A child with sore throat comes to us

80% are caused by viral

15-20% by GAS

- RF developes in 3% and .3% cases of GAS pharyngitis in epidemic & endemic areas respectively.
- If h/o previous RF then 50% incidence

How to know whether it can be GAS

Features suggestive of GAS

- Sudden-onset
- Pain on swallowing
- Fever
- Scarlet fever rash
- Headache
- Nausea, vomiting, and abdominal pain
- Tonsillopharyngeal erythema
- Tonsillopharyngeal exudates
- Soft palate petechiae (“doughnu lesions)
- Beefy, red, swollen uvula
- Tender, enlarged anterior cervica nodes
- Patient 5 to 15 years of age
- Presentation in winter or early spring (in temperate climates)
- History of exposure
- Absence of cough

Features suggestive of viral origin

- Conjunctivitis
- Coryza
- Hoarseness
- Cough
- Diarrhea
- Characteristic exanthems
- Characteristic enanthems

If four or five of the factors are present, the likelihood ratio of streptococcal infection is 4.9 (approximately 50% of cases); if 3 factors are present the ratio decreases to 2.5 (approximately
[illegible]); and if only 2 are present, to

Now this seems to be a probable case of

GAS pharyngitis

- We need to detect the presence of GAS in throat
- Two options-

Throat Culture

RADT

CULTURE

- Gold standard for detecting *Streptococcus pyogenes* remains a throat swab cultured on blood agar
- It takes 24–48 hours to produce a result, (consequent delay in starting antibiotic)
- Vigorous swabbing of both tonsils and the posterior pharyngeal wall has almost 100% yield
- During transportation avoid high temperatures and moisture
- Cultures negative for *S. pyogenes* after an overnight incubation should be incubated for another 24 hours.

RADT

- Detecting the antigen is the most specific method
- Kits have reported specificities in the range 85–100%,
- False-positive results are unusual
- Sensitivity less (31–95%) and false negatives can occur
- Hence they cannot be used to replace standard blood agar cultures, particularly in populations at high risk for RF.
- In such circumstances, it is recommended that negative kit results should be confirmed by culturing

Now we found GAS

So this patient can have-

- Chronic carrier state -Normal serology
- Recent infection -Elevated serology
- Active infection -Rising serology

SEROLOGY

- Generally antistreptolysin O (ASLO) is the commonest antibody measured.
- It appears in about 1wk and peaks in 3-6wk.
- Anti-DNAase B appears in 1-2wk & peaks in 6-8wks.
- Normal value for a population is that which is not crossed by more than 20% of the population
- These ab persist for months and hence remain positive when RF develops

Normal cut-offs

- In endemic areas the baseline ASLO could be 250 Todd (333 for children) units or more whereas in non-endemic areas it could be as low as 50 Todd units.

- Normal values of Anti DNase B titer 1:60 unit in preschool, 1:480 units in school children & 1:340 in adults

ASO & Anti-DNAase B

- Both can be positive following erysipelas (streptococcal skin infection)

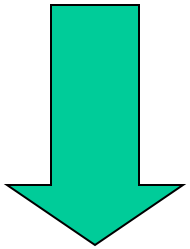
- Both can be positive following GCS/ GGS

Recent interest- Streptozyme test

- Often used as a screening test for antibodies to the strepto coccal antigens NADase, DNase, streptokinase,streptoly sin O, hyaluronidase.
- It can detect several antibodies in a single assay
- It is technically quick& easy,
- It is not as sensitive in children as in adults.
- Still not standardized

- So we can start antibiotics or wait for serology if time permits
- Starting antibiotics within 9 days of initiation of symptoms can prevent RF
- After starting antibiotics the patient becomes non-infective within 24 hours

Suppose culture is negative but this pharyngitis has high probability of GAS
Should we start empirical antibiotic



