
Bronquiolitis Obliterante

Pos-infecciosa:



Hospital de Niños R. Gutiérrez
Buenos Aires

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Centro Respiratorio



Bronquiolitis Obliterante

Pos-infecciosa:

desarrollo y pronóstico



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Bronquiolitis Obliterante

Injuria de la vía aérea

Transplante

- Injerto contra huesped postransplante de medula osea
- Rechazo crónico postransplante pulmonar

Miscelaneas

- Enfermedades del Tejido conectivo
- Drogas
- Inhalacion de tóxicos
- Aspiracion

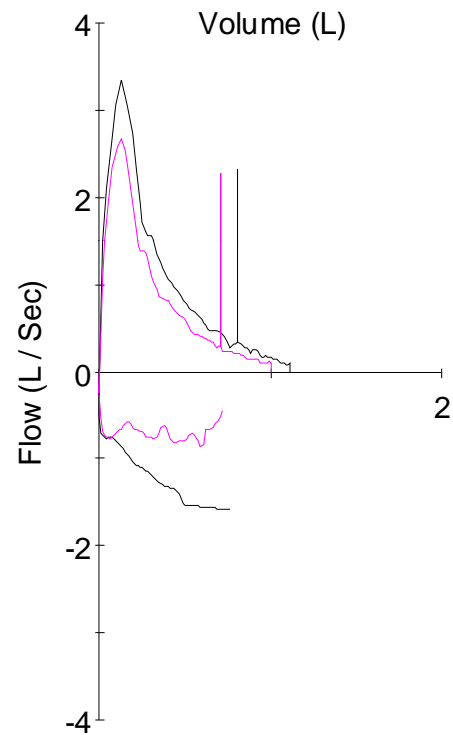
Infecciones

- Adenovirus
- Influenza
- Parainfluenza
- Mycoplasma
- Sarampion
- B. Pertusis

EB

- I. **Historia típica:** Internado durante 2 meses al año de vida por bronquiolitis, ARM 18 días y oxígeno suplementario durante 5 años.
 - II. **No se identifico Adenovirus.**
 - III. **TAC** con patrón en mosaico.
-

