



Università degli Studi di Chieti

Corso di aggiornamento Reumatologia pediatrica (2° parte)



**Luciana Breda
Manuela Marsili**

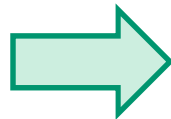
CASO CLINICO

Francesco, 9 anni

Febbre



Faringodinia



**Non eseguito test rapido,
né tampone faringeo**

Astenia

**Terapia intrapresa su consiglio del pediatra
di fiducia:**

Artralgie

- Azitromicina per 3 giorni
- Amoxicillina e ac. clavulanico per 7 giorni

CASO CLINICO

Dopo 3 giorni di benessere clinico, ricomparsa di **febbre** e **malessere generale**...

Ricoverato presso
altra sede

ESAME OBIETTIVO:

Soffio sistolico 1-2/6 al mesocardio.

Faringe iperemico con ipertrofia tonsillare

- ✓ VES 120 mm/h
- ✓ PCR 101.2 mg/L
- ✓ TAS 1010 UI/ml
- ✓ AntiDnaseB 2370 UI/ml
- ✓ Tampone faringeo negativo per SBEA
- ✓ Esame urine e urinocoltura negativi
- ✓ Negativa sierologia per complesso TORCH, Adenovirus, Mycoplasma, EBV
- ✓ Negativi Weil-Felix e Widal-Wright

CASO CLINICO

- ✓ Rx torace: **diffusa accentuazione della trama bronchiale; tenue ipodiafania basale dx**; cavità pleuriche libere da versamento; **lieve prominenzza del II arco a sinistra (a. polmonare)**
- ✓ ECG: nella norma
- ✓ Ecocardio: nella norma
- ✓ Ecoaddome: nella norma

CASO CLINICO

3) Quale diagnosi?

- A) Polmonite streptococcica
- B) Faringotonsillite con bronchite da SBEA
- C) Cardite Reumatica
- D) Endocardite batterica

CASO CLINICO

Terapia praticata durante la degenza:

- Amoxicillina e ac. clavulanico
- Claritromicina

Gli esami ematici predimissione:

- Emocromo nella norma
- VES 112 mm/h
- PCR 77,8 mg/L
- TAS 1057 UI/ml

Veniva dimesso a distanza di 2 giorni dalla defervescenza con diagnosi di «**Polmonite - Infezione streptococcica**»

Terapia consigliata a domicilio:

- ✓ amoxicillina e ac. clavulanico
- ✓ ibuprofene



CASO CLINICO

Dopo alcuni giorni...

Il bambino presenta nuovamente febbre, associata ad artralgie e malessere generale

Prosegue la terapia antibiotica con amoxicillina e ac. clavulanico e per il **TAS aumentato** vengono effettuate due somministrazioni di **Penicillina G Benzatina**

Vengono eseguiti:

- Rx torace di controllo**: refertato nella norma
- Esami ematici**: VES (n.d) - PCR 26 mg/l – TAS 1133 UI/ml

CASO CLINICO

2° Ecocardio

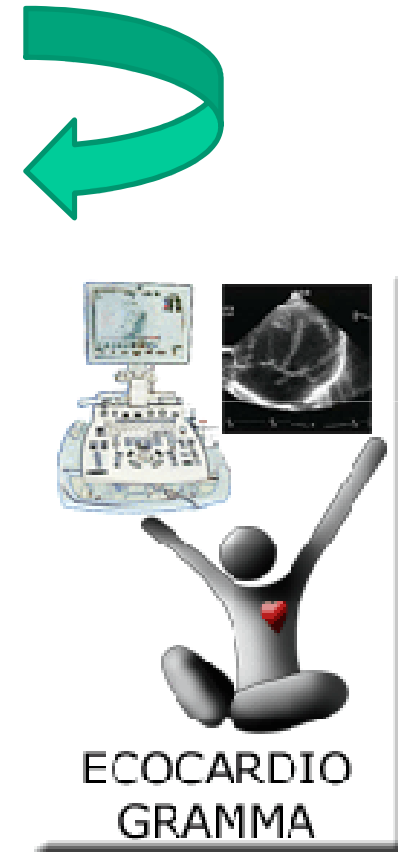
Insufficienza aortica moderata con prolasso delle cuspidi che appaiono iperriflettenti ed ispessite

Lembi mitralici fibrotici, iperriflettenti con

insufficienza mitralica moderata

Insufficienza tricuspidalica lieve con
Ipertensione polmonare moderata PAPs:52 mmHg

- Prednisone 2 mg/kg/die dosaggio a scalare
- Profilassi con Penicillina G Benzatina



CASO CLINICO

3) Quale diagnosi?

Cardite Reumatica

CASO CLINICO

A distanza di poche settimane...

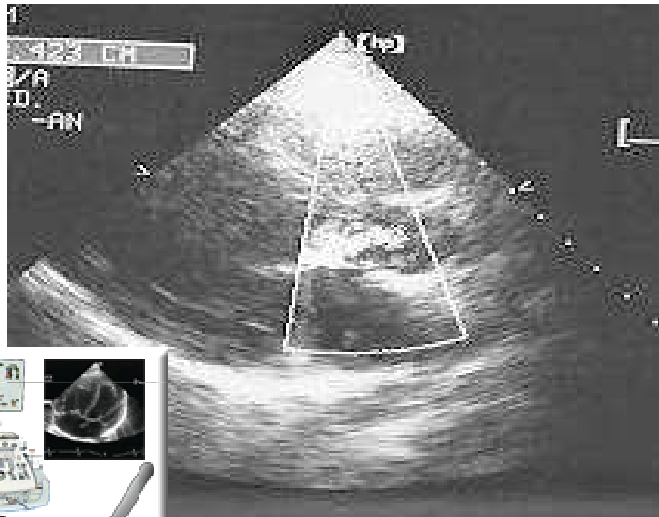


Francesco viene ricoverato nuovamente per lipotimia con riscontro di **BAV di I grado** (PR 0,24 sec)

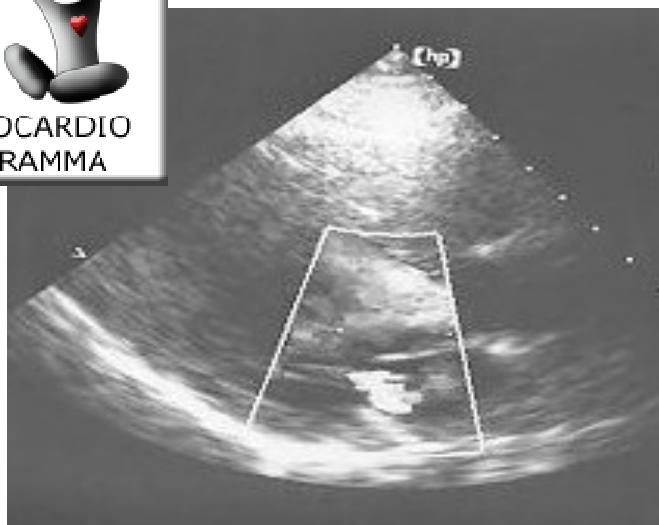
Associato ASA ad alto dosaggio

Il bambino viene quindi inviato presso un centro di cardiocirurgia pediatrica per approfondimento diagnostico

CASO CLINICO



Insufficienza valvolare aortica severa
(finestra asse lungo parasternale)



Insufficienza mitralica lieve
(finestra asse lungo parasternale)

