Ocrelizumab en EM
(sobre un efecto adverso letal)

Maitines en el Hospital de León

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S. de Neurología

28 de enero de 2020

Caso JDA

Varón, 48 a

- 2008: Ablación por TSV
- EcoCG: Vena cava superior izquierda persistente, que drena en seno venoso coronario dilatado.

Dco de EM en 2009

- Tto con Avonex en 2013 y con Copaxone desde 2014

Caso JDA

2017: EDSS, 6

- 2017: RM con alta carga lesional. Gd (-).

Inicio de Tto con Ocrevus en Febrero 2019

- Ocrevus: 2º ciclo en Agosto 2019. Fallece durante su administración.

AUTOPSIA JDA

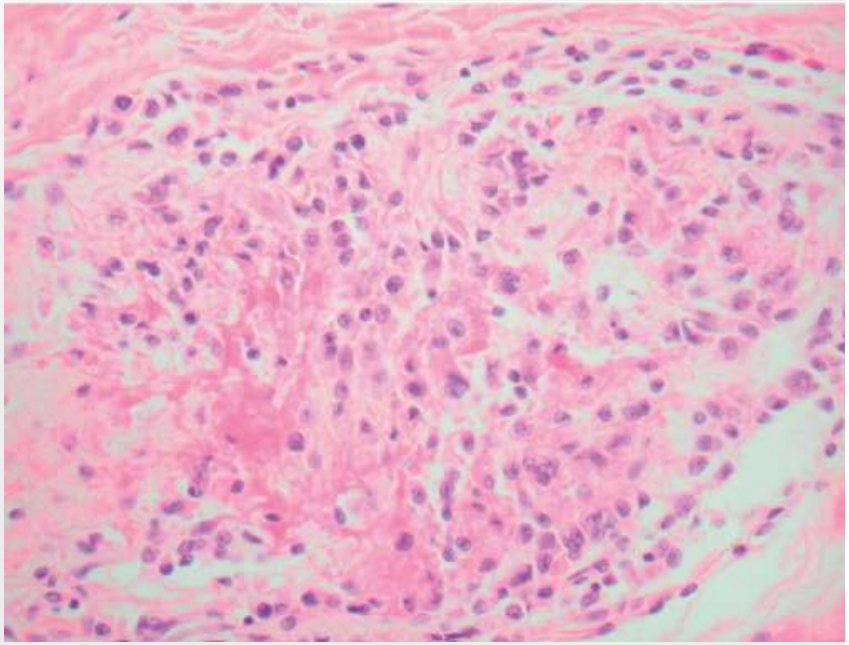
1. MASIVO EDEMA Y HEMORRAGIA PULMONAR (BILATERAL)

2. SEVERA PANCARDITIS REUMÁTICA

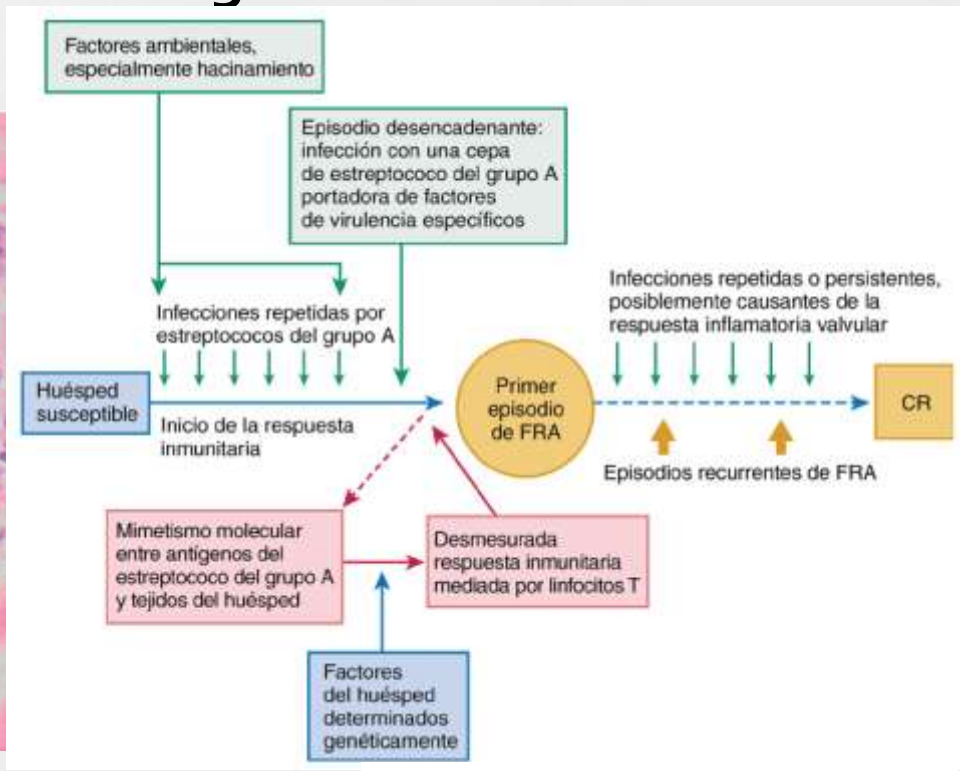
3. CONGESTIÓN Y HEMORRAGIA RENAL (BILATERAL)

Cardiopatía reumática

Nódulos de Aschoff y células de Anitschkow



Patogenia

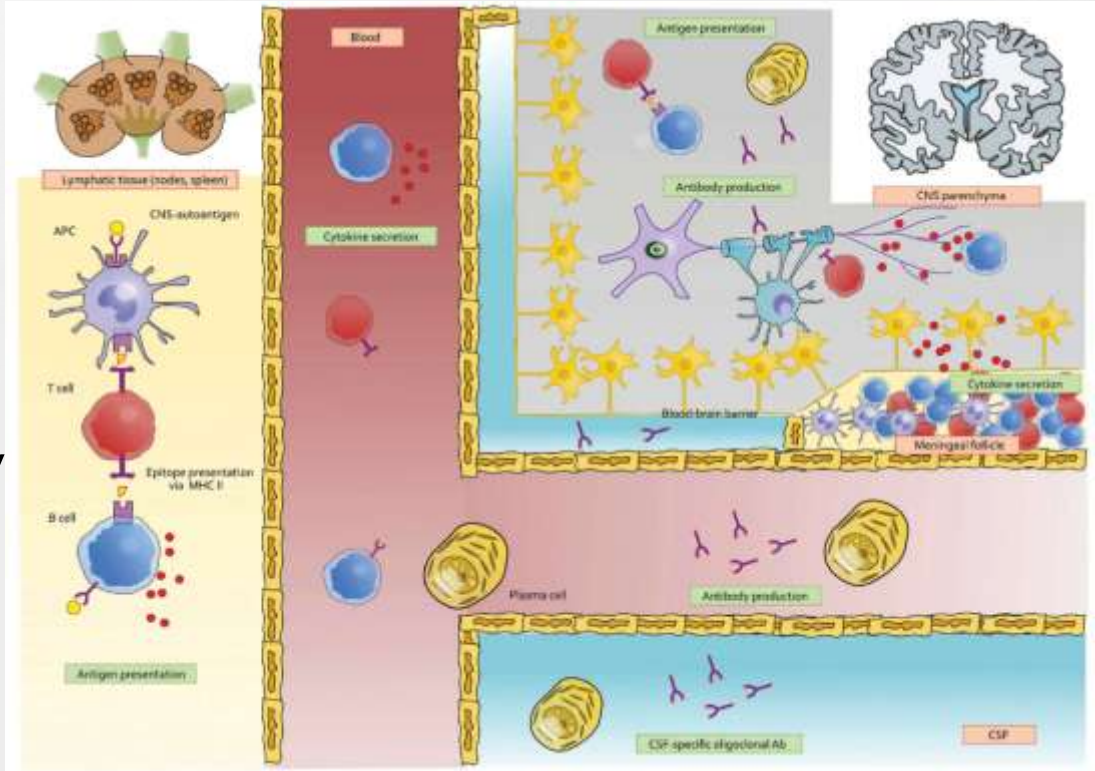


Lancet 2005;366:155

B cells in multiple sclerosis therapy—A comprehensive review

Acta Neurol Scand. 2018;1–13.