EB



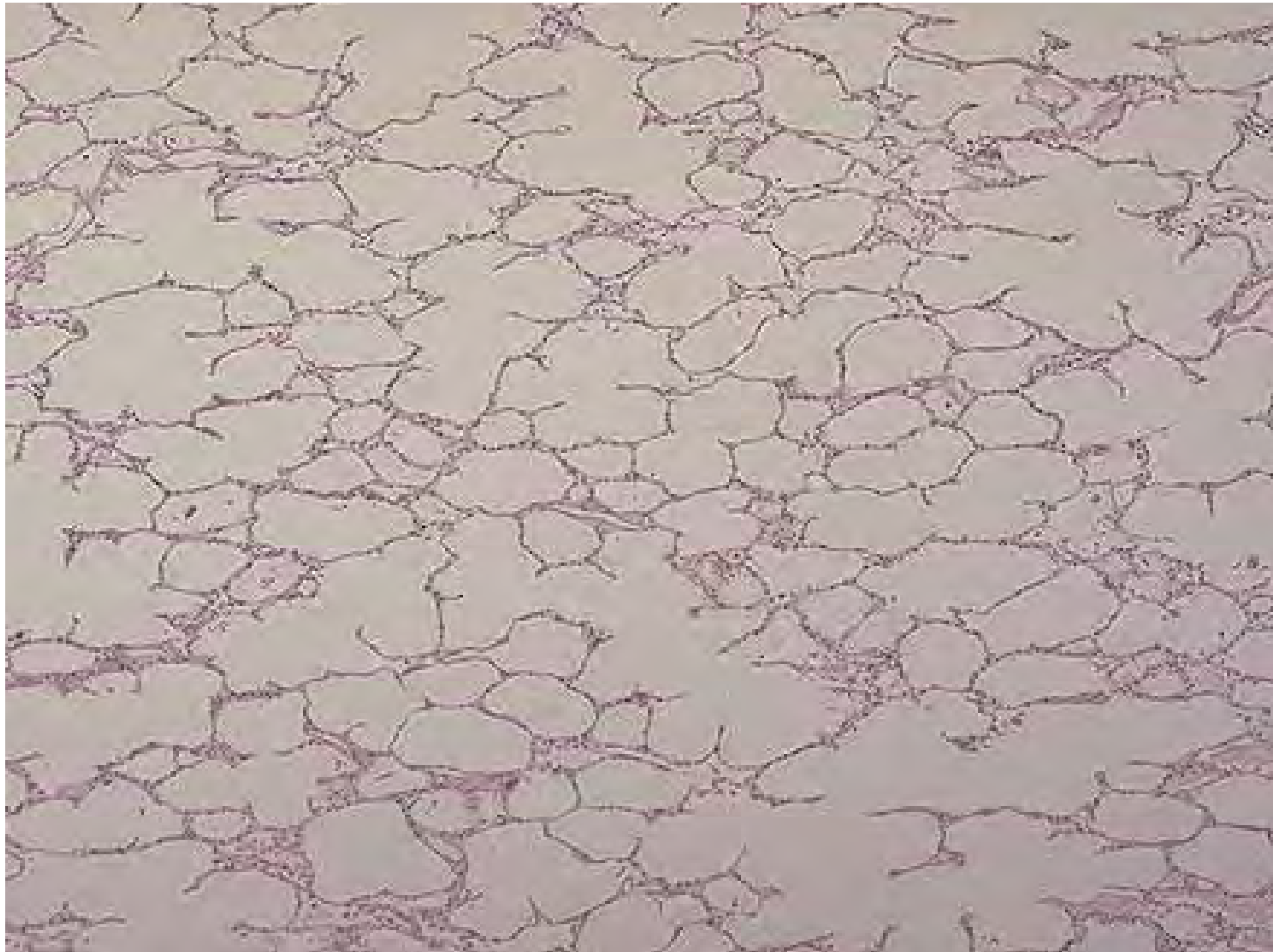
Variable

CVF 55 %

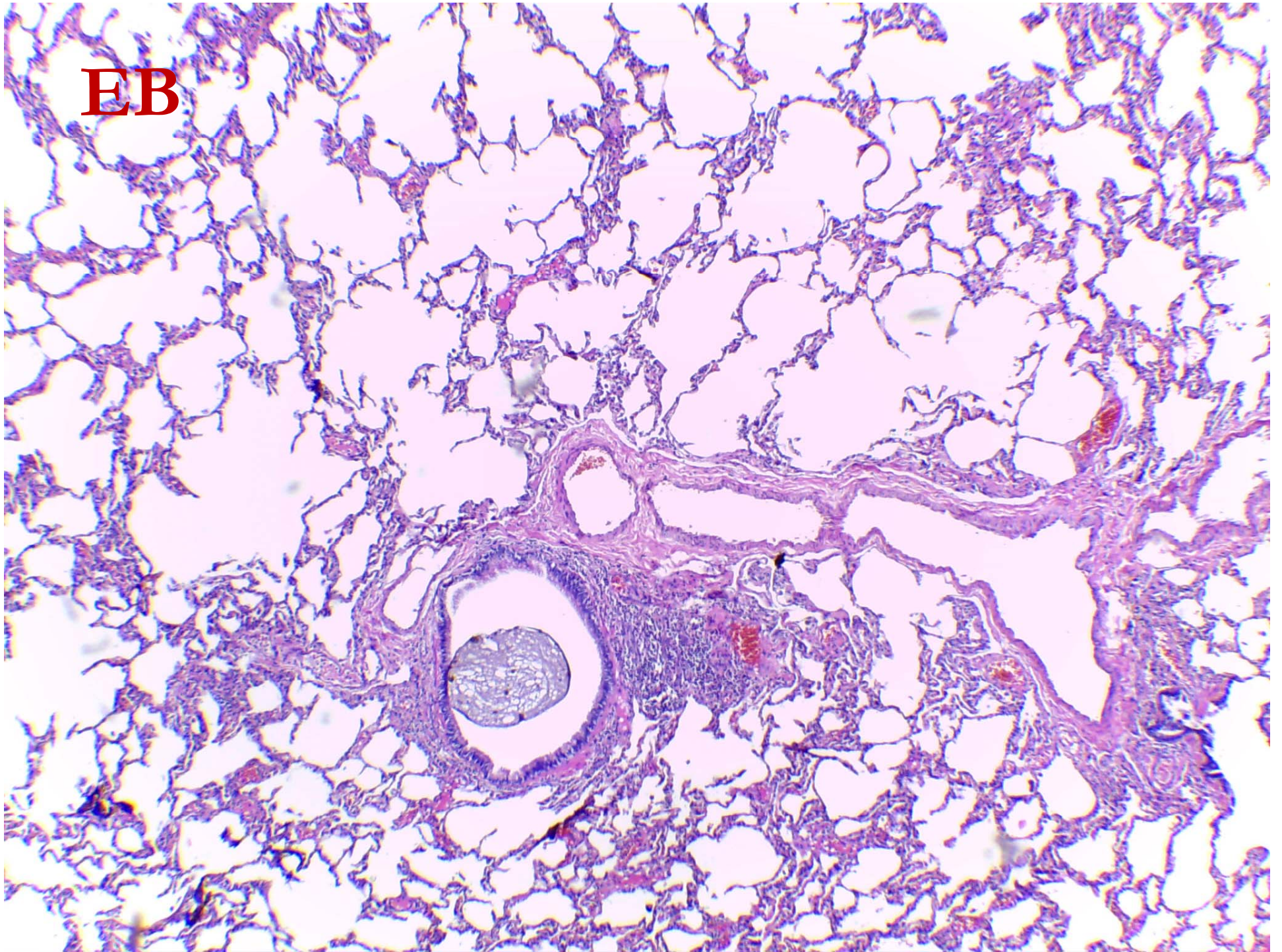
VEF₁ 42 %

VEF₁/CVF 68

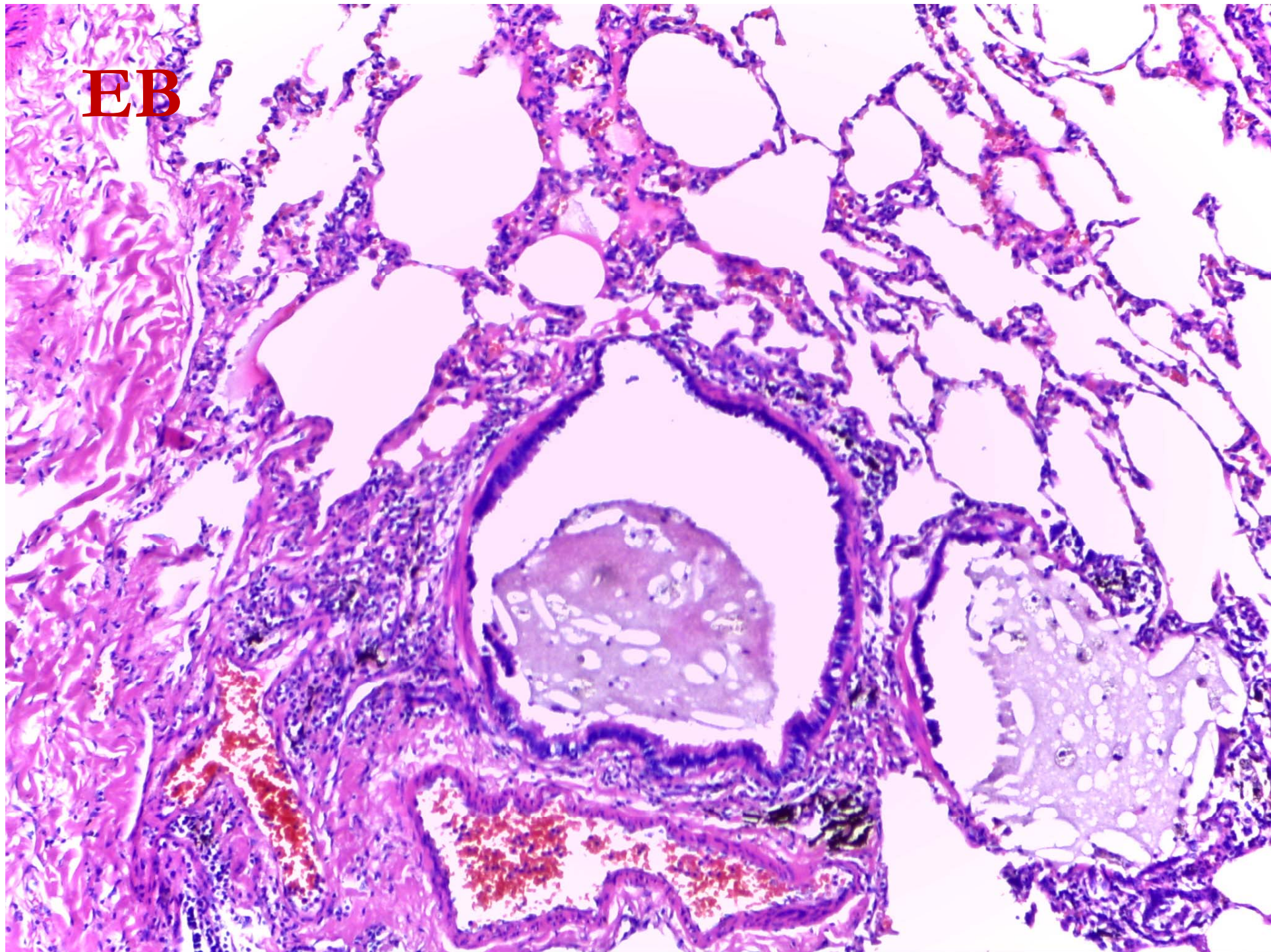