No clear cut recommendation

Now which antibiotic to start

- No clinical isolate of group A beta-hemolytic streptococcus (*Streptococcus pyogenes*) has been shown to be resistant to penicillin in vitro.
- However no treatment regime eradicates GAS in 100% cases in vivo
- Penicillin is inexpensive and available in most countries, it remains the drug of choice
- A single intramuscular injection of Benzathine benzylpenicillin can be used to treat the infection
- Oral penicillin (penicillin V or penicillin G) can be given for a full 10 days
- First-generation cephalosporin(Cefadroxil or cephalexin) have also been used successfully.
- Oral macrolide (resistance 5-8%) & clindamycin (resistance ~1%) have Class IIa indication for treatment

Agent	Dose	Mode	Duration	Rating
Penicillins				
Penicillin V (phenoxymethyl penicillin)	Children: 250 mg 2 to 3 times daily for ≤27 kg (60 lb); children >27 kg (60 lb), adolescents, and adults: 500 mg 2 to 3 times daily	Oral	10 days	IB
	or			
Amoxicillin	50 mg/kg once daily (maximum 1 g)	Oral	10 days	IB
	or			
Benzathine penicillin G	600 000 U for patients ≤27 kg (60 lb); 1 200 000 U for patients >27 kg (60 lb)	Intramuscular	Once	IB
For individuals allergic to penicillin				
Narrow-spectrum cephalosporin† (cephalexin, cefadroxil)	Variable	Oral	10 days	IB
	or			
Clindamycin	20 mg/kg per day divided in 3 doses (maximum 1.8 g/d)	Oral	10 days	IIaB
	or			
Azithromycin	12 mg/kg once daily (maximum 500 mg)	Oral	5 days	IIaB
	or			
Clarithromycin	15 mg/kg per day divided BID (maximum 250 mg BID)	Oral	10 days	IIaB

Remember

- Amoxicillin for >12 yrs.
- Allergy to penicillin more common in adults
- QT prolongation & Cyt P interaction for macrolide
- Suphonamides/ Tetracyclins/ TMP-SMX/ FQ- Contraindicated

Treatment completed for 10 days

Send repeat culture 2-7 days after completion of treatment if –

- Symptoms persists
- Symptoms recur
- Previous h/o RF/RHD

Post-treatment culture comes to be positive

- M-typing can be done to know whether it is treatment failure or re-infection with other strain
- Treatment required if symptoms persist or h/o RF/RHD of self/family member
- Treat with same antibiotic/ alternate oral agent/ i.m. penicillin
- Amox-Clav/ Penicillin+rifampicin can be given(class IIa)

Should we screen family members?

- If patient had developed RF then routinely
- But since patient has only GAS pharyngitis then screening required only if he had past h/o RF/RHD

So this is how we prevented risk of development of RF by around 70% (80% for inj. BPG)

But suppose the patient had developed RF

GAS pharyngitis was undiagnosed or untreated

GAS pharyngitis was assymptomatic (1/3 in endemic and ½ in epidemic)

Treatment failure

It takes 2-3 weeks to develop RF from onset of GAS pharyngitis

How does GAS cause RF

- M-proteins have different epitopes against which Ab are produced & they cross-react with body tissues (**α- helical coil dimers**)
- Myosin, tropomyosin, laminin, N-acetyl glucosamine, ganglioside, dopamine receptors, vimentin, keratin.
- Collagen damage leads to auto-ab against collagen

This dev. of RF from untreated GAS pharyngitis depends on

- Agent
- Host
- Environment

Beta-haemolytic streptococci

- Divided into a number of serological groups on the basis of cell-wall polysaccharide antigen.
- Group A further subdivided into more than 130 distinct M types
- Only pharyngitis caused by group A streptococci has been linked with the etiopathogenesis of RF and RHD.
- Streptococci in groups C and G can produce extracellular antigens (including streptolysin-O) with similar characteristics.
- Further studies are warranted into the role of groups C and G in the pathogenesis of RF

“Rheumatogenicity”

- M types such as 1, 3, 5, 6, 14, 18, 19 and 24
- Such serotypes are usually heavily encapsulated, and form large, mucoid colonies that are rich in M-protein.
- These enhance the ability of the bacteria to adhere to tissue, as well as their ability to resist phagocytosis.

