Infecciones perinatales: ¿Que hay de nuevo en toxoplasmosis y CMV?

Dra Fabiana García

FUNCEI
FUNDACION CENTRO DE ESTUDIOS INFECTOLOGICOS

3er Congreso de Neonatología
Junio 2016

Toxoplasmosis aguda y embarazo: Riesgo de infección fetal

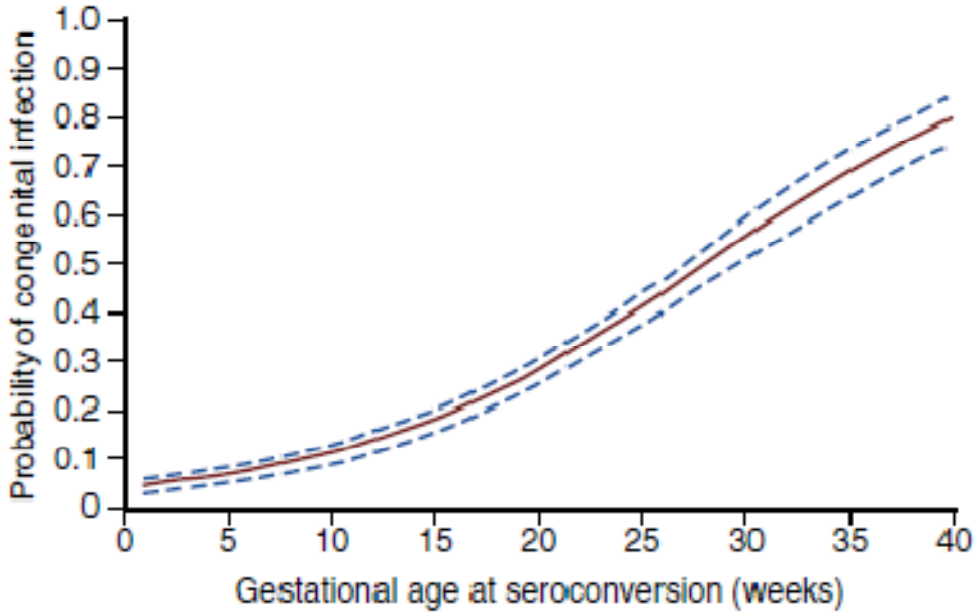
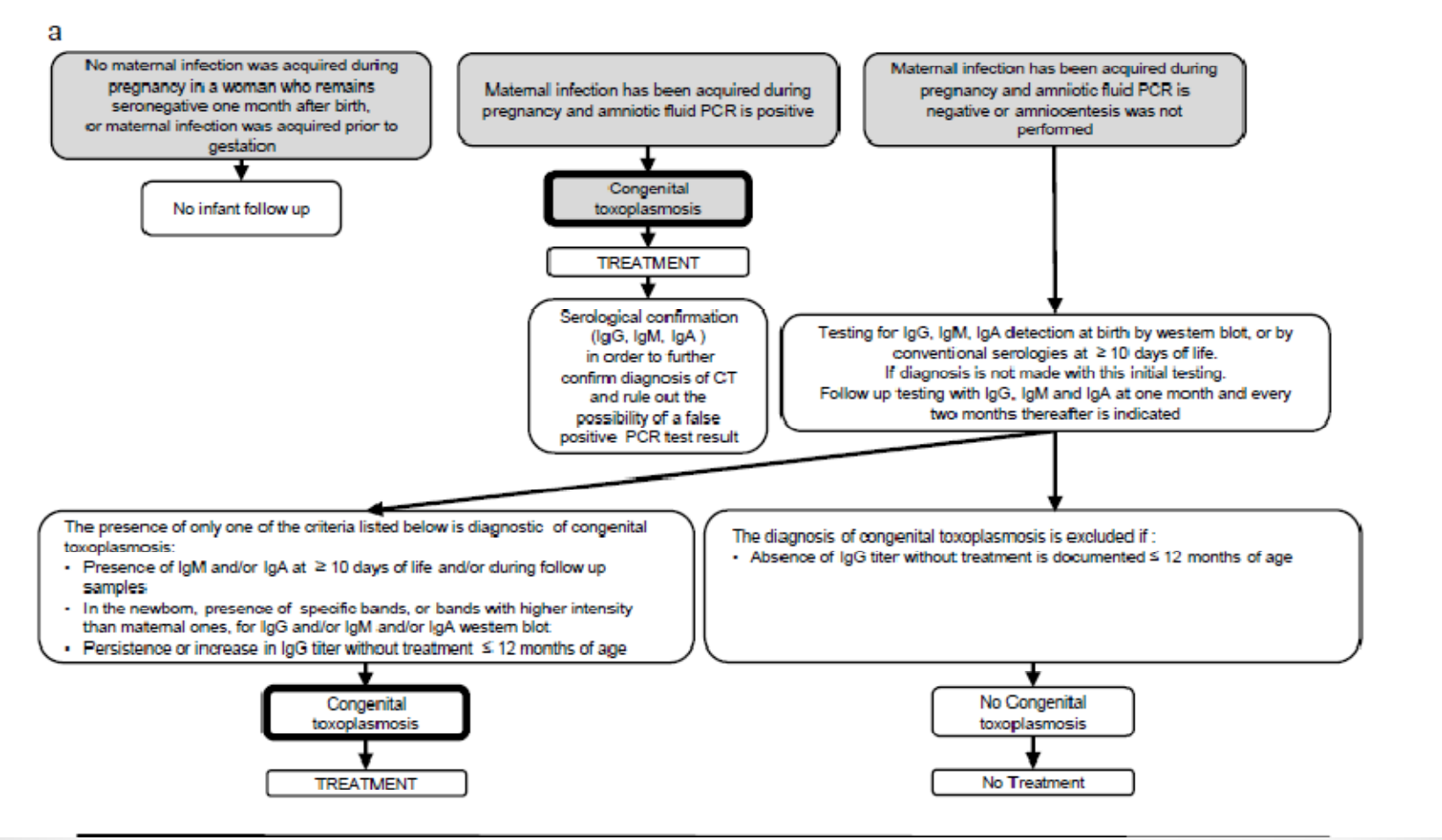


Figure 31-25 Risk of mother-to-child transmission of *Toxoplasma gondii* by gestational age at maternal seroconversion ($n = 1721$). *Dotted lines* are bounds of 95% confidence interval. (Modified from SYROCOT (Systematic Review on Congenital Toxoplasmosis) Study Group; Thiébaut R, Leproust S, Chêne G, Gilbert R: Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data, *Lancet* 369:115-122, 2007; with permission.)