FEF₂₅₋₇₅ 21 %



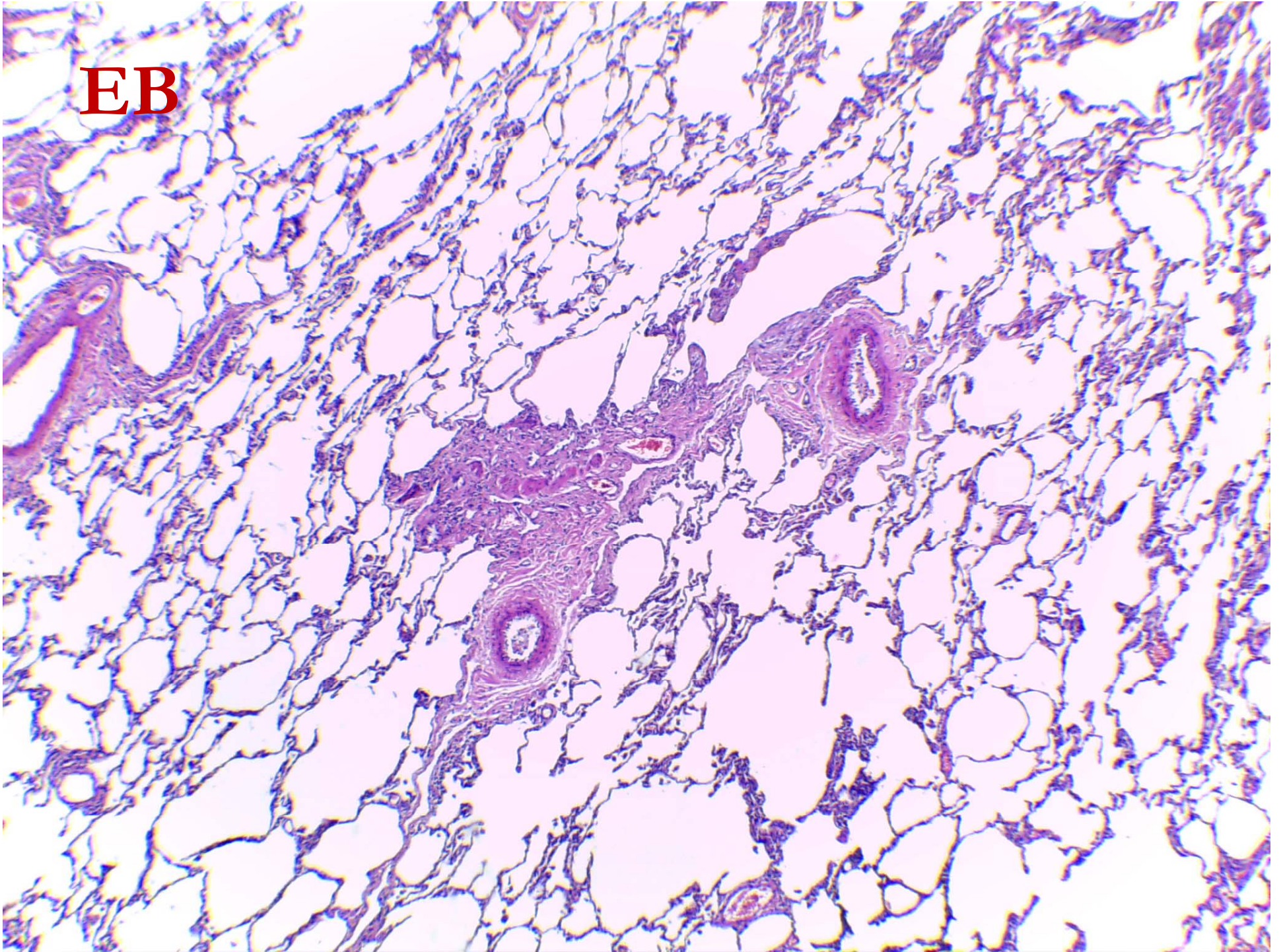
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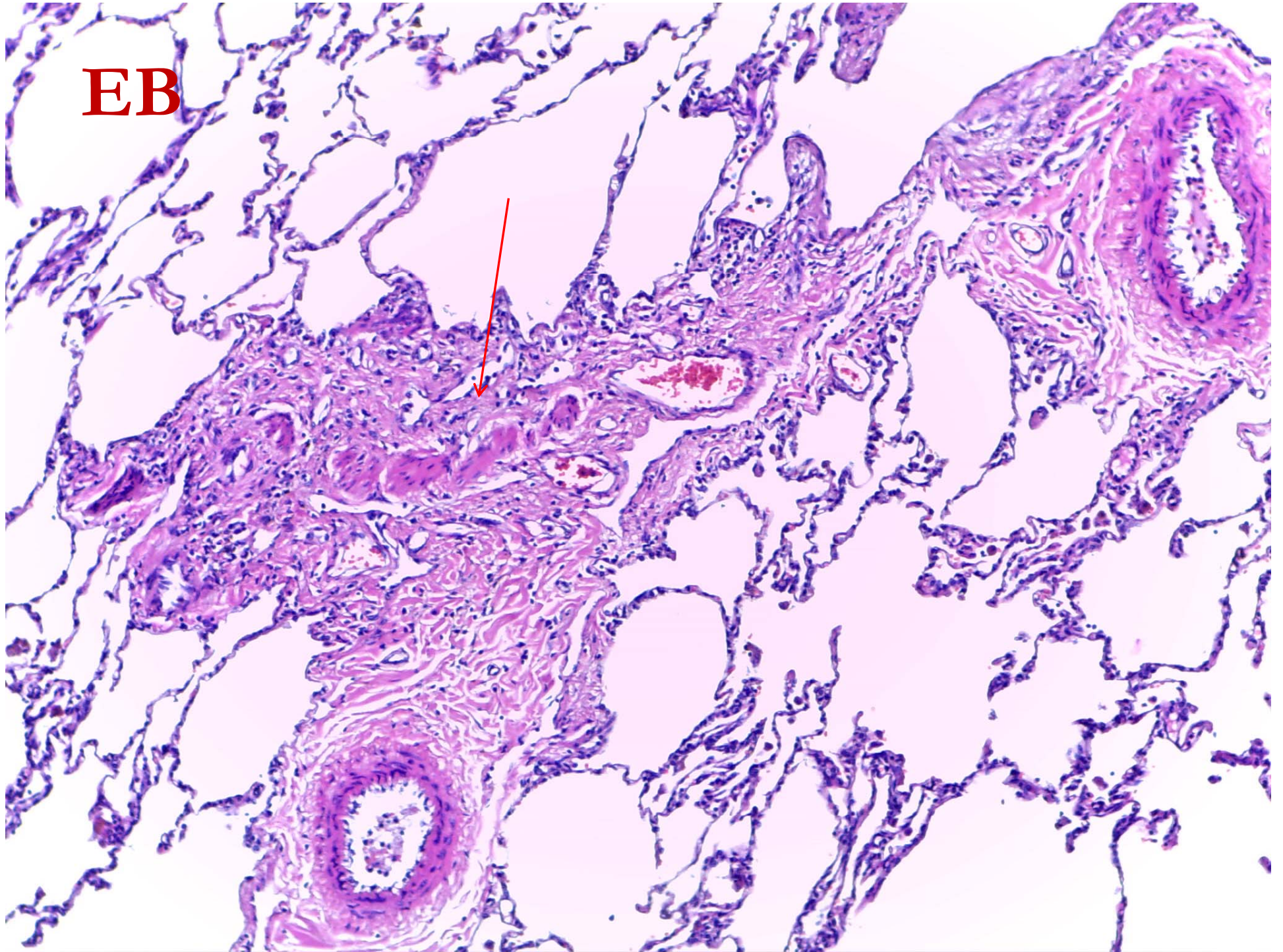
EB



