CARDIAC INFECTIONS: ARF AND ENDOCARDITIS

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Acute Rheumatic fever (ARF)

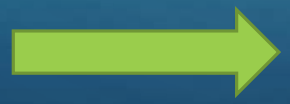
OUTLINES

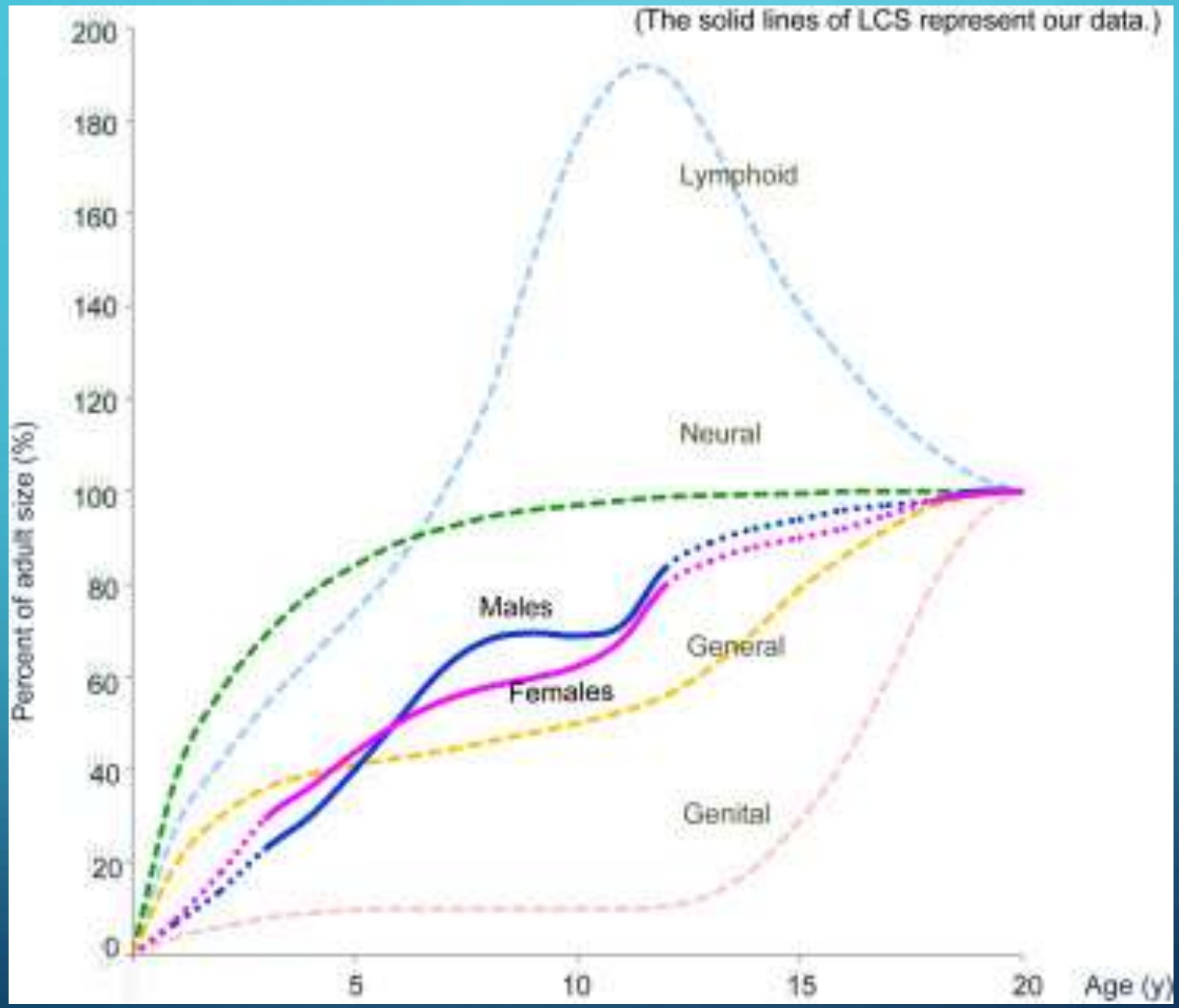
- *Etiolgy.*
- *Epidemiology*
- *Pathophysiology*
- *Jones criteria*
- *Diagnosis*
- *Treatment*
- *Complications*
- *Prevention*
- *Prognosis*

ETIOLOGY

- Proceeded by GAS pharyngitis.
- ABT to treat GAS pharyngitis prevents rheumatic fever.
- ABT prophylaxis prevents ARF recurrence
- serotypes of GAS (M types 1, 3, 5, 6, 18, 29) are more frequently isolated

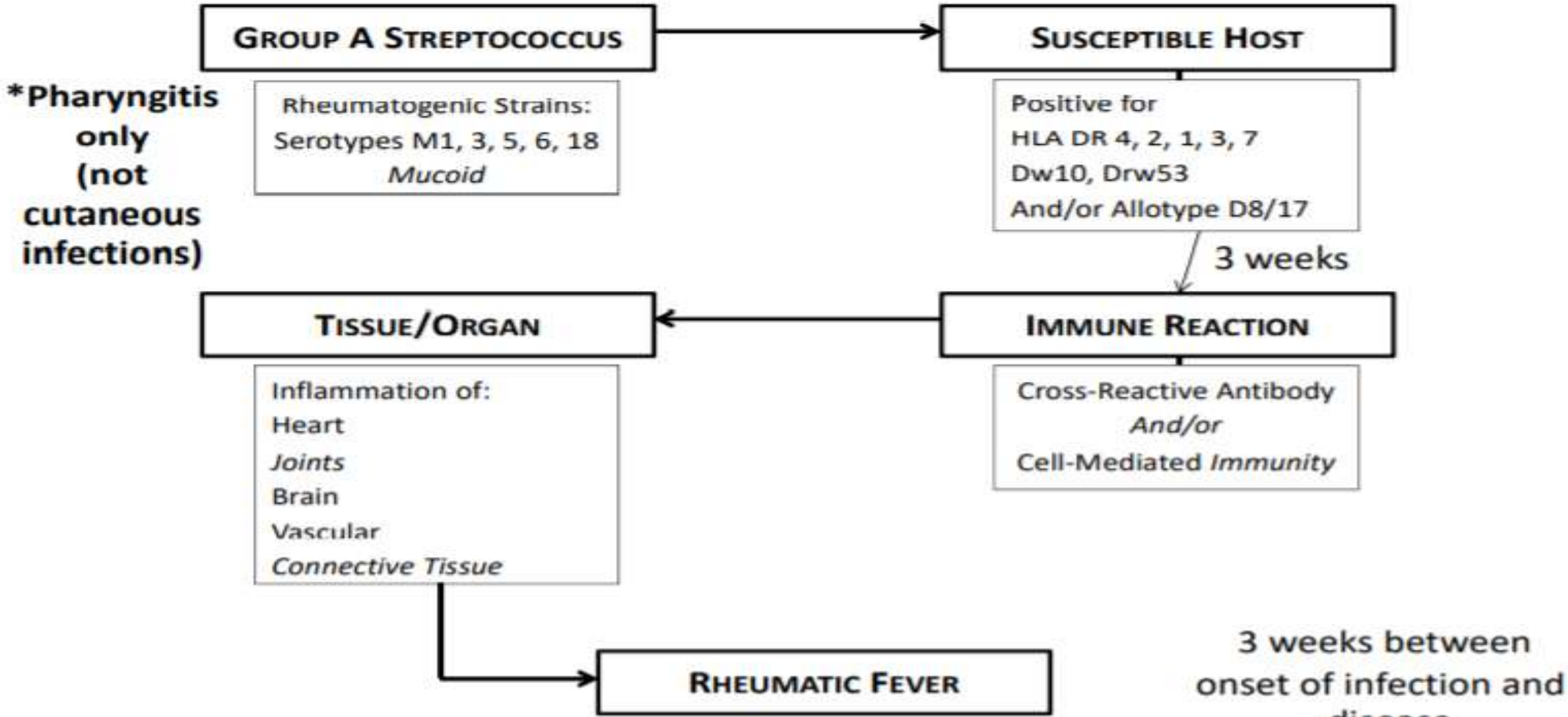
EPIDEMIOLOGY

- Why more frequent in developing countries:
  - Host factors:
    - genetic susceptibility
    - Lack of appropriate medical care.
    - Poverty and crowding.
  - Pathogen factors
    - Certain GAS are rheumatogenic serotypes (types 1, 3, 5, 6, and 18)
- Most common form of acquired heart disease
- peaks : 5-15 yr of age
- Once happened  increased risk of recurrence


(The solid lines of LCS represent our data.)
Percent of adult size (%)
200
180
160
140
120
100
80
60
40
20
0
Lymphoid
Neural
Males
Females
General
Genital
5
10
15
20
Age (y)