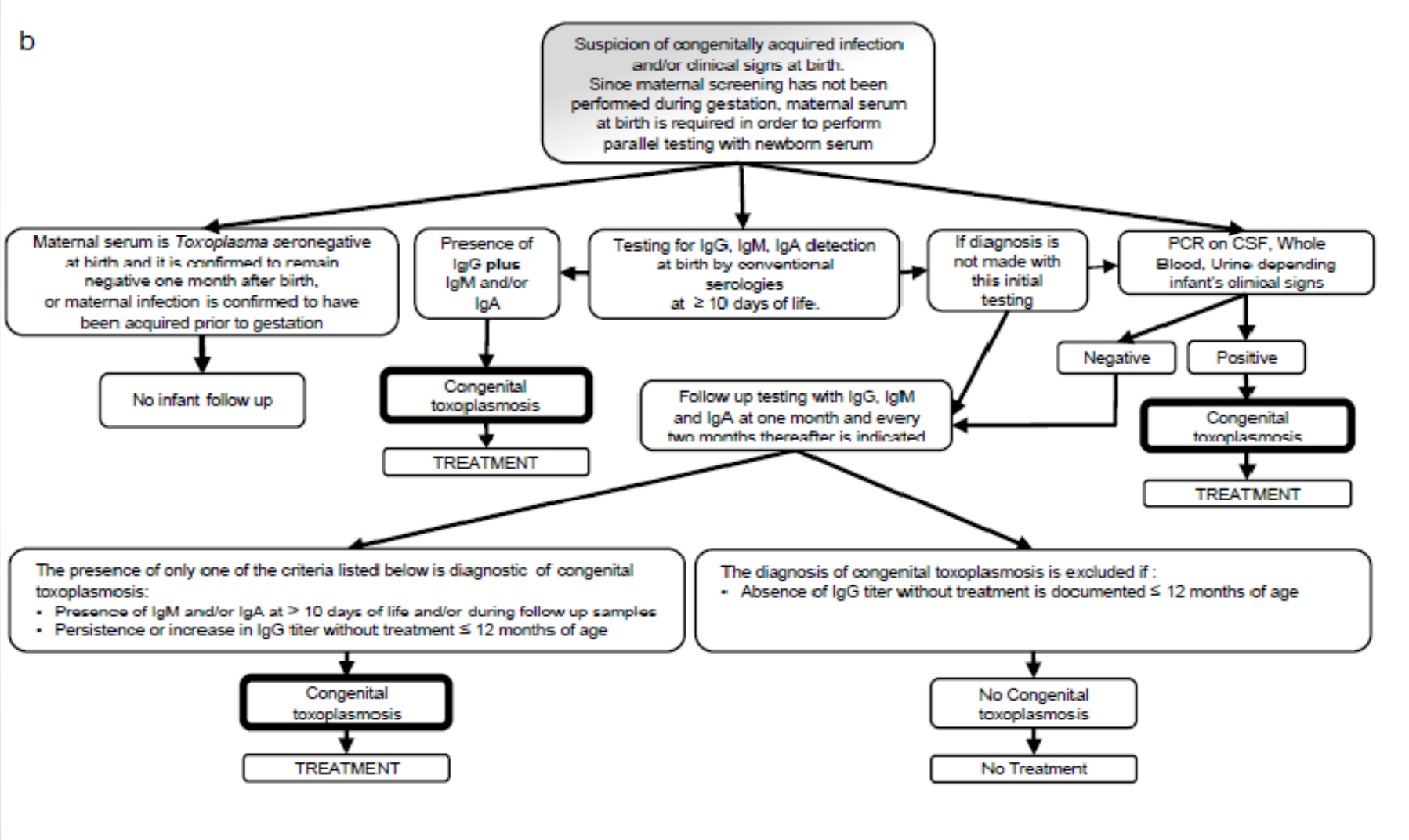
- Remmington&Klein 2016. Peyron F (Cap 31)Toxoplasmosis

Laboratory diagnosis of congenital toxoplasmosis



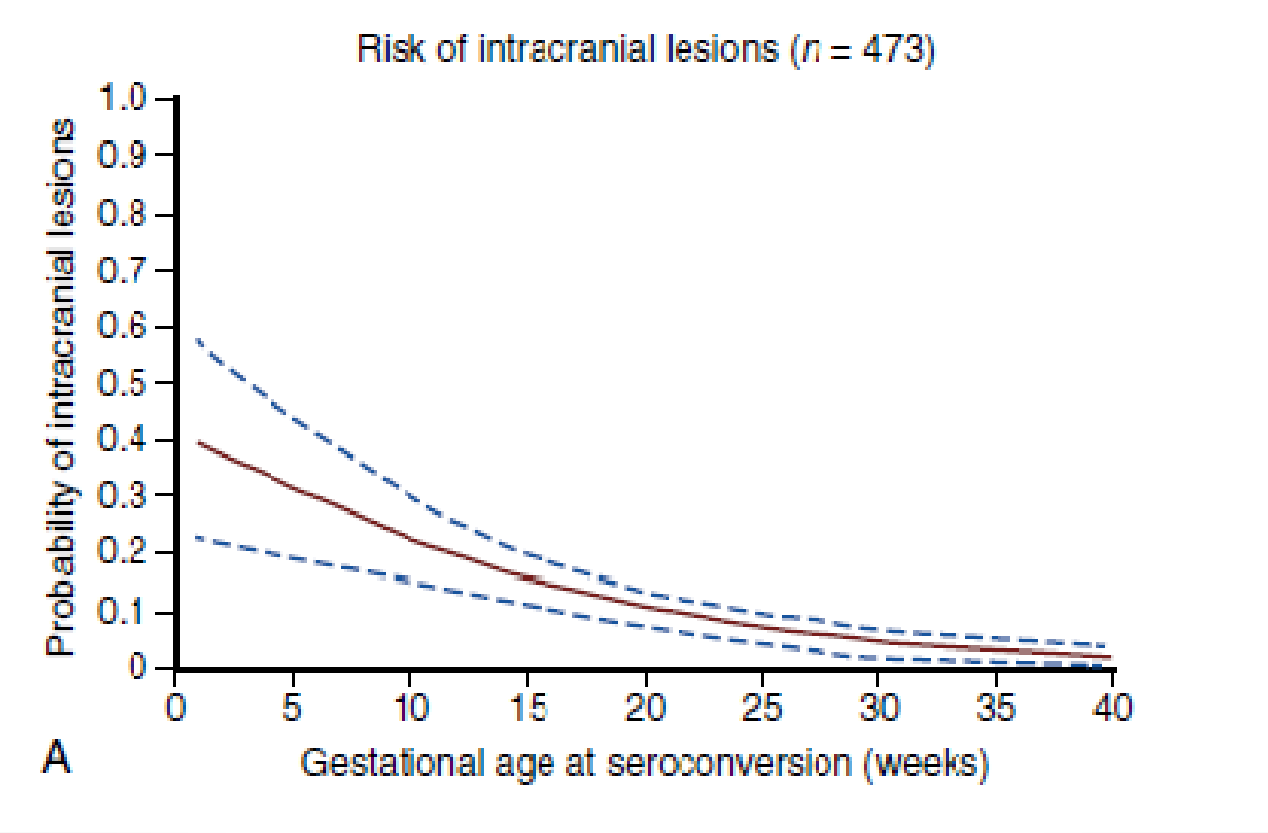
J. Clin. Microbiol. doi:10.1128/JCM.00487-16

Laboratory diagnosis of congenital toxoplasmosis.



