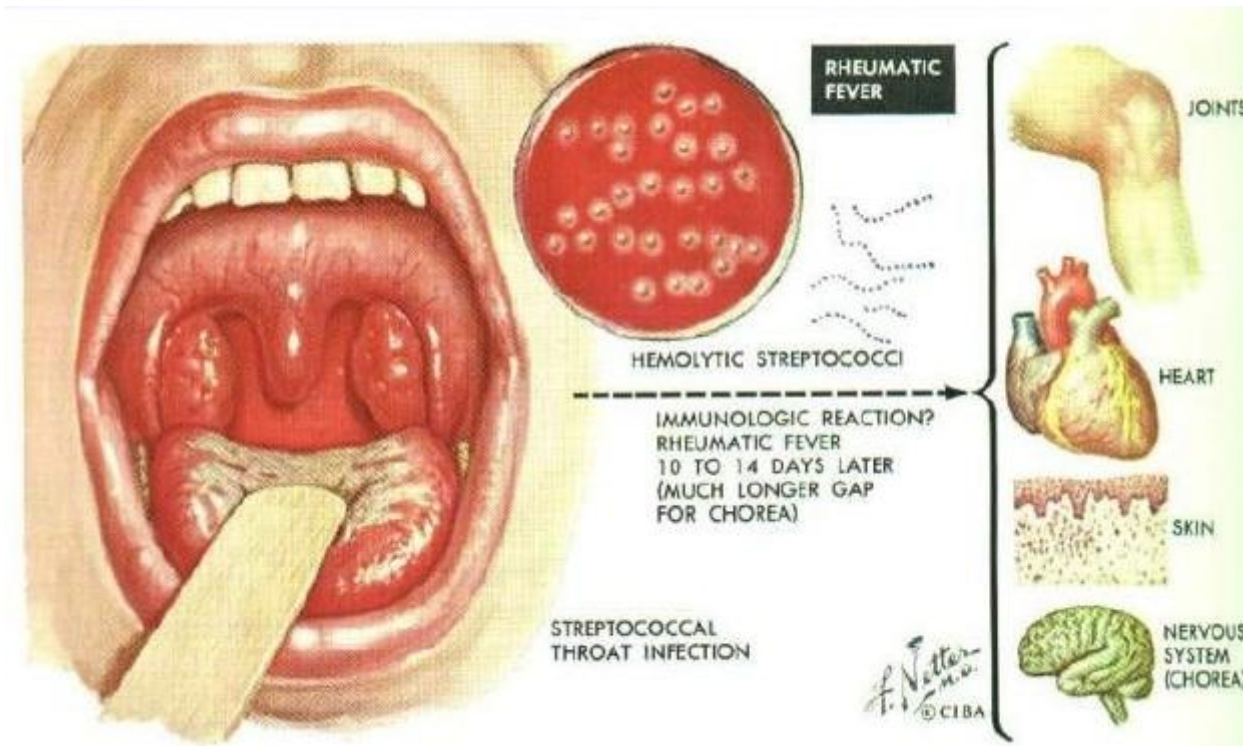
- Significant global burden
- Low-resource populations
- ARF incidence poorly documented
- 155/100.000 children aged 5-14 ys in indigenous populations in Australia
- Global disease in 2005 estimated 471000 cases annually
- Diagnosis of ARF difficult and problematic