- Hay LB activados en las lesiones de EM
- En EM existe secreción de Ig autorreactivas
- Los LB son potentes presentadores de Ag
- Los LB producen citoquinas pro y anti-inflamatorias
- Los fármacos que favorecen la deplección de LB son eficaces



EXPERT OPINION ON BIOLOGICAL THERAPY
2019, VOL. 19, NO. 8, 829–843

CD20 monoclonal antibodies for the treatment of multiple sclerosis: up-to-date

EXPERT OPINION ON BIOLOGICAL THERAPY
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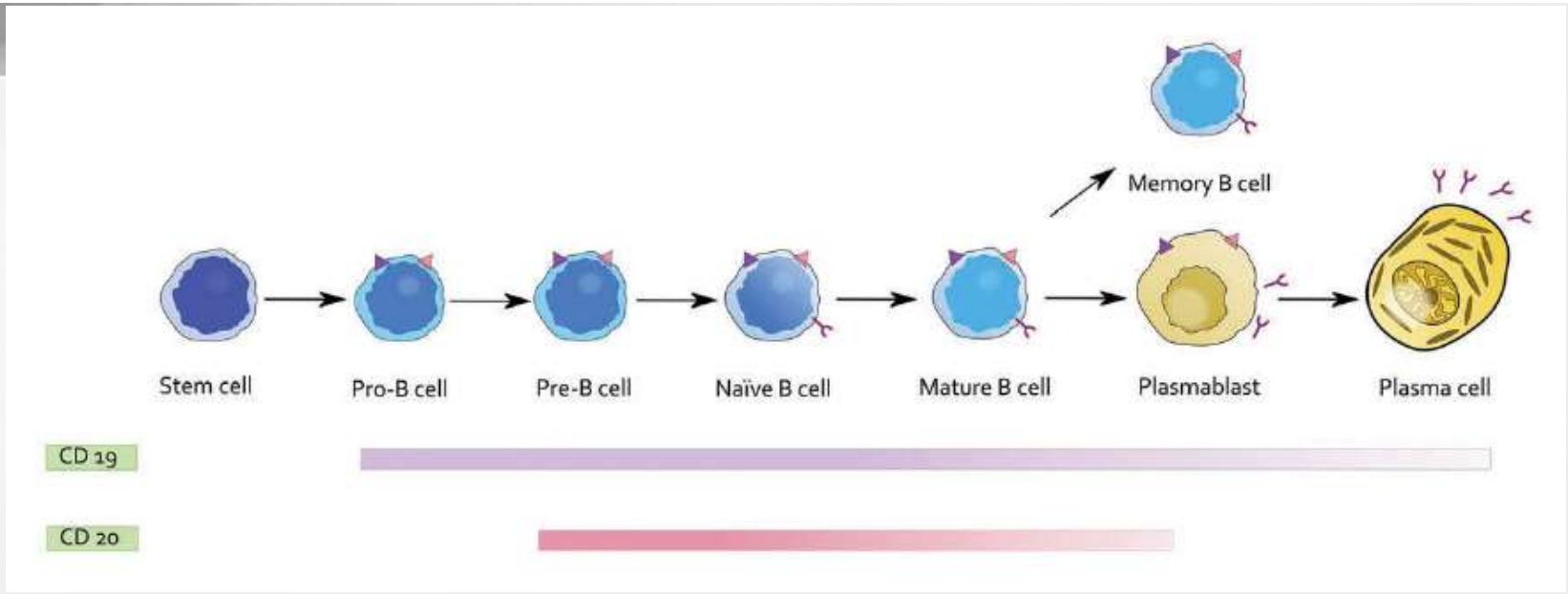

Table 1. Overview of CD20-monoclonal antibodies currently implemented in Multiple Sclerosis.

	Rituximab (RTX)	Ocrelizumab (OCR)	Ofatumumab (OFA)	Ublituximab (UTX)
Structure	Chimeric IgG1 (65% human)	Humanized IgG1 (>90% human)	Recombinant fully human IgG1	Glycoengineered chimeric IgG1
Regimen	1 g i.v. d. 1 & d. 15, followed by 1 g every 24 weeks.	300 mg i.v. d. 1 & d. 15, followed by 600 mg every 24 weeks.	20 mg s.c. every 4 weeks.	450 mg i.v. d. 1 & d. 15, followed by 450 mg i.v. every 24 weeks.
Primary mechanism of action	CDC	ADCC	CDC	ADCC
Generation	1st	2nd	3rd	3rd
Immunogenicity	+++	++	+	++

