Rheumatic Heart Disease in Sub-Saharan Africa

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Clinical Assistant Professor of Medicine, Brown University

Global Health Conference
May 8, 20012
“A lecture on rheumatic heart disease in sub-Saharan Africa, is a lecture on rheumatic fever and its prevention”

“let nature take its course”
Rheumatic Fever

Inflammatory disease following Streptococcal infection

- Pharyngitis – clinical features
- Scarlet fever → rheumatic fever (3% cases, untreated)
- Delayed immune response to Lancefield group A \( B \) hemolytic strep (humoral/cellular) M serotypes
  - antigenic mimicry in assoc with abnormal host response
- 1-5 week latency period
- Children 80% cases
- 1/3 episodes rheumatic fever result from subclinical streptococcal infections (echo)
- streptococcal skin infections ? assoc with rheumatic fever (rheumatogenic M serotypes infrequently found in areas with high burden RF)

Heart 2007;93:1510-1519
Lancet 2012;379:953-964
<table>
<thead>
<tr>
<th>Features suggestive of GAS as causative agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden-onset sore throat</td>
</tr>
<tr>
<td>Pain on swallowing</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Scarlet fever rash</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Nausea, vomiting, and abdominal pain</td>
</tr>
<tr>
<td>Tonsillopharyngeal erythema</td>
</tr>
<tr>
<td>Tonsillopharyngeal exudates</td>
</tr>
<tr>
<td>Soft palate petechiae (&quot;doughnut&quot; lesions)</td>
</tr>
<tr>
<td>Beefy, red, swollen uvula</td>
</tr>
<tr>
<td>Tender, enlarged anterior cervical nodes</td>
</tr>
<tr>
<td>Patient 5 to 15 years of age</td>
</tr>
<tr>
<td>Presentation in winter or early spring (in temperate climates)</td>
</tr>
<tr>
<td>History of exposure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Features suggestive of viral origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Coryza</td>
</tr>
<tr>
<td>Hoarseness</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Characteristic exanths</td>
</tr>
<tr>
<td>Characteristic enanths</td>
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Heart 2007;93:1510-1519
Lancet 2012;379:953-964
Modified Jones Criteria
(1944 T. Duckett Jones)

◆ Major

✓ polyarthritis (ascending/migratory/large joints)
✓ carditis (all layers of cardiac tissue)
✓ subcutaneous nodules (painless/collagenous/tendons)
  ✓ always assoc with severe carditis
✓ erythema marginatum
✓ often assoc with chronic carditis
✓ Syndenham’s chorea (St Vitus dance)

◆ Minor

✓ fever
✓ arthralgia
✓ laboratory
✓ ECG
✓ previous rheumatic fever/RHD

Guidelines revised to establish the initial attack of rheumatic fever

subcutaneous nodule
Modified Jones Criteria
(1944 T. Duckett Jones)

◆ Major

✓ polyarthritis
(ascending/migratory/large joints)

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✓ previous rheumatic fever/RHD

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Guidelines revised to establish the initial attack of rheumatic fever

erythema marginatum
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✓ carditis (all layers of cardiac tissue)

✓ subcutaneous nodules(painless/collagenous/tendons)

✓ always assoc with severe carditis

✓ erythema marginatum

✓ often assoc with chronic carditis

✓ Sydenham’s chorea (St Vitus dance)—may be only manifestation

◆ Minor

✓ fever

✓ arthralgia

✓ ECG

✓ previous rheumatic fever/RHD

✓ laboratory

Guidelines revised to establish the initial attack of rheumatic fever

Laboratory Findings

- High ESR
- Anemia, leukocytosis
- Elevated CRP
- ASO titre >200
- Anti-DNAse B test
- Throat cx pos GABH streptococcus
- ECG: 1st degree AVB, Echo: valve edema, effusion
Confirmation of Diagnosis