J. Clin. Microbiol. doi:10.1128/JCM.00487-16

Toxoplasmosis congenita: morbilidad



Remmington&Klein 2016. Peyron F (Cap 31)Toxoplasmosis

Toxoplasmosis congénita: morbilidad

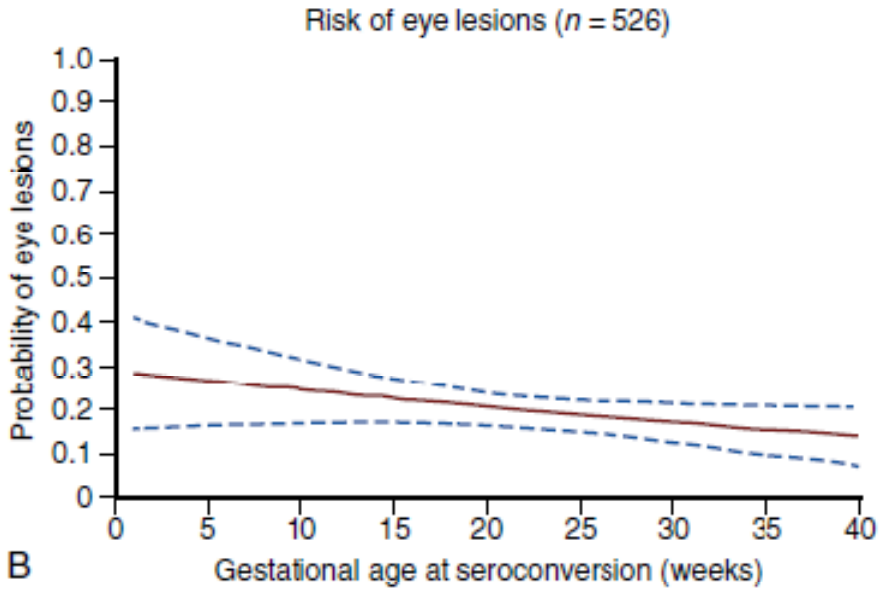


Figure 31-26 A, Risk of clinical manifestation in children infected by *Toxoplasma gondii* gestational age at maternal seroconversion: intracranial lesions. *Dotted lines* are bounds of 95% confidence interval. **B,** Risk of clinical manifestation in children infected *by T. gondii* gestational age at maternal serocorversion: risk of eye lesions. *Dotted lines* are bounds of 95% confidence interval. (Modified from SYROCOT (Systematic Review on Congenital Toxoplasmosis) Study Group; Thiébaut R, Leproust S, Chêne G, Gilbert R: Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data, *Lancet* 369:115-122, 2007; with permission.)

Ophthalmic Outcomes of Congenital Toxoplasmosis Followed Until Adolescence

Estudio prospectivo realizado en Htal de la Saint Croix Lyon desde 1987 a 2010 en **477 niños con infección confirmada en el 1er mes de vida(con tratamiento durante 12 meses). Las embarazadas evaluadas recibieron tratamiento antiparasitario**.

- El 29.8% de los pacientes evidenció lesiones oculares. Algunos pacientes manifestaron la 1ra lesión a los 22 años. Muchas de esas lesiones fueron unilaterales y periféricas. Se detectaron 2 picos de edades en el diagnóstico de anomalìas oculares 3 y 12 años.
- El 35% de los pacientes presentaron recurrencias.
- Los autores recomiendan realizar chequeos oftalmológicos anuales.

PEDIATRICS Volume 133, Number 3, March 2014

Ophthalmic Outcomes of Congenital Toxoplasmosis Followed Until Adolescence

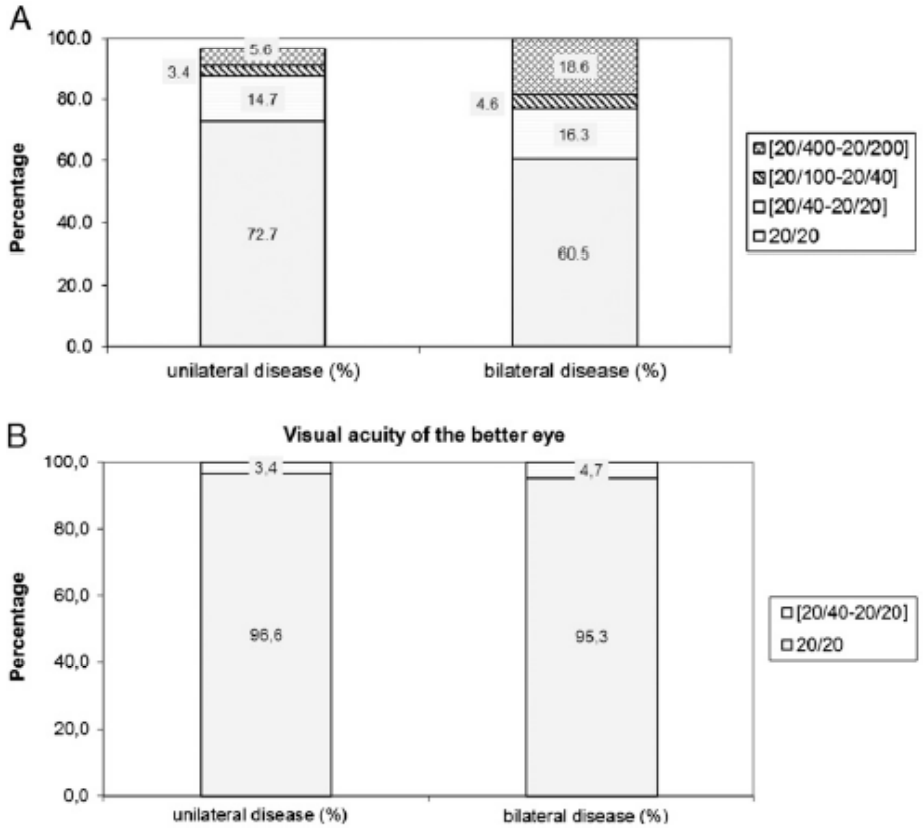
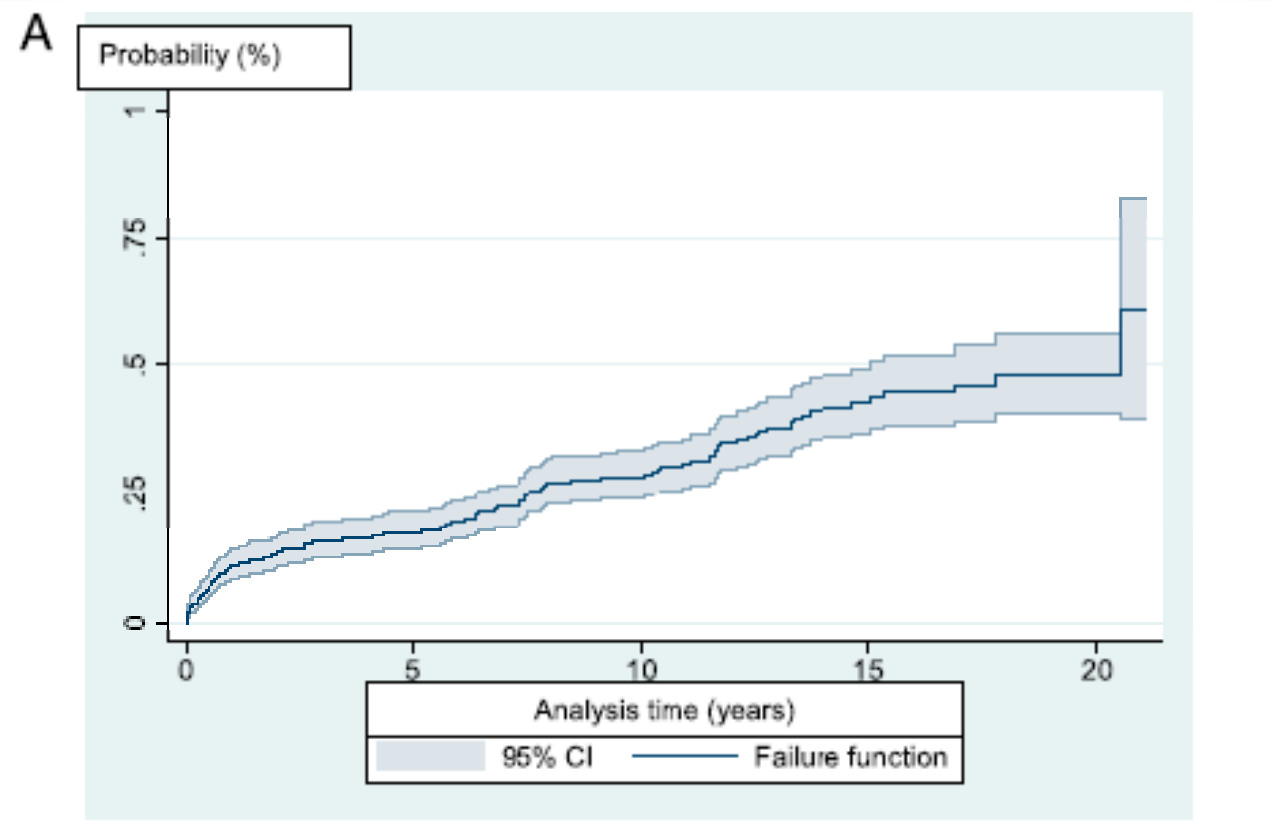


FIGURE 2
Visual acuity of the weaker (A) and better (B) eyes (Lyon Cohort Study 1987–2010).