PATHOGENESIS

- Cytotoxicity theory:
  - GAS toxin leads to ARF and rheumatic heart disease.
- **Immunologic theory**
  - Latency.
  - Cross antigenicity of several GAS and tissues (e.g., heart valve, sarcomere, brain, joint)


*Pharyngitis only (not cutaneous infections)
GROUP A STREPTOCOCCUS
Rheumatogenic Strains:
Serotypes M1, 3, 5, 6, 18
Mucoid
SUSCEPTIBLE HOST
Positive for
HLA DR 4, 2, 1, 3, 7
Dw10, Drw53
And/or Allotype D8/17
3 weeks
IMMUNE REACTION
Cross-Reactive Antibody
And/or
Cell-Mediated Immunity
TISSUE/ORGAN
Inflammation of:
Heart
Joints
Brain
Vascular
Connective Tissue
RHEUMATIC FEVER
3 weeks between onset of infection and disease

JONES CRITERIA

MAJOR MANIFESTATIONS	MINOR MANIFESTATIONS	EVIDENCE OF GAS INFECTION
1. Carditis 2. Polyarthritis 3. Erythema marginatum 4. Subcutaneous nodules 5. Chorea	1. Arthralgia 2. Fever 3. High ESR or CRP 4. Prolonged P-R	1. Positive throat culture 2. or rapid strep. test 3. or ASO titer

- Guidelines for the Diagnosis of Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)
- 2 major or 1 major and 2 minor criteria PLUS evidence of preceding GAS infection needed to diagnose ARF
- recurrent ARF: presence of 3 minor criteria PLUS evidence of preceding GAS infection.

JONES CRITERIA

- Initial attack:
  - 2 major manifestations, plus evidence of recent GAS infection.
  - Or 1 major and 2 minor manifestations, plus evidence of recent GAS infection.
  - Chorea alone, plus evidence of recent GAS infection.
- Recurrent attack: 2 major, or 1 major and 2 minor, or 3 minor manifestations , plus evidence of recent GAS infection
- Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis)
- Arthritis: monoarthritis or polyarthralgia

Revised Jones Criterion

Major manifestations

- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

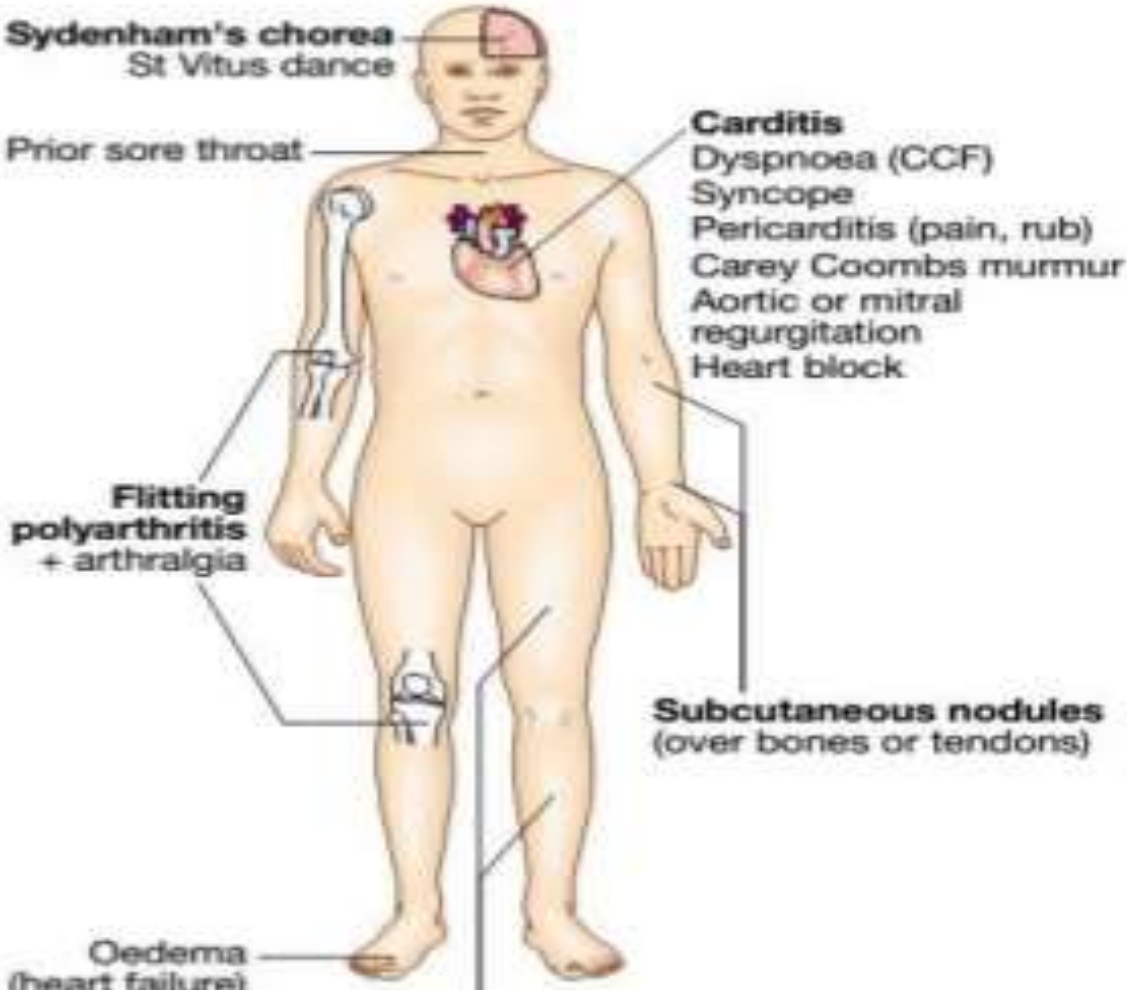
Minor manifestations

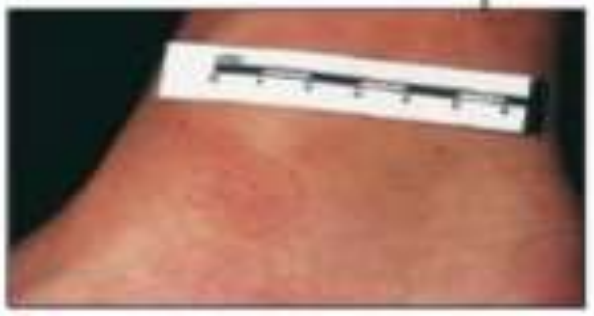
- Fever
- Arthralgia
- Previous rheumatic fever
- Raised ESR or CRP
- Leucocytosis
- First-degree AV block

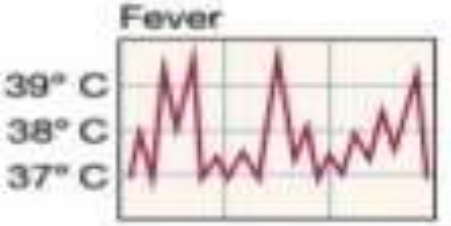
Plus

- Supporting evidence of preceding streptococcal infection: recent scarlet fever, raised antistreptolysin O or other streptococcal antibody titre, positive throat culture

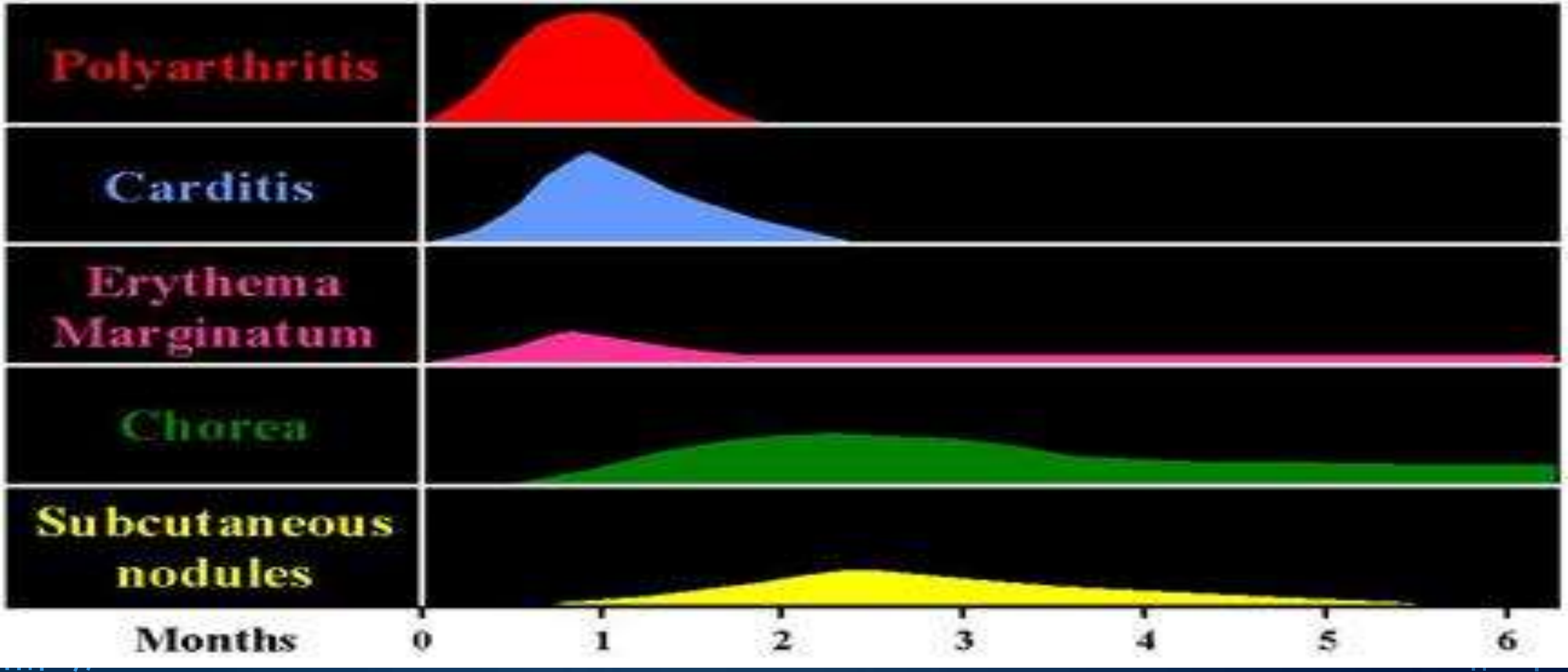
N.B. Evidence of recent streptococcal infection is particularly important if there is only one major manifestation.