* difficult on clinical grounds alone
* Two major criteria or one major and two minor criteria
* supported by GABH strep infection
* laboratory studies rarely available in developing countries
### Primary Prevention of Rheumatic Fever (Treatment of Strep Tonsillopharyngitis)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Mode</th>
<th>Duration</th>
</tr>
</thead>
</table>
| Benzathine PCN G | 600,000U <27 kg  
1,200,000U >27 kg  
OR  
50mg/kg once daily(max1g) OR | IM      | Once    |
| Amoxacillin | <27 kg 250mg 2-3 times per day  
>27 kg  
500mg 2-3 times/day | Oral    | 10 days |
| PCN V      | <27 kg 250mg 2-3 times per day  
>27 kg  
500mg 2-3 times/day | Oral    | 10 days |


WHO 1999; Drugs used in the treatment of strep pharyngitis/prevention of RHD
## Primary Prevention of Rheumatic Fever (penicillin allergic)

<table>
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<tr>
<th>Agent</th>
<th>Dose</th>
<th>Mode</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>20 mg/kg per day divided in 3 doses (max 1.8g/day) OR</td>
<td>Oral</td>
<td>10 days</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>12mg/kg once daily (max 500mg) OR</td>
<td>Oral</td>
<td>5 days</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>15mg/kg per day BID (max 500mg total dose) OR</td>
<td>Oral</td>
<td>10 days</td>
</tr>
<tr>
<td>Cephalosporin (cephalexin/cefadroxil)</td>
<td>Variable</td>
<td>Oral</td>
<td>10 days</td>
</tr>
</tbody>
</table>


WHO 1999; Drugs used in the treatment of strep pharyngitis/prevention of RHD
Secondary Prevention of Rheumatic Fever

- Previous attack of rheumatic fever-high risk for recurrent attack
- Recurrent attack assoc with worsening of the severity of RHD developed with initial attack
- Rheumatic fever can occur with optimal RX of GABHS
- Prevention of recurrent episodes of GABHS
  - most effective method to prevent severe RHD
  - continuous antimicrobial prophylaxis required
  - detection of subclinical disease is critical (echo)

NEJM 2007; 357:439-441
## Secondary Prevention of Rheumatic Fever (Prevention of Recurrent Attacks)

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<tr>
<th>Agent</th>
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<tr>
<td>Benzathine PCN G</td>
<td>&lt;27 kg 600,000U, &gt;27 kg 1,200,000U q 3-4 wks</td>
<td>IM</td>
</tr>
<tr>
<td>PCN V</td>
<td>250mg bid</td>
<td>Oral</td>
</tr>
<tr>
<td>sulfadiazine</td>
<td>&lt;27 kg 500mg daily, &gt;27 kg 1g daily</td>
<td>Oral</td>
</tr>
<tr>
<td>Emycin</td>
<td>250mg bid</td>
<td>Oral</td>
</tr>
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WHO 1999; Drugs used in the treatment of strep pharyngitis/prevention of RHD
Duration of prophylaxis

- Risk of recurrence of rheumatic fever
  - increases with multiple previous attacks
  - decreases as interval since most recent attack lengthens
  - increases with exposure to GABHS
    - children, teachers, health professionals, military
    - economically disadvantaged

- Presence of rheumatic valvular disease/carditis

- Lifelong prophylaxis ➔ prosthetic valves, high risk pts
## Duration of Secondary Rheumatic Fever Prophylaxis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic fever without carditis</td>
<td>5 yrs or until age 21 (whichever is longer)</td>
</tr>
<tr>
<td>Rheumatic fever with carditis without RHD</td>
<td>10 yrs or until age 21 (whichever is longer)</td>
</tr>
<tr>
<td>Rheumatic fever with carditis and RHD</td>
<td>10 yrs or until age 40 (whichever is longer), sometimes life long</td>
</tr>
<tr>
<td>Artificial valves</td>
<td>For life</td>
</tr>
</tbody>
</table>

Circulation 2009; 119: 1541-1551
AHA Scientific Statement: Prevention of Rheumatic fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis
WHO 1999; Drugs used in the treatment of strep pharyngitis/prevention of RHD
Rheumatic Heart Disease