EB



EB



Bronquiolitis Obliterante

Anatomía Patológica

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graph TD; A[Bronquiolitis Obliterante Anatomía Patológica] --> B[Proliferativa]; A --> C[Constrictiva];
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Proliferativa

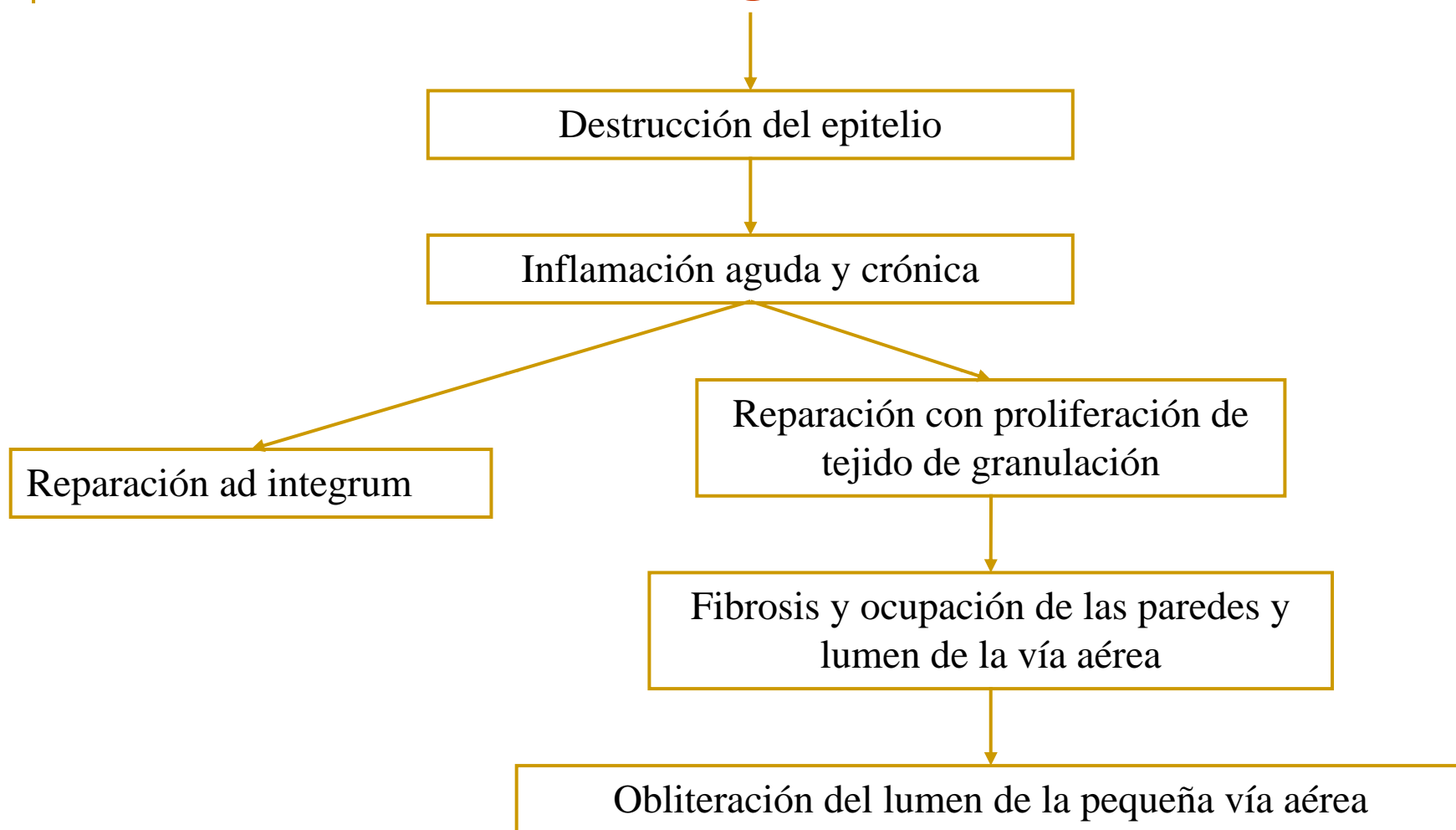
Obstrucción del lumen de la pequeña vía aérea por pólipos constituidos por tejido de granulación.

Constrictiva

Fibrosis peribronquiolar con diferentes grados de estrechamiento del lumen

Como se produjo el daño
pulmonar...

Patogenia



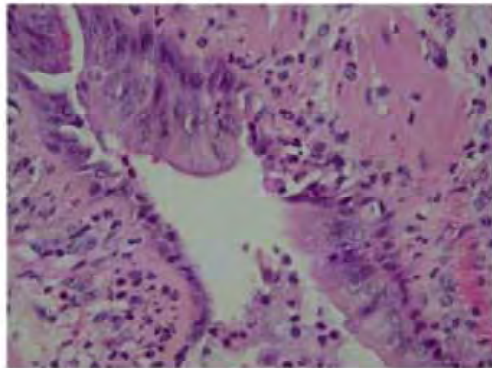
Mechanisms of Airway Obliteration after Lung Transplantation

Laurent P. Nicod

Clinic and Policlinic of Pneumology, Inselspital, Bern, Switzerland

allo-antigen dependent
allo-antigen independent
injury

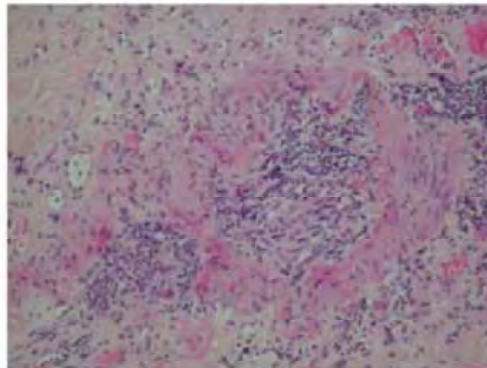
Damage



epithelial cells/
endothelial cells

inflammatory/
infiltrative response

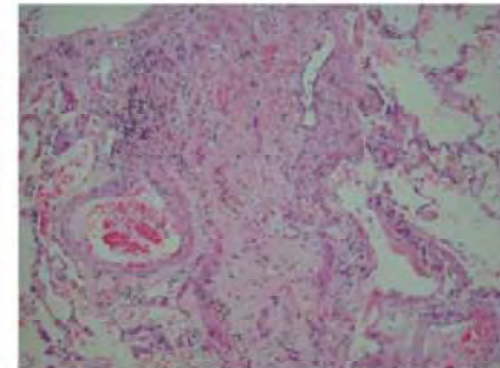
Cellular infiltration



T cells (CD8/CD4)
dendritic cells/ Mo
neutrophils/ eosin.