Ocrelizumab for the treatment of multiple sclerosis

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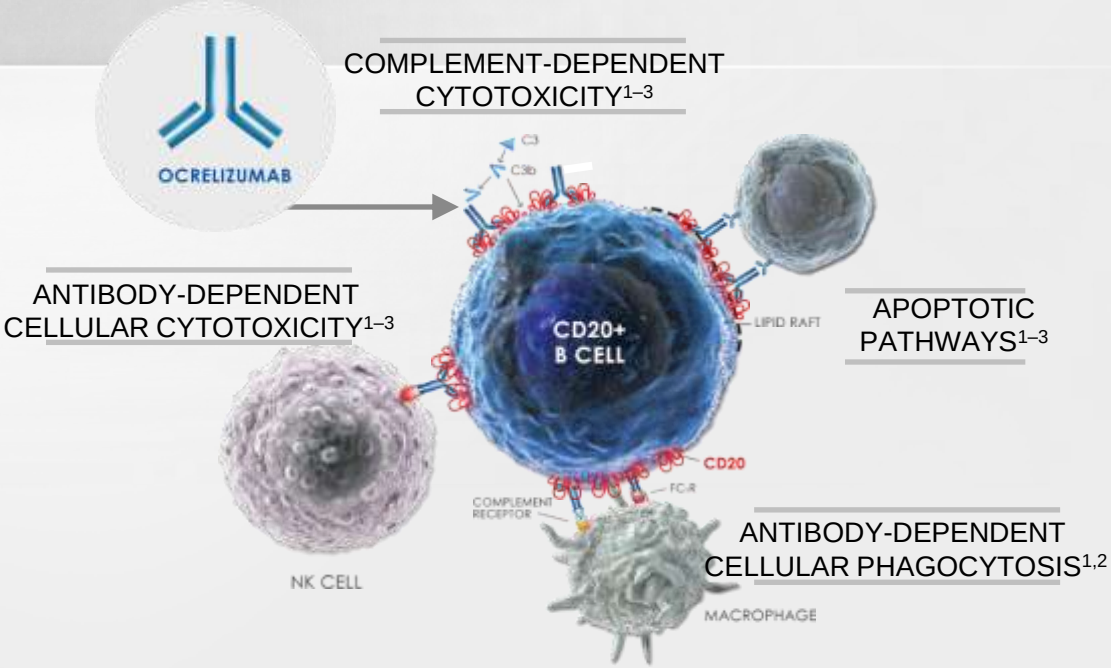
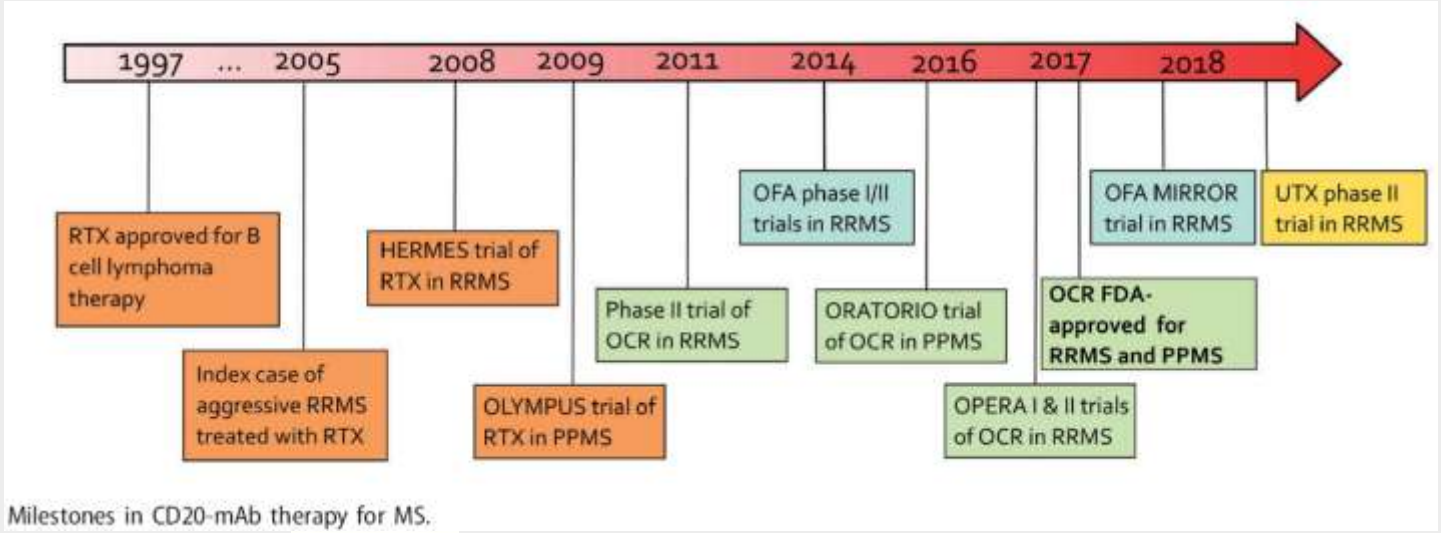
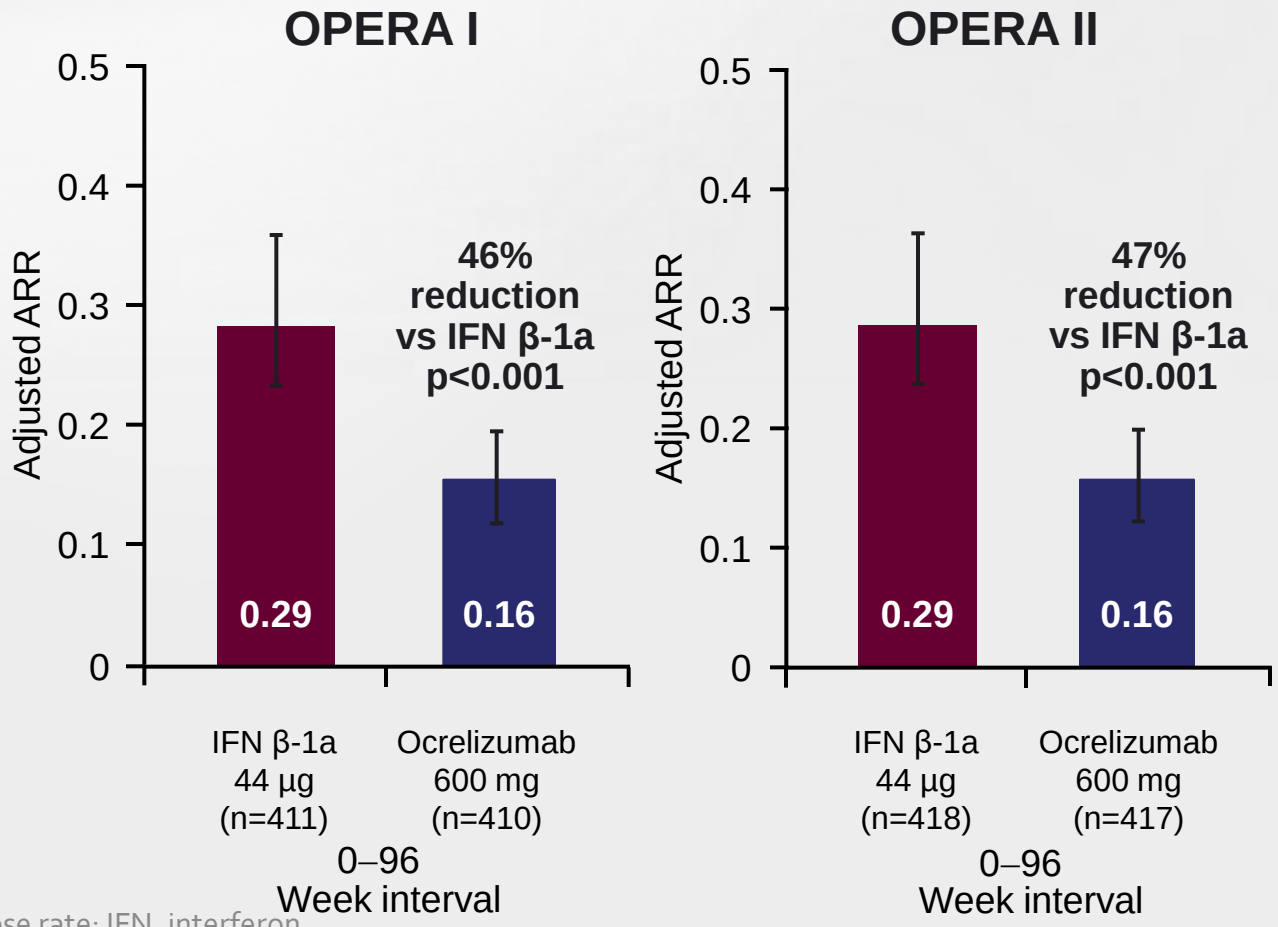




Milestones in CD20-mAb therapy for MS.

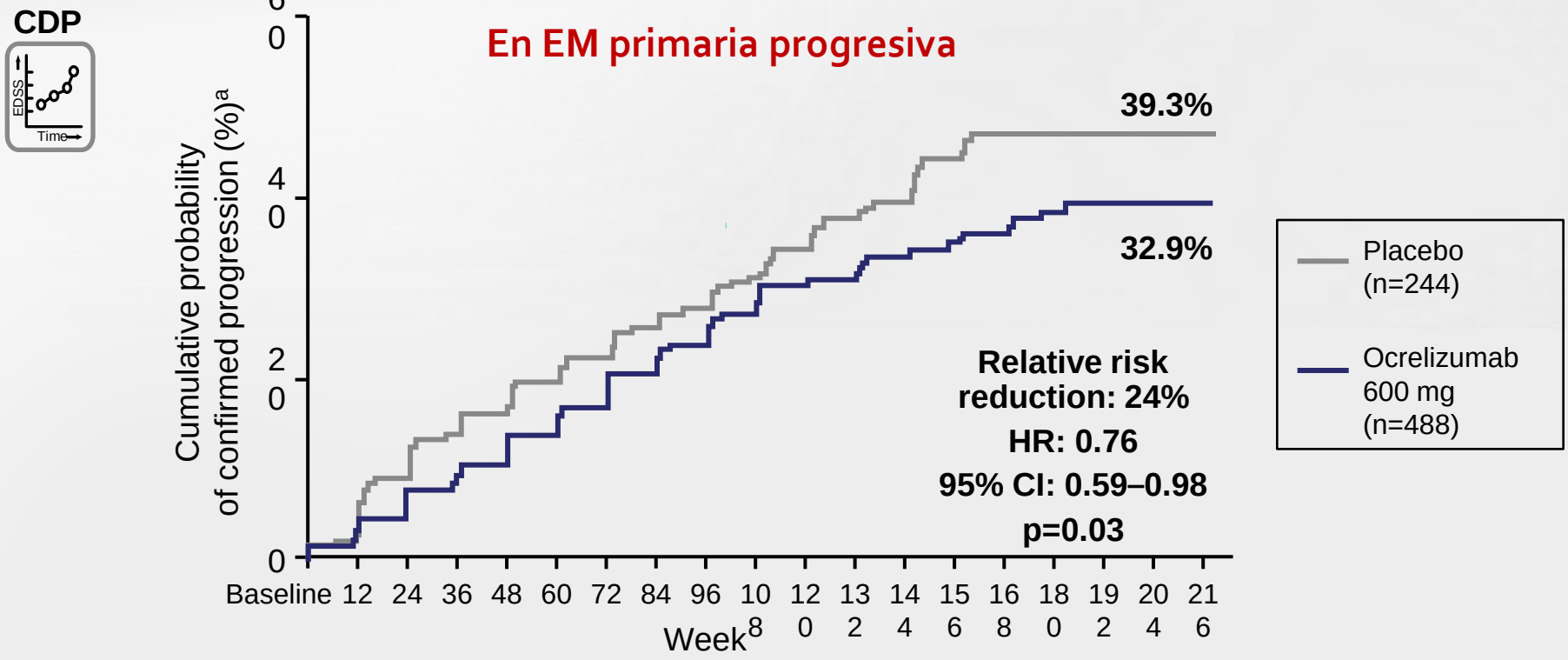
OPERA I and OPERA II: Ocrelizumab significantly reduced ARR vs IFN β-1a (primary endpoint)



ARR, annualised relapse rate; IFN, interferon.

Hauser SL et al. *N Engl J Med* 2017;376:221–234.

ORATORIO: Ocrelizumab significantly decreased the risk of 12-week CDP vs placebo (primary endpoint)



	Baseline	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204	216
Placebo (n)	244	232	229	219	189	180	172	162	153	145	136	120	85	66	46	30	20	7	2
Ocrelizumab (n)	487	462	450	431	414	391	376	355	338	319	304	281	207	166	136	80	47	20	7

Montalban X, et al. *N Engl J Med* 2017;376:209–220.