Role of other virulence factors

- Superantigen-like activity of M-protein fragments (PeP M5, in particular)
- Streptococcal pyrogenic exotoxin
- GRAB (an alpha-2 macroglobulin-binding protein)
- Streptococcal fibronectin-binding protein 1 (sfb1),
- Streptococcal C5a peptidase (SCPA)

Susceptibility gene

- Particular allele at, or nearby, the HLA-DR locus(Class II HLA).
- DR4 was present more frequently in Caucasian RF patients
- DR2 more frequently in African-American populations
- DR1 and DRw6 in RF patients from South Africa
- HLA-DR3 was present more frequently in RF patients in India (who also had a low frequency of DR2)
- HLA-DQW2 was present more frequently in Asian RF patients

Many other genes related to…

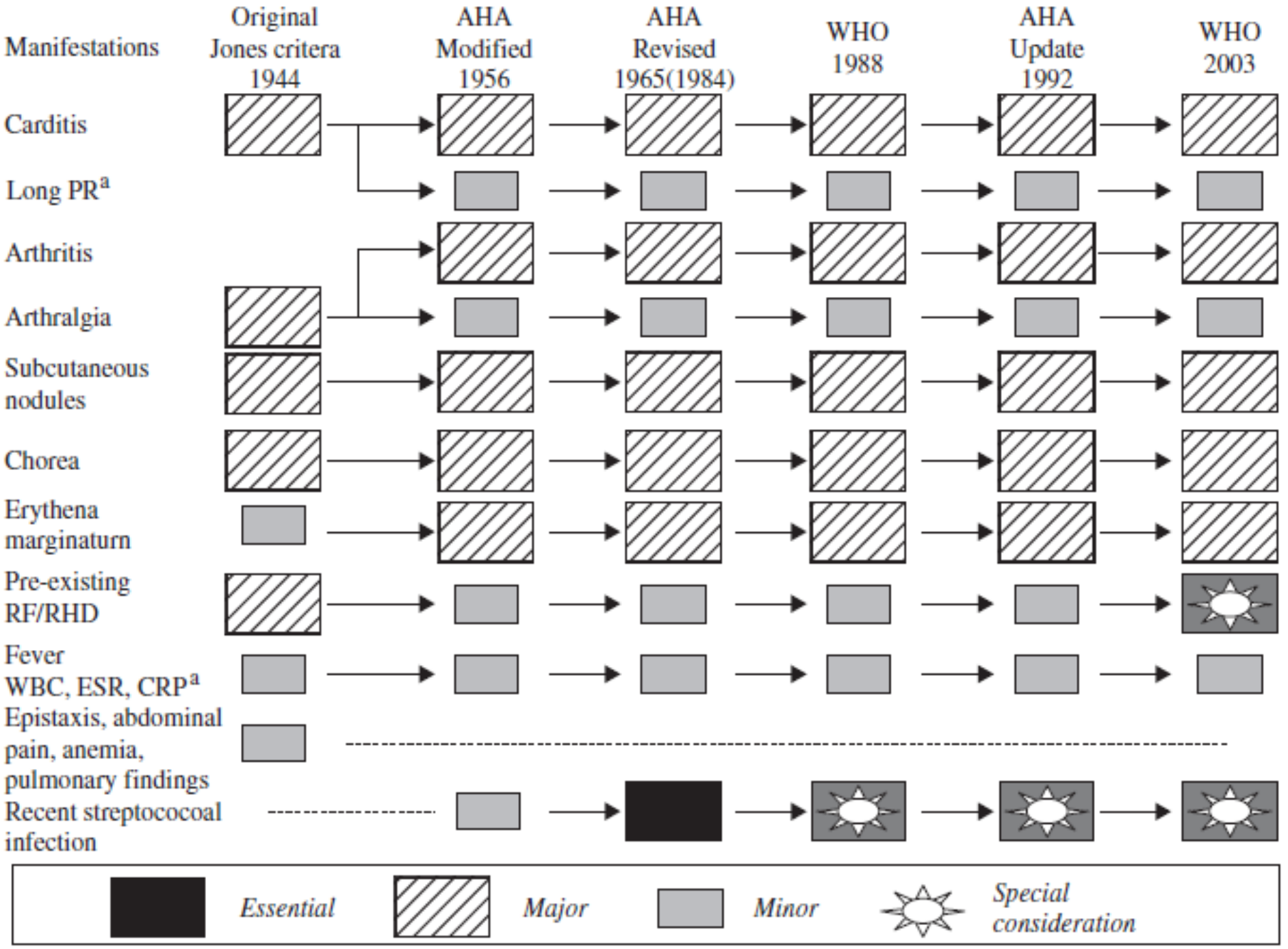
- CLA 4
- MBL 2
- FcR of IgG
- TNF α
- IL 1
- TGF β