CASO CLINICO

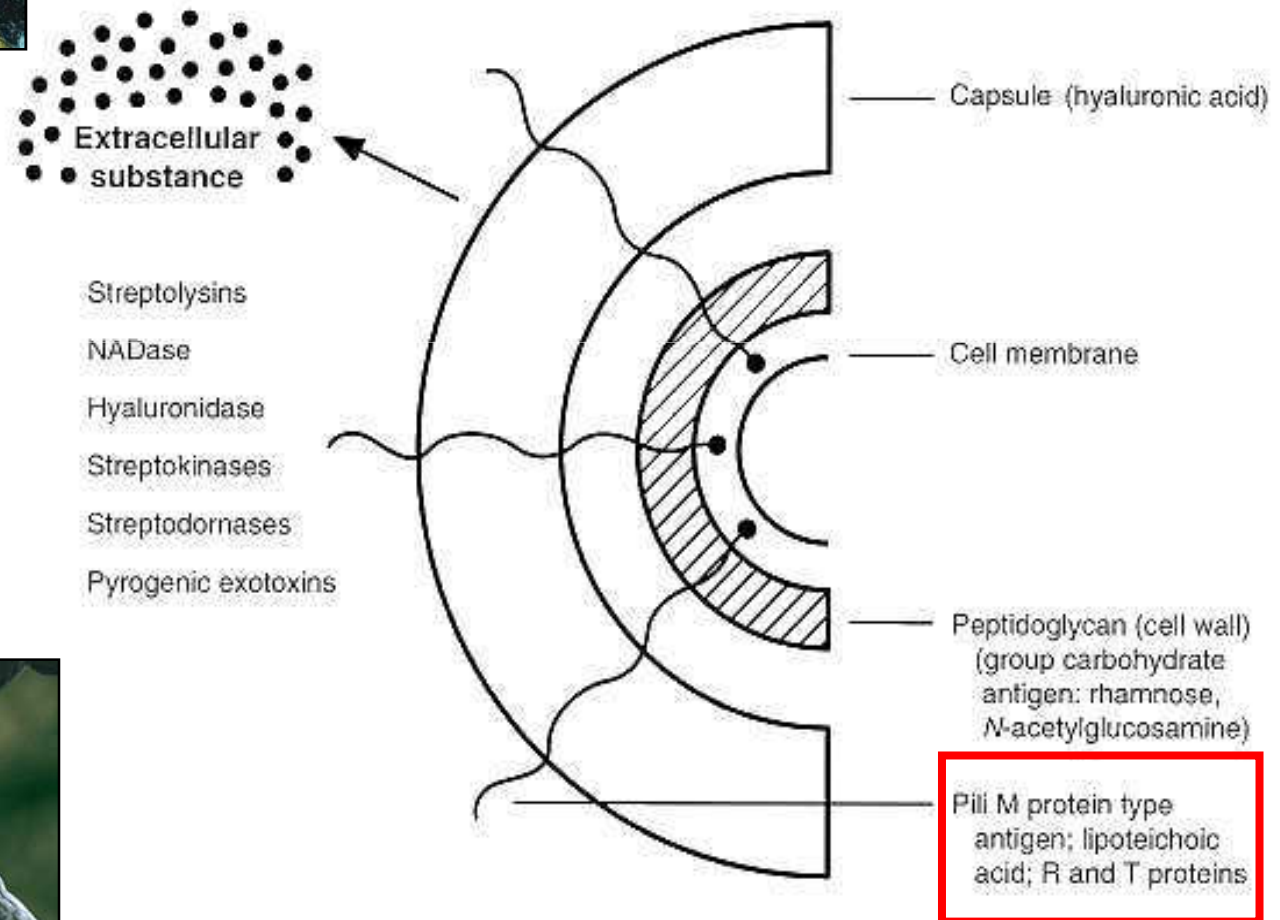
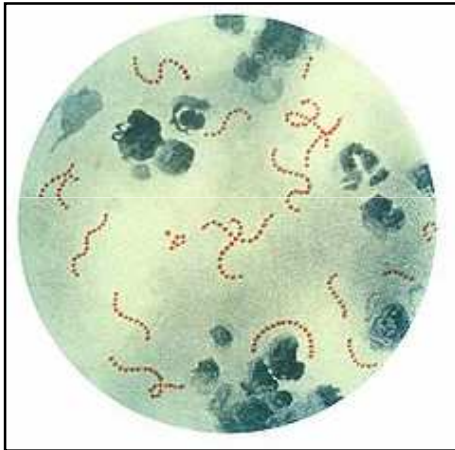
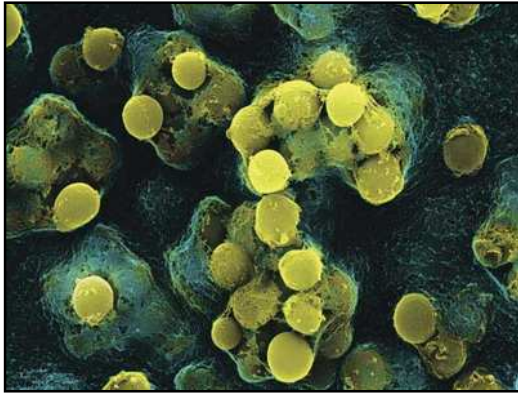


Viene intrapresa terapia con:

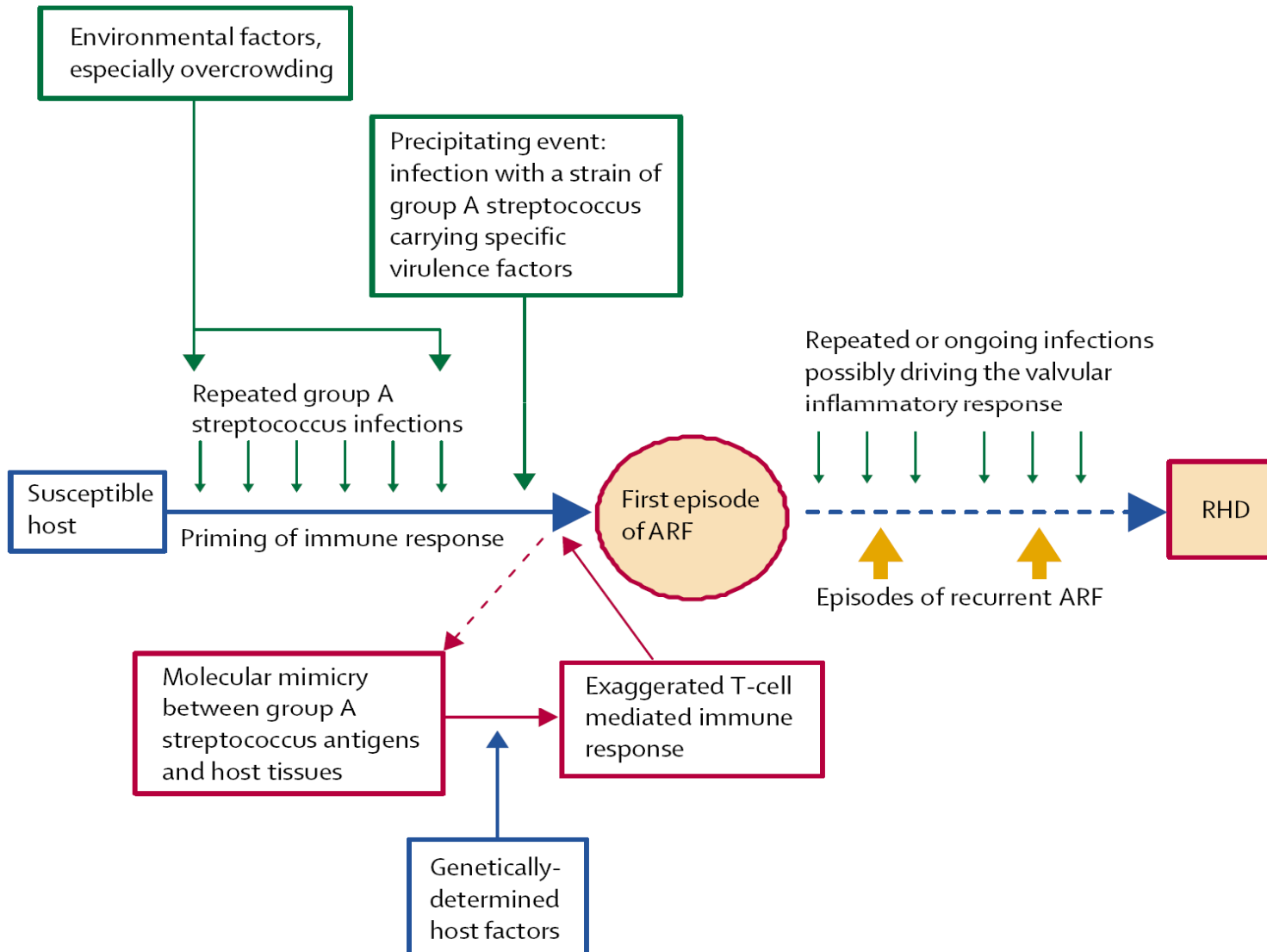
- **Prednisone** (2 mg/Kg/die a scalare per 2 mesi), successivamente sostituita da **ASA** (100 mg/Kg/die per 4 settimane)
- **ACE inibitori e diuretici**

Dopo 6 mesi e circa un anno dalla diagnosi di Febbre Reumatica, il bambino viene sottoposto a **intervento di sostituzione valvolare aortica**

Lo Streptococcus Pyogenes



ARF and RHD pathogenesis





Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev



Acute rheumatic fever and its consequences: A persistent threat to developing nations in the 21st century

Jennifer L. Lee, Stanley M. Naguwa, Gurtej S. Cheema, M. Eric Gershwin *

Division of Rheumatology. Allergy and Clinical Immunology. University of California at Davis School of Medicine. 451 Health Sciences Drive, Suite 6510, Davis, CA 95616, United States

Disease	Number of existing cases	Number of new cases each year	Number of deaths each year
Severe GAS diseases			
Rheumatic heart disease	15.6 million	282 000*	233 000†
History of acute rheumatic fever without carditis, requiring secondary prophylaxis	1.88 million	188 000*	..
RHD-related infective endocarditis	..	34 000	8000
RHD-related stroke	642 000	144 000	108 000
Acute post-streptococcal glomerulonephritis	‡	472 000	5000
Invasive group A streptococcal diseases	..	663 000	163 000
Total severe cases	18.1 million	1.78 million	517 000
Superficial GAS diseases			
Pyoderma	111 million	..	..
Pharyngitis	..	616 million	..

“Rheumatic heart disease is a marker of inequity, of social injustice, and of neglect of vast populations living in poverty...”