OPERA I and OPERA II, and ORATORIO: Infusion-related reactions

	OPERA I and OPERA II (RMS)[1]		ORATORIO (PPMS)[2] (2:1 randomisation)	
	IFN β-1a 44 µg (n=826)	Ocrelizumab 600 mg (n=825)	Placebo (n=239)	Ocrelizumab 600 mg (n=486)
Patients with at least one IRR	82 (9.9)	283 (34.3)	61 (25.5)	194 (39.9)
Total number of IRR events reported	112	505	145	485
CTCAE severity grade				
1 – Mild	56 (6.8)	179 (21.7)	38 (15.9)	129 (26.5)
2 – Moderate	24 (2.9)	83 (10.1)	19 (7.9)	59 (12.1)
3 – Severe	2 (<1)	20 (2.4)	4 (1.7)	6 (1.2)
4 – Life-threatening	0	1 (<1)	0	0
5 – Death	0	0	0	0

CTCAE, Common Terminology Criteria for Adverse Events; IFN β-1a, interferon β-1a; IRR, infusion-related reaction; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis.

1. Hauser SL, et al. *N Engl J Med.* 2017;376:221–234 [Suppl Appendix]; 2. Montalban X, et al. *N Engl J Med.* 2017;376:209–220.

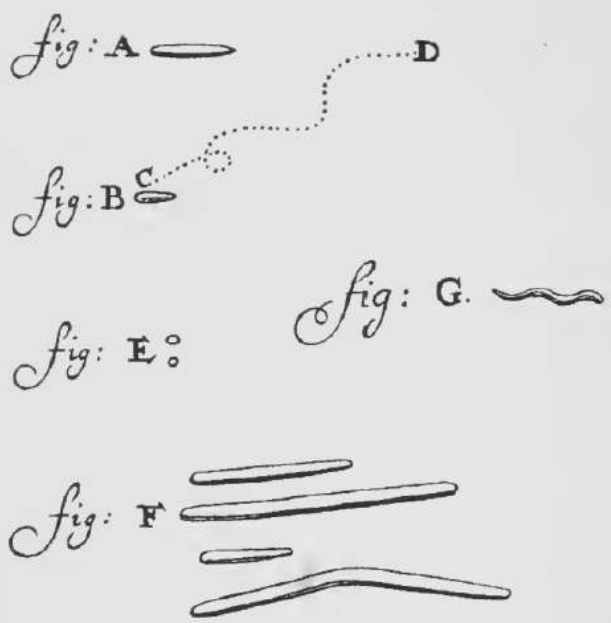
Overview of infections and serious infections *OPERA I and OPERA II, and ORATORIO*

Patients, n (%)	Pooled OPERA I and OPERA II (96-week controlled period)		ORATORIO (2:1 randomisation)	
	IFN β-1a 44 µg N=826	Ocrelizumab 600 mg N=825	Placebo N=239	Ocrelizumab 600 mg N=486
Patients with infections	433 (52.4)	482 (58.4)	162 (67.8)	339 (69.8)
Patients with serious infections	24 (2.9)	11 (1.3)	14 (5.9)	30 (6.2)
Most common types of infections (serious and non-serious)	87 (10.5)	125 (15.2)	14 (5.9)	53 (10.9)
Upper respiratory tract infection	84 (10.2)	122 (14.8)	65 (27.2)	110 (22.6)
Nasopharyngitis	100 (12.1)	96 (11.6)	54 (22.6)	96 (19.8)
Urinary tract infection	–	–	21 (8.8)	56 (11.5)
Influenza				

IFN β-1a, interferon β-1a.

Hartung H-P, et al. Presented at: ECTRIMS 2016 (Poster P1248).

Streptococcus pyogenes



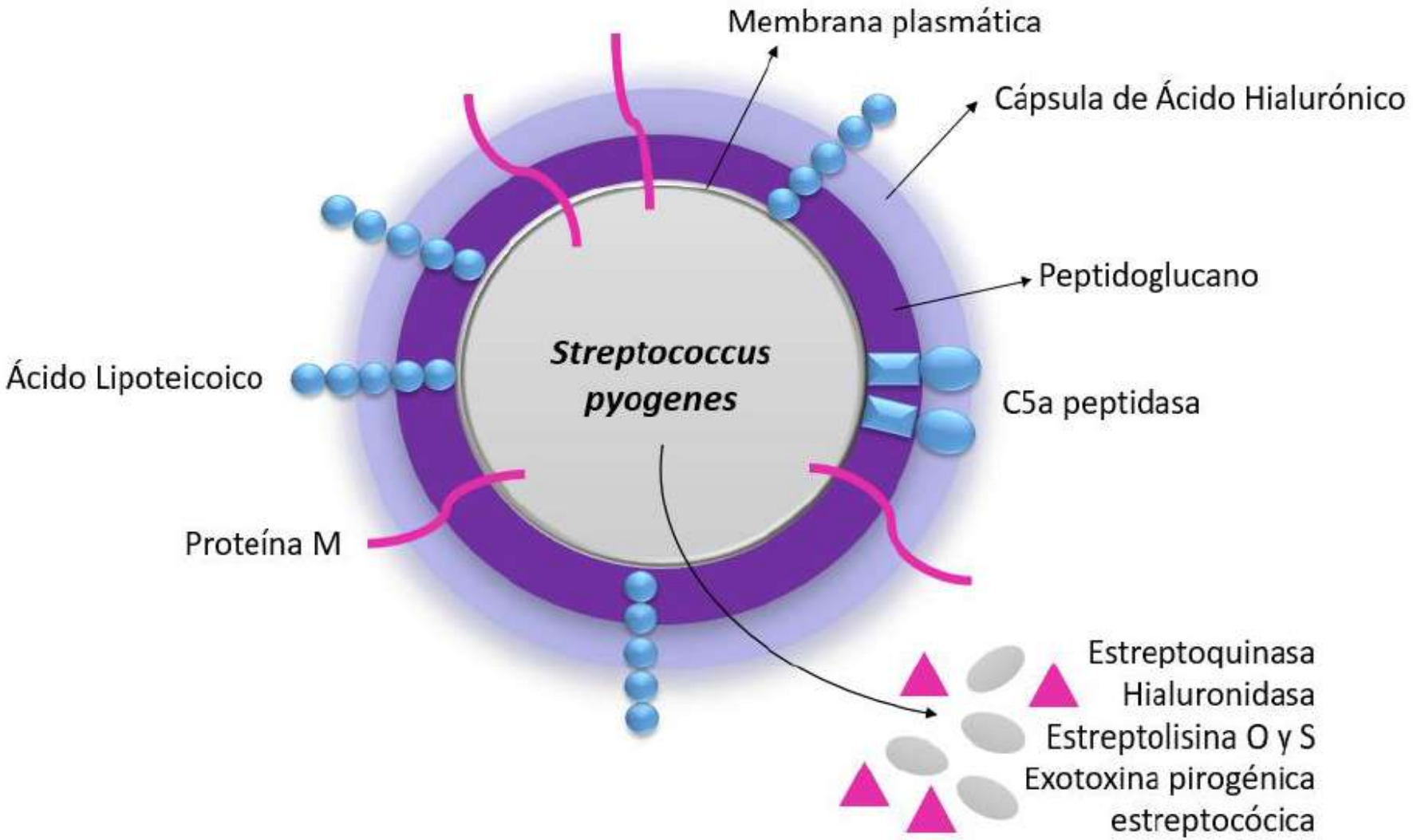
LEEUWENHOEK'S FIGURES OF BACTERIA FROM THE HUMAN MOUTH
(Letter 39, 17 Sept. 1683)
Enlarged (× 1½) from the engravings published in *Arc. Nat. Det.*, 1695.