Epidemiology - data scarce in Africa

- acute rheumatic fever/RHD
  - commonest form of heart disease in Africa
- 20 million affected in developing world
  - →highest prevalence sub-Saharan Africa
- 2 million children worldwide/ 1 million sub-Saharan Africa
  - leading cause of death during 1st 5 decades of life
  - mortality 20% at 6 yr follow up Nigeria; 12.5%/yr Ethiopia
- 200,000 new cases per yr Kenya
- acute rheumatic carditis in Africa - more fulminant and malignant course
  - most cases undiagnosed/subclinical →echo

Heart 2009;95:1559-1560
Lancet 2012;379:953-964
Circulation 2009; 119: 1541-1551

AHA Scientific Statement: Prevention of Rheumatic fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis
Figure 5: Rheumatic heart disease (RHD) prevalence rates in children: echocardiography-based screening versus clinical examination.

Lancet 2012;379:953-964
Rheumatic Heart Disease Prevalence Data

- guide regional health service planning
- identify affected children to be targeted for secondary prophylaxis
Number of rheumatic fever cases notified per year to the National Department of Health, South Africa.
Determinants of persistence of RF and RHD in Africa

- poverty, overcrowding
- malnutrition
- cultural aspects, low level of disease awareness
- shortage of resources
- inadequate healthcare expertise
- more virulent GABHS, genetic susceptibility

leads to increased transmission of strep infections, inadequate diagnosis/treatment and poor adherence to secondary measures

Heart 2007;93:1510-1519
Rheumatic Heart Disease

- Rheumatic Valvulitis
  - may resolve spontaneously
  - may progress into young adulthood
  - prophylactic antibiotic therapy (primary/secondary prevention)
  - medical surveillance/echo
    - limit dx progression
    - identify subclinical disease
    - endocarditis prophylaxis
Rheumatic Heart Disease

- Mitral valve
  - most common lesion is pure MR (young)
- Mixed aortic and mitral
- Aortic valve (rare in isolation)
- Pulmonic
- Tricuspid
  - common, late diagnosis
  - Tricuspid regurgitation related to:
    - severe MV/AV disease
    - pulmonary HTN/dilated RV

Isolated pulmonary or tricuspid regurgitation are not typical of RHD

Lancet 2012;379:953-964
Cardiovasc J Africa 2012;23:165-167
Heart 2005;91:e50
Mitral Valve Disease

- Heart failure and LV dilation rarely occur in the absence of mitral regurgitation
- Mitral regurgitation during active carditis
  - annular dilation
  - chordal elongation
  - anterior leaflet prolapse
- Surgical correction leads to ventricular remodeling and improvement in symptoms

Heart 2007;93:1510-1519
Time-course analysis (by decade) of the relative prevalence of pure mitral regurgitation (MR), mixed mitral valve (MV) disease, and pure mitral stenosis (MS).
Relations among age, disease activity, and valve lesion.

Nkomo V T Heart 2007;93:1510-1519
Rheumatic MS
Rare case of 35 yo female with all four valves involved:
Transthoracic echocardiogram showing thickened and doming aortic valve (A) and thickened mitral valve (B).

Jai Shankar K et al. Heart 2005;91:e50-e50
Transthoracic echocardiogram showing thickened and doming pulmonary valve (A) and thickened tricuspid valve (B).
Challenges for Cardiac Surgery in African Children

- Poor general health/nutritional condition increases operative risk
- Multiple valve lesions $\rightarrow$ suboptimal operative solutions
- Anticoagulation management
  - contraception
- Recurrent RF
- endocarditis prophylaxis post op
- Valve repair during active RF not a long term result

surgical correction for RHD is essentially a palliative procedure

Cardiovasc J Africa 2012;23:165-167
Anticoagulation Management

Performance outcomes of a pharmacist-managed anticoagulation clinic in the rural, resource-constrained setting of Eldoret, Kenya.