Clinical Manifestations of Acute Rheumatic Fever



MIGRATORY POLYARTHRITIS

- In 75% of ARF.
- larger joints (knees, ankles, wrists, and elbows
- Migratory
- Arthritis is the earliest manifestation
- Last weeks if untreated.
- **Response to salicylates is characteristic**
- Not deforming
- inverse relationship between the severity of arthritis and severity of cardiac involvement

CARDITIS

- 50-60% of all ARF
- subclinical carditis accepted in revised jones criteria 2015.
  - subclinical carditis defined: without a murmur but with echocardiographic evidence of valvulitis
  - clinical carditis (with a valvulitis murmur)
- Pancarditis: but mainly Endocarditis (valvulitis)
- **MR** or MR+AR
- insufficiency is characteristic
- mitral and/or aortic valvular stenosis usually appears in years
- tachycardia and cardiac murmur
- Most serious ARF complication, May require valve replacement, if recurrent

SYDENHAM CHOREA

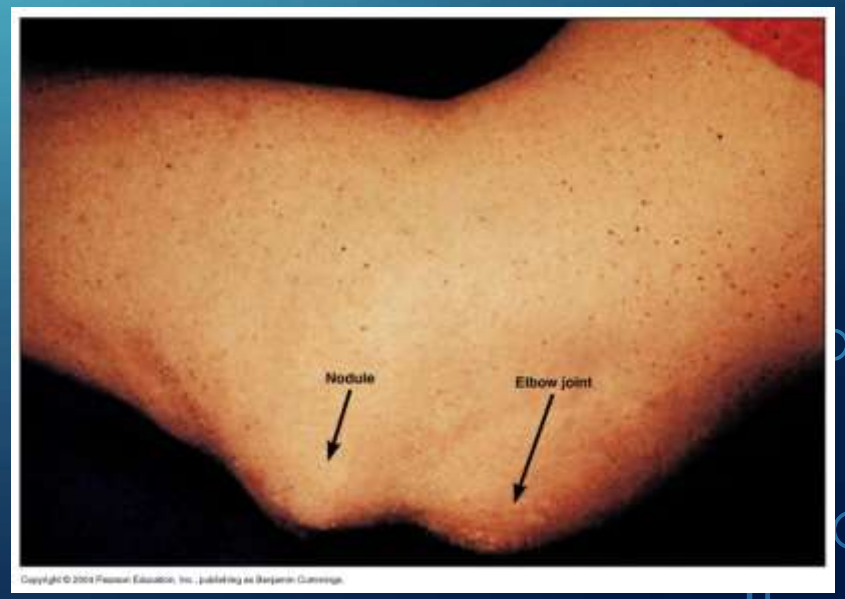
- 10-15% of ARF.
- could be Isolated, frequently subtle
- Emotional lability, incoordination, poor school performance, uncontrollable movements, and facial grimacing, all exacerbated by stress and disappearing with sleep, are characteristic.
- Later than arthritis or carditis (ASO may disappear when chorea presents)
- Occurs in 10-15% of pts with acute RF

- Occasionally unilateral

-lasts 3 m to 2-3 yrs , no permeant *damage*

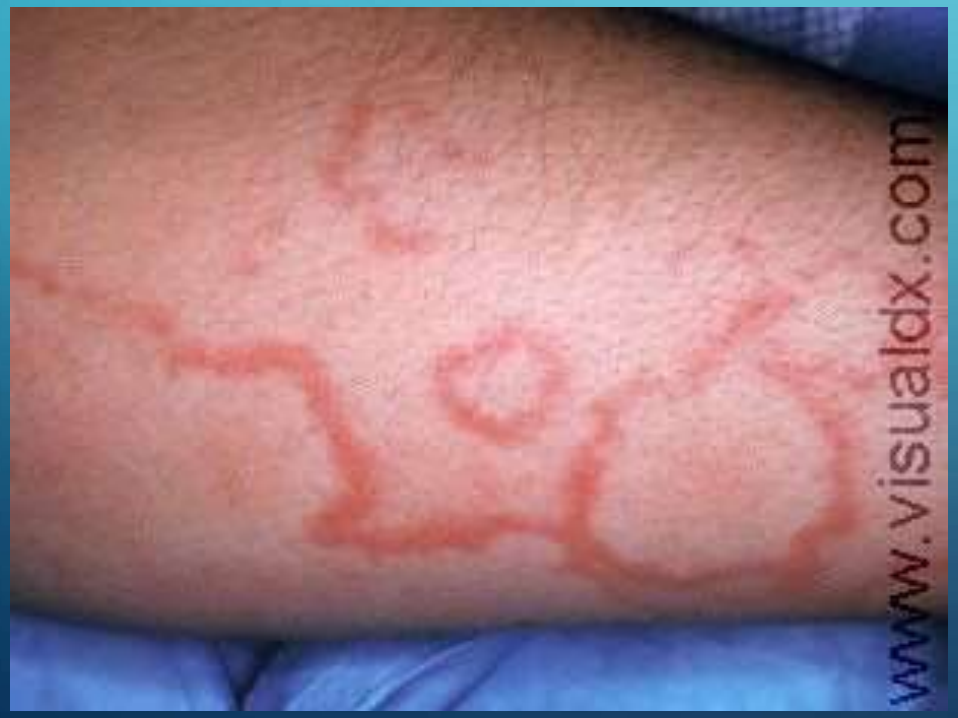
SUBCUTANEOUS NODULES

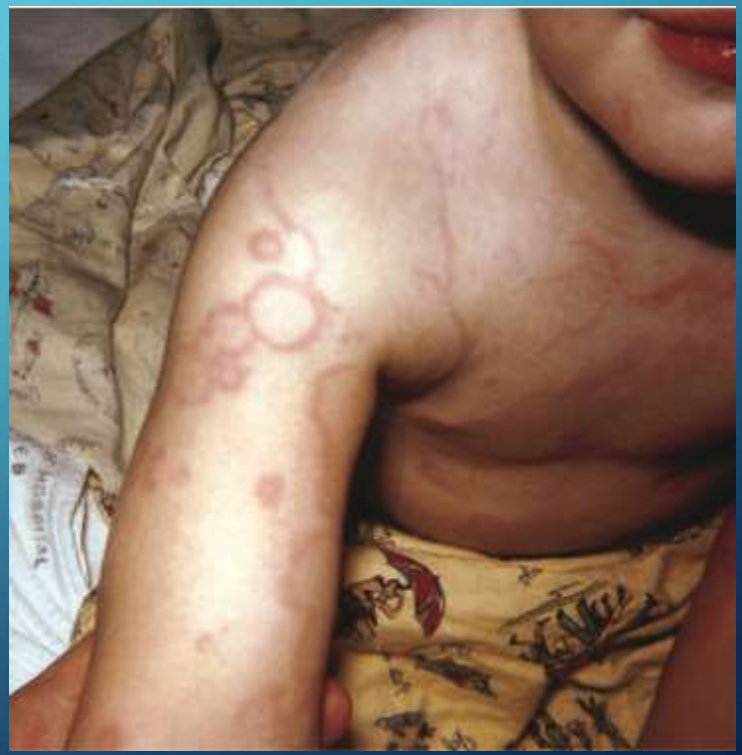
- rare (≤1%
- firm nodules
- along the extensor surfaces of tendons near bony prominences
- Corollates with significant rheumatic heart disease.