Maurice J, Lancet 2013

The global burden of group A streptococcal diseases

Jonathan R Carapetis, Andrew C Steer, E Kim Mulholland, Martin Weber

Lancet Infect Dis 2005;

5: 685–94

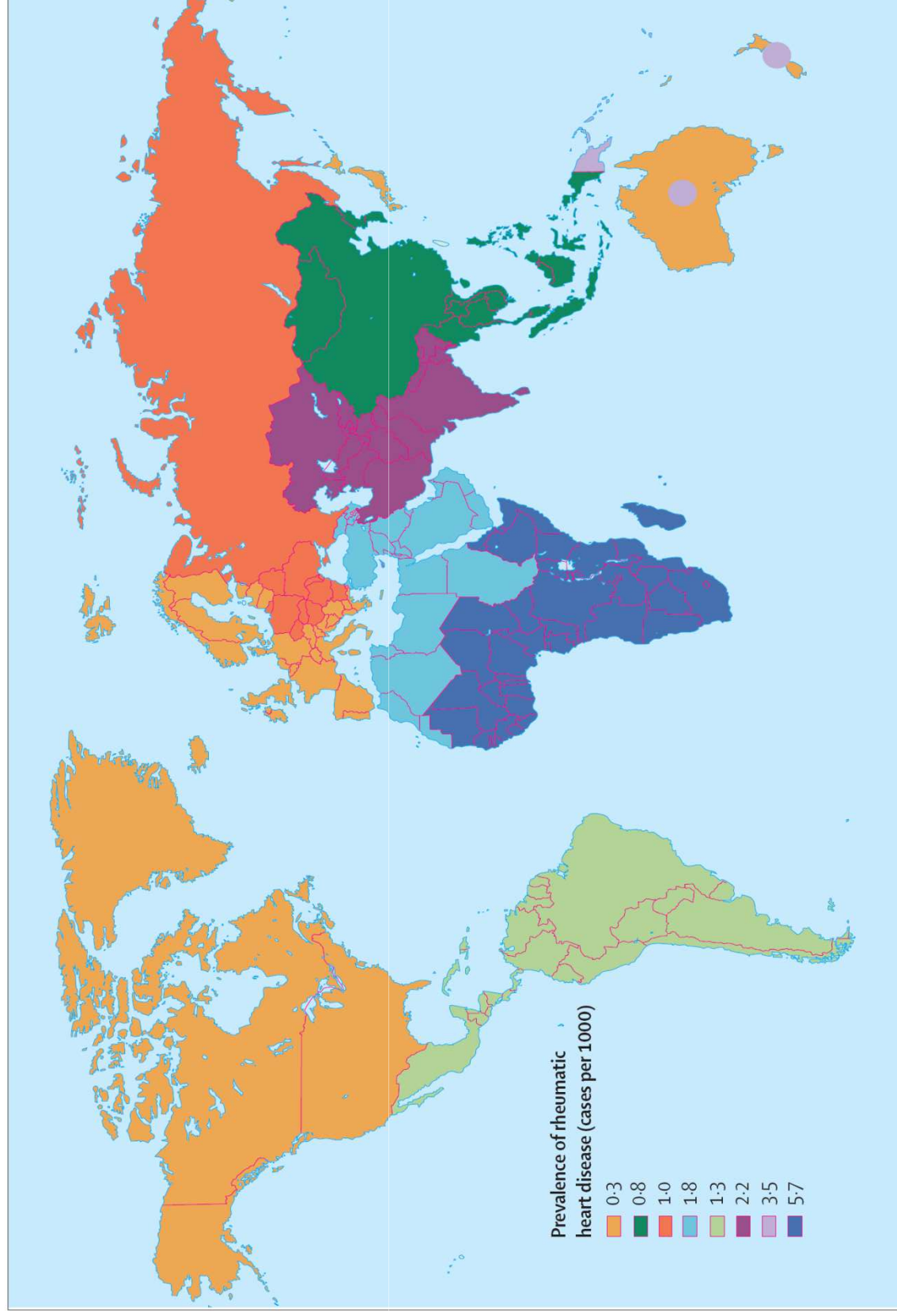


Figure 1: Prevalence of rheumatic heart disease in children aged 5–14 years

Incidence of acute rheumatic fever in the world: a systematic review of population-based studies



Incidence of first attack acute rheumatic fever by geographical region

Study	Study period	Geographic al region	Country	Overall mean annual incidence (per 100000 population)	Age group studied (years)	Version of Duckett-Jones diagnostic criteria
Quinn, 1967	1963-5	America	USA	10	All	Revised
Berrios, 1984	1976-81		Chile	5	All	Modified
Bach, 1996	1981-92		Martinique and Gouadaloupe	8	< 20	Modified
Grover, 1993	1988-91	Asia	India	51	5-18	Revised
Talbot, 1984	1978-82	Australasia	New Zealand	22	< 30	Revised
Ekelund, 1967	1952-61	Europe	Sweden	5	0-15	Modified
Sramek, 1981	1961-72		Czechoslovakia	16	All	Modified
Gharagozioo, 1976	1971-3	Middle East	Iran	35	All	Modified
Majeed, 1987	1980-3		Kuwait	18	< 14	Revised
Majeed, 1993	1984-8		Kuwait	23	5-14	Revised

Tibazarwa KB et al. Heart 2008

Acute rheumatic fever

Jonathan R Carapetis, Malcolm McDonald, Nigel J Wilson

Lancet 2005; 366: 155-68

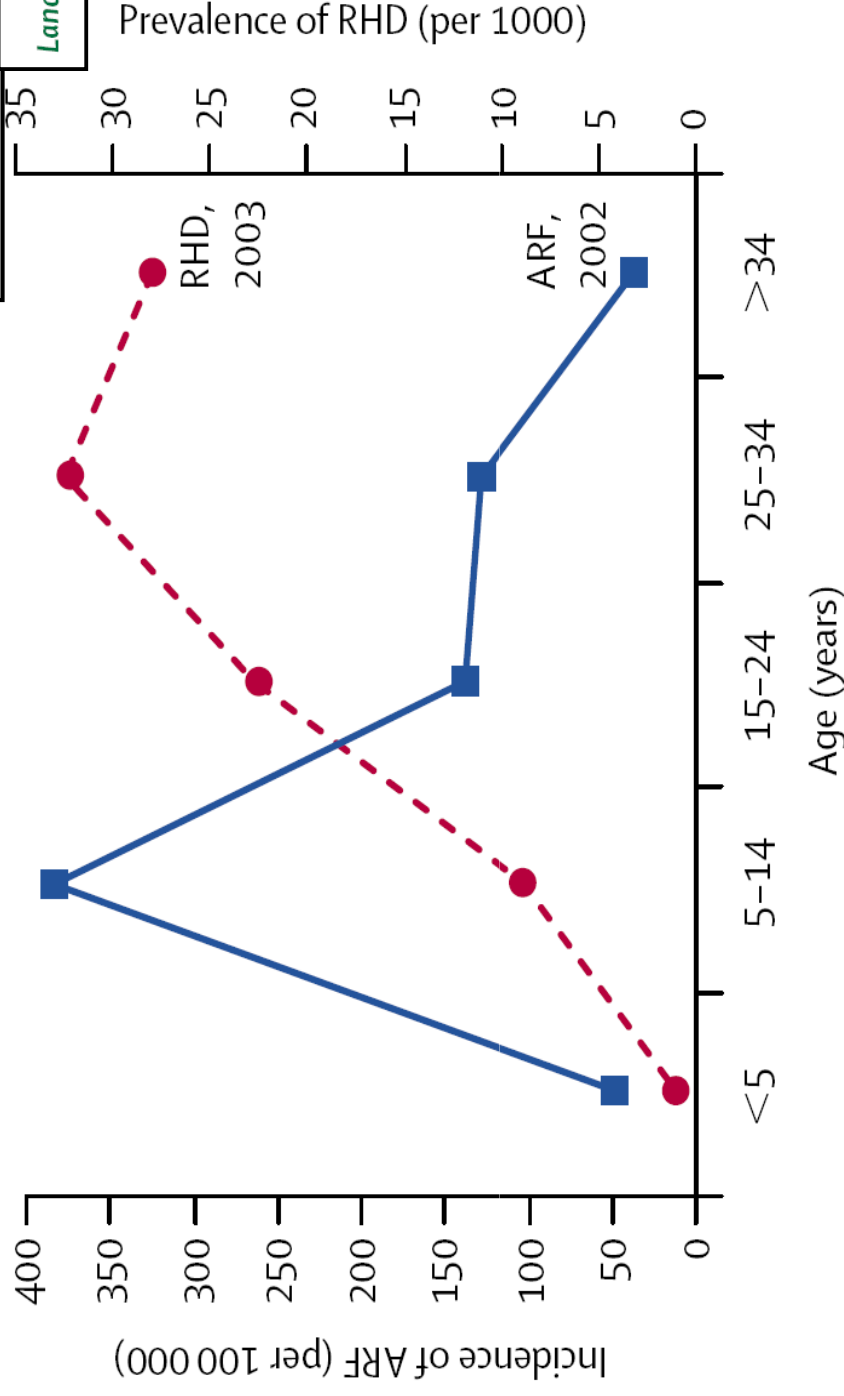
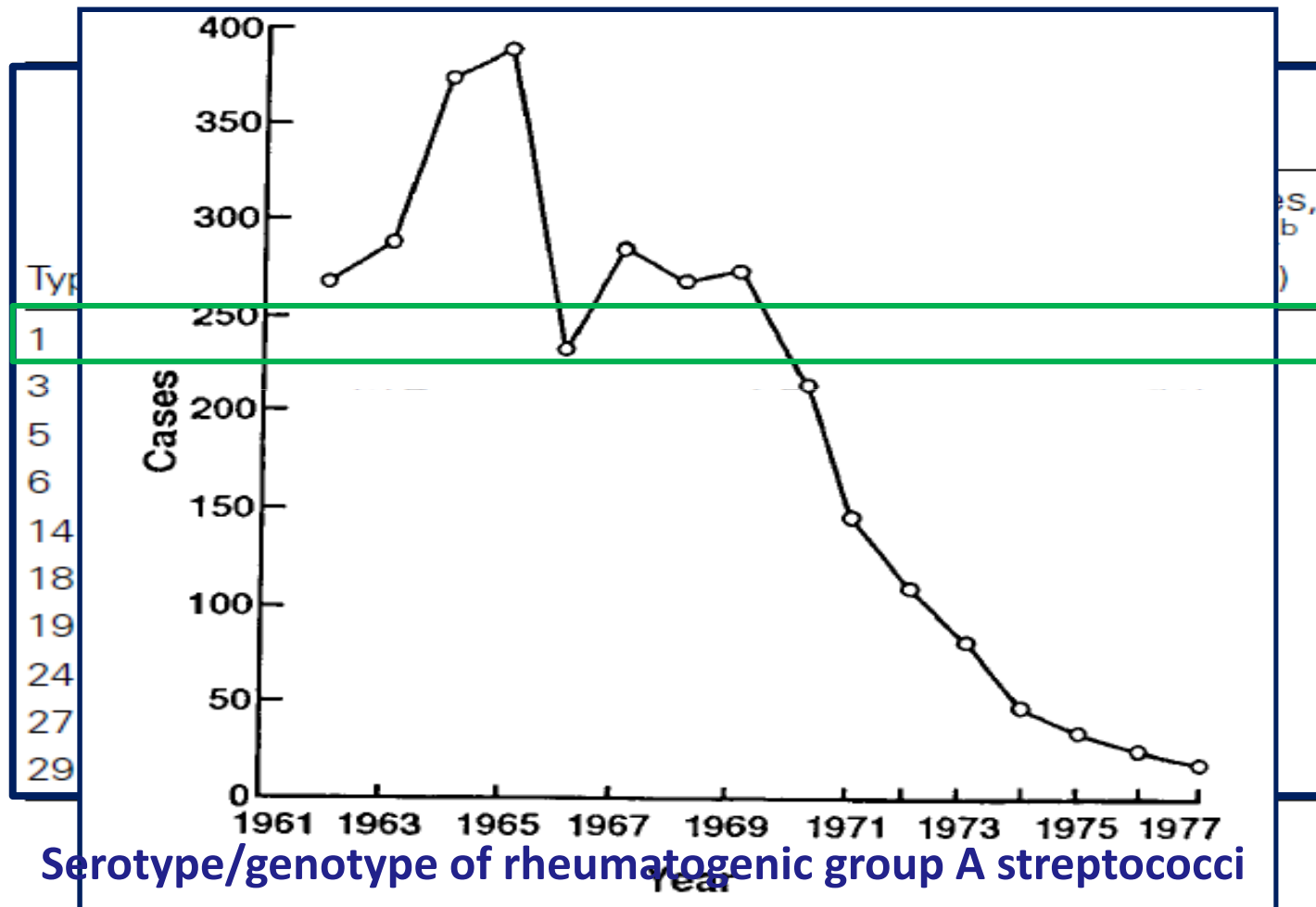