fibrosis/
bronchiolitis obliterans

*Matrix deposition
Vascular remodeling*



fibroblasts
mesenchymal cells
endothelial cells

Mediators: Cytokines: IL-2; TNF α -b; IFN γ ; IL-12; IL-6
chemokines: IL-8; Rantes; MCP-1; ...
prostaglandines; leukotrienes; endothelin
reactive oxygen metabolites (H₂O₂; O₂⁻)
metallo-proteinases

Growth factors:
CXCR2-ligands; PDGF;
IGF; FGF; TGF β ;
endothelin

Acute Inflammatory Response and Remodeling of Airway Epithelium After Subspecies B1 Human Adenovirus Infection of the Mouse Lower Respiratory Tract

Adriana E. Kajon, Andrew P. Gigliotti, and Kevin S. Harrod*

Lovelace Respiratory Research Institute, Albuquerque, New Mexico

Our findings indicate that Ad3 and Ad7 of subspecies B1, represented in our experiments by the prototype strain GB of serotype 3 (Ad3p) and by the field strain 87–922 corresponding to genome type 7h, do not replicate in the mouse but induce lung disease with a distinct inflammatory infiltrate, lung epithelial injury, and mucous cell metaplasia. Expression of putative immunoregulatory genes encoded in the E3 region of these viruses was detected in infected lungs indicating the feasibility of in vivo studies of the role of early gene products unique to species B adenoviruses in the pathogenesis of respiratory disease. These studies

Dra Alicia S. Mistchenko y cols.

Participation of immune complexes in adenovirus infection

Demuestra la circulación de *inmunocomplejos* conteniendo antígenos de adenovirus, en pacientes con infección de la vía aérea baja que presentan diferente evolución.

Acta Paediatr 81: 983-8. 1992

Cytokines in adenoviral disease in children: Association of interleukin 6, interleukin-8, and tumor necrosis factor alpha levels with clinical outcome

La presencia de *IL-6*, *IL-8*, y *TNF- α* se asocia en forma significativa con infecciones severas y fatales por adenovirus.

J Pediatr 1994;124:714-20.

Lymphocyte subsets and cytokines in adenoviral infection in children

La relación entre el recuento total de linfocitos, linfocitos T, CD4 β , CD8 β y células NK y la severidad se asocia en forma lineal y negativa.

Acta Paediatr 87: 933-9. 1998

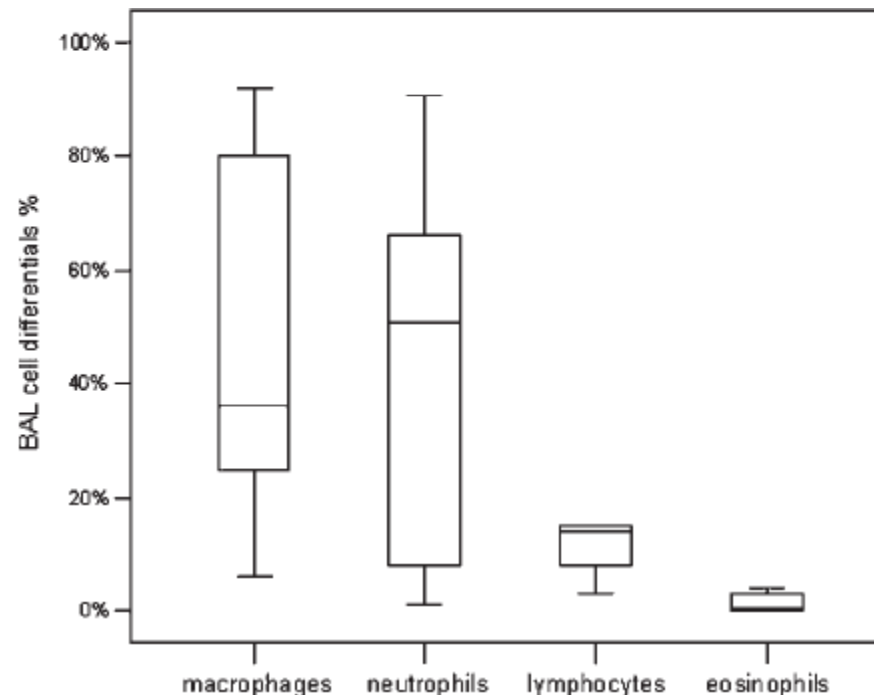
Bronchoalveolar Cellularity and Interleukin-8 Levels in Measles Bronchiolitis Obliterans*

Young Yull Koh, MD; Da Eun Jung, MD; Ji Yeon Koh, MD; Jung Yeon Kim, MD; Young Yoo, MD; and Chang Keun Kim, MD

Characteristics	Measles BO (n = 12)	Control (n = 10)
<u>Total cells</u> , 10 ⁴ /mL	38.5† (18.2–159.0)	15.6 (7.9–18.1)
Macrophages, %	71.0† (40.8–84.3)	85.0 (81.5–89.0)
Lymphocytes, %	4.0 (1.0–10.0)	7.5 (5.0–10.8)
<u>Neutrophils</u> , %	16.0‡ (4.3–56.5)	2.3 (1.0–3.9)
Eosinophils, %	0.0 (0.0–0.8)	0.0 (0.0–0.1)
Epithelial cells	3.5 (2.3–4.2)	3.2 (1.7–9.9)
Lymphocyte subsets		
CD3+, %	88.0 (84.0–91.8)	82.0 (78.0–88.5)
CD4+, %	23.3 (23.0–34.0)	28.0 (28.0–34.0)
<u>CD8+</u> , %	62.0‡ (55.0–65.0)	46.0 (38.8–50.5)
<u>CD4/CD8</u> ratio	0.41‡ (0.36–0.55)	0.65 (0.57–0.79)