Risk Factors

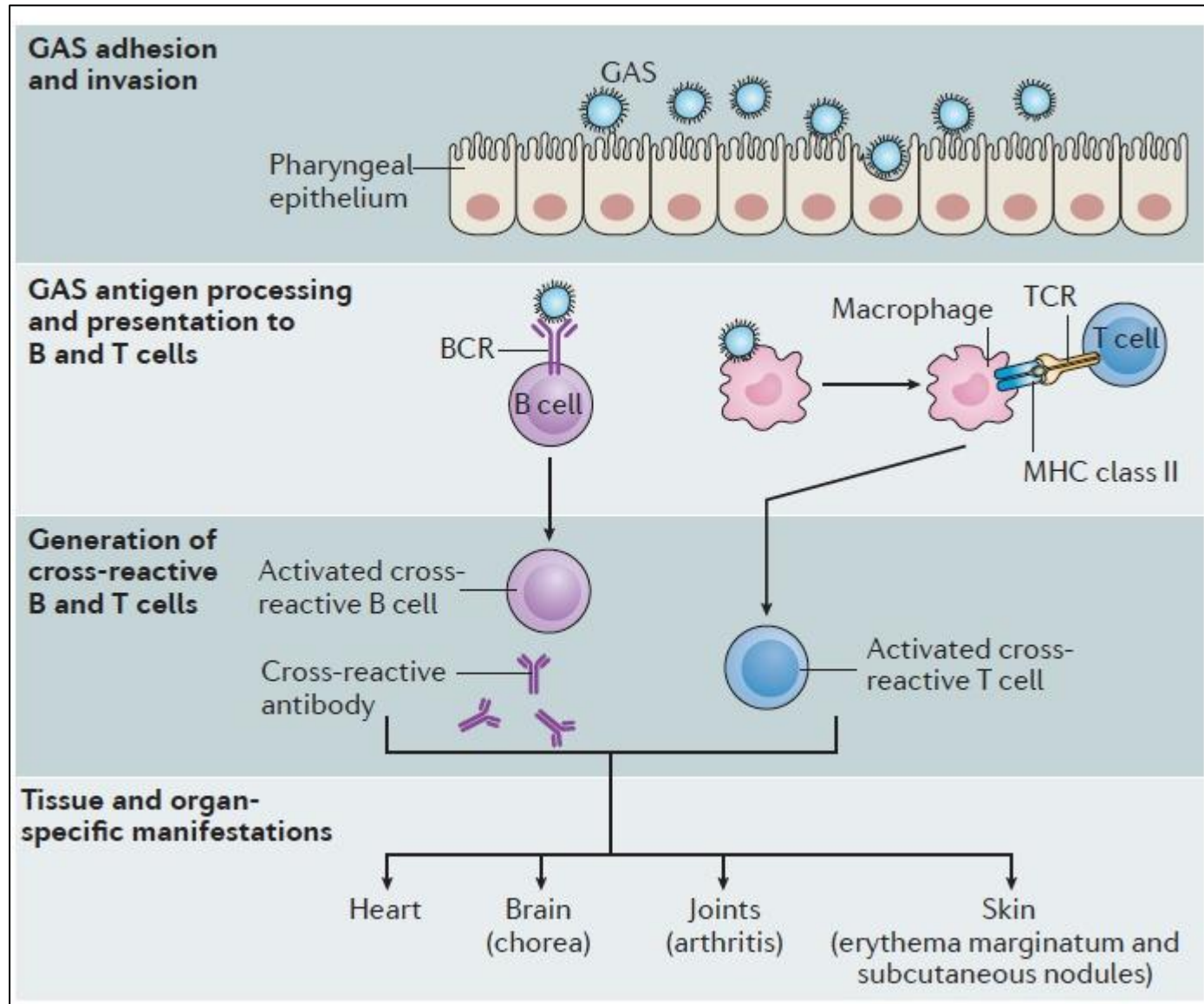
- Age: 5-14 ys children
- Gender: M=F for ARF, F>M for RHD
- **Environmental Factors** increasing exposure to *S. pyogenes*:
 - Household crowding
 - rural and remote areas
 - insufficient nutrition in childhood
- **Genetic susceptibility**:
 - Polygenic
 - Polymorphisms in several genes

Pathophysiology

- Starts from a pharyngeal infection by *S. pyogenes* in a host with a genetic susceptibility to the disease
- Activation of the immune system: presentation of Group A Streptococcus to T and B cells
- **Molecular Mimicry**