Figure 1: Incidence of ARF in 2002 and prevalence of RHD in 2003 by age in Aboriginal Australians from the top end of the Northern Territory (personal communication, Top End RHD Control Program, Department of Health and Community Services, Darwin, Australia)

The decline of RF in industrialized countries



The resurgence of ARF in the USA



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

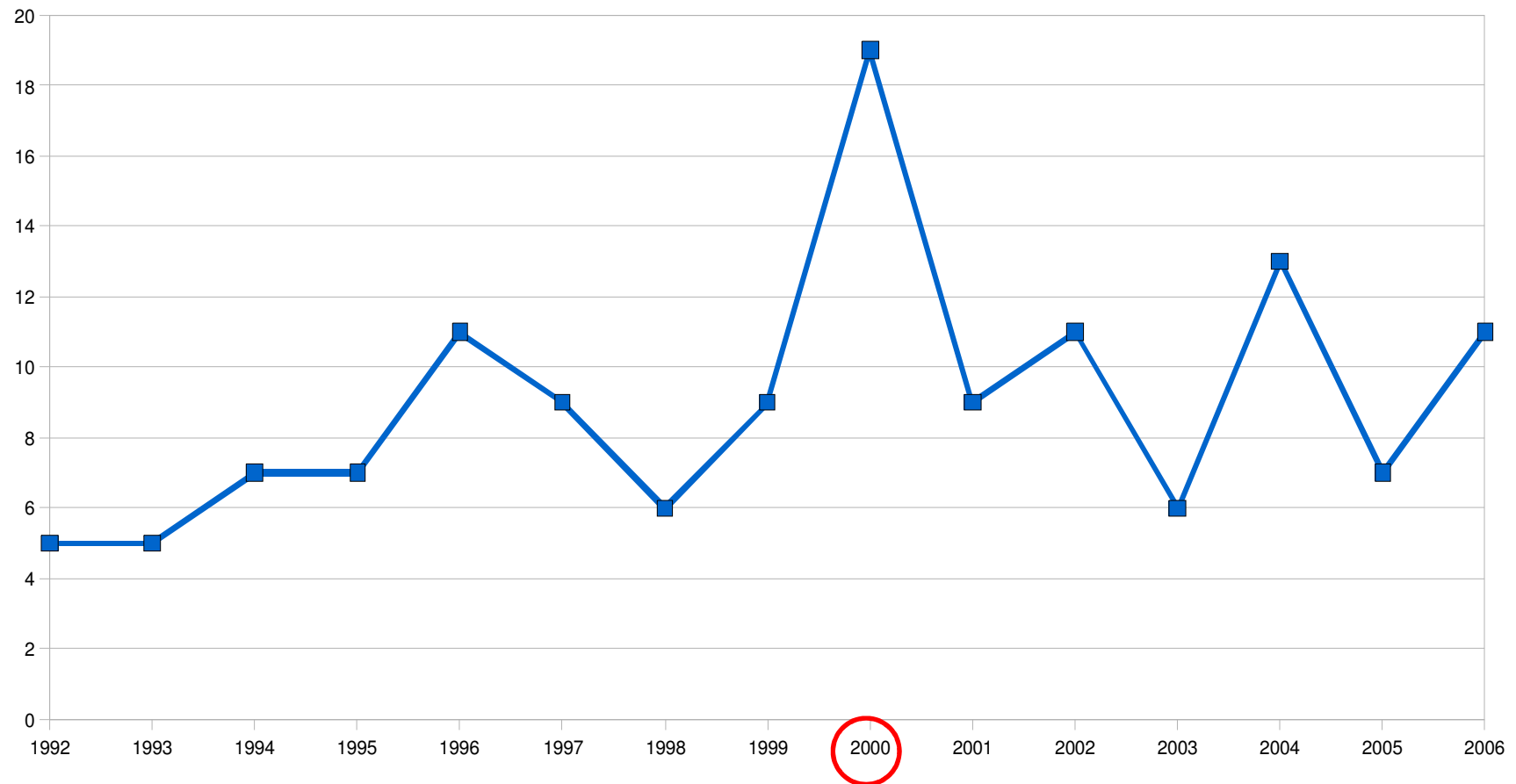
ARCHIVE

Resurgence of Acute Rheumatic Fever in the Intermountain Area of the United States

L. George Veasy, M.D., Susan E. Wiedmeier, M.D., Garth S. Orsmond, M.D., Herbert D. Ruttenberg, M.D., Mark M. Boucek, M.D., Stephen J. Roth, M.D., Vera F. Tait, M.D., Joel A. Thompson, M.D., Judy A. Daly, Ph.D., Edward L. Kaplan, M.D., and Harry R. Hill, M.D.

N Engl J Med 1987; 316:421-427 | [February 19, 1987](#) | DOI: 10.1056/NEJM198702193160801

Rheumatic Fever in Italy (1)



Grassi A et al. Clin Exp Rheumatol 2009

Rheumatic Fever in Italy (2)

RHEUMATOLOGY

Rheumatology 2011;50:396–400
doi:10.1093/rheumatology/keq290
Advance Access publication 3 November 2010

Concise report

The resurgence of rheumatic fever in a developed country area: the role of echocardiography

Serena Pastore¹, Angela De Cunto¹, Alessandra Benettoni², Emanuela Berton²,
Andrea Taddio¹ and Loredana Lepore¹

RHEUMATOLOGY

1) Quale tra questi fattori è il maggiormente imputato nella riduzione della Malattia Reumatica negli ultimi decenni?

- A) Ampia diffusione terapia antibiotica**
- B) Diagnosi tempestiva faringiti da SBEA**
- C) Miglioramento delle condizioni igieniche e socioeconomiche**
- D) Tutte le precedenti**