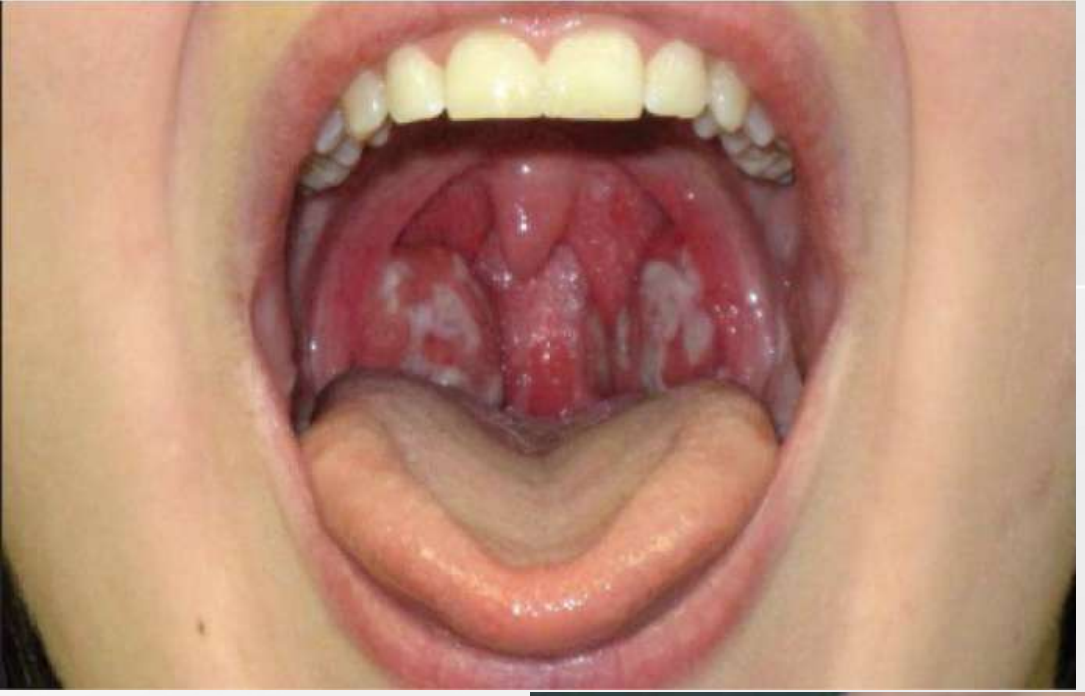
Fig. A, a motile *Bacillus.*
Fig. B, *Selenomonas sputigena.* C . . . . D, the path of its motion.
Fig. E, Micrococci.
Fig. F, *Leptothrix buccalis.*
Fig. G, A spirochæte—probably "*Spirochaeta buccalis,*" the largest form found in this situation.

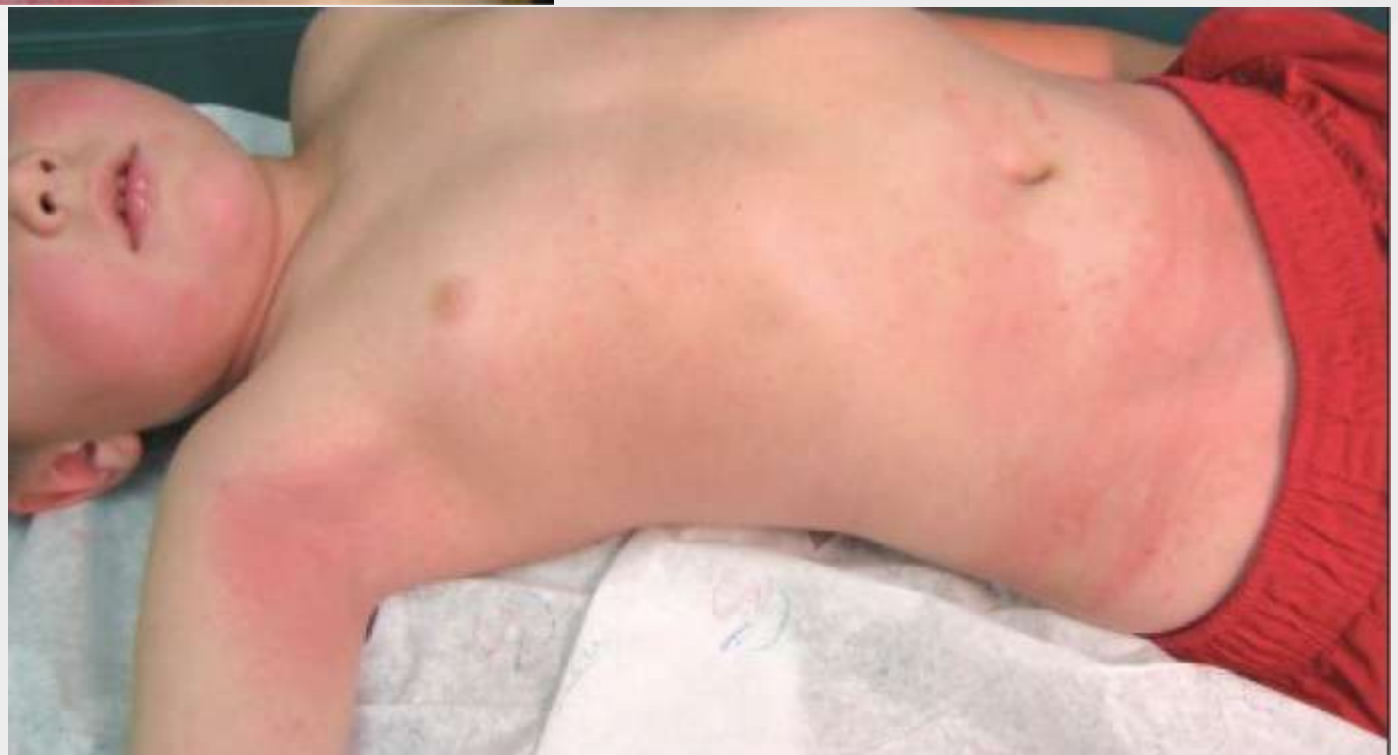
Louis Pasteur, 1822–1895.

Walter Bauer, Rebecca Lancefield, and Maclyn McCarty at the Rockefeller Institute.

Streptococcus pyogenes







Faringitis estreptocócica

Table 2. Clinical Scoring System and Likelihood of Positive Throat Culture for Group A Streptococcal Pharyngitis.*

Criteria	Points†
Fever (temperature >38°C)	1
Absence of cough	1
Swollen, tender anterior cervical nodes	1
Tonsillar swelling or exudate	1
Age	
3 to <15 yr	1
15 to <45 yr	0
≥45 yr	−1

N ENGL J MED 364;7

LABORATORIO

1. Cultivo.
2. Test de detección rápida de antígeno
   (S: 70-90% E: 95%)

Primary prevention (treatment of GAS pharyngitis)

Agent	Dose	Route	Duration
Benzathine penicillin G	≥27 kg: 1.2 million units	IM injection	Once
	<27 kg: 600,000 units		
Penicillin V	Children 250 mg, × 2-3/d	Oral	10 d
	Adults 500 mg, × 2-3/d		

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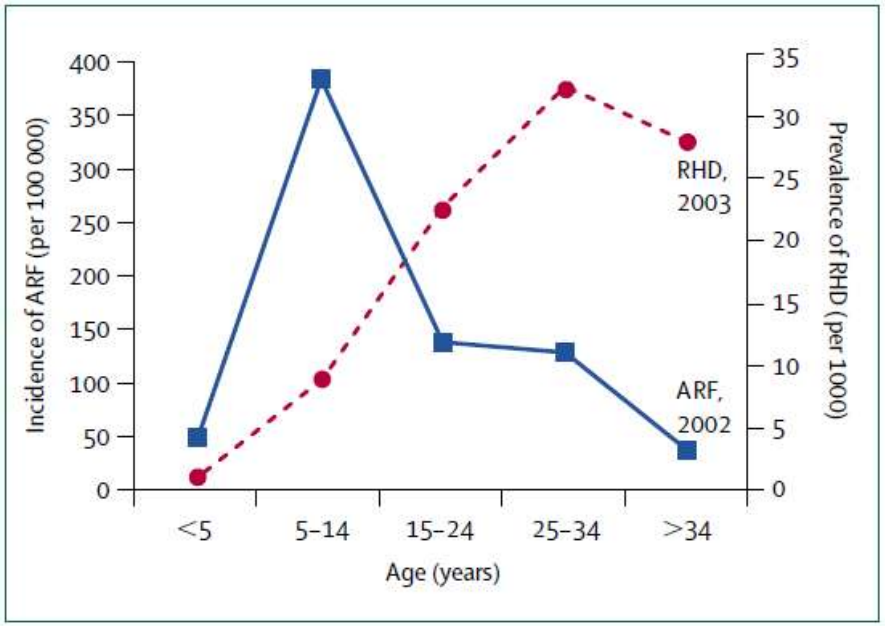
Fiebre reumática aguda



Evidence of Preceding GAS Infection (at least one of the following)

1. Increased or rising anti-streptolysin O titer or other streptococcal antibodies*(anti-DNASE B)*. A rise in titer is better evidence than a single titer result
2. A positive throat culture for group A [beta]-hemolytic streptococci
3. A positive rapid group A streptococcal carbohydrate antigen test in a child whose clinical presentation suggests a high pretest probabilityof streptococcal pharyngitis