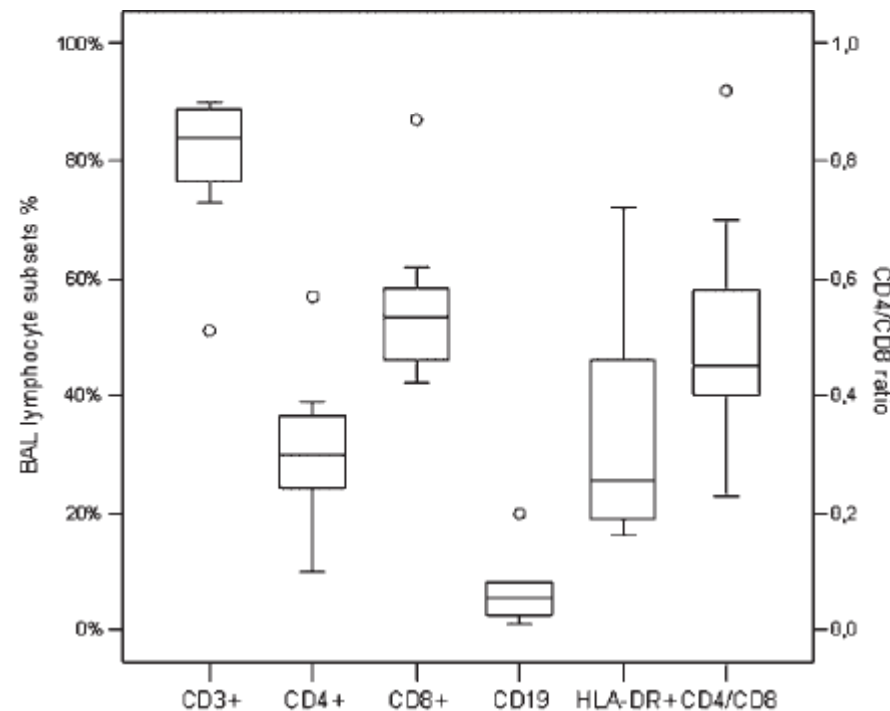
Airway Inflammation and Lung Function Decline in Childhood Post-Infectious Bronchiolitis Obliterans

Salvatore Cazzato, MD, PhD,^{1*} Venerino Poletti, MD,² Filippo Bernardi, MD,¹
Leonardo Laroni, MD,³ Luca Bertelli, MD,¹ Stefano Colonna, MD,¹ Franco Zappulla, MD,¹
Giuseppe Timoncini, MD,⁴ and Alessandro Cicognani, MD¹



Airway Inflammation and Lung Function Decline in Childhood Post-Infectious Bronchiolitis Obliterans

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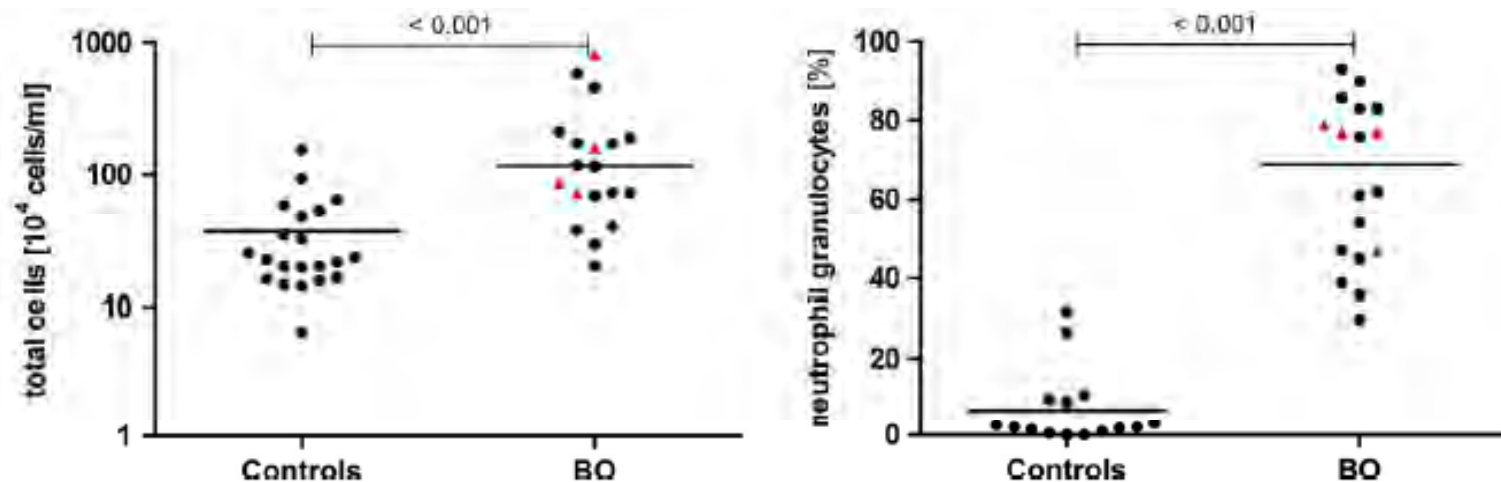
Airway inflammation in children and adolescents with bronchiolitis obliterans

Martin Rosewich^{a,*}, Ulrich M. Zissler^b, Tanja Kheiri^a, Sandra Voss^a, Olaf Eickmeier^a, Johannes Schulze^a, Eva Herrmann^c, Ruth Pia Dücker^a, Ralf Schubert^a, Stefan Zielen^a

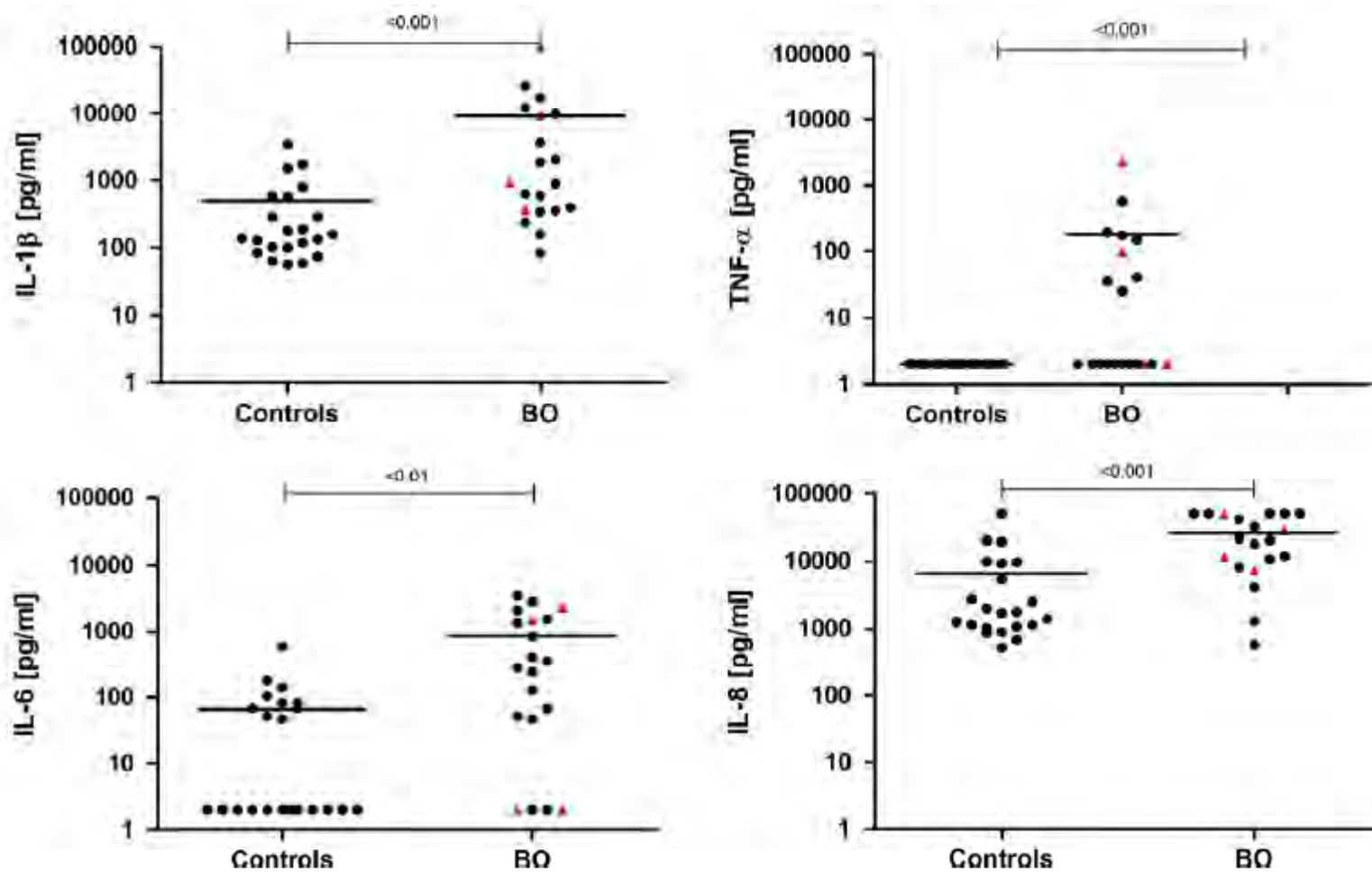
^a Department of Paediatric Pulmonology, Allergy and Cystic Fibrosis, Children's Hospital, Goethe-University, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany

^b Center of Allergy and Environment (ZAUM), Technical University and Helmholtz Center Munich, Germany

^c Institute of Biostatistics and Mathematical Modelling, Goethe-University, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany



Airway inflammation in children and adolescents with bronchiolitis obliterans





Risk factors for the development of bronchiolitis obliterans in children with bronchiolitis

Table 2 Multivariate logistic regression analysis of risk factors for BO

Variable	OR	95% CI	p value
Age (<6 v ≥6 months)	1.4	0.4 to 5.4	0.6
Sex (male v female)	0.8	0.2 to 2.6	0.7
ETS at present	1.4	0.4 to 4.5	0.5
ETS during pregnancy	0.4	0.1 to 3.2	0.4
Adenovirus infection	49	12 to 199	<0.001
Mechanical ventilation	11	2.6 to 45	0.001

ETS, environmental tobacco smoke.



Como podríamos evitar el
daño pulmonar...

¿ Que utilizar y cuando ?



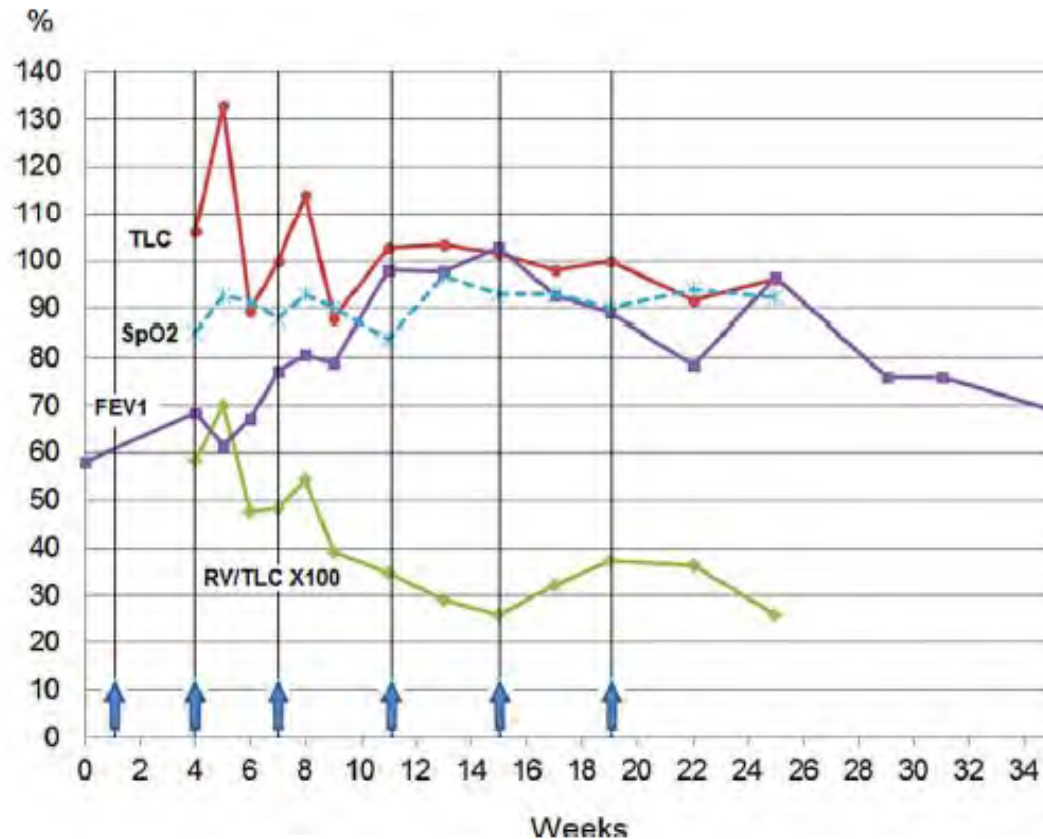
POSIBLES TRATAMIENTOS

1. Corticoides



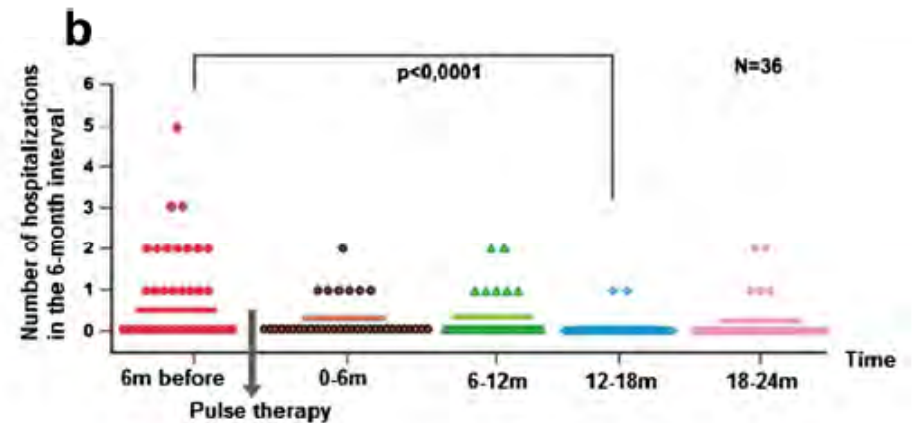
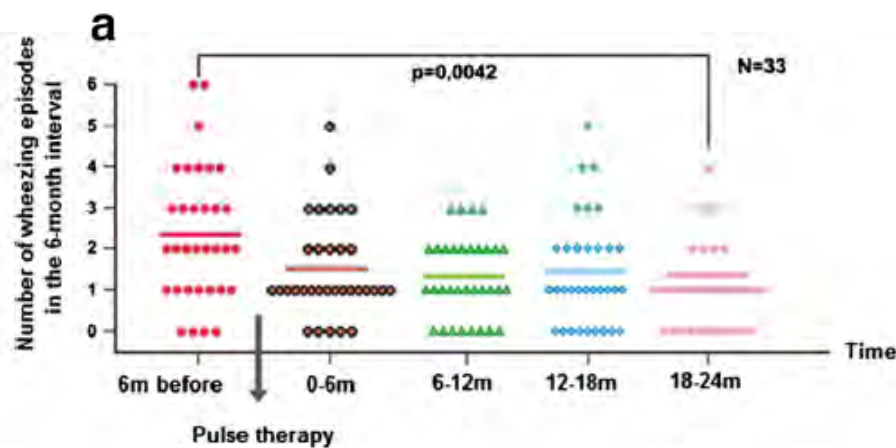
Efficacy of Pulse Methylprednisolone in a Pediatric Case of Postinfectious Bronchiolitis Obliterans