Rheumatic fever ... in Abruzzo

ORIGINAL
ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

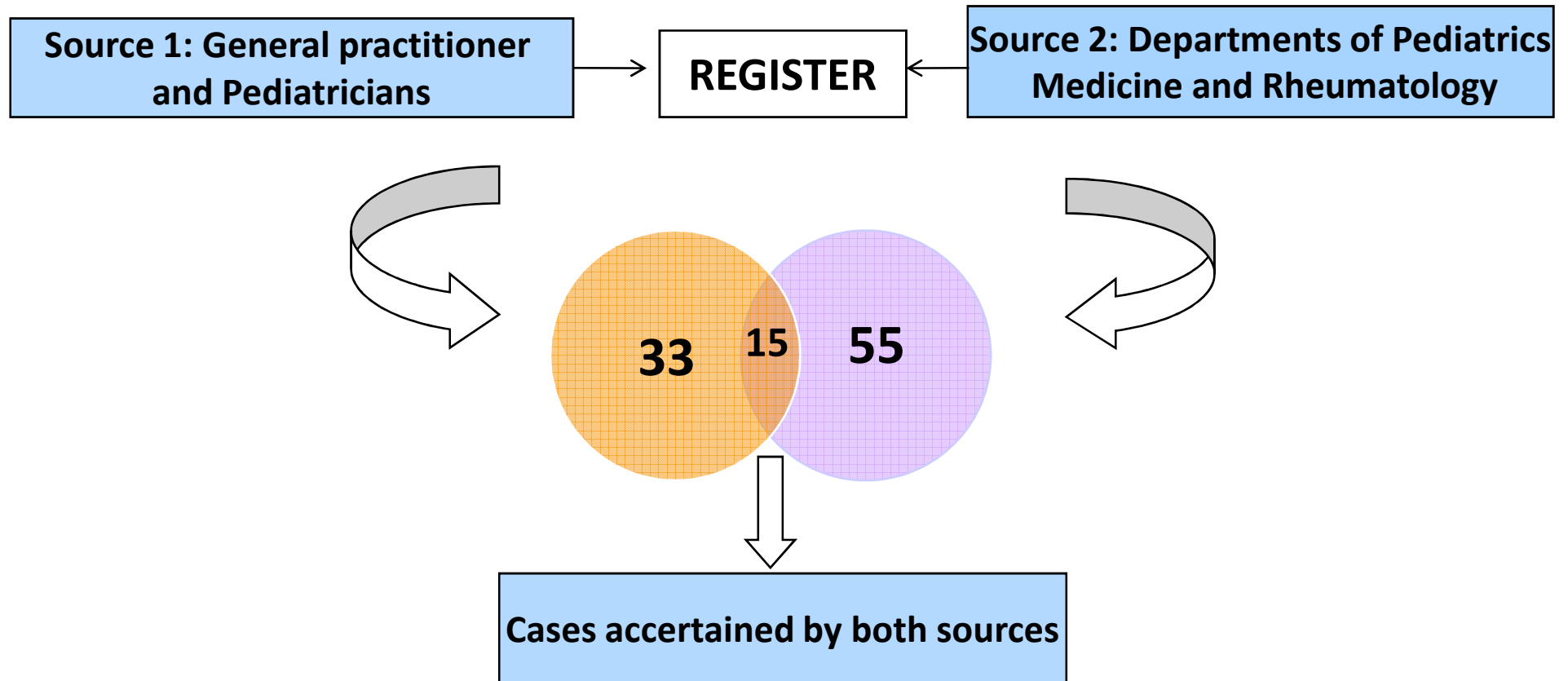
Population-Based Study of Incidence and Clinical Characteristics of Rheumatic Fever in Abruzzo, Central Italy, 2000-2009

Luciana Breda, MD¹, Valentina Marzetti, MD¹, Stefania Gaspari, MD¹, Marianna Del Torto, MD¹, Francesco Chiarelli, PhD¹,
and Emma Altobelli, MD²

L. Breda et al. J Pediatr. 2012

Rheumatic Fever in Abruzzo

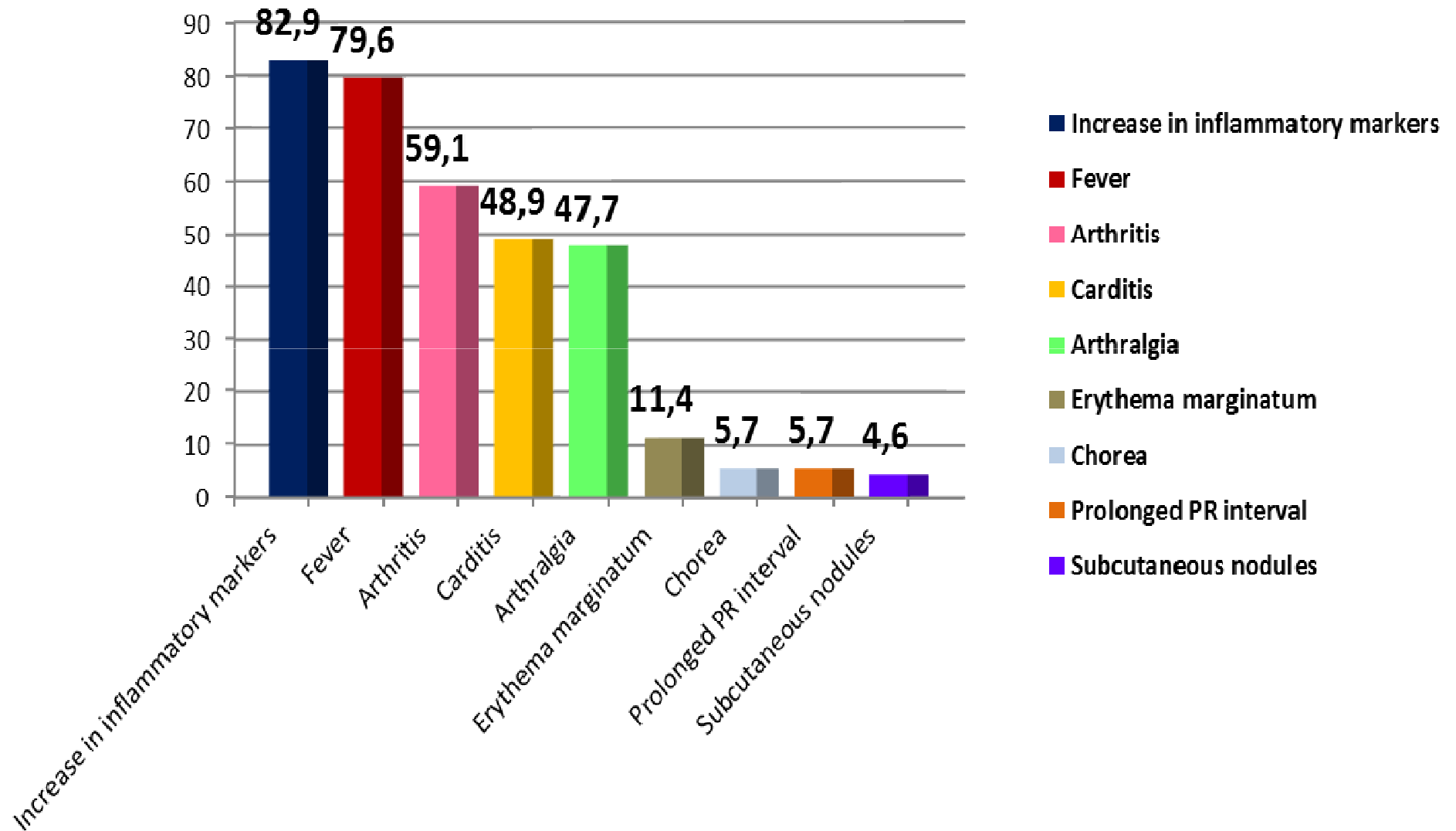
Years	Source 1	Source 2	Source 1 + 2	Total cases	Estimated total cases	Ascertainment probability, %
2000-2009	33	55	15	88	118.0	74.6



Incidence of Rheumatic Fever in Abruzzo

Years	No. Cases	RATE·100000	%	Population	% annual increase
2000	5	2.26	5.7	221702	
2001	7	3.20	7.9	218731	41.90
2002	6	2.80	6.8	216423	10.87
2003	5	2.30	5.7	215481	-0.58
2004	11	5.12	12.5	214732	14.10
2005	11	5.12	12.5	214992	16.45
2006	12	5.58	13.6	214905	16.48
2007	10	4.68	11.4	213473	13.36
2008	11	5.13	12.5	214233	11.67
2009	10	4.67	11.4	214257	9.59
	Tot. Cases	RATE·100000		Population	
2000-2009	88	4.1		2158929	

DISTRIBUTION OF JONES CRITERIA



Rheumatic Fever in Abruzzo

✓ **Recurrence: 6 patients (6.8%).**

1→secondary prophylaxis with an oral

antibiotic: 5 patients did not receive
Conclusion: Our data indicate that ARF has not
secondary prophylaxis.
disappeared in industrialized countries and still

✓ **Residual valvular damage: 39 patients (44.3%)**
causes significant residual rheumatic heart

disease.
✓ **History of rheumatic fever: 5 patients**

✓ **Prosthetic replacement of mitral valve: 2
patients**

Rheumatic Fever in the Marche region

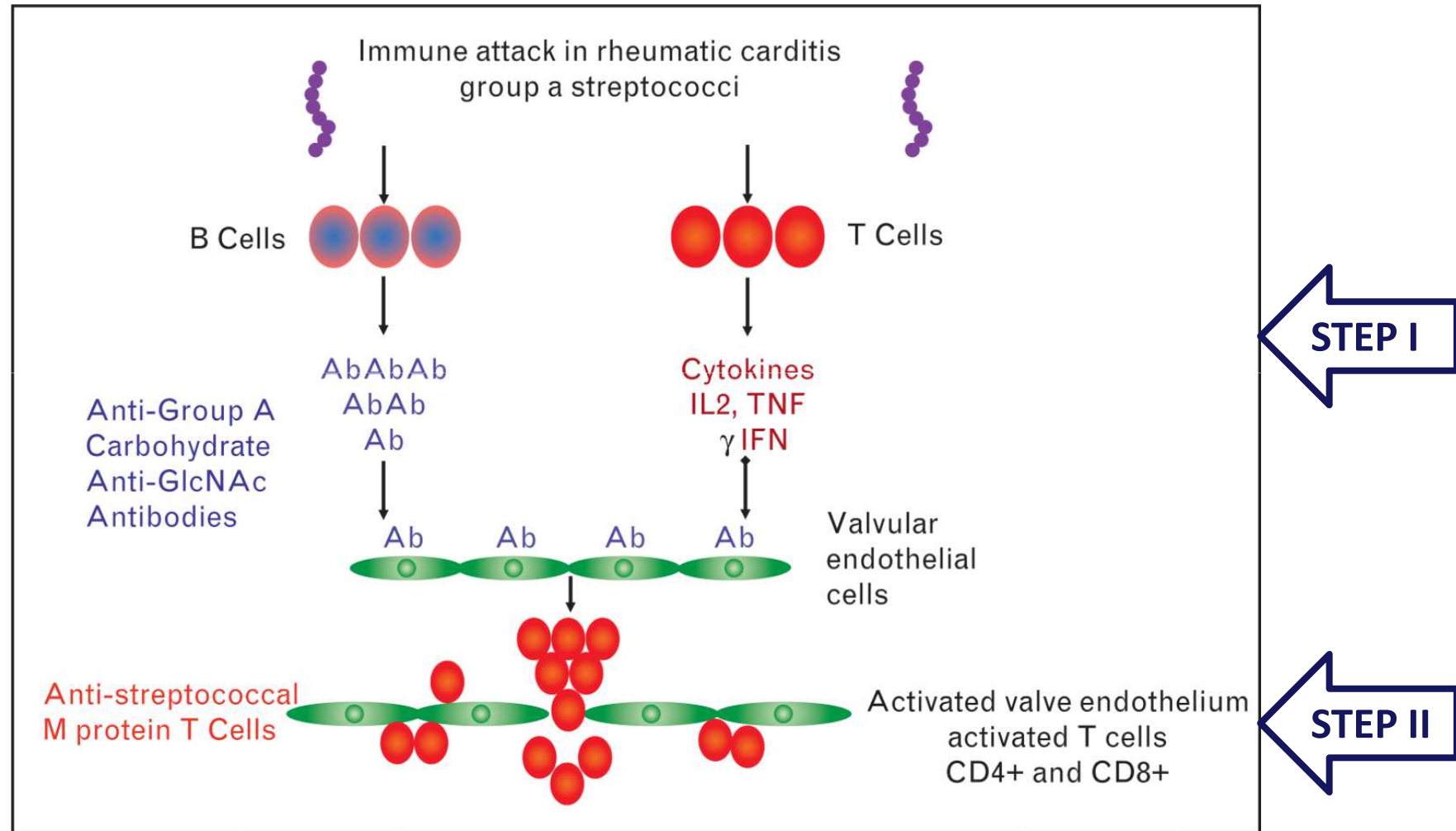
Ascertainment period: 1 January 2007- 31 December 2011
Overall incidence rate: 3.2/100000/year