Heredity

- Proportion of susceptible patients are same in all ethnicities (3-5%)
- Hereditary trait increases risk of RF by 5 times
- Monozygotic twins have 6 times increased risk

Environmental factors

- poor living conditions,
- overcrowding
- poor access to health care
- Seasonal variations (early fall, late winter and early spring)


Manifestations
Original Jones critera 1944
AHA Modified 1956
AHA Revised 1965(1984)
WHO 1988
AHA Update 1992
WHO 2003
Carditis
Long PR[a]
Arthritis
Arthralgia
Subcutaneous nodules
Chorea
Erythena marginaturn
Pre-existing RF/RHD
Fever
WBC, ESR, CRP[a]
Epistaxis, abdominal pain, anemia, pulmonary findings
Recent streptococoal infection
Essential
Major
Minor
Special consideration

Revised Jones Criteria- WHO 2003

* Major manifestations	— carditis — polyarthritis — chorea — erythema marginatum — subcutaneous nodules
** Minor manifestations	— clinical: fever, polyarthralgia — laboratory: elevated acute phase reactants (erythrocyte sedimentation rate or leukocyte count) — electrocardiogram: prolonged P-R interval
*** Supporting evidence of a preceding streptococcal infection within the last 45 days	— elevated or rising antistreptolysin-O or other streptococcal antibody, or — a positive throat culture, or — rapid antigen test for group A streptococci, or — recent scarlet fever.

Diagnostic categories	Criteria
Primary episode of RF.[a]	Two major *or one major and two minor** manifestations **plus** evidence of a preceding group A streptococcal infection***.
Recurrent attack of RF in a patient **without** established rheumatic heart disease.[b]	Two major or one major and two minor manifestations **plus** evidence of a preceding group A streptococcal infection.
Recurrent attack of RF in a patient **with** established rheumatic heart disease.	Two minor manifestations **plus** evidence of a preceding group A streptococcal infection.[c]
Rheumatic chorea. Insidious onset rheumatic carditis.[b]	Other major manifestations or evidence of group A streptococcal infection not required.
Chronic valve lesions of RHD (patients presenting for the first time with pure mitral stenosis or mixed mitral valve disease and/or aortic valve disease).[d]	Do not require any other criteria to be diagnosed as having rheumatic heart disease.

“probable rheumatic fever”

- Several (3 or more) minor manifestations, together with evidence of recent group A streptococcal infection.

- Some of these cases may later turnout to be rheumatic fever.