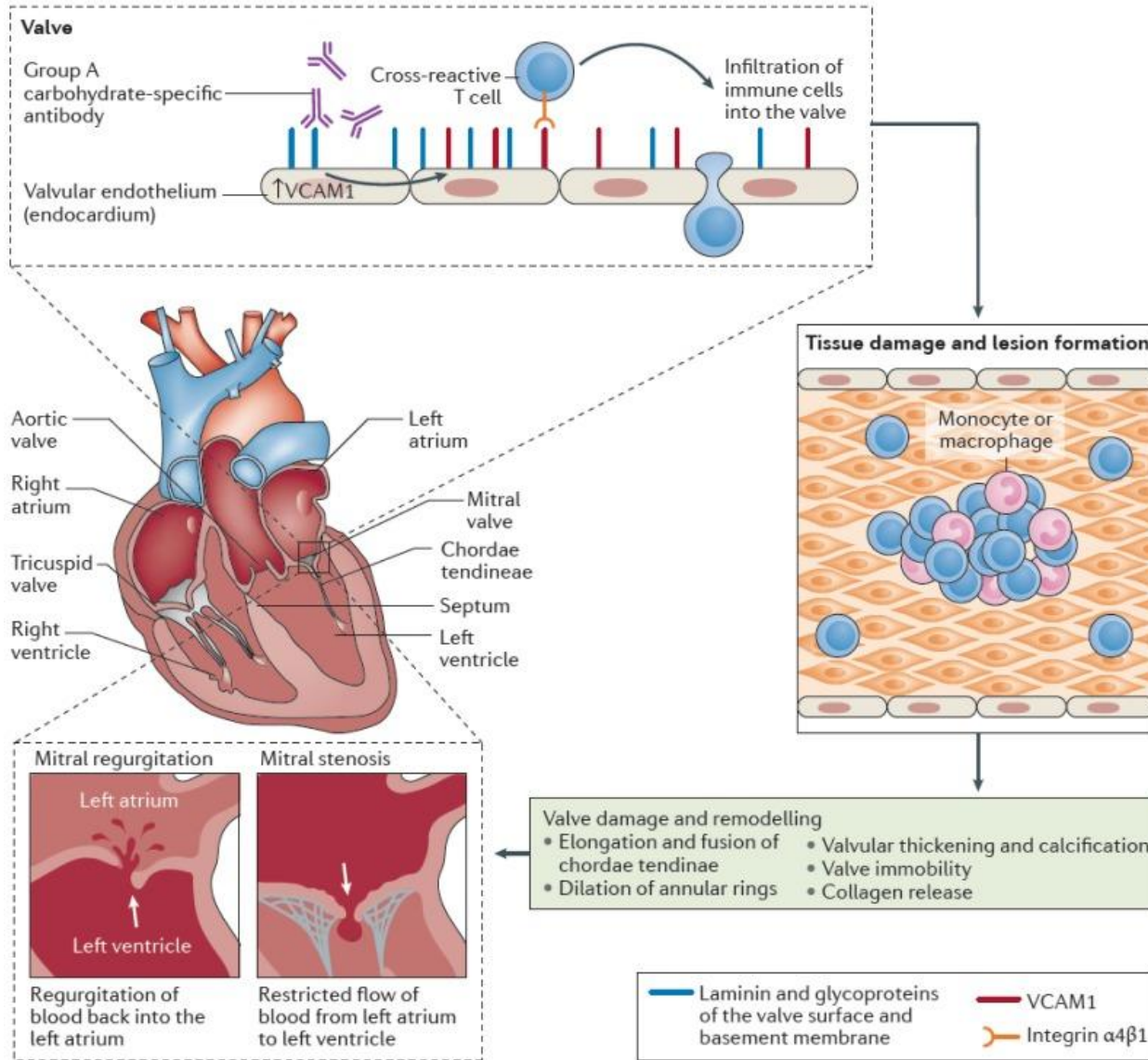
Pathophysiology



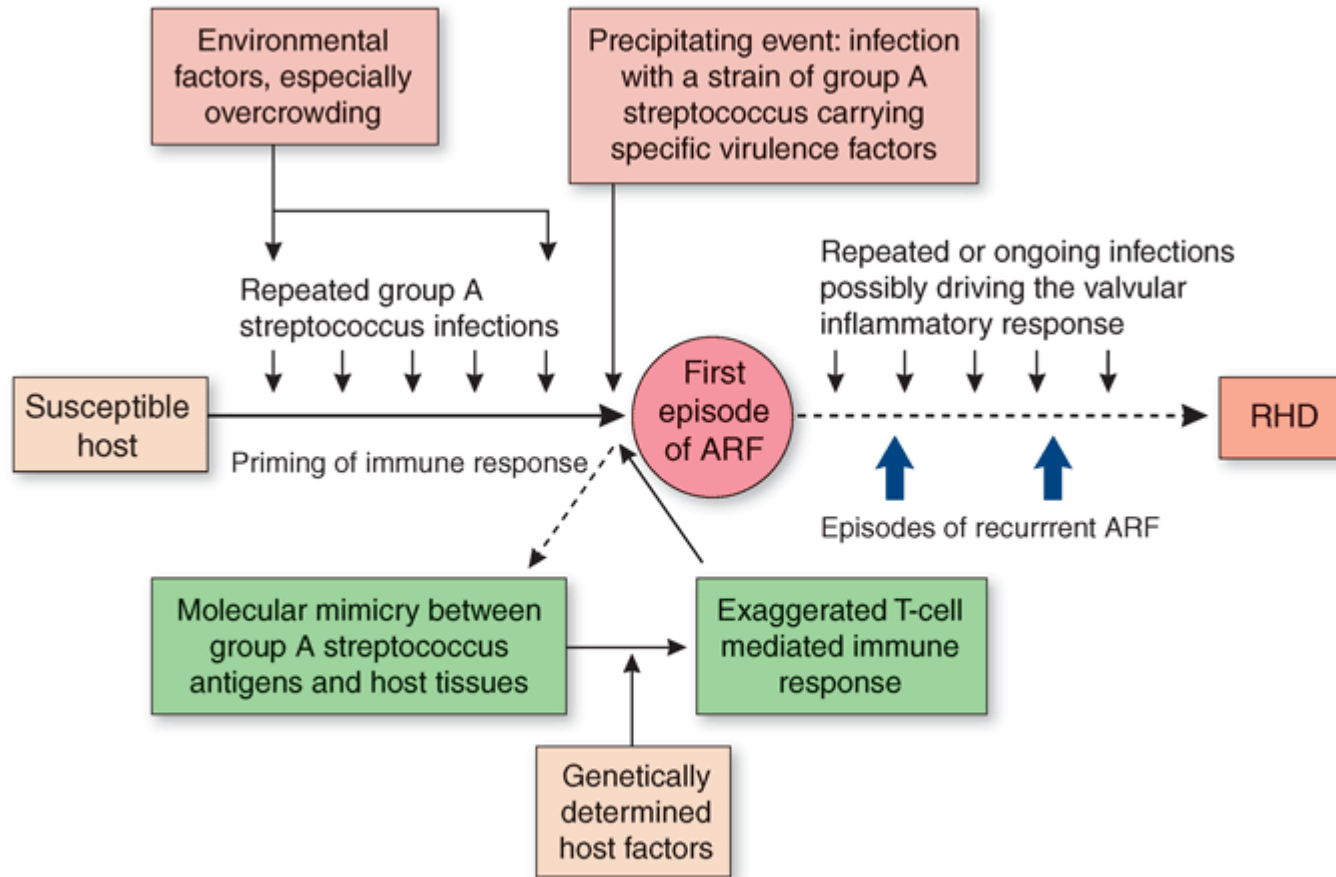
Molecular Mimicry

- The alpha-helical protein structures of **protein M and N-acetyl-beta-D-glucosamine** (the carbohydrate antigen of GAS) share epitopes with **myosin**, and antibodies against both of these antigens cross-react against human tissues
- Monoclonal antibodies from GAS-infected patients cross-react with myosin
- Monoclonal Antibodies directed against myosin and N-acetyl-beta-D-glucosamine react against valvular endothelium in patients with ARF

Pathogenesis of Carditis in ARF



Pathophysiology



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

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Clinical Manifestations

- In the weeks following an episode of *S. pyogenes* pharyngitis
- Fever (90%) and arthritis (75%)
- The most serious is carditis (>50%) because can lead to RHD, while all others fully resolve within weeks



Clinical Manifestations:

Arthritis

- Large joints: knees, ankles, elbows, wrists
- «Migratory» or «Additive» polyarthritis
- Each joint affected for few days to a week and complete resolution without treatment in a month
- Joint pain can be severe
- Rapid response to anti-inflammatory therapy
- No response in 48h: reconsider diagnosis
- DD with septic arthritis (joint aspiration)

Clinical Manifestations:

Carditis

- Pancarditis involving pericardium, epicardium, myocardium and endocardium
- The main clinical manifestation involves endocardium: valvulitis of mitral valve (mitral regurgitation) and less frequently aortic valve (aortic regurgitation)
- Mitral regurgitation: typical pansystolic murmur
- Pericardial rub may be heard when pericardium is affected
- Cardiomegaly in more severe mitral regurgitation
- **To do:** echocardiogram

Clinical Manifestations:

Chorea

- Sydenham's chorea or St. Vitus dance
- Up to 30% of ARF patients
- Involuntary, non-rhythmic and purposeless movements of the trunk and limbs, which are often more pronounced on one side of the body
- Disappears with sleep
- Emotional instability
- Can occur many months after the streptococcal infection
- Strongly associated with carditis

Clinical Manifestations:

Skin findings



- Less than 10%
- **Erythema marginatum or annulare**
 - Bright pink, blanching, non-pruritic macules or papules that spread outwards in a serpiginous pattern, usually on the trunk or proximal limbs
- **Subcutaneous nodules**
 - small, painless, round nodules over bony prominences (elbows) or extension tendons and usually symmetric
 - one-two weeks duration