DISTRIBUTION OF JONES CRITERIA

- ✓ **CARDITIS 76.2% → 45.2% CHRONIC HEART DISEASE**
- ✓ **ARTHRITIS 52.4%**
- ✓ **CHOREA 7.15%**

RHEUMATOLOGY

RHD pathogenesis

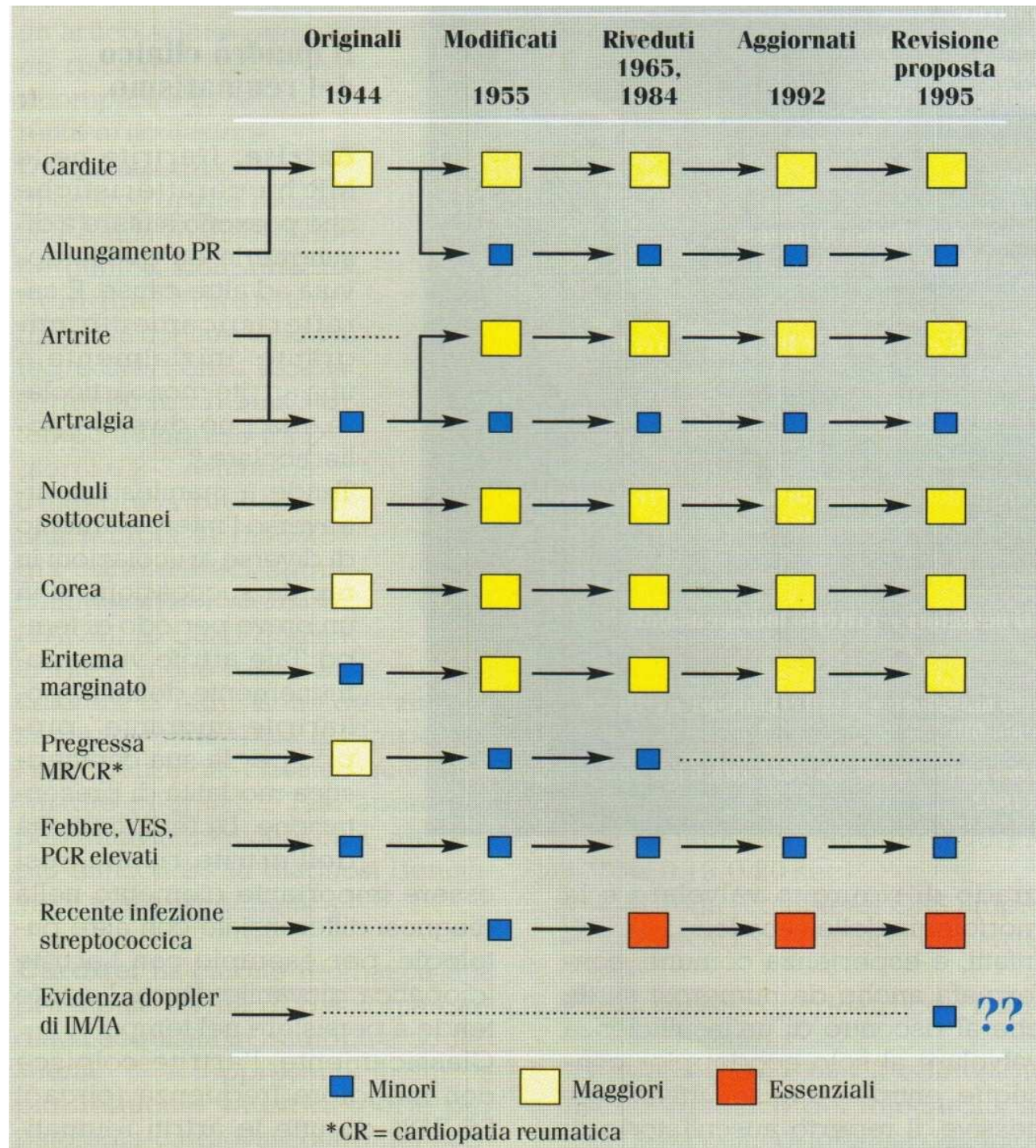


Criteri di Jones nel tempo



Thomas Duckett Jones
1899-1954

Narula J et al. Circulation 1999



Febbre Reumatica: Diagnosi

Criteri di Jones

MAGGIORI

Cardite

Poliartrite

Eritema marginato

Noduli sottocutanei

Corea

MINORI

Artralgia

Febbre

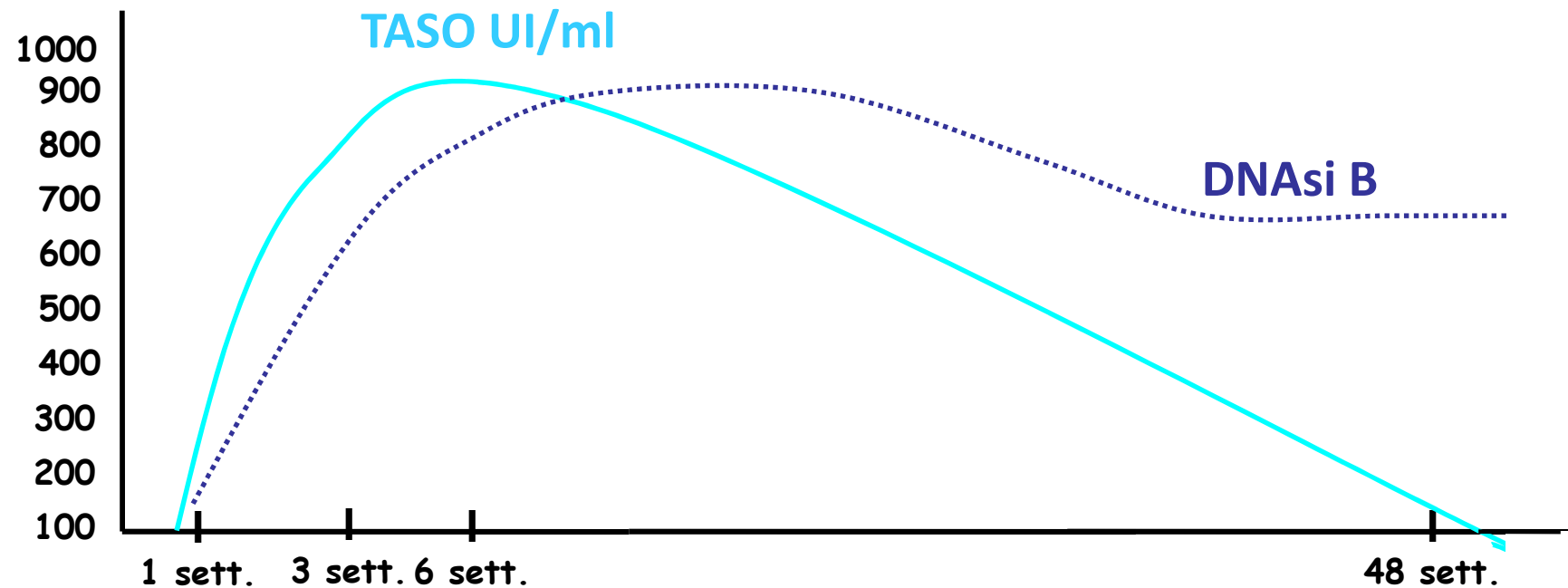
Aumento VES e PCR

Allungamento P-R all'ECG

**Due criteri maggiori o un criterio maggiore + due criteri minori
+
evidenza di recente infezione da SBEA**

Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. JAMA 1992

TASO, DNAsi, test rapido per SBEA, TF



FARINGITE DA SBEA

Test rapido

Tampone faringeo

Sensibilità

87%

95%

Specificità

96%

96%

Jones criteria: Update 2015

Revision of the Jones Criteria for the Diagnosis of Acute Rheumatic Fever in the Era of Doppler Echocardiography **A Scientific Statement From the American Heart Association**