PEDIATRICS Volume 133, Number 3, March 2014

Ophthalmic Outcomes of Congenital Toxoplasmosis Followed Until Adolescence



PEDIATRICS Volume 133, Number 3, March 2014

Toxoplasmosis congénita: morbilidad

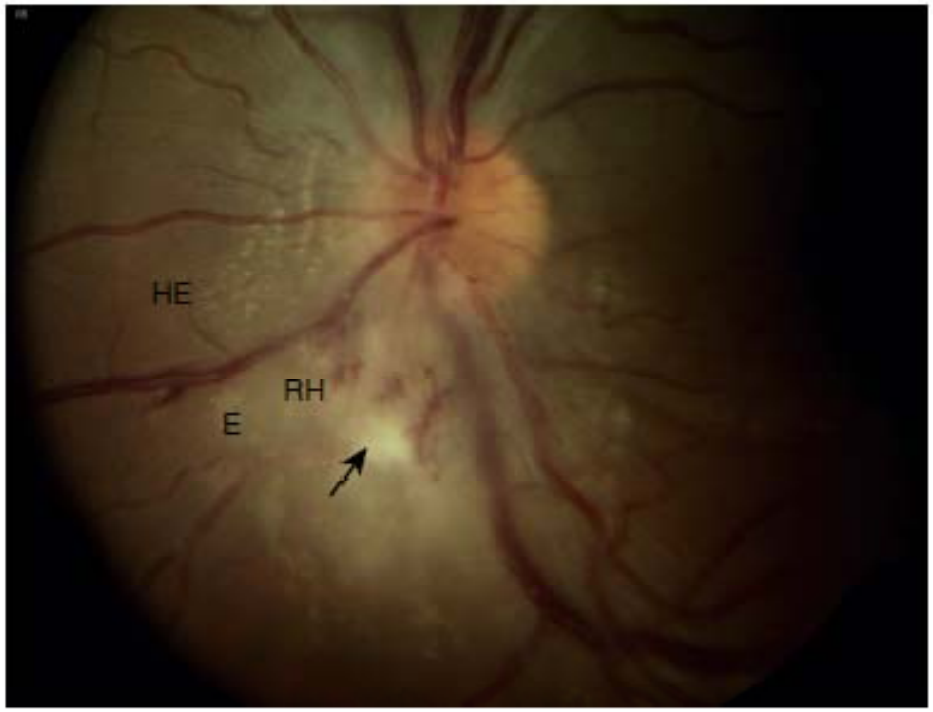


Figure 31-46 Young male with confirmed congenital toxoplasmosis who developed a first ocular lesion at the age of 17 years close to the optic nerve head (arrow). Note the surrounding edema *(E)*, hard exudates *(HE)* and retinal hemorrhage *(RH)*, together with the hyperemic vessels indicative of vasculitis, which contrasts with discrete (here not visible) areas of vitreal infiltration.

Remmington&Klein 2016. Peyron F (Cap 31)Toxoplasmosis

Tratamiento

FOR SEVERE FORMS OF CONGENITAL TOXOPLASMOSIS (HYDROCEPHALUS, >3 CEREBRAL CALCIFICATIONS, MACULAR CHORIORETINITIS)[a]	
Pyrimethamine	1 mg/kg/day for 6 months, then 0.5 mg/kg/day for 6 months
Sulfadiazine	100 mg/kg/day in two daily divided doses, 1 year
Folinic acid	10 mg 3x weekly or 25 mg 2x weekly, 1 year

Remmington&Klein 2016. Peyron F (Cap 31)Toxoplasmosis

Tratamiento

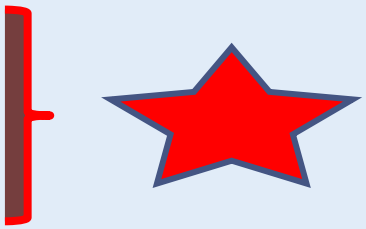
FOR SUBCLINICAL AND MILDER FORMS OF CONGENITAL TOXOPLASMOSIS:

Two possible protocols:

Protocol A[†]

Primary regimen:

Pyrimethamine	1 mg/kg/day for 2 months, then 0.5 mg/kg/day for 10 months
Sulfadiazine	100 mg/kg/day in two daily divided doses, 1 year
Folinic acid	10 mg 3× weekly or 25 mg 2× weekly, 1 year



Alternative regimen: May be used for subclinical/mild forms, and/or for difficulties in compliance, and/or frequent hematologic adverse effects

Pyrimethamine and sulfadoxine (Fansidar)	1.25 mg/kg every 10 days 25 mg/kg every 10 days, 1 year
Folinic acid	10 mg 3× weekly or 25 mg 2× weekly, 1 year

The authors recommend starting with the primary regimen of pyrimethamine plus sulfadiazine for the first 2 months then continuing treatment with pyrimethamine plus sulfadoxine, which has a longer half-life and is more convenient as it is administered every 10 days.

With either regimen, leukocyte counts should be checked at day 0 and 15 and monthly thereafter. Therapy should be discontinued (but folinic acid continued) whenever neutrophils decrease below 750/mm^3. Monthly tests for proteinuria are recommended in children treated with pyrimethamine and sulfadiazine.

Remmington&Klein 2016. Peyron F (Cap 31)Toxoplasmosis

Tratamiento

Protocol B[‡]

Postnatal treatment of the infant and child

Medication	Dosage Therapy	Indication for Therapy	Duration of Therapy
Pyrimethamine	Loading dose: 1 mg/kg every 12 hours for 2 days; then beginning on day 3, 1 mg/kg per day for 2 or 6 months; then this dose every Monday, Wednesday, and Friday	When congenital toxoplasmosis diagnosed in infant	1 year
Sulfadiazine *plus*	50 mg/kg every 12 hours		1 year
Folinic acid (Leucovorin)	10 mg 3×/week		1 year
Corticosteroids[§] (prednisone)	0.5 mg/kg every 12 hours	When CSF protein is ≥1 g/dL or when active chorioretinitis threatens vision	During and for 1 week after

Toxoplasmosis congénita: seguimiento serológico en el 1er año de vida de niños NO infectados