2012- AUSTRALIAN GUIDELINES

	High-risk groups[†]	All other groups
Major manifestations	Carditis (including subclinical evidence of rheumatic valvulitis on echocardiogram)	Carditis (excluding subclinical evidence of rheumatic valvulitis on echocardiogram)
	Polyarthritis[‡‡] or aseptic mono-arthritis or polyarthralgia	Polyarthritis[‡‡]
	Chorea[§]	Chorea[§]
	Erythema marginatum[¶]	Erythema marginatum[¶]
	Subcutaneous nodules	Subcutaneous nodules
Minor manifestations	Monoarthralgia	Fever[‡‡]
	Fever[‡‡]	Polyarthralgia or aseptic mono-arthritis
	ESR ≥30 mm/h or CRP ≥30 mg/L	ESR ≥30 mm/h or CRP ≥30 mg/L
	Prolonged P-R interval on ECG[§§]	Prolonged P-R interval on ECG[§§]

High-risk groups are those living in communities with high rates of ARF (incidence >30/100,000 per year in 5–14 year olds) or RHD (all-age

CARDITIS

- **Valvulitis/endocarditis**
- More common in children
- New MR(with or without MS), and/or AR.
- an individual with previous RHD, a definite change in the character of any of these murmurs or the appearance of a new significant murmur
- Cardiomegaly due to valvular pathology
- Heart Block may develop (any degree)

Pericarditis

- Up to 15% cases
- Audible friction rub, chest pain
- Mild/Mod effusion
- Large effusion/ tamponade rare
- Simultaneous demonstration of valvular involvement generally considered essential
- electrocardiogram may show low-voltage QRS complexes and ST-T changes
- Heart may appear enlarged in an Xray silhouette
- No sequelae

Studies strongly suggest that RF does **not** cause myocarditis

(i) absence of increase in markers of myocardial damage - CK-MB, troponin I & T and myoglobin

(ii) normal left ventricular systolic function and myocardial contractility by echocardiographic studies

(iii) radionuclide studies using technetium pyrophosphate scanning and indiumIII labelled anticardiac myocin Fab (FAB) do not indicate presence of myocardial damage

(iv) myocardial biopsy studies have not been able to identify the presence of myocarditis

(v) normalization of heart size and disappearance of congestive failure following surgical mitral and/or aortic valve replacement in patients deteriorating in spite of aggressive medical management

(vi) histopathology of the left ventricular myocardium showing absence of myocardial or inter-myocardial connective tissue damage

(vii) immunopathology of Ashoff nodule (AN) shows complete absence of cells of myocardial origin

Arthritis

- Arthritis is the most frequent major manifestation of RF, occurring in up to 75% of patients in the first attack of RF
- More common in adults
- It occurs early in the course of the disease
- Migratory polyarthritis,most often in the larger joints, assymmetric distribution
- synovial fluid may reveal a high leukocyte count Tenderness in rheumatic arthritis may be out of proportion to the objective findings
- Additive arthritis / monoarthritis may occur

…contd

- Inflammation in a particular joint usually resolves within two weeks and the entire bout of polyarthritis in about a month if untreated.
- Inverse relationship between the severity of arthritis and carditis

Poststreptococcal reactive arthritis

- Short latency period(~10 days vs 2-3 wks for RF)
- May be persistent or relapsing
- Symmetric, additive, mostly monoarthritis, may involve axial/upper limb
- Does not respond dramatically to anti-inflammatory
- Soetimes renal involvement
- A number of patients presenting initially as PSRA have later manifested RHD
- Rheumatic prophylaxis for 1 year and then discontinue if no cardiac involvement (IIb)

Sydenham's chorea

- Prevalence 5–36%
- Chorea occurs primarily in children and is rare after the age of 20
- Primarily in females, and almost never occurs in postpubertal males.
- When the tongue is protruded it resembles a "bag of worms,"
- speech is jerky and staccato
- When the hands are extended, the dorsum assumes a "spoon" or "dish" configuration
- "pronator sign"
- "milkmaid grip"
- "Jack in the box" tongue (motor impersistence)

Subcutaneous nodules

- Up to 20% of cases
- Round, movable, painless lesions
- Size from 0.5–2.0 cm
- Overlying skin not inflamed
- Over bony prominences or extensor tendons, occiput, and the spinous processes of the vertebrae
- Persist upto 1–2 weeks

Erythema marginatum

- Up to 15% of RF patients
- Bright pink macule/papule that spreads outward in a circular or seripiginous pattern.
- Multiple
- On the trunk or proximal extremities,
- Never on the face.
- Nonpruritic and nonpainful,
- Blanch under pressure,
- Rarely raised