Endorsed by the World Heart Federation

Michael H. Gewitz, MD, FAHA, Co-Chair; Robert S. Baltimore, MD, Co-Chair;
Lloyd Y. Tani, MD, FAHA; Craig A. Sable, MD, FAHA; Stanford T. Shulman, MD;
Jonathan Carapetis, MBBS; Bo Remenyi, MBBS; Kathryn A. Taubert, PhD, FAHA;
Ann F. Bolger, MD, FAHA; Lee Beerman, MD; Bongani M. Mayosi, MBChB; Andrea Beaton, MD;
Natesa G. Pandian, MD; Edward L. Kaplan, MD, FAHA; on behalf of the American Heart
Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease
of the Council on Cardiovascular Disease in the Young



Gewitz MH et al. Circulation 2015

A. For all patient populations with evidence of preceding GAS infection

Diagnosis: initial ARF

Diagnosis: recurrent ARF

2 Major manifestations or 1 major plus 2 minor manifestations

2 Major or 1 major and 2 minor or 3 minor

B. Major criteria

Low-risk populations*

Carditis†

- Clinical and/or subclinical

Arthritis

- Polyarthritis only

Chorea

Erythema marginatum

Subcutaneous nodules

Moderate- and high-risk populations

Carditis

- Clinical and/or subclinical

Arthritis

- Monoarthritis or polyarthritis
- Polyarthralgia‡

Chorea

Erythema marginatum

Subcutaneous nodules

C. Minor criteria

Low-risk populations*

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)

Moderate- and high-risk populations

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)



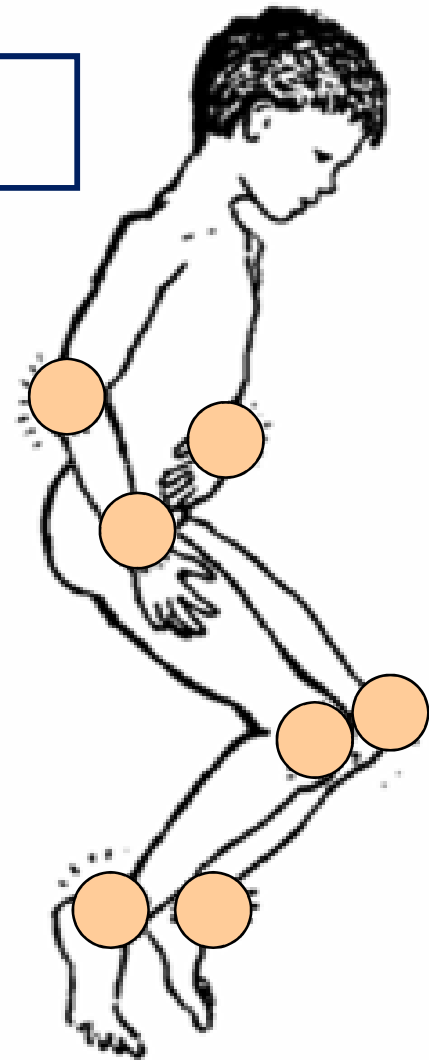
Gewitz MH et al. Circulation 2015

Arthritis



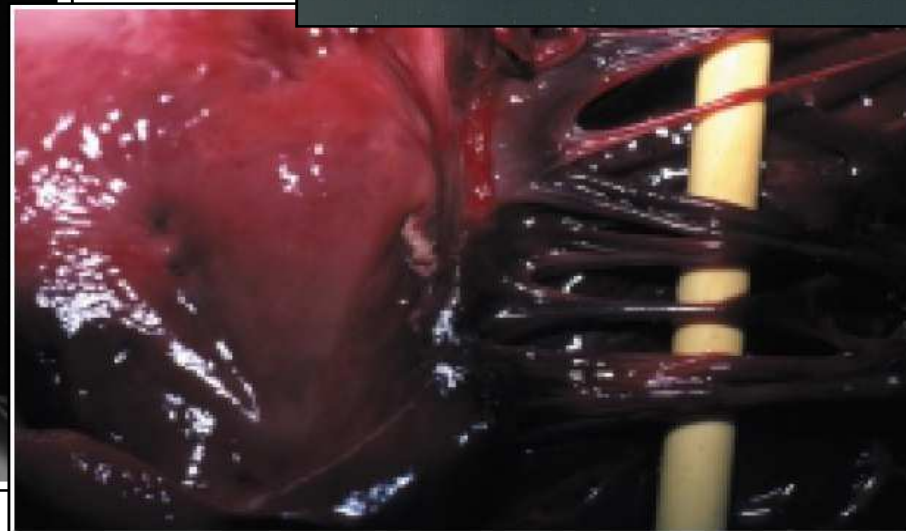
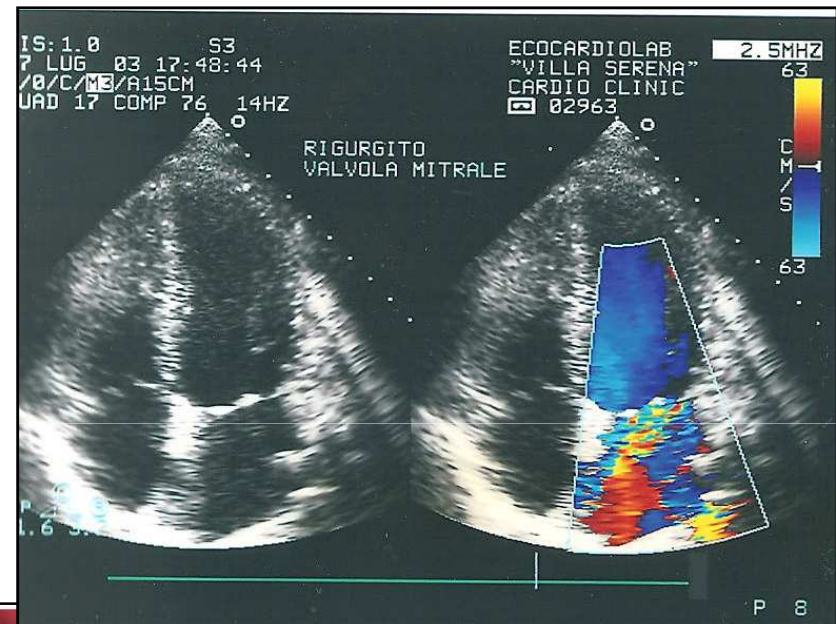
Arthritis

- Occurs in 60-80% of patients
- Large joints are mostly affected
- Lasting to 2-3 days in each joint
- Lasts a maximum of 4 weeks
- Is migratory and polyarticular
- Rapid response to ASA



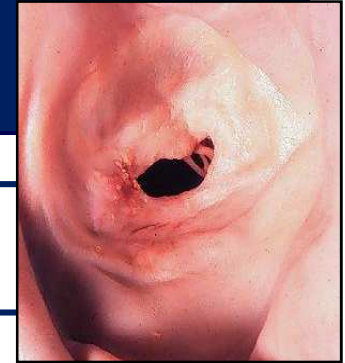
Carapetis JR et al. Lancet 2005
Lee JL et al. Autoimmunity reviews 2009

Carditis



Carditis

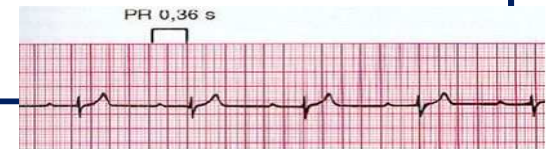
- Occurs in 30-45% of patients with ARF



- May follow arthritis after 2-3 weeks

- Valvular involvement causes regurgitation (94% mitral regurgitation) and later stenosis

- Myocarditis is responsible of arrhythmias



- Subclinic carditis is present in about 17% of cases

Sydenham's chorea

- Occurs in 10% of patients with ARF

- Late manifestation of ARF

- Most often seen in older children and young adolescents

- Clinical characteristics:

Involuntary purposeless non rhythmic movements (face and extremities)

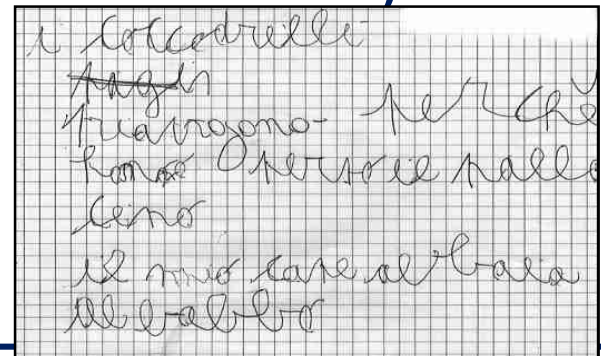
Weakness

Emotional lability

Frequent falls

Dysarthria

Difficulties in concentrations



Erythema marginatum



Erhytema marginatum

- Occurs in about 5% of cases



- Usually found on the trunk and extremities and spares the face



- Evanescent pink rash with erythematous edge



Subcutaneous nodules

- Rare and painless
- Localized on the extensor surfaces of the wrists, elbows, knees and ankles