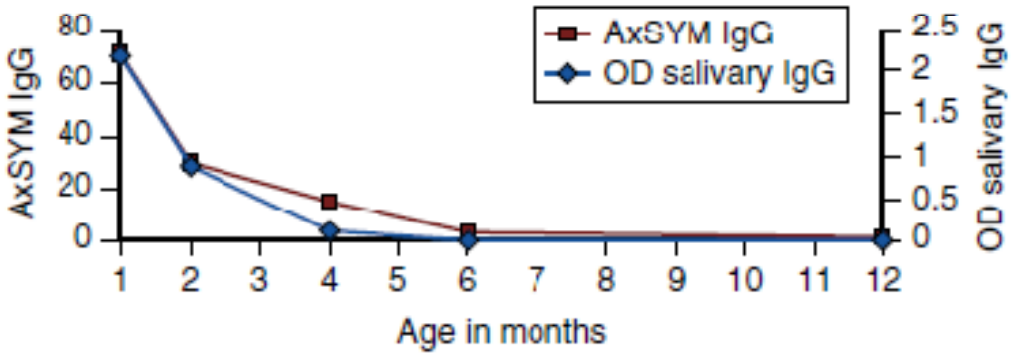
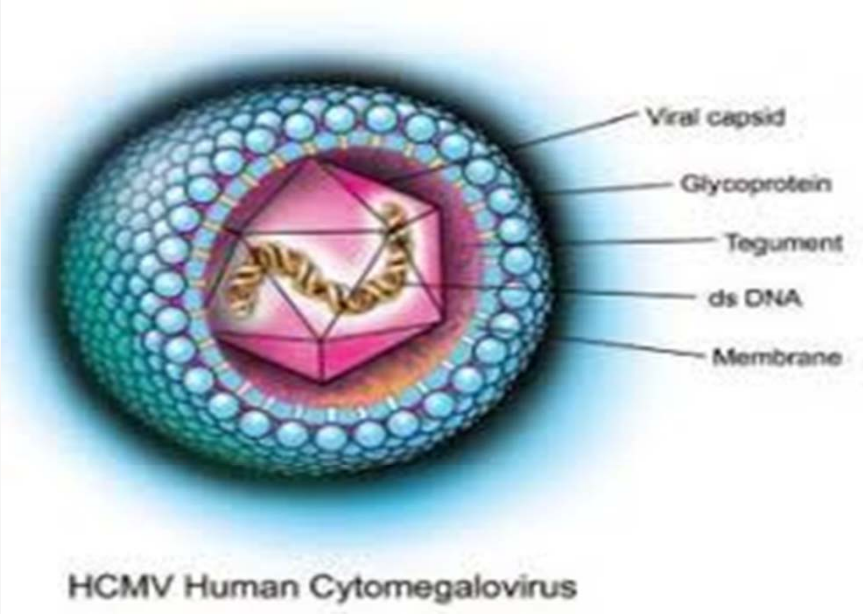
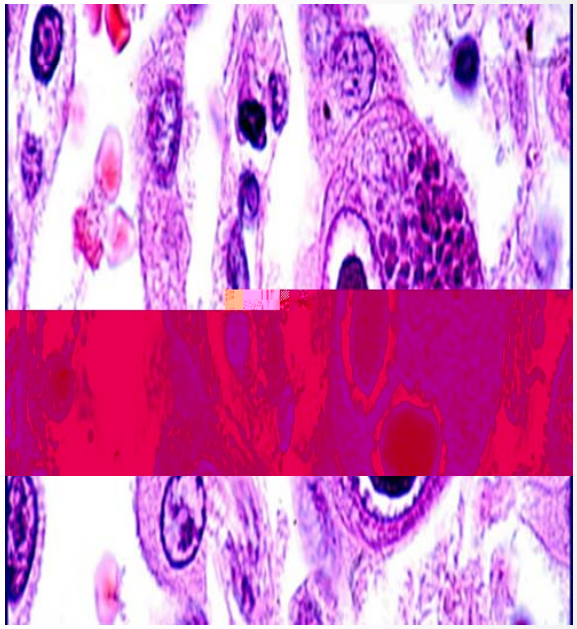


Figure 31-44 Similar pattern of immunoglobulin G disappearance in blood (ELISA AxSYM, Abbott Diagnostics, Abbott Park, Ill) and optical density (OD) in saliva in an uninfected infant. *IgG*, Immunoglobulin G.

Remmington&Klein 2016. Peyron F (Cap 31)Toxoplasmosis

Citomegalovirus: Familia herpesvirus



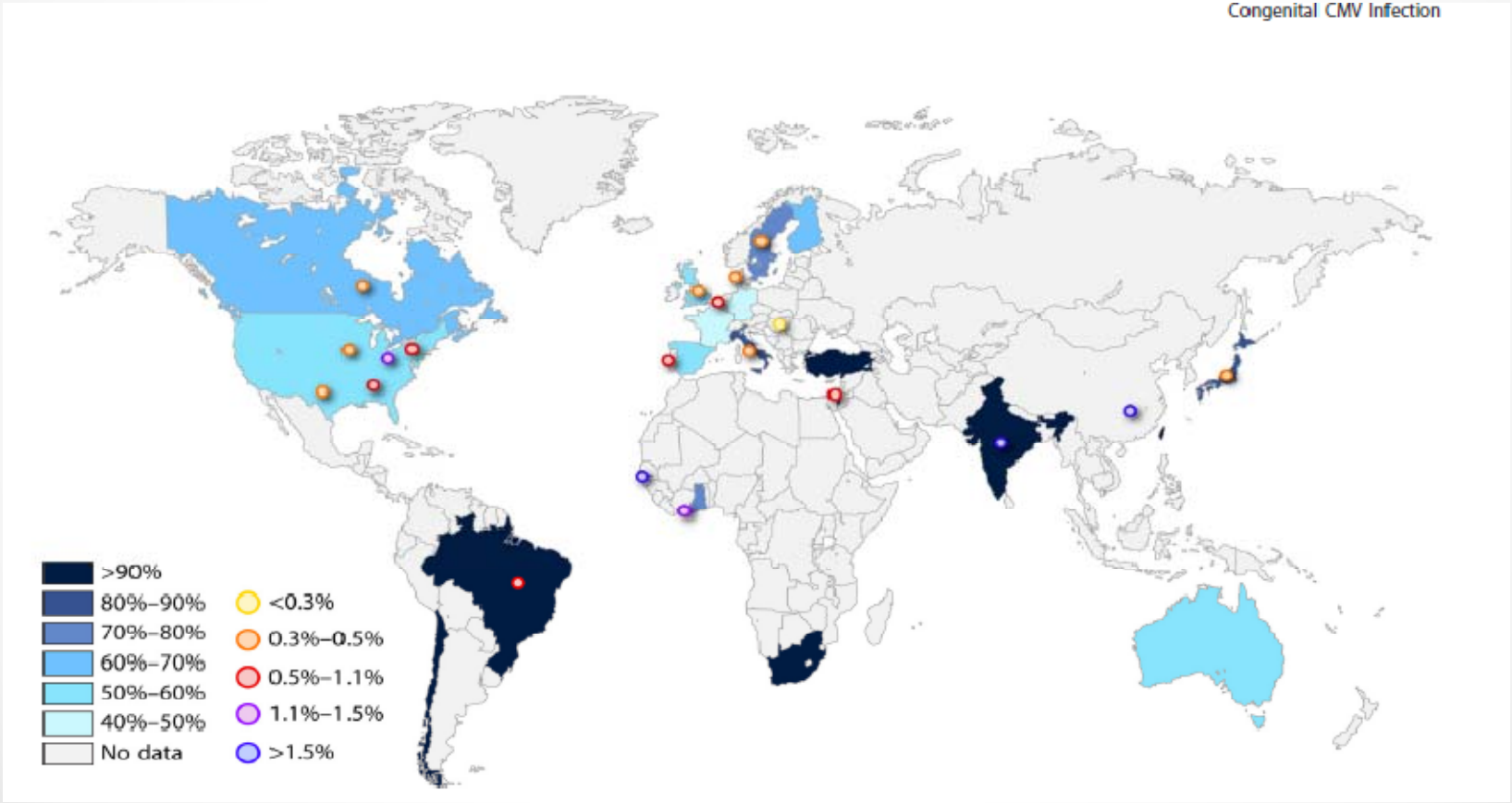


- Existen varios genotipos
- Genera infección latente.
- Inmunidad parcial. El huésped infectado puede presentar reactivaciones (recurrencias) o reinfecciones

The "Silent" Global Burden of Congenital Cytomegalovirus

Sheetal Manicklal,[a] Vincent C. Emery,[b] Tiziana Lazzarotto,[c] Suresh B. Boppana,[d] Ravindra K. Gupta[b]