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2015 Jones criteria

Risk Stratification	
Low-Risk Population ARF incidence ≤ 2 per 100,000 school-aged children or all-age RHD prevalence of ≤ 1 per 1000 population year	Moderate/High Risk Population Children not clearly from a low-risk population.
Major Criteria	
Clinical and/or Subclinical Carditis	Clinical and/or Subclinical Carditis
Polyarthritis	Monoarthritis, Polyarthritis, and/or Polyarthralgia
Chorea	Chorea
Erythema Marginatum	Erythema Marginatum
Subcutaneous Nodules	Subcutaneous Nodules
Minor Criteria	
Prolonged PR interval	Prolonged PR interval
Polyarthralgia	Monoarthralgia
≥ 38.5°C	≥ 38°C
Peak ESR ≥ 60mm in 1 hour and/or CRP ≥ 3.0 mg/dL	Peak **ESR ≥ 30mm** in 1 hour and/or CRP ≥ 3.0 mg/dL

Fiebre reumática aguda

2 criterios mayores

O

1 criterio mayor y 2 menores

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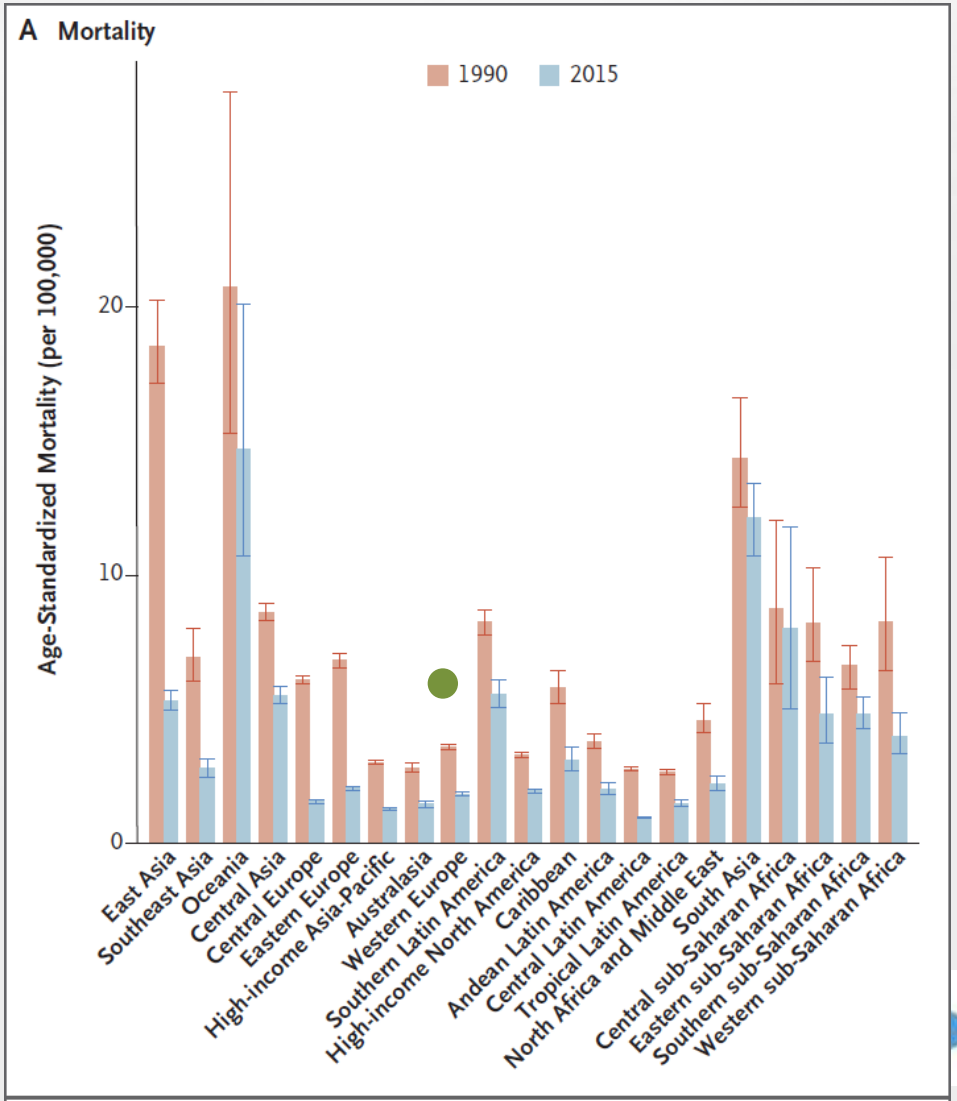
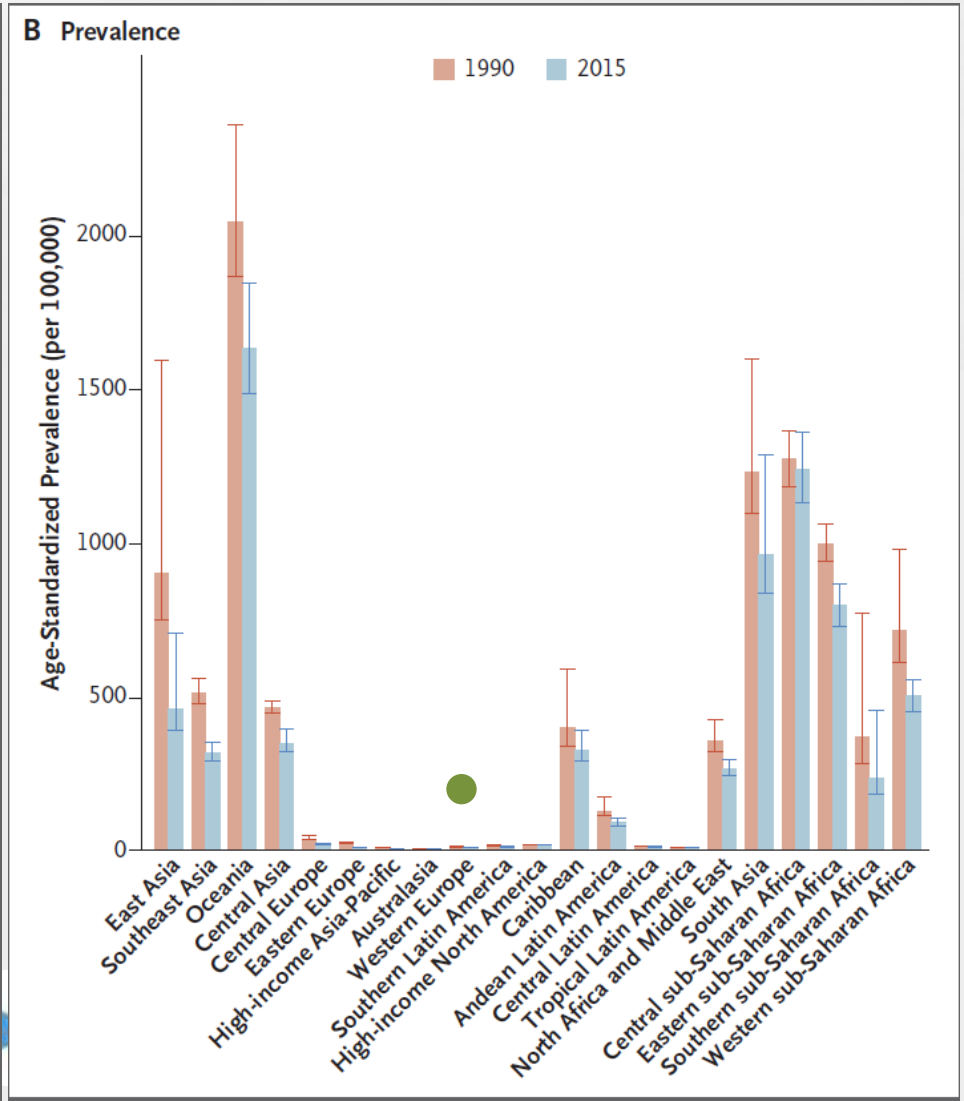
Cardiopatía reumática. Prevalencia y mortalidad

N ENGL J MED 377;8





33 millones de personas afectadas por CR (en zonas endémicas)