ERYTHEMA MARGINATUM

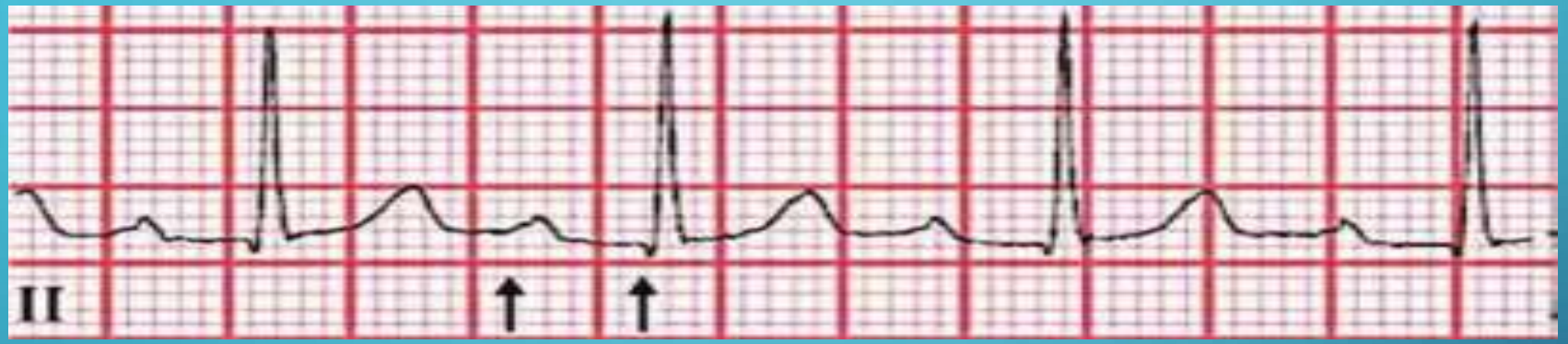
- On trunk and extremities, but not on the face
- accentuated by warming the skin





MINOR CRITERIA

- Arhtralgia: (only if arthritis is not used as a major criterion)
- Fever, more than 38.0°
- elevated acute phase reactants
- prolonged P-R interval on ECG (unless carditis is a major criterion)



- *First-degree heart block with prolonged PR interval (interval between arrows), which may be present as a minor criterion for acute rheumatic fever.*

RECENT GAS INFECTION

- Must have.
- ARF devlpes 2-4 wk post GAS pharyngitis.
- 1/3 have no Hx of pharyngitis.
- 80-85% have high ASO.
- 95-100% have an elevation if 3 different antibodies (antistreptolysin O, anti–DNase B, antihyaluronidase)
- Clinical findings of acute rheumatic fever generally coincide with peak antistreptococcal antibody responses.

DDX OF ARF

ARTHRITIS	CARDITIS	CHOREA
Juvenile idiopathic arthritis	Viral myocarditis	Huntington chorea
Reactive arthritis (e.g., Shigella, Salmonella, Yersinia)	Viral pericarditis	Wilson disease
Serum sickness	Infective endocarditis	SLE
Sickle cell disease Malignancy SLE Lyme disease (Borrelia burgdorferi) Pyogenic arthritis Post strep RA	Kawasaki disease Congenital heart disease Mitral valve prolapse Innocent murmurs	Cerebral palsy Tic disorder Hyperactivity

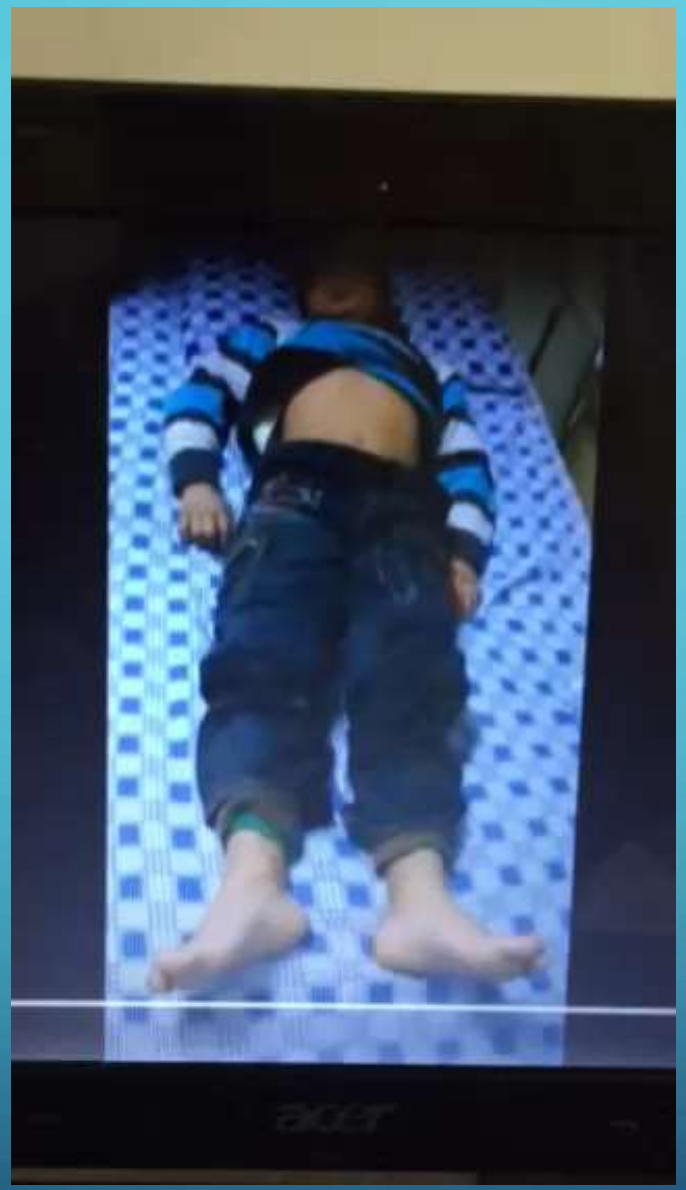
- bed rest (esp if caditis present).
- ABT:
  - PCV V K 10 days.
  - Or Amoxcillin oral for 10 days
  - Or Benzathenine Penicillin G X 1 intramuscular
  - If PCN allergic: erythromycin, azithromycin or clindamycin

ANTIINFLAMMATORY THERAPY

- Early treatment may mask the disease.
- Use Acetaminophen early if still unsure if DX.
- Salicylates.:
  - 50-70 mg/kg/day QID PO X 3-5 days
  - Then 50 mg/kg/day in 4 QID PO X 3 wk
  - Then half that 2-4 wk
- Corticosteroids. If Carditis present.
  - prednisone is 2 mg/kg/day QID X 2-3 wk
  - followed by half the dose for 2-3 wk
  - then by 5 mg/24 hr every 2-3 days.
- Repeat if ARF rebounded
- *Carditis Rx: Steroid, Digoxcin, fluid and salt restriction, diuretics, and oxygen*

SYDENHAM CHOREA RX

- Late: usually anti-inflammatory not needed.
- Sedatives:
  - phenobarbital, drug of choice
  - Alternate choices: haloperidol or chlorpromazine
  - Plus minus corticosteroids.


acer

COMPLICATIONS

- *"Acute Rheumatic Fever licks the joints and bites the heart" (Laseque 1884)*

PROGNOSIS

- 50-70% of carditis recover.
- Worsoning carditis may occur in subsequent attacks.
- ARF recurrence 50% risk with each GAS pharyngitis
- ARF Recurrence is highest in the 1st 5 yr
- 20% of patients who present with “pure” chorea who are not given secondary prophylaxis develop rheumatic heart disease within 20 yr.

PREVENTION

- primary prevention:
  - DX and treat GAS pharyngitis X 10 days before ARF appears.
  - Effective if PCN given in first 9 days of pharyngitis
- secondary prevention:
  - Maitance ABT since recurrence likely.
  - Benzathine PCN G IM X 1 Q 4 weeks
  - Or PCV V K PO
  - Or Sulfa
  - Macrolide if PCN allergic

DURATION OF PROPHYLAXIS BY AHA

CATEGORY	DURATION
Rheumatic fever without carditis	5 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis but without residual heart disease (no valvular disease)	10 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis and residual heart disease (persistent valvular disease)	10 yr or until 40 yr of age, whichever is longer; sometimes