Division of Medical Virology, Department of Clinical Laboratory Sciences, National Health Laboratory Service, Groote Schuur Hospital/University of Cape Town, Cape Town, South Africa[a]; Division of Infection and Immunity, University College London, London, United Kingdom[b]; Operative Unit of Microbiology, St. Orsola Malpighi General Hospital/University of Bologna, Bologna, Italy[c]; Pediatrics and Microbiology, University of Alabama School of Medicine, Birmingham, Alabama, USA[d]



Cytomegalovirus Strain Diversity in Seropositive Women[▽]

Zdenek Novak,[1]* Shannon A. Ross,[1] Raj Kumar Patro,[2] Sunil Kumar Pati,[2] Rekha A. Kumbla,[1] Sallie Brice,[1] and Suresh B. Boppana[1]

Department of Pediatrics, The University of Alabama at Birmingham, Birmingham, Alabama,[1] and All India Institute of Medical Sciences, New Delhi, India[2]

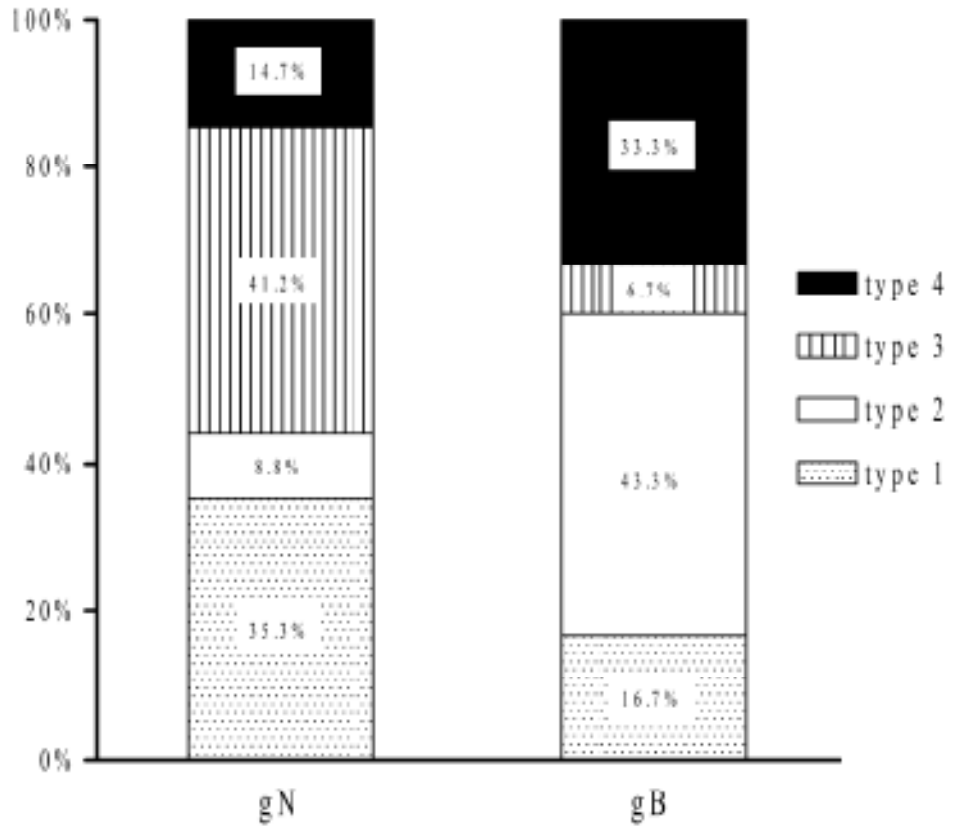


FIG. 3. Relative frequencies of CMV gN and gB genotypes in urine and blood samples from CMV-seropositive women.

J. Clin. Microbiol. 2008, 46(3):882

The "Silent" Global Burden of Congenital Cytomegalovirus

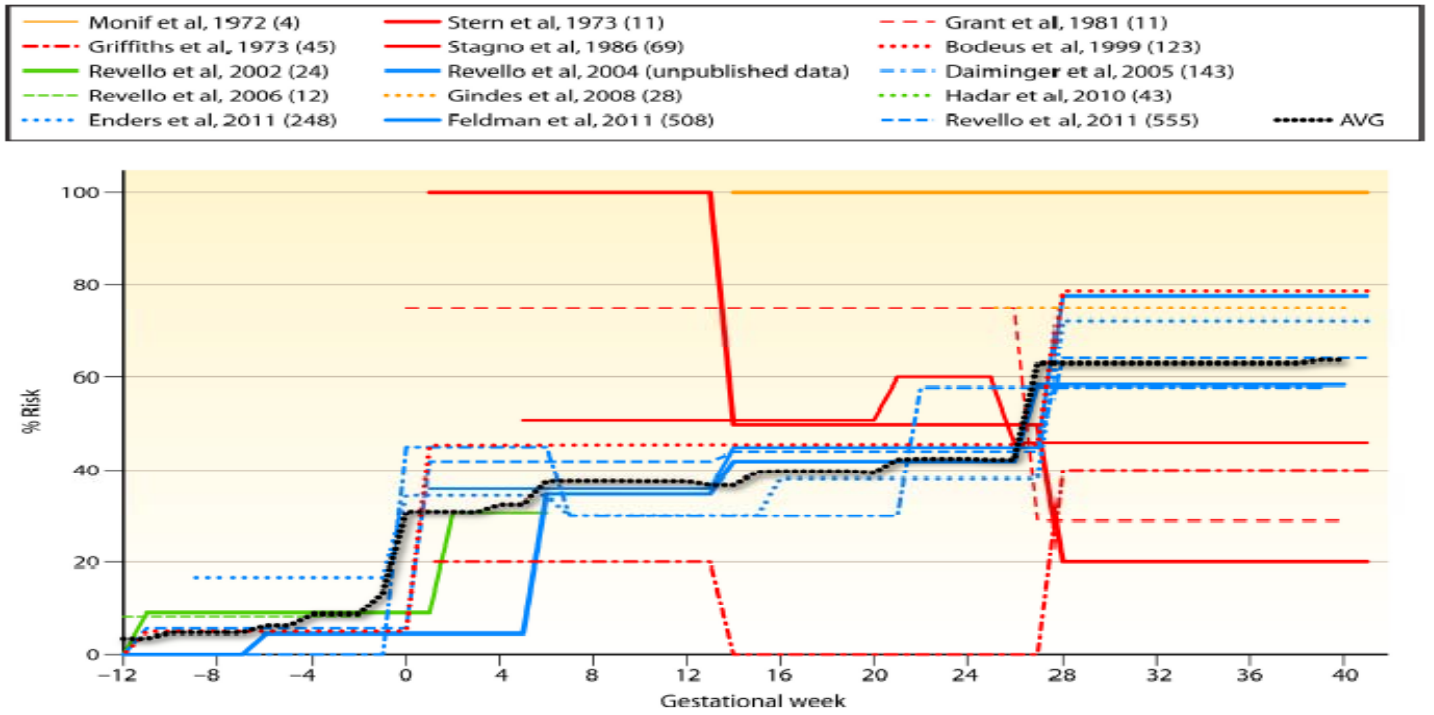


FIG 3 Graph representing the risk of intrauterine CMV transmission following maternal primary infection from 15 studies. The transmission risk is the proportion of mothers undergoing a primary infection in a given trimester and/or the preconception period who transmitted CMV to the fetus. The risk is therefore uniform (represented by a flat line) for the time period defined as preconception (from 12 or more weeks prior to conception), first trimester (up to the 12th gestational week), second trimester (from 12 to 26 weeks), and third trimester (26 weeks to delivery) in each of the studies. Studies were grouped according to the number of weeks for which data were collected and are represented by lines of different colors: yellow, studies with late-gestation data; green, studies with preconception and/or first-trimester data; red, studies with first-, second-, and third-trimester data; blue, studies with preconception and first-, second-, and third-trimester data. The black dotted line represents pooling of the data (excluding unpublished data) for each gestational week. The denominator is the sum of mothers undergoing a primary infection from studies with data available for a particular gestational week. The numerator is the total number of transmitter mothers across these studies for that gestational week. Risks are shown as percentages. The number of women undergoing a primary infection in each study is shown in parentheses. (See references 43, 54, 55, 56, 71, 137, 143, 184, 209, 210, 211, 212, 213, and 214.)