Manji I, Pastakia SD, DO AN, Ouma MN, Schellhase E, Karwa R, Miller ML, Saina C, Akwanalo Moi Teaching and Referral Hospital, Eldoret, Kenya

- 178 pts enrolled
- mean TTR 64.6%
- rates of major bleeding 1.25%, thromboembolic events 5%
- performance of MTRH anticoagulation clinic non-inferior to results in resource rich settings

fixed dose warfarin is associated with increased thromboembolic events
MV repair preferable to replacement
- concern with inadequate secondary prophylaxis, recurrent RF

Bioprostheses - rapid deterioration in the young
- Antunes cohort 135 pts, 80% valve failure at 7 yrs

Mechanical prostheses
- thromboembolic events
- hemorrhage
- infective endocarditis

Heart 2007;93:1510-1519
Aortic valve – Ross procedure
- allows for tissue growth
- no anticoagulation
- aortic insufficiency 18% at 2.4 yrs
- rheumatic involvement of autograft (pulmonic)

Cardiovasc J Africa 2012;23:165-167
Governmental challenges in RHD

- Building local capacity/expertise in disease management
- Training local cardiologists/surgeons
- Research infrastructure
- Financial support
- Increasing commitment from policy makers/governance
- Collaborations ie Brown/Duke/Indiana
  - Community acceptance
  - Regional referral centers
Prevention of RHD

- teaching - health care professionals/community
- cultural change - fear of allergic rxn/barriers
- sick isolation/awareness
- rapid strep testing ? eliminate (cost/barrier to care)
- treating pharyngitis early – single injection benzathine penicillin G IM for compliance

Clinical Consortium - comprehensive primary health care program
  - Brown/Duke/Indiana
Potential Preventive Measures for Rheumatic Fever and Rheumatic Heart Disease.

Causal Pathway

Group A streptococcal infection

Acute rheumatic fever

Rheumatic heart disease

Cardiac failure

Stroke, endocarditis

Death

Preventive Measures

“Primordial” prevention
Housing
Hygiene

Primary prevention
Sore-throat treatment
Vaccine (unavailable)
Control of skin infections (unproved)

Secondary prevention
Secondary prophylaxis

“Tertiary” prevention
Medication for heart failure
Valve surgery
Anticoagulation
FUTURE

- Streptococcal clinics/primary prevention (AMPATH)
- New anticoagulants
- Early diagnosis
  - Mobile echocardiography
- Increasing cardiology presence on site
- Local surgical/percutaneous intervention capabilities
- Vaccine
  - Pathogenesis of RF→Ab against GABHS react with human heart preparations (myosin, tropomyosin, keratin, laminin)

Lancet 2012;379:953-964
Vaccine: surface M protein

Development

- Targets the variable region of M protein
- Phase 2 trials completed in adults

Obstacles

- Limited number of >80 distinct GABS serotypes are rheumatogenic
- Require highly complex mixture of M proteins (associated with adherence to epithelial cells) from multiple serotypes
- M protein contains epitopes cross react with human tissue
- Antibodies against these epitopes may produce RF

Ann Intern Med. 1994;120:243-245
Lancet 2012;379:953-964
“A lecture on rheumatic heart disease in sub-Saharan Africa, is a lecture on rheumatic fever and its prevention”

“let nature take its course”

African healthcare infrastructure financial allocation:

HIV
tuberculosis
leprosy
parasitic/diarrheal diseases
The Drakensberg Declaration on the Control of Rheumatic Fever and Rheumatic Heart Disease in Africa

(i) raising the **awareness** of the public and health care workers with regard to RF and RHD

(ii) *(ii)* improving the quality of information available on the incidence, prevalence and burden of RF/RHD through epidemiological **surveillance**

(iii) *(iii)* working together as **advocates** to change public policy for the improvement of health care facilities needed to treat and prevent the disease

(iv) *(iv)* working towards the establishment of national primary and secondary **prevention** programmes for RF and RHD.

*SAMJ* March 2006, Vol. 96, No. 3