Endocarditis

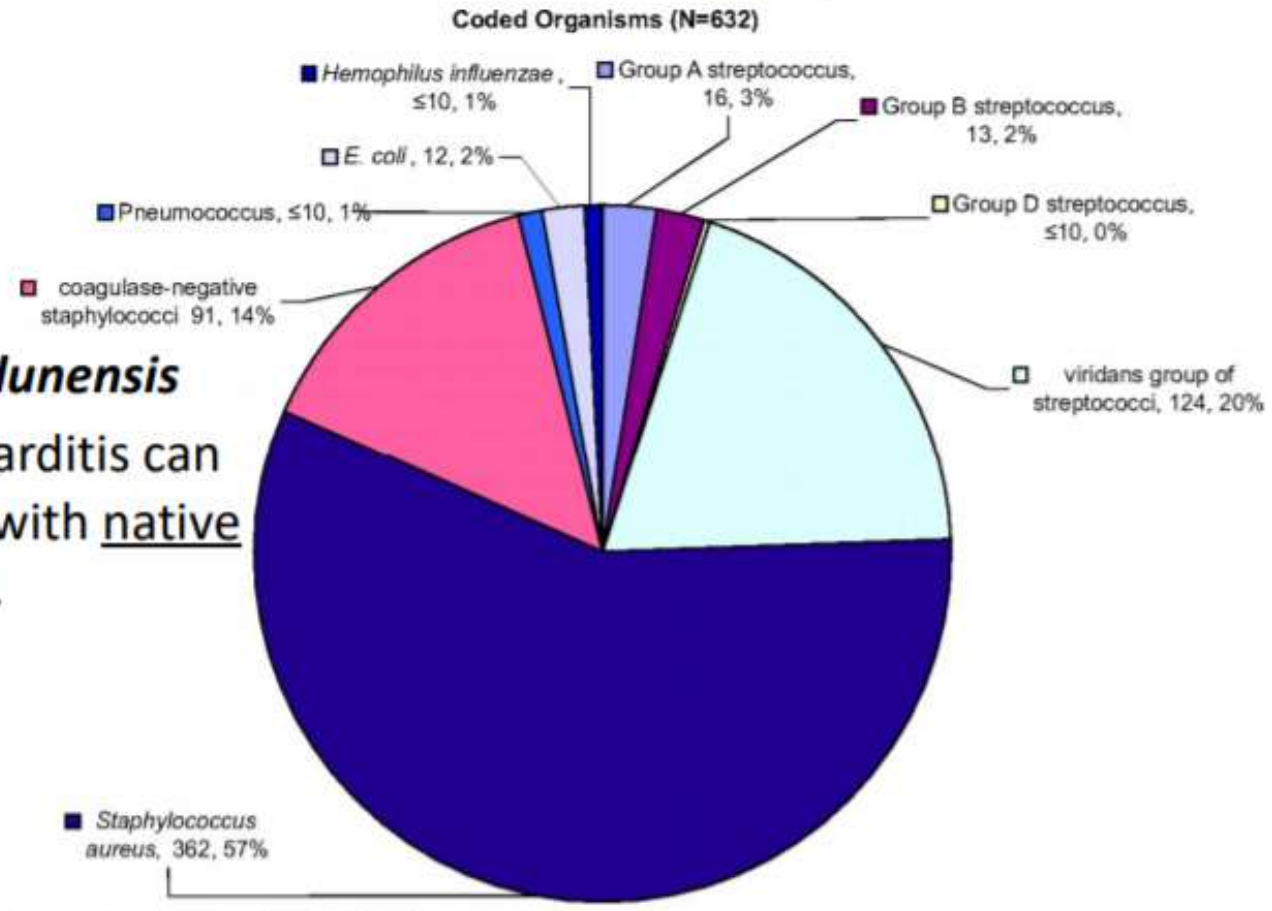
WHO DEVELOPS PEDIATRIC ENDOCARDITIS?

- Marked decline in Rheumatic HD
- 80-90% occur in congenital HD
  - (VSD, PDA, TOF, aortic valve abnormalities; operated patients with S-P shunts, prosthetic material)
  - Not ASD
- Central venous catheters, pacemakers, IV drug users
- 10% in normal hearts
- Highest risk: Aortic valve prosthesis or systemic-pulmonary shunt

ETIOLOGY

- **STREPTOCOCCI** (~ 45%)
  - **Viridans** 35%
  - Enterococci ~ 5%
  - *S. pneumoniae*, beta streptococci (GBS) - ~ 7%
- **STAPHYLOCOCCI**: especially post-op, foreign body-associated or in normal hearts (~ 40%)
  - *S. aureus* ~ 30%
  - Coagulase-negative staph ~ 10%

Pie chart showing the number and percentage of IE admissions in the KID from 2000 and 2003 with a coded causative organism.



S. lugdunensis

Endocarditis can occur with native valves.

Day M D et al. Circulation 2009;119:865-870

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Learn and Live

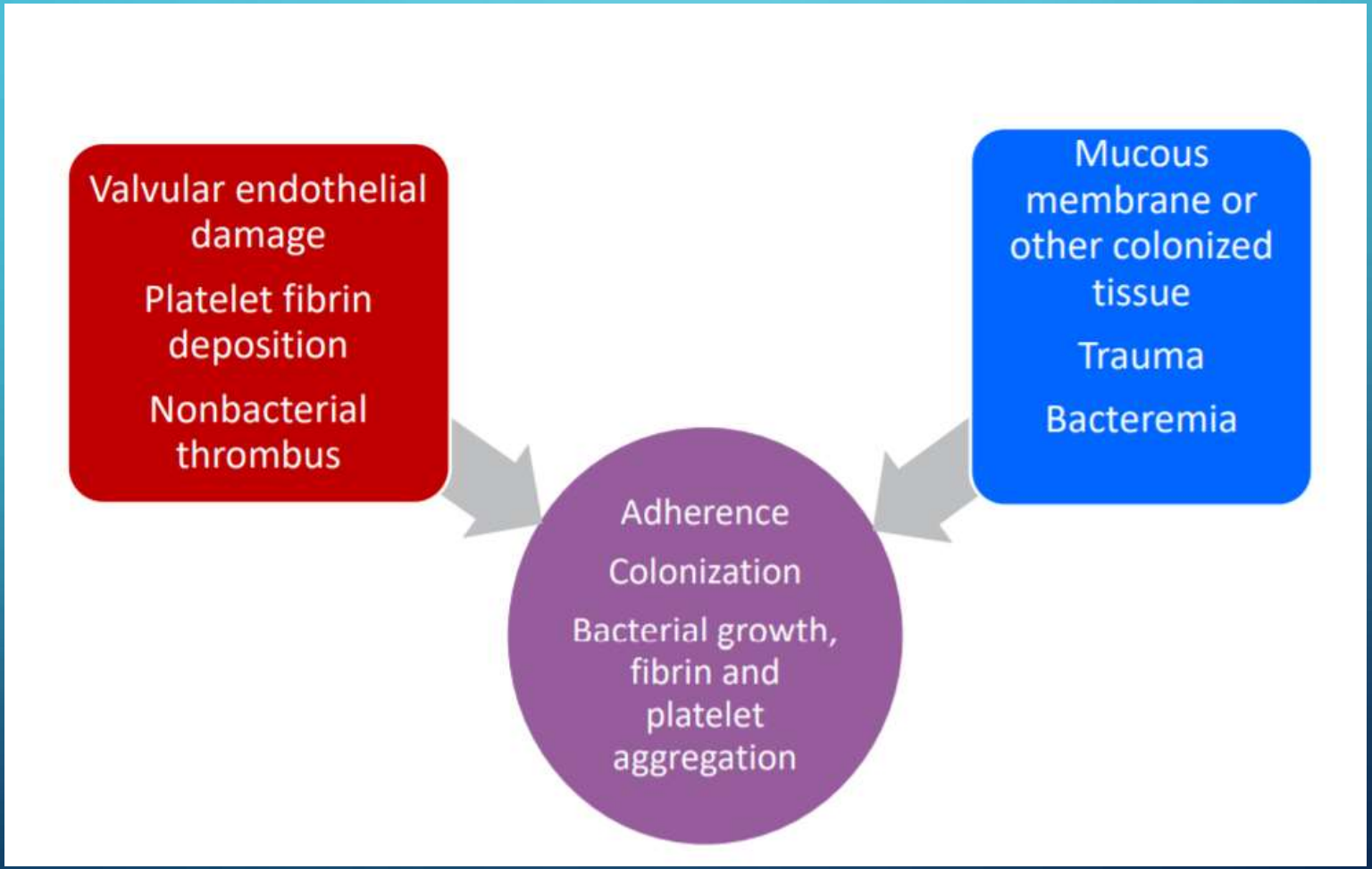
ETIOLOGY

- **HACEK** group: ~ 5%:
  - ***H****aemophilus* species, *Actinobacillus actinomycetemcomitans, **C**ardiobacterium hominis, **E**ikenella corrodens, **K**ingella kingae*
  - fastidious Gram-negative coccobacilli
- Others ~ 5-7%
  - Fungi, especially Candida ~ 2-5%
  - Gram-negative enterics ~ 3%
- Culture-negative ~ 5%

INFECTIVE ENDOCARDITIS PATHOGENESIS

- Areas of turbulent flow (jet effect, eddies)
  - Stenosis (valves, coarct)
  - Small VSD
- Endothelial disruption results (also occurs with indwelling line)
- Sterile fibrin-platelet thrombus develops on the disrupted surface
- Entrapment of bacteria from “stray bacteremia” initiates focus of infection; platelets and fibrin deposit to form vegetation. Receptors are involved (MSCRAMM’s).