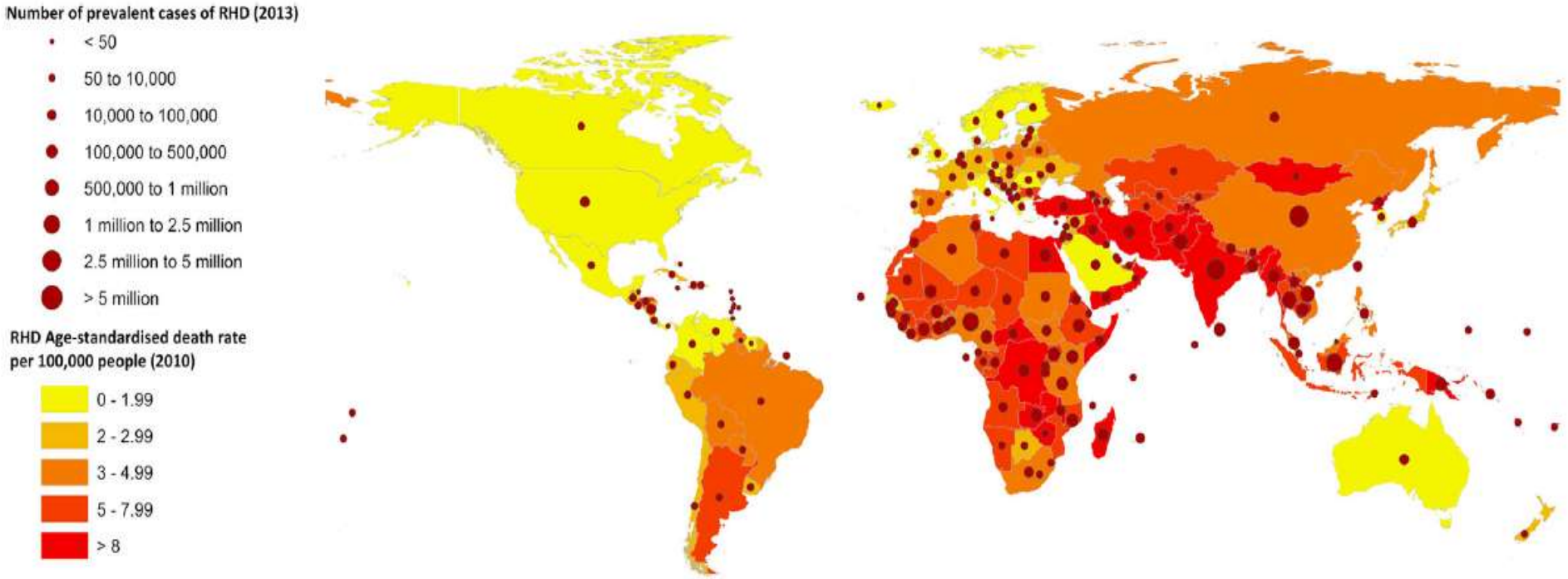


Fig. 1. Global prevalence and mortality rates. Source: data derived from Global Burden of Disease data 2010/2013.

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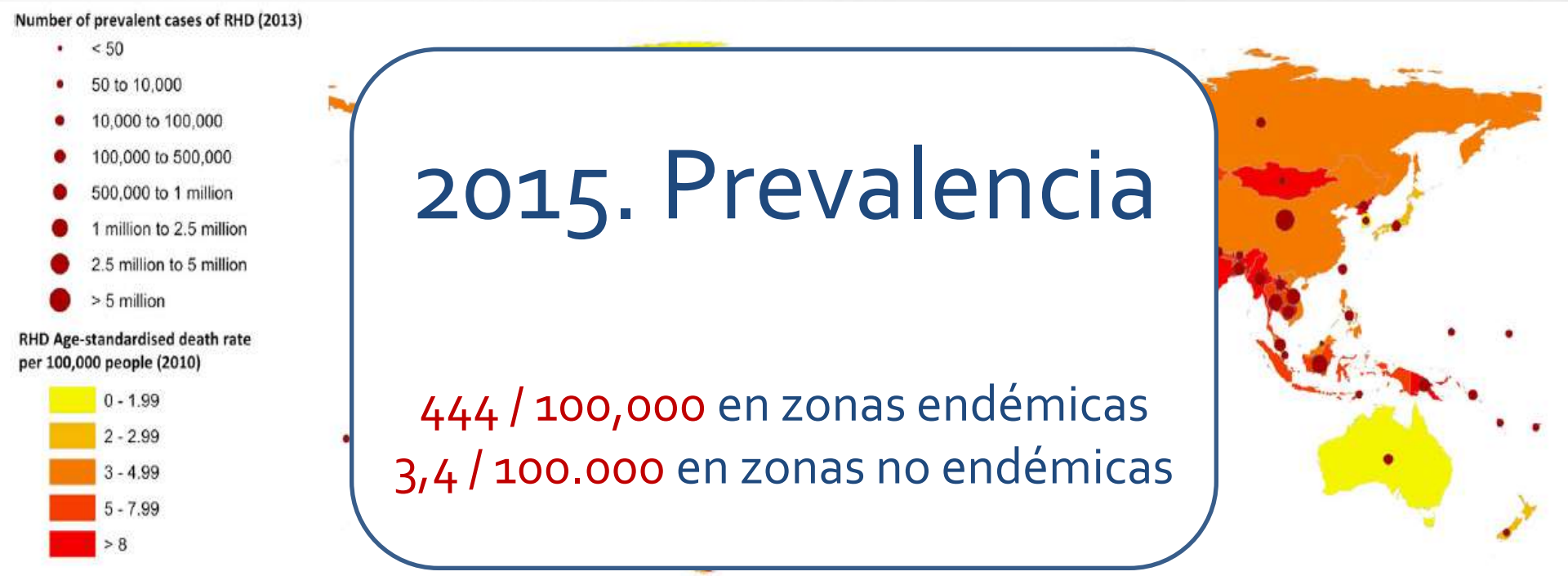

2015. Prevalencia

444 / 100,000 en zonas endémicas

3,4 / 100.000 en zonas no endémicas

Fig. 1. Global prevalence and mortality rates. Source: data derived from Global Burden of Disease data 2010/2013.

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0,6% del total de muertes son por CR (en zonas endémicas)

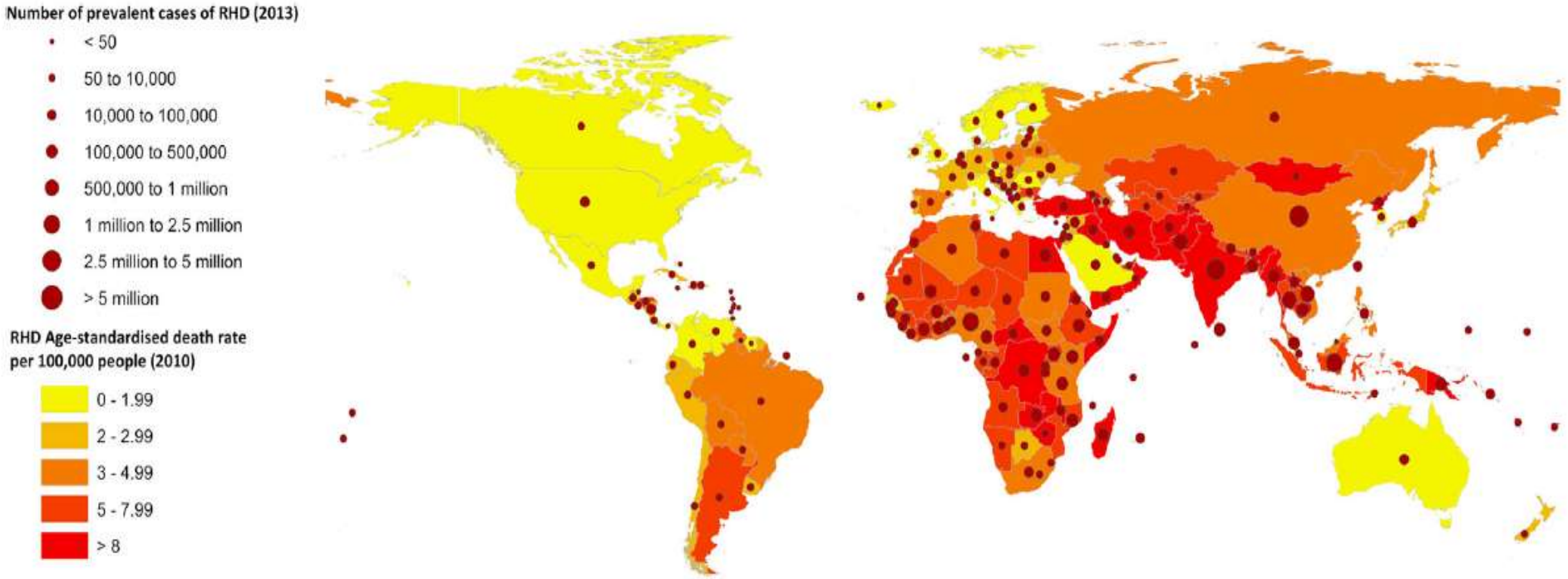

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TABLE 2 World Heart Federation Criteria for the Diagnosis of RHD