Clinical Manifestations:

Others

- Fever
- Arthralgia
- Elevated acute phase reactants
- Prolonged PR interval on ECG

- Lethargy
- Abdominal pain
- Epistaxis
- Anemia (normocytic and normochromic) and leukocytosis

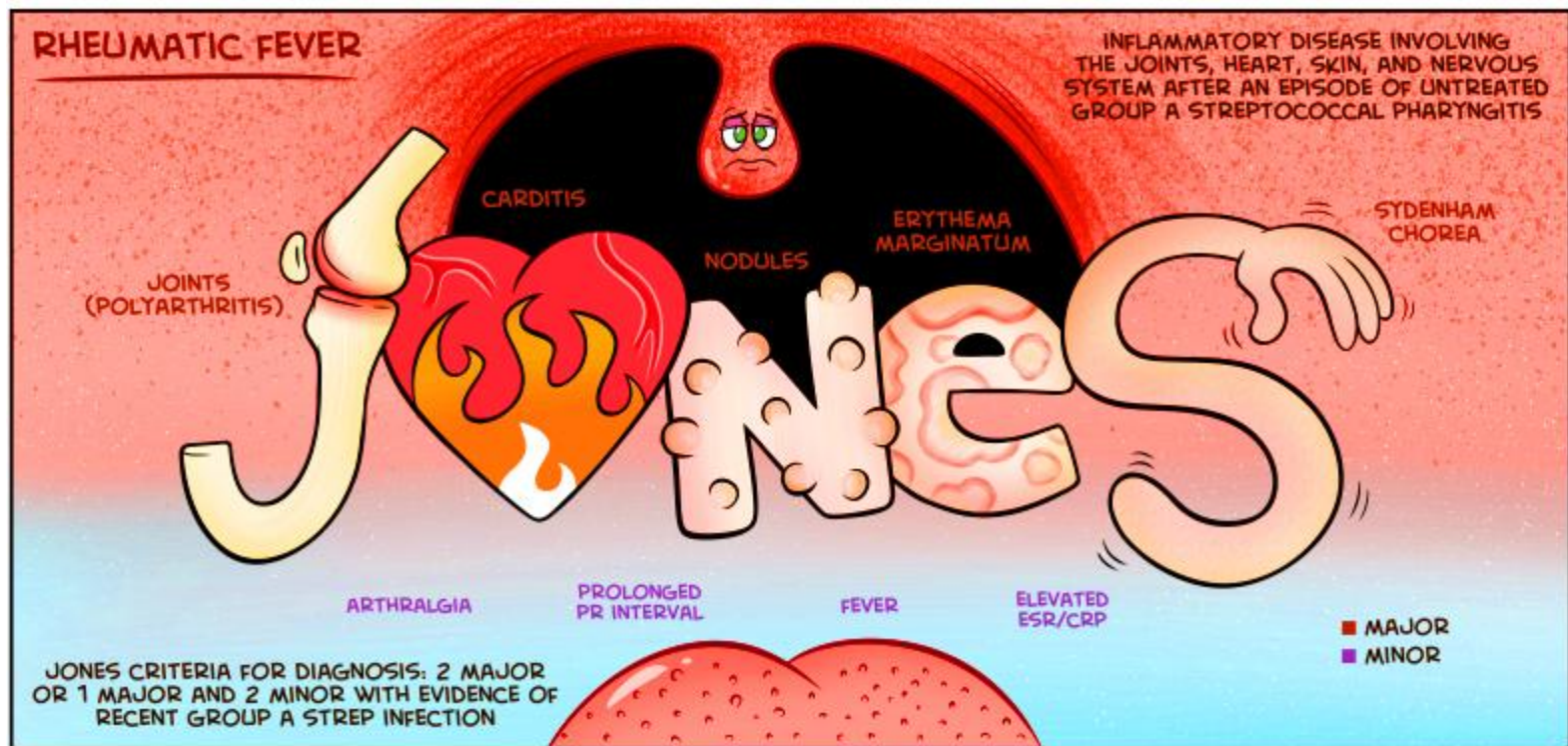
Clinical Manifestations:

Diagnosis

<p>MAJOR CRITERIA</p> <p><u>Low-risk populations</u></p> <p>Carditis</p> <ul style="list-style-type: none">• Clinical and/or subclinical <p>Arthritis</p> <ul style="list-style-type: none">• Polyarthritits only <p>Chorea</p> <p>Erythema marginatum</p> <p>Subcutaneous nodules</p> <p>MINOR CRITERIA</p> <p><u>Low-risk populations</u></p> <p>Polyarthralgia Fever ($\geq 38.5^{\circ}\text{C}$) ESR ≥ 60 mm in the first hour and/or CRP ≥ 3.0 mg/dL Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)</p>	<p>MAJOR CRITERIA</p> <p><u>Moderate- and high-risk populations</u></p> <p>Carditis</p> <ul style="list-style-type: none">• Clinical and/or subclinical <p>Arthritis</p> <ul style="list-style-type: none">• Monoarthritis or polyarthritits• Polyarthralgia <p>Chorea</p> <p>Erythema marginatum</p> <p>Subcutaneous nodules</p> <p>MINOR CRITERIA</p> <p><u>Moderate- and high-risk populations</u></p> <p>Monoarthralgia Fever ($\geq 38^{\circ}\text{C}$) ESR ≥ 30 mm/h and/or CRP ≥ 3.0 mg/dL Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)</p>
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2 major or 1 major + 2 minor criteria

Clinical Manifestations: Diagnosis



Clinical Manifestations:

Diagnosis

Key investigations for the diagnosis of acute rheumatic fever

- Full blood count
- Acute phase reactants: C-reactive protein and erythrocyte sedimentation rate
- Echocardiogram
- Electrocardiogram
- Chest radiograph
- Throat swab for bacterial culture
- Streptococcal serology (anti-streptolysin O titer and anti-deoxyribonuclease B titer)

Medical Management

- Eradication of GAS from the throat and secondary prophylaxis
- Symptomatic treatment of arthritis and/or arthralgia
- Management of carditis and/or heart failure
- Management of chorea
- Patient and family education

Medical Management: Primary Prevention

<i>AGENT</i>	<i>DOSAGE</i>	<i>EVIDENCE RATING</i>
Amoxicillin	50 mg per kg (maximum, 1 g) orally once daily for 10 days	1B
Penicillin G benzathine	Patients weighing 27 kg or less: 600,000 units IM once Patients weighing more than 27 kg: 1,200,000 units IM once	1B
Penicillin V potassium	Patients weighing 27 kg or less: 250 mg orally 2 or 3 times daily for 10 days Patients weighing more than 27 kg: 500 mg orally 2 or 3 times daily for 10 days	1B
For patients allergic to penicillin		
Azithromycin	12 mg per kg (maximum, 500 mg) orally once daily for 5 days	2aB
Clarithromycin	15 mg per kg orally per day, divided into 2 doses (maximum, 250 mg twice daily), for 10 days	2aB
Clindamycin	20 mg per kg orally per day (maximum, 1.8 g per day), divided into 3 doses, for 10 days	2aB

Adapted from Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation. 2009;119(11):1544.

Medical Management

- Symptomatic treatment of arthritis and/or arthralgia
 - Aspirin, NSAIDs
- Management of carditis and/or heart failure
 - CCS, HF treatment (diuretics, fluid restriction, bed rest, ACE-I)
 - valve surgery when necessary
- Management of chorea
 - Usually benign and self-limiting
 - Valproic acid and carbamazepine
- Patient and family education

Medical Management: Secondary Prevention

Secondary Prevention of Rheumatic Fever (Prevention of Recurrent Attacks)

Agent	Dosage	Route of Administration	Rating
Benzathine Penicillin G	Children (<27kg) 600 000 U Those (>27kg) 1 200 000 U Every 4 weeks*	Intramuscular	IA
Penicillin V	250 mg twice daily	Oral	IB
Sulfadiazine	Patients (<27kg) 0.5 g once daily Patients (>27kg) 0.5 g once daily	Oral	IB
For patients allergic to penicillin and sulfadiazine			
Macrolide	Variable	Oral	IC

*In high risk situations, administration every 3 weeks is justified and recommended.

Medical Management: Secondary Prevention

Duration of Secondary Prophylaxis for Rheumatic Fever

<i>TYPE</i>	<i>DURATION AFTER LAST ATTACK</i>	<i>EVIDENCE RATING</i>
Rheumatic fever with carditis and residual heart disease (persistent valvular disease†)	10 years or until age 40 years	1C
Rheumatic fever with carditis but no residual heart disease (no valvular disease†)	10 years or until age 21 years	1C
Rheumatic fever without carditis	5 years or until age 21 years	1C

†—*Clinical or echocardiographic evidence.*

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Prevention and Clinical Management