INFECTIVE ENDOCARDITIS PATHOGENESIS



ASYMPTOMATIC BACTEREMIA OCCURS IN:

Initiating Event	Percentage of Positive Blood Cultures (%)	Predominant Organisms
Dental extraction (children)	30-65	*Streptococcus*, diphtheroids
Chewing gum, candy, paraffin	0-51	*Streptococcus, Staphylococcus epidermidis*
Tooth brushing	0-26	*Streptococcus*
Tonsillectomy	28-38	*Streptococcus, Haemophilus*, diphtheroids
Bronchoscopy (rigid scope)	15	*Streptococcus, S. epidermidis*
Bronchoscopy (fiberoptic)	0	
Orotracheal intubation	0	
Nasotracheal intubation/suctioning	16	*Streptococcus*, aerobic gram-negative rods
Sigmoidoscopy/colonoscopy	0-9.5	*Enterococcus*, aerobic gram-negative rods
Upper gastrointestinal endoscopy	8-12	*Streptococcus, Neisseria, S. epidermidis*, diphtheroids, other
Percutaneous liver biopsy	3-14	Pneumococcus, aerobic gram-negative rods, *Staphylococcus aureus*, other
Urethral catheterization	8	Not stated
Manipulation of *S. aureus* suppurative foci	54	

From Everett ED, Hirschmann JU. Transient bacteremia and endocarditis prophylaxis: a review. *Medicine (Baltimore)* 1977;**56**:61–77.
© 1977, The Williams & Wilkins Company, Baltimore.

INFECTIVE ENDOCARDITIS CLINICAL SYNDROMES

- Acute Presentation
  - High fever, toxicity, ± CHF
  - *S. aureus* most common; β strep, *S. pneumoniae*
  - Early post-op; normal heart; indwelling lines
- Subacute Presentation (more common)
  - Insidious, non-toxic, malaise, immune phenomena
  - Viridans strep most common pathogen
  - Also fungal, HACEK agents, coagulase-negative staph
  - Extracardiac manifestations are less common than in adults (splenomegaly, hematuria, immune phenomena)

C/P

- Causes of the clinical picture and complications:
  - Embolization
  - Heart damage
  - Circulating immune complexes

C/P

Symptom	Average (%)	Range (%)	Physical Finding	Average (%)	Range (%)
Fever	90	56-100	Splenomegaly	55	36-67
Malaise	55	40-79	Petechiae	33	10-50
Anorexia/weight loss	31	8-83	Embolic phenomena	28	14-50
Heart failure	30	9-47	New or change in heart murmur	24	9-44
Arthralgia	24	16-38	Clubbing	14	2-42
Neurologic findings	18	12-21	Osler nodes	7	7-8
Gastrointestinal findings	16	9-36	Roth spots	5	0-6
Chest pain	9	5-20	Janeway lesion	5	0-10
			Splinter hemorrhages	5	0-10

INFECTIVE ENDOCARDITIS EVALUATION

- 3 or more blood cultures (separate venipunctures) over 6-24 hours before therapy:
  - Continuous bacteremia is the rule in endocarditis
- Trans-thoracic Echo (~ 80% sensitive, higher than in adults)

INFECTIVE ENDOCARDITIS EVALUATION

- Role of Trans-esophageal Echo (TEE) in kids is evolving:
  - Better imaging of aortic root structures
  - Superior in individuals with thick chest walls, obesity
  - Superior with prosthetic valves
  - Superior for vegetations, abscesses

SELECTED LABORATORY FINDINGS OF BACTERIAL ENDOCARDITIS IN CHILDREN

Laboratory Finding	Average (%)	Range (%)
Positive blood culture	87	68-98
Elevated erythrocyte sedimentation rate	80	71-96
Low hemoglobin (anemia)	44	19-79
Positive rheumatoid factor	38	25-55
Hematuria	35	28-47

INFECTIVE ENDOCARDITIS DIAGNOSTIC CRITERIA

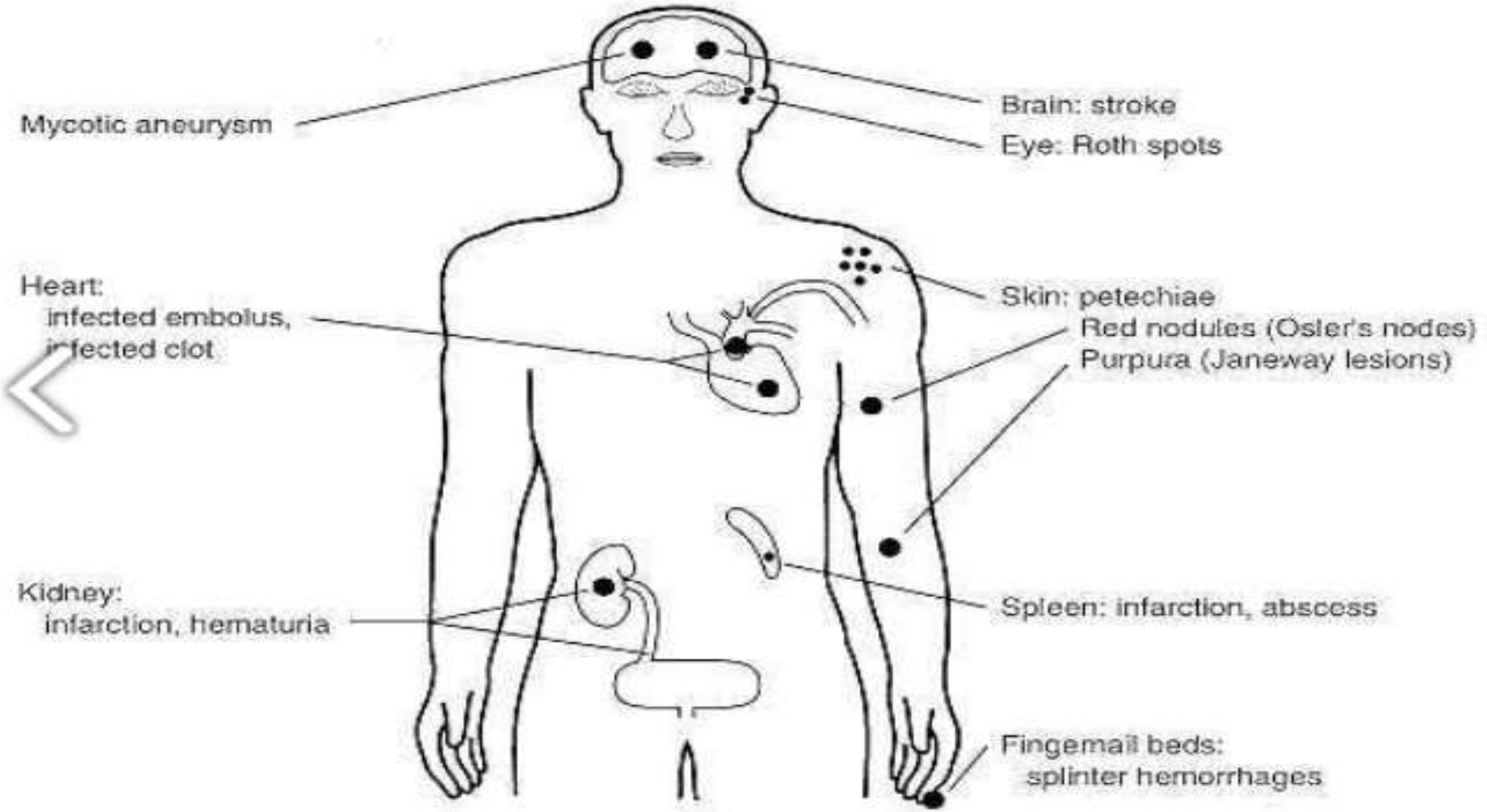
- Duke Criteria:
  - **Definite IE:** Pathologic evidence, or 2 majors, or 1 major and 3 minors, or 5 minors
  - **Possible IE:** 1 major and 1 or 2 minors, or 3-4 minors alone
  - **Rejected:** Firm alternate diagnosis; or resolution of illness or absence of evidence of IE at surgery or autopsy after ≤ 4 days of antibiotics