Minor Criteria

- Fever > 37.5º C ; usually subsides by 1 wk, max 4 wks
- Elevated erythrocyte sedimentation rate (ESR) is a nonspecific evidence for an active disease. It is elevated in acute RF but can be normal if the patient has congestive failure and can be high in the presence of anaemia.
- Normal CRP is against the diagnosis of active RF.
- Prolonged PR interval is a non specific finding and does not indicate the presence of myocarditis.
- If carditis is present as a major manifestation, a prolonged P-R interval cannot be considered an additional minor manifestation(Australian guidelines)

Few terminologies

Recurrence: A new episode of rheumatic fever following another GABHS infection; occurring after 8 week following stopping treatment.

Rebound: Manifestations of rheumatic fever occurring within 4-6 wk of stopping treatment or while tapering drugs.

Relapse: Worsening of rheumatic fever while under treatment and often with carditis.

Sub clinical carditis: When clinical examination is normal but echocardiogram is abnormal.

Indolent carditis: It is a common entity in our country. Patient presents with persistent features of CHF, murmur and cardiomegaly.There are no or very few features of active carditis.

Now this patient satisfies the criteria

He should now be treated

Aspects of treatment

- Stop inflammation in joints & heart
- Treat other symptoms
- Eradicate GAS
- Secondary Prophylaxis

Suppression of the inflammatory process

- Aspirin,100 mg/kg-day divided into 4–5 doses, is the first line of therapy
- Given for ten weeks and tapered in the next two weeks.
- Patients without carditis can have weekly follow up of ESR and CRP. If they normalize, the course can be reduced to a shorter period.
- Aspirin is preferred over steroids as long as the carditis is mild and the patient is not in congestive failure.

Role of corticosteroids

- Patients with pericarditis or heart failure respond favorably to corticosteroids
- advisable in patients who donot respond to salicylates and who continue to worsen and develop heart failure despite anti-inflammatory therapy .
- Prednisone (1–2mg/kg-day, to a maximum of 80mg/day given once daily, or in divided doses)
- In life-threatening circumstances, therapy may be initiated with intravenous methyl prednisolone
- After 2–3 weeks of therapy the dosage may be decreased by 20–25% each week
- While reducing the steroid dosage, a period of overlap with aspirin is recommended to prevent rebound of disease activity

Management of chorea

- Self-limiting benign, requiring no therapy.
- Rarely can lead to disability and/or social isolation.
- Neuroleptics, benzodiazepines and antiepileptics
- Haloperidol, diazepam, carbamazepine
- Supportive measures such as rest in a quiet room. in the treatment of chorea
- Resistant cases can be treated with plasmapheresis or pimozide

Antibiotic therapy

- Ideally, throat cultures should be performed before starting antibiotics.
- Throat culture is positive in only 11% cases
- However, antibiotic therapy is warranted even if the throat cultures are negative.
- Antibiotic therapy does not alter the course, frequency and severity of cardiac involvement

- Inj. BPG
    - » 1st dose on Day 1
    - » 2nd dose on day 10
    - » Then every 3 weekly
- Oral PV
- Erythromycin
- Others?

Secondary prophylaxis: general principles

- Intramuscular injection of benzathine benzylpenicillin every three weeks is the most effective strategy for preventing recurrent attacks of RF
- (every four weeks in low-risk areas or low risk patients)
- Oral penicillin may also be used as an alternative in secondary prophylaxis
- Penicillin prophylaxis for recurrent attacks of RF should be continued during pregnancy.
- There is no evidence of teratogenicity associated with benzathine benzylpenicillin.

Oral penicillin : Disadvantages

- Noncompliance,
- Serum penicillin levels are less predictable
- RF recurs more frequently

- For those patients who are known to be, or are suspected of being, allergic to penicillin, oral sulfadiazine or oral sulfasoxazole represent optimal second choices

- Where patients are allergic both to penicillin and the sulfa drugs, or if these drugs are not available, oral erythromycin may be used.