Clin Microb Rev 2013

Pesquiza (screening) en el embarazo

- NO (contra)
- SI (pro)

2016: NO aún!!!!

DEBE SOLICITARSE ante: - S.mononucleòsico o S gripal
- Alteraciones ecográficas fetales
- Conviviente con CMV agudo

Guías de prevención de la TV del CMV

1) No se recomienda el screening en el embarazo (III-B)
2) Solicitar serología ante S.gripal, S.mononucleosico o alteraciones ecográficas sugestivas (III-B)
3) La confirmación diagnóstica se jerarquizara en seroconversión (IgG (+), IgM pos y baja avidez) (II2A)
4) En caso de infección materna se informara a la pareja que el riesgo de infección fetal es del 30 a 40%, y, de secuelas post-natales del 20 al 30%(II-2A)
5) Si se sugiere amniocentesis indicarlo > S21 y después del 5 -7ma S de la infección(II-2ª)
6) La infección 2ria se confirmará con títulos de IgG e IgM en ascenso y alta avidez. Puede considerarse la amniocentesis.(IIIC)
7) Seguimiento ecográfico cada 2 a 3 semanas en infecciones agudas confirmadas(II-B).
8) El estudio cuantitativo de L.amniótico puede predecir infección fetal(II3B)
9) Los trabajadores de la salud, de guarderías y madres con hijos en guarderías requieren evaluación serológica pre e intra-embarazo(III-B)

J Obstet Gynaecol Can. 2010 Apr;32(4):348-54

Identification of Symptomatic Fetuses Infected with Cytomegalovirus Using Amniotic Fluid Peptide Biomarkers

Cyrille Desveaux[1☯¤], Julie Klein[2,3☯], Marianne Leruez-Ville[4,5], Adela Ramirez-Torres[6], Chrystelle Lacroix[3,7], Benjamin Breuil[2,3], Carine Froment[3,7], Jean-Loup Bascands[2,3], Joost P. Schanstra[2,3], Yves Ville[1,5]*

Table 5. Sensitivity, specificity, AUC, positive predictive value (PPV) and negative predictive value (NPV) of CMV34 and other clinical parameters associated to postnatal outcome.

	Sensitivity (% [95% CI])	Specificity (% [95% CI])	AUC [95% CI]	PPV* (% [95% CI])	NPV* (% [95% CI])
CMV34 °	89 [51.8–99.7]	75 [42.8–94.5]	0.90 [0.68–0.98]	0.35 [0.03–0.85]	0.98 [0.62–1.00]
CMV DNA levels in amniotic fluid °°	79 [54.4–93.9]	84 [63.9–95.5]	0.84 [0.70–0.93]	0.42 [0.05–0.88]	0.96 [0.72–1.00]
CMV DNA levels in fetal blood °°	92 [64.0–99.8]	59 [36.4–79.3]	0.81 [0.65–0.92]	0.25 [0.02–0.71]	0.98 [0.55–1.00]
Fetal platelet count °°	82 [48.2–97.7]	70 [45.7–88.1]	0.77 [0.58–0.90]	0.29 [0.01–0.83]	0.96 [0.54–1.00]

° Data given for validation cohort only.

°° Data given for both discovery and validation cohort since missing values did not allow a separate analysis of the discovery and validation cohort.

* Based on a prevalence of 13% [1] of symptomatic CMV infected individuals; confidence intervals were calculated using variable numbers of cases: 22 for CMV34; 19 for CMV DNA levels in amniotic fluid, 13 for CMV DNA levels in fetal blood and 11 for fetal platelet count.

CMV congénito: aporte de la RMN en el embarazo

121 bebes por nacer con infección confirmada por CMV fueron estudiados pre-nacimiento con RMN.

Las alteraciones de la RMN se clasificaron en:
Grado 1: Normal
Grado 2: Hiperintensidad frontal, parieto-occipital
Grado 3: Hiperintensidad temporal periventricular
Grado IV: quistes o tabiques intraventriculares temporo-paritales.
Grado V: Alteraciones de la migración neuronal

La realización del estudio entre S27 y S33 brindó información con respecto a pronóstico con respecto a alteraciones auditivas y neurológicas.

Se hizo seguimiento post-natal de los niños con RMN patològicas y se confirmò en 18 alteraciones auditivas y en 10 neurològicas (p0.001).
Las RMN repetidas post-nacimiento fueron comparables.

Eur Radiol. 2016 Mar 17

Uso de ɣ-globulina hiperinmune para CMV en el embarazo

Table 1. Clinical studies having investigated the effect of HIG treatment for the prophylaxis of vertical CMV transmission

Author, year [Ref.]	Design	n	Dosing regimen (PEIU/kg/dose)[a]	Newborn follow-up (years)	Outcome parameter	Results	
						HIG group	control group
Nigro et al., 2005 [46]	Prosp., nrd	84	100 q4w 2–7 doses	2	Percentage of congenitally infected live births	6/37 (16%), p = 0.02 0 symptomatic[b]	19/47 (40%) 3 symptomatic
Buxmann et al., 2012 [64]	Retrosp.	38	100–200[c] 1–3 doses	1–3	Percentage of congenitally infected neonates/fetuses	9/38[d] (24%) 0 symptomatic, 1 induced abortion	–
Revello et al., 2014 [65]	Prosp., rd, db	123	100 q4w 3–6 doses	0	Percentage of congenitally infected neonates/fetuses	18/61 (30%), p = 0.13 3/10 symptomatic (8 abortions)[e]	27/62 (44%) 4/17 symptomatic (10 abortions)[e]

Uso de -ɣglobulina hiperinmune para CMV en el embarazo

Table 2. Clinical studies having investigated the therapeutic effect of HIG on CMV-related fetal anomalies and clinical outcome of evidently infected newborns

Author, year [Ref.]	Design	n	Dosing regimen (PEIU/kg/dose)[a]	Newborn follow-up (years)	Outcome parameter	Results	
						HIG group	control group
Nigro et al., 2005 [46]	Prosp., nrd	45	200 q2–6w (plus 400 i.a. or i.u. in 9 subjects) 1–3 doses	2	Resolution or regress of fetal sonographic anomalies incl. IUGR	14/15 (93%)	0/7
					Percentage of symptomatic newborns	1/31 (3%)[b], p < 0.001	7/14 (50%)
Buxmann et al., 2012 [64]	Retrosp.	3	180–220[c] plus ~500[e] i.a. or i.u. 1–3 doses	1–3	Percentage of symptomatic newborns	0/3[d]	
Nigro et al., 2012 [72]	Retrosp., case-control	64	200 q2–4w 1–4 doses	1–5	Resolution or regress of fetal sonographic anomalies incl. IUGR	9/14 (64%)	5/17 (29%)
					Percentage of infants with sequelae	4/31 (13%), p < 0.001	28/33 (85%)
Nigro et al., 2012 [70]	Prosp., nrd	16[f]	200 q4w 1–3 doses	2–8	Resolution of hyperechogenic bowel	7/9 (78%), p = 0.15	3/8 (38%)
					Percentage of infants with sequelae	1/9 (11%), p < 0.0004	8/8 (100%) incl. 1 stillbirth
Visentin et al., 2012 [71]	Prosp., nrd	68	200 1 dose	1	Resolution or regress of fetal sonographic/MRI anomalies incl. IUGR	0/4	0/5
					Percentage of infants with sequelae	4/31 (13%), p < 0.01	16/37 (43%)
JCCHFTSG 2012 [73]	Prosp., uncontrolled	12	~100–200[g] q1w 1–5 doses and/or ~500–1,800[e,g] q1w 2–6 doses i.p.	2–6	Resolution or regress of fetal sonographic anomalies incl. IUGR	9/12[h] (75%)	–
					Percentage of infants with sequelae	9/12[h] (75%) incl. 2 neonatal deaths	