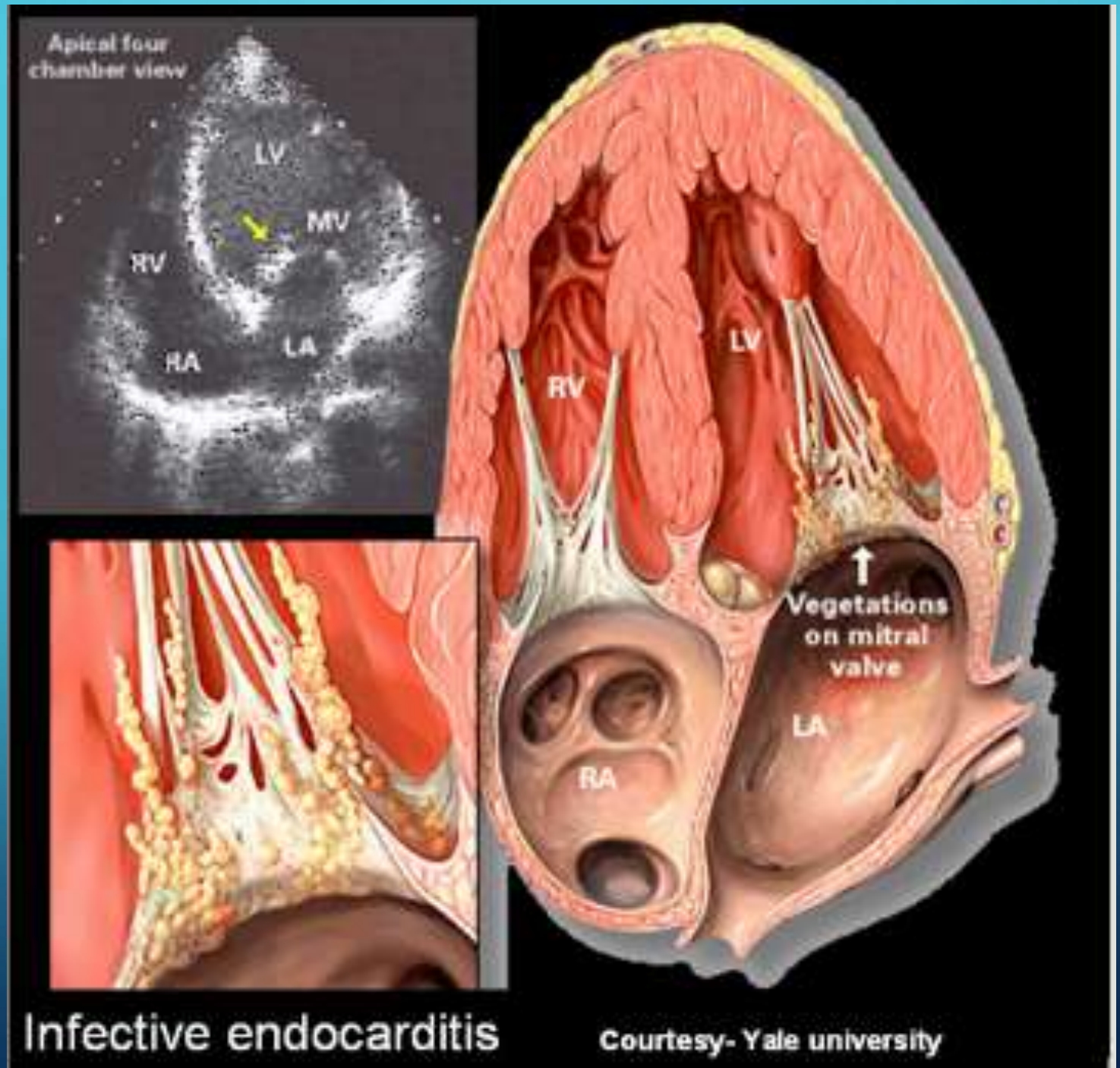
INFECTIVE ENDOCARDITIS
REVISED DUKE CRITERIA (2000)

- **MAJOR CRITERIA**
  - Positive blood cultures
    - Typical IE organism from ≥ 2 cultures or
    - Persistently positive cultures (≥ 2 BC at least 12 hr apart or all of 3 or majority of ≥ 4 BC at least 1 hr apart)
    - Single positive for *C. burnetii* or IgG > 1:800
  - Evidence of endocardial involvement
    - Positive echocardiogram or
    - New valvar regurgitation

INFECTIVE ENDOCARDITIS
REVISED DUKE CRITERIA (CONT.)

- **MINOR CRITERIA**
  - Predisposing heart disease or IVDA
  - Fever 38° C
  - Vascular phenomena (Janeway lesions, emboli, conjunctival hemorrhages, mycotic aneurysms, strokes)
  - Immunologic phenomena (nephritis, Osler nodes, Roth spots, rheumatoid factor)
  - Positive blood cultures not meeting major criterion


Mycotic aneurysm
Brain: stroke
Eye: Roth spots
Heart:
infected embolus,
infected clot
Skin: petechiae
Red nodules (Osler's nodes)
Purpura (Janeway lesions)
Kidney:
infarction, hematuria
Spleen: infarction, abscess
Fingernail beds:
splinter hemorrhages

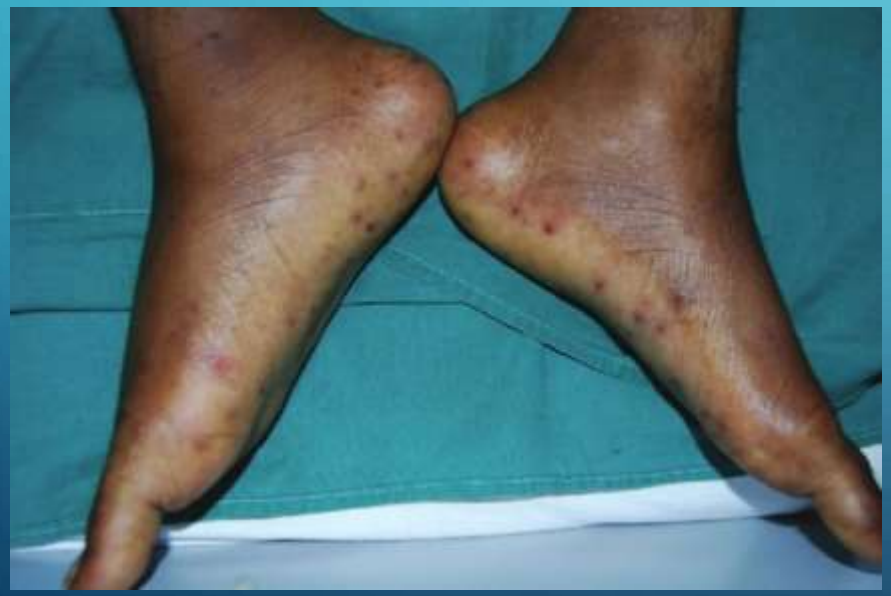

Apical four chamber view
LV
MV
RV
RA
LA
RV
LV
Vegetations on mitral valve
LA
RA
Infective endocarditis
Courtesy- Yale university

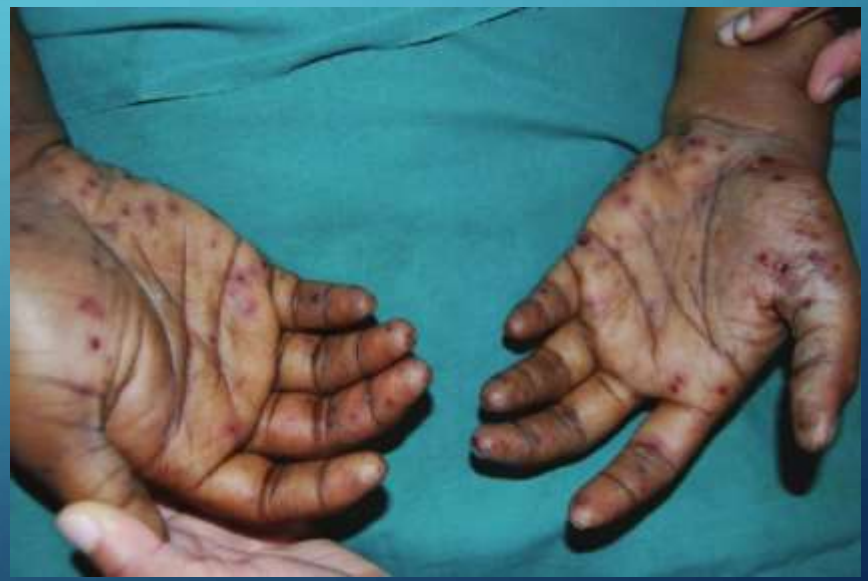
VASCULAR PHENOMENA

- Janeway lesions
- Emboli
- Conjunctival hemorrhages
- Mycotic aneurysms
- Strokes