Screening of family members

- Routine screening of household contacts-
- Treatment to be offered if Culture/RADT positive(even if they are carriers)

Subclinical carditis

- Evaluation of data indicates that about 60 per cent patients get clinically recognizable RHD following RF.
- This suggests that at least 40 per cent patients who have had RF could be potentially patients of subclinical carditis.
- On the basis of Utah study, 27 per cent patients had subclinical carditis.
- Secondly, most prevalence figures indicate that the prevalence of RF in surveys is about one tenth or even less than that of RHD (0.1/1000 vs 1/1000).
- The inference could be that the diagnosis of RF is being missed more often than desirable or acceptable.

Magnitude of the problem

- A review of SC involving more than 1700 patients found overall prevalence to be 16.8 per cent.
- Around 30 percent of patients having chorea present as sub clinical carditis
- WHO criteria for the identification of SC by E&D were satisfied by 10 studies which gave a prevalence of 18.1 per cent. Of the 99 patients whose follow up of up to 2 years was available, 48 per cent showed improvement and 52 per cent either no change or became worse indicating variable course of SC

SUBCLINICAL CARDITIS

- Most available echocardiographic evaluation studies for the presence of RHD in school children suggest more than 10 to 20 times higher prevalence of clinically “silent” RHD

2012 WHF criteria for echocardiographic diagnosis of RHD

Echocardiographic criteria for individuals aged ≤20 years

Definite RHD (either A, B, C, or D):

- A) Pathological MR and at least two morphological features of RHD of the MV
- B) MS mean gradient ≥4 mmHg*
- C) Pathological AR and at least two morphological features of RHD of the AV‡
- D) Borderline disease of both the AV and MV§

Borderline RHD (either A, B, or C):

- A) At least two morphological features of RHD of the MV without pathological MR or MS
- B) Pathological MR
- C) Pathological AR

Normal echocardiographic findings (all of A, B, C, and D):

- A) MR that does not meet all four Doppler echocardiographic criteria (physiological MR)
- B) AR that does not meet all four Doppler echocardiographic criteria (physiological AR)
- C) An isolated morphological feature of RHD of the MV (for example, valvular thickening) without any associated pathological stenosis or regurgitation
- D) Morphological feature of RHD of the AV (for example, valvular thickening) without any associated pathological stenosis or regurgitation

Criteria for pathologic regurgitation

Pathological mitral regurgitation
(All four Doppler echocardiographic criteria must be met)

- Seen in two views
- In at least one view, jet length ≥2 cm*
- Velocity ≥3 m/s for one complete envelope
- Pan-systolic jet in at least one envelope

Pathological aortic regurgitation
(All four Doppler echocardiographic criteria must be met)

- Seen in two views
- In at least one view, jet length ≥1 cm*
- Velocity ≥3 m/s in early diastole
- Pan-diastolic jet in at least one envelope

*A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant color (blue or red).

Disadvantages of Echo as a diagnostic tool

- Overdiagnosis of physiological valvular regurgitation as an organic dysfunction
- Use of echo-Doppler echocardiography resulted in a diagnosis of carditis in 90–100% of RF patients. This prevalence of carditis in RF patients is significantly higher than that reported clinically,
- Finally, in developing countries, echo is not widely available

Assymptomatic carriers

- 10-15% of school children
- In tropics ~60% type C/G streptococci
- In temperate zones ~60% type A
- Throat swab culture/ RADT/ Single raised Ab titre can be positive in Carriers.
- Antibiotics are not recommendeds

RF Vaccine

Attempts to develop a safe and effective M-protein vaccine encountered considerable difficulties because of

- multiplicity of M-protein serotypes (and genotypes),
- the toxicity of early M-protein preparations,
- and the immunological cross-reactivity between M-protein and human tissues, including heart tissue

Targets other than streptococcal M-protein for immunization

- C5a peptidase
- Streptococcal pyrogenic exotoxin B