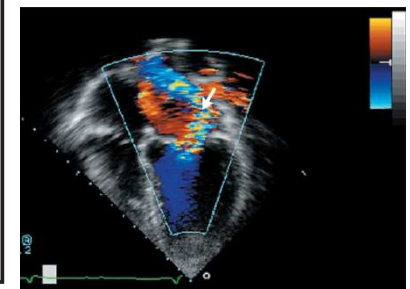
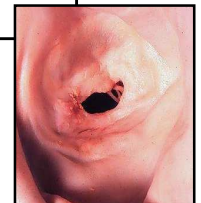
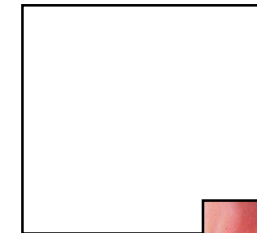
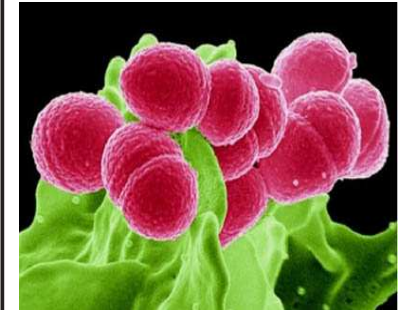
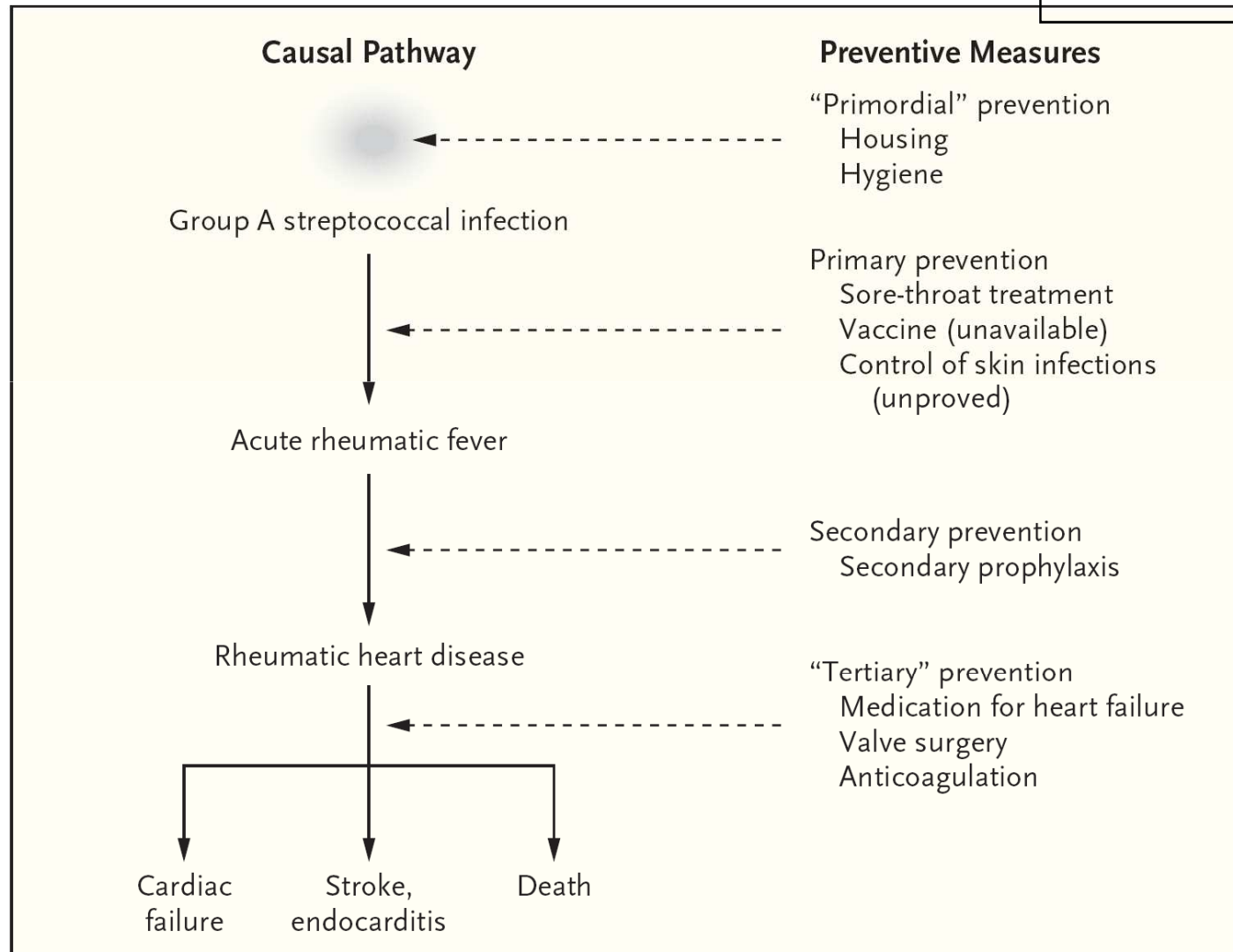
Treatment

A) ERADICATE THE STREPTOCOCCAL INFECTION (PENICILLIN)

B) TREAT THE SYMPTOMS OF ARF

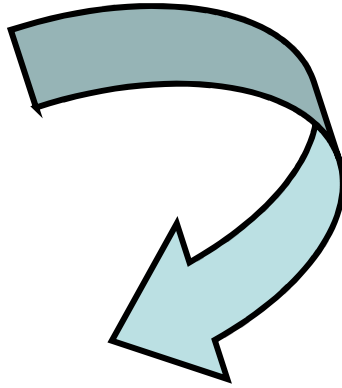
- **ARTHRITIS** → *Salycilates* (80-100 mg/kg/day for 2 weeks then decreases to 60-70 mg/Kg/day for 3-6 weeks)
- **CARDITE** → *Salycilates* (80-100 mg/kg/day 4-8 weeks)
Steroids (PDN 1-2 mg/kg/day for 2-3 weeks for severe)
- **CHOREA** → *VALPROIC ACID, CARBAMAZEPINE, STEROIDS*

Rheumatic Fever prevention



Carapetis JR. NEJM 2007

Rheumatic Fever: the future



Vaccine



Febbre Reumatica

Take home messages

- 1) La Febbre Reumatica colpisce in modo particolare i bambini dei paesi poveri ma è ancora presente nei Paesi Industrializzati, anche se con bassa incidenza ($< 10/100000$ anno)
- 2) La cardiopatia è la più importante sequela e causa di morbidità e mortalità
- 3) Un'accurata diagnosi (faringite streptococcica e Febbre Reumatica) e la compliance alla terapia sono i cardini della prevenzione primaria e secondaria
- 4) Il vaccino rappresenta una speranza per le popolazioni a rischio



**Servizio di Reumatologia
Pediatria
Università degli Studi di Chieti**

Luciana Breda

Debora d'Angelo
Caterina Di Battista
Giuseppe Lapergola
Manuela Marsili
Roberto Troiani

**GRAZIE PER
L'ATTENZIONE**

Febbre reumatica



***La connessione
streptococcica***

**Artrite
post-streptococcica**

**Cardite
indolente e
subclinica**

Artrite Post-Streptococcica (APS)

Criteri diagnostici proposti da *Ayoub and Ahmed nel 1997*

- 1) Artrite ad insorgenza acuta, simmetrica o asimmetrica, di solito non migrante, che può colpire ogni articolazione, persistente o ricorrente, scarsamente responsiva ai saliciati ed ai FANS
- 2) Evidenza di una precedente infezione streptococcica
- 3) Non aderenza ai criteri di Jones per la diagnosi di FR

Ricardo G et al. American Family Physician 2005

Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. JAMA 1992

Ayoub EM et al. Curr Probl Pediatr 1997

Confronto tra APS e FR



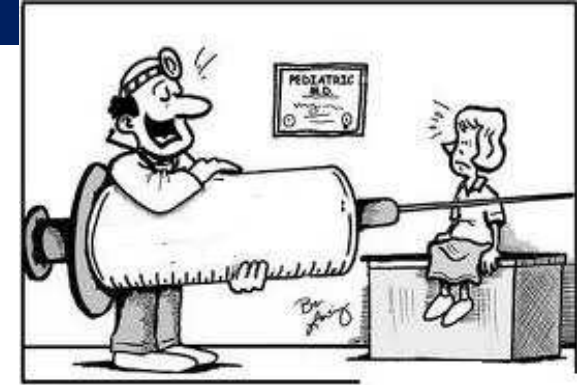
PEDIATRIC
RHEUMATOLOGY

	<i>PSRA</i>	<i>ARF</i>
Age	Bimodal: 8-14 years and 21-37 years	5-15 years with peak incidence around 12 years
Disease onset post streptococcal infection	7-10 days	10-28 days
Joint involvement	Additive and persistent; large, small and axial joints	Migratory, transient; mainly large joints
Acute phase reactants	Moderately elevated	Markedly elevated
Response of arthritis to acetylsalicylic acid or NSAID treatment	Poor to moderate	Dramatic
Genetic markers	Increased frequency of HLA DRB1*01	Increased frequency of the HLA DRB1*16 allele
Carditis	Conflicting reports, but uncommon	Major diagnostic criteria, between 60-70%
Antibiotic prophylaxis	Antibiotic prophylaxis for one year if echocardiogram is normal	Long-term secondary antibiotic prophylaxis

NSAID: Non-steroidal antiinflammatory drugs

Profilassi Antibiotica?

- L'efficacia della profilassi nell'APS non è stata ancora definita
- Secondo l'**American Heart Association** la profilassi secondaria è raccomandata fino a un anno dall'esordio (raccomandazione di classe II – livello di evidenza C)
- Successivamente, se non si riscontra evidenza clinica di **cardite**, la profilassi può essere sospesa (*raccomandazione di classe I*)
- In caso di **dubbio diagnostico** è preferibile effettuare diagnosi di FR e somministrare la profilassi secondaria raccomandata



JAMA 1992;68:2069-7

Barash J et al. J Pediatr 2008; 153:696-9