JANEWAY LESIONS

painless small erythematous or hemorrhagic lesions on the palms and soles





IMMUNOLOGIC PHENOMENA

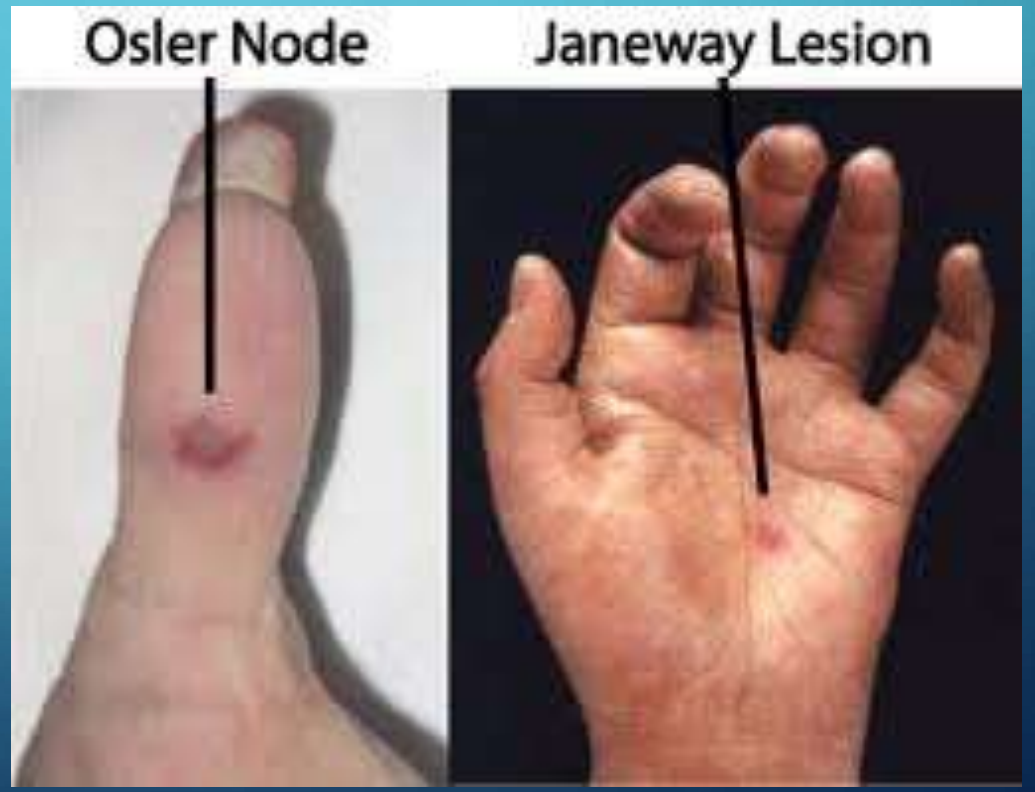
- Nephritis
- Osler nodes
- Roth spots
- Rheumatoid factor
- Splinter hemorrhages

Roth Spots

- "white-centered" hemorrhages
- not specific for endocarditis

OSLER NODES

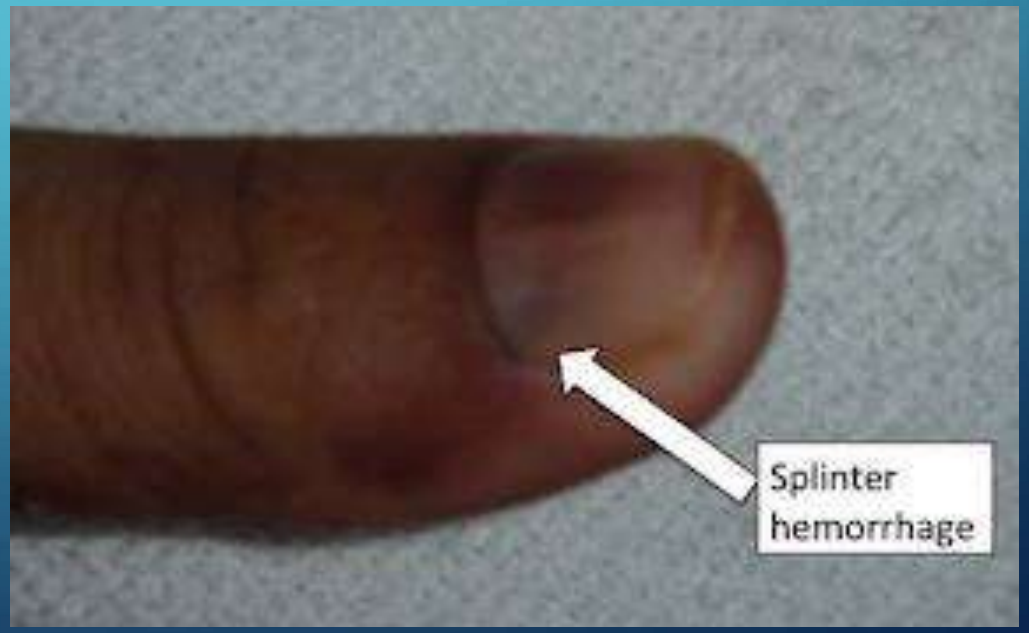
Osler nodes :tender, pea-sized intradermal nodules in the pads of the fingers and toes



SPLINTER HEMORRHAGES

linear lesions beneath the nails.

- may present vasculitis produced by circulating antigen-antibody complexes..



INFECTIVE ENDOCARDITIS TREATMENT I

- PROLONGED
- PARENTERAL
- BACTERICIDAL ANTIBIOTICS

RX IN NATIVE VALVE IE

	Sensitivity	Drug/duration	Alternative
Viridans group Streptococci	PCN sen (MIC <0.12 mcg/mL)	Pen G x 4 weeks OR Ceftriaxone x 4 weeks OR Pen or Ceftriaxone + gent x 2 weeks	Vancomycin x 4 weeks (only to use if patient unable to tolerate beta lactams)
	PCN somewhat resistant (MIC 0.12-0.5)	Pen G x 4 weeks and add gent x 2 weeks OR can consider ceftriaxone alone	
	PCN MIC >0.5 mcg/mL	Pen G or Ampicillin x 4 weeks, gent for two Ceftriaxone + gent	Vancomycin + ~~gent x 6 weeks~~
S. aureus	MSSA	Nafcillin or oxacillin x 6 weeks ~~Option to add gent~~	Cefazolin ~~+ option to add gent~~
	MRSA	Vancomycin x 6 weeks	Daptomycin for MSSA, endocarditis

RX IN NATIVE VALVE IE

Organism	Sensitivity Pattern	Regimen	Alternate agents
Enterococci	PCN sensitive	Amp or Pen G gentamicin or streptomycin x 4-6 weeks OR amp + ceftriaxone	Vancomycin + gentamicin x 6 weeks
	Intrinsic PCN resistance	Vancomycin + gentamicin x 6 weeks	Linezolid x ≥6 weeks
	Ampicillin, vancomycin and AG resistant enterococci	Linezolid or daptomycin	Quinupristin-dalfopristin limited due to toxicity

RX IN POSTHETIC VALVE IE

	Sensitivity	Drug/duration	Alternative
Viridans group Streptococci	PCN sen (MIC <0.12 mcg/mL)	Pen G x 4 weeks OR Ceftriaxone x 6 weeks OR Pen or Ceftriaxone + optional gent x 2 weeks	Vancomycin x 6 weeks (only to use if patient unable to tolerate beta lactams)
	PCN somewhat resistant (MIC 0.12-0.5)	Pen G or ceftriaxone x 6 weeks and add gent x 2 weeks	
	PCN MIC >0.5 mcg/mL	Pen G or Ampicillin plus Gentamicin x 6 weeks	Vancomycin + gent x 6 weeks
S. aureus	MSSA	Nafcillin or oxacillin x ≥6 weeks+ rifampin +gent (x 2 weeks)	Cefazolin + Gentamicin + rifampin
	MRSA	Vancomycin + rifampin x 6 weeks and gentamicin x 2 weeks	Daptomycin for right sided endocarditis,

INFECTIVE ENDOCARDITIS TREATMENT II

- HACEK Agents
  - Ceftriaxone 4 weeks, or Ampicillin and Gentamicin 4 weeks

"CULTURE - NEGATIVE" ENDOCARDITIS INCLUDES

- Partially treated endocarditis
- Nutritionally deficient streptococci
- Fungal endocarditis
- Q fever (rare) Chlamydia
- Bartonella quintana
- Rx: 4-6 weeks of amp-sulbactam or vancomycin and gentamicin, possibly with cipro. Ceftriaxone and gentamicin ± doxycycline if Bartonella suspected

HIGH RISK FOR COMPLICATIONS

- Prosthetic valve IE
- Left-sided IE
- *Staphylococcus aureus* IE
- Fungal IE
- Previous episode of IE
- Prolonged symptoms (≥3 months)
- Cyanotic CHD
- Systemic-pulmonary shunts
- Poor clinical response to antibiotics

PREVENTION OF IE

- Maintain good oral hygiene
- Antibiotic prophylaxis now recommended only for dental procedures in those with:
  - Prosthetic valve
  - History of previous IE
  - Congenital heart disease
    - Unrepaired cyanotic CHD
    - Repaired CHD in 1st 6 months after repair
    - Repaired CHD with residual defect
  - Heart transplant with valve dysfunction

Wilson: Circulation 2007; 115

ENDOCARDITIS PROPHYLAXIS REGIMENS FOR A DENTAL PROCEDURE

Situation	Agent	Regimen: Single Dose 30 to 60 Minutes Before Procedure	
		ADULTS	CHILDREN
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	or		
	Cefazolin *or* Ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins oral	Cephalexin*	2 g	50 mg/kg
	or		
	Clindamycin	600 mg	20 mg/kg
	or		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins and unable to take oral	Cefazolin		
	or		
	Ceftriaxone*	1 g IM or IV	50 mg/kg IM or IV
	or		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation* 2007;**116**:1736–54.


THANK
YOU