Definite RHD (A, B, C, D) Age ≤20 yrs	Definite RHD (A, B, C, D) Age >20 yrs
A. Pathological MR and at least 2 morphological features of RHD of the MV	A. Pathological MR and at least 2 morphological features of RHD of the MV
B. MS mean gradient ≥4 mm Hg*	B. MS with mean gradient ≥4 mm Hg*
C. Pathological AR and at least 2 morphological features of RHD of the AV	C. Pathological AR and at least 2 morphological features of RHD of the AV in those age <35 yrs
D. Borderline disease of both the AV and MV	D. Pathological AR and at least 2 morphological features of RHD of the MV

Borderline RHD (A, B, C)	Borderline Not Applicable to Those Age >20 yrs
A. At least 2 morphological features of RHD of the MV without pathological MR or MS	
B. Pathological MR	
C. Pathological AR	

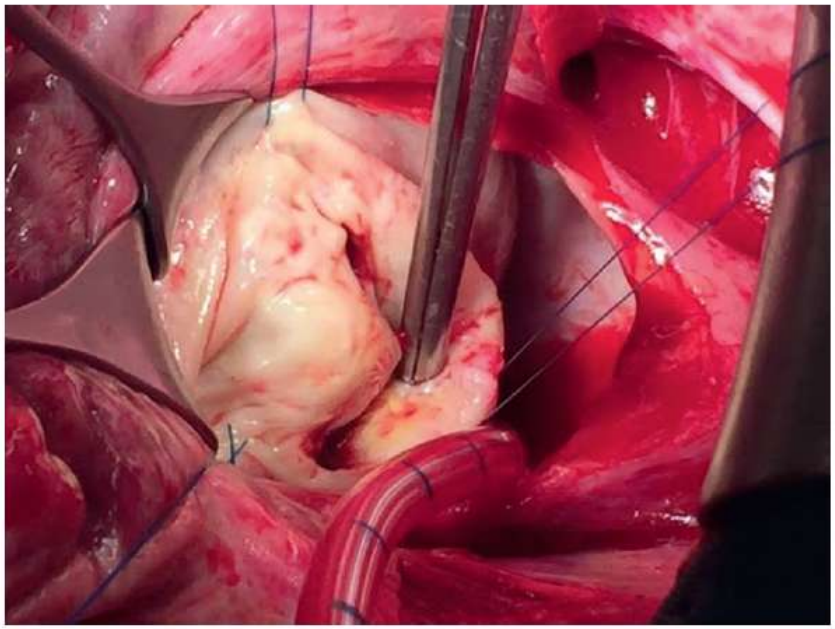
Pathological Mitral Regurgitation	Pathological Aortic Regurgitation
Seen in 2 views	Seen in 2 views
In at least 1 view, jet length ≥2 cm†	In at least 1 view, jet length ≥1 cm†
Velocity ≥3 m/s for 1 complete envelope	Velocity ≥3 m/s in early diastole
Pan-systolic jet in at least 1 envelope	Pan-diastolic jet in at least 1 envelope

Mitral Valve	Aortic Valve
AMVL thickening ≥3 mm (age ≤20 yrs), ≥4 mm (age 21 to 40 yrs), ≥5 mm (age >40 yrs)	Irregular or focal thickening
Chordal thickening	Coaptation defect
Restricted leaflet motion	Restricted leaflet motion
Excessive leaflet tip motion during systole	Prolapse

*Must rule out congenital anomalies of the mitral and aortic valve. †Jet to be measured from vena contracta to last pixel of color. Modified with permission from Remenyi et al. (24).

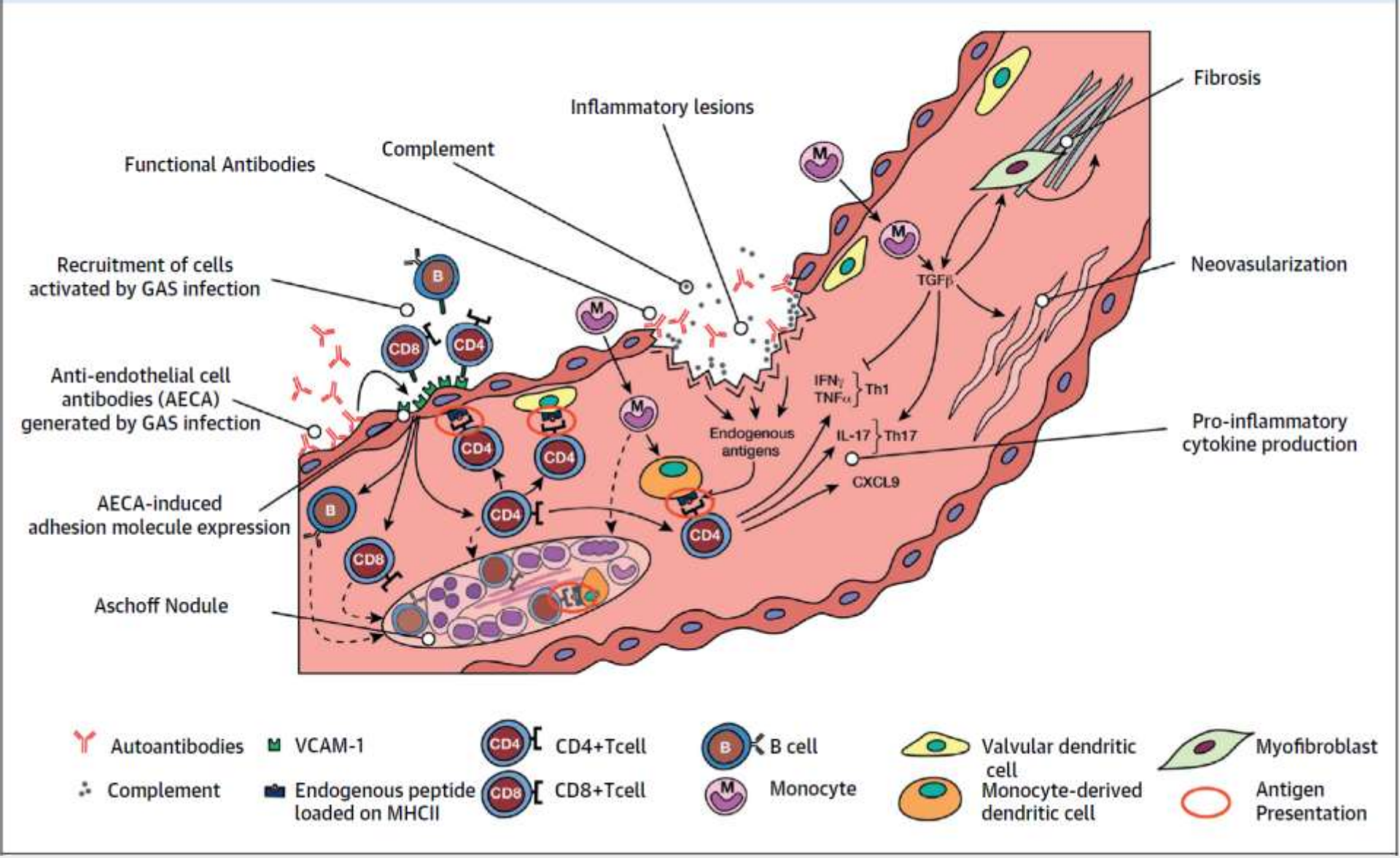
AMVL = anterior mitral valve leaflet; AR = aortic regurgitation; AV = aortic valve; MR = mitral regurgitation; MS = mitral stenosis; MV = mitral valve; RHD = rheumatic heart disease.

FIGURE 6 Effect of Rheumatic Heart Disease on the Mitral Valve



Pre-operative photograph of a stenotic, regurgitant mitral valve, showing fused commissures and thickened cusps.

FIGURE 1 Possible Pathogenic Mechanisms in Rheumatic Heart Disease



Ahora vienen los interrogantes

1. ¿Podemos atribuir este caso de cardiopatía reumática al Ocrelizumab?

2. ¿Los hallazgos microscópicos que vemos a nivel cardiaco se pueden producir en 6 meses?

3. ¿Cuál pudo ser la "causa inmediata" de la muerte en este enfermo?