Gamma globulina st y prevención CMV perinatal estudios preliminares

TABLE 1 Characteristics of the 113 consecutive enrolled pregnant women

Variable	Value
Age in yrs of pregnant women, mean (SD)	32.3 (5.5)
Gestational week at diagnosis, mean (SD)	15.7 (7.2)
No. of weeks after diagnosis at first infusion, mean (SD)	5.6 (4.3)
Pregnancy order, %	
First	37.2
Second	47.1
Third	15.7
Gestational age at diagnosis, %	
First trimester	39.8
Second trimester	45.1
Third trimester	15.1
No. of infusions, %[a]	
One	30.1
Two	27.4
Three or more	42.5
Outcome at birth, no. (%) (data available for 67 newboms)	
Infected	27 (40.3)
Asymptomatic	22 (81.5)
Impaired otoemissions	2 (7.4)
Mild growth retardation	3 (11.1)

[a] Reinfusions were delivered approximately 4 weeks after the previous one.

TABLE 2 CMV IgG titers and avidity indexes at investigated time points

	Mean CMV IgG titer, U/ml (SD) by no. of paired observations			Mean % avidity index (SD) by no. of paired observations		
Time point	87	55	57	85	55	59
Pre-1st infusion	81.8 (67.3)			38.9 (14.4)		
Post-1st infusion	134.3 (72.4)	146.5 (81.3)		57.2 (12.1)	58.4 (10.8)	
Pre-2nd/3rd infusion[a]		90.4 (46.7)	89.4 (46.5)		45.3 (12.9)	45.8 (13.1)
Post-2nd/3rd infusion[a]			127.1 (53.2)			58.4 (13.4)
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[a] Reinfusions were delivered approximately 4 weeks after the previous one.

Clin Vaccine Inmunol 2012

Infección materna por VIH y TV de CMV

RESULTADOS: Durante 8 años se realizò un estudio prospectivo que incluyò 125.781 RNs. **367 niños (0.3%) hijos de 303 mujeres VIH(+)**

En los 333 HIV-expuestos en los que se realizò screening de CMV **10 (3%) tuvieron infecciòn congenita** . **Seis de ellos fueron identificados a traves de este protocolo** . Cuatro niños tuvieron infectados por VIH, ninguno con infecciòn por CMV.

Los RNs infectados por CMV tuvieron peso promedio de (2508 versus 3148 g, P < 0.01), EG menor (37 vs. 39 weeks, P < 0.01), y > CV materna para VIH(en el 1er control prenatal,15.411 vs. 2209 copies/mL, P = 0.02).

Los niños con CMV congènito fueron hijos de madres con diagnòstico de VIH en el embarazo o el parto. (P = 0.03).

CONCLUSIONES: **En esta poblaciòn la prevalencia de CMV congènito fue 3%.La solicitud de test *diagnòsticos* para CMV en hijos de madres VIH (+) debe ser considerada.**

Duryea y col. 2010

Tratamiento del RN sintomático

Antivirales:

Ganciclovir 5-7,5mg/kg cada 12hs EV

Valganciclovir 16mg/kg cada 12hs VO

Duración: 6 meses

El tratamiento prolongado demostró mejor evolución auditiva y del desarrollo madurativo en los pacientes con CMV sintomáticos que iniciaron tratamiento en el 1er mes de vida

Uso de valganciclovir para tratamiento de CMV congénito sintomático

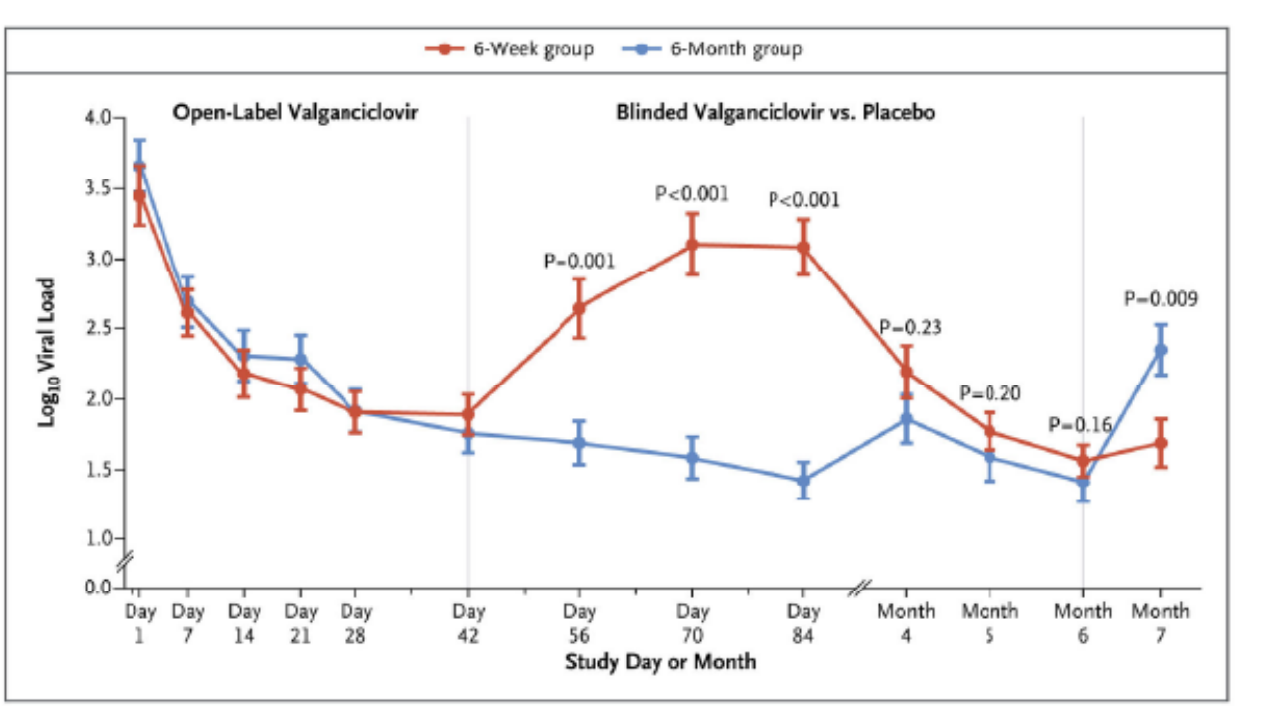


Figure 2. Cytomegalovirus DNA Viral Load in Whole Blood in Participants Receiving the Study Therapy

Participants with a viral load of less than 100 were assessed as having a viral load of 10 (i.e., 1.0 in the graph). P values are for the between-group comparisons at the respective time points.

N Engl J Med. 2015 March 5; 372(10): 933–943.

CMV congénito

Prevención

Evitar el contacto con saliva y orina, de niños que aún no controlan esfínteres (< 3 años aprox)

- No comparta los utensillos de cocina.
- No coma los restos de comida que dejan en el plato.
- No limpie con su boca el chupete de su hijo.
- Lávese las manos luego de cambiarle los pañales, acompañarlo al baño o limpiarle la nariz.
- Lave periódicamente los juguetes que se llevan a la boca.

¡ Muchas gracias por su atención!

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