Kalliopi Tanou, MD, Athina Xaidara, MD, and Athanasios G. Kaditis, MD*



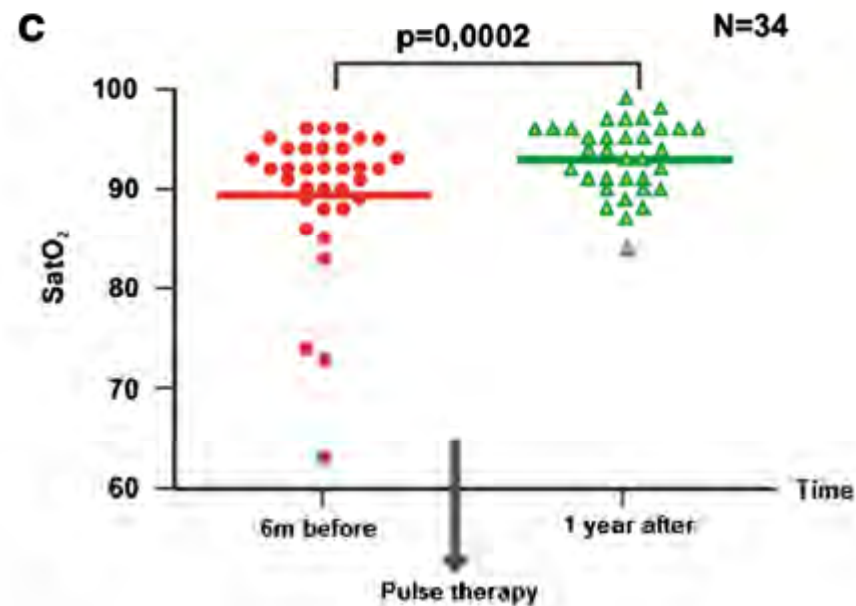
Follow-up on pediatric patients with bronchiolitis obliterans treated with corticosteroid pulse therapy

Silvia Onoda Tomikawa^{1,3*}, Fabíola Villac Adde¹, Luiz Vicente Ribeiro Ferreira da Silva Filho¹, Claudio Leone² and Joaquim Carlos Rodrigues¹



Follow-up on pediatric patients with bronchiolitis obliterans treated with corticosteroid pulse therapy

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Tratamiento con Metilprednisolona

Evolución	Pre TTO			Pos TTO		
	Sao ₂	FR	Pulsos	Sao ₂	FR	
1	3	90 %	45	6	90 %	40
2	1	93 %	40	6	94 %	36
3	4	90 %	40	4	90 %	32
4	1	89 %	36	2	90%	40
5	1	90 %	60	1	90%	60
6	5	90%	50	1	91%	50

POSIBLES TRATAMIENTOS

1. Corticoides



POSIBLES TRATAMIENTOS

1. Corticoides
2. Macrólidos



Macrólidos
Efectos antiinflamatorios
in vitro

a. Liberación de citocinas y quimiocinas

Supresión de IL-1B y TNF en monocitos
IL-1B, IL-6, TNF α y GM-CSF en células cebadas
IL-8, ENA-78 y MIP-1 en macrófagos y leucocitos.
Inhibición de eotaxina, GM-CSF

Expresión de moléculas de adhesión

< e-selectina
< ICAM1 y SICAM-1
Dism. β -2 integrinas (CD11b*/CD18)
Disminución de VCAM 1
Disminución de función de linfocitos asociada a LAF3.

PMN

Inhibición de elastasa de neutrófilos
Inhibición de aniones superóxido
Est. desgranulación de PMN
Incremento de AMPc en PMN acelerando su apoptosis
Promueven fagocitosis de PMN por los macrófagos

Células T

Inhibición de IL-4 e IL-5
dosis dependiente

Clinical features of post-infectious bronchiolitis obliterans in children undergoing long-term azithromycin treatment

XUEYAN WANG¹, CHANGSHAN LIU¹, MENGJUAN WANG¹, YI ZHANG¹, HEWEN LI² and GELI LIU³

Departments of ¹Pediatrics and ²Radiology, The Second Hospital of Tianjin Medical University, Heping, Tianjin 300211;

³Department of Pediatrics, The General Hospital of Tianjin Medical University, Heping, Tianjin 300052, P.R. China

Patient	Age (month)	Gender	Predisposing factors	Diagnostic method	Treatment		Hospital stay (days)	Disease course (months)	Outcomes
					Steroid	Azithromycin			
1	24	M	<i>Mycoplasma pneumoniae</i>	HRCT	+	+	39	20	Exacerbation
2	12	M	<i>Mycoplasma pneumoniae</i>	HRCT	+	+	33	17	No improvement
3	7	M	Adenovirus	HRCT	+	+	54	13	Improved
4	7	M	Adenovirus	HRCT	+	+	57	13	Improved
5	3	M	Adenovirus	HRCT	+	+	22	13	Improved
6	5	M	Unknown	HRCT	+	+	26	14	Improved
7	36	M	<i>Mycoplasma pneumoniae</i>	HRCT	+	+	23	10	No improvement
8	24	M	Epstein-Barr virus	HRCT	+	+	19	7	Improved
9	51	F	<i>Mycoplasma pneumoniae</i>	HRCT	+	+	16	26	Improved
10	30	F	<i>Mycoplasma pneumoniae</i>	HRCT	+	+	15	12	Improved
11	10	M	Adenovirus	HRCT	+	+	28	18	No improvement
12	72	F	<i>Mycoplasma pneumoniae</i>	HRCT	+	+	20	22	Improved
13	8	M	Unknown	HRCT	+	+	21	12	Improved
14	16	M	Adenovirus	HRCT	+	+	23	18	No improvement
15	5	M	Adenovirus	HRCT	+	+	30	31	Exacerbation
16	13	M	Unknown	HRCT	+	+	26	19	Improved

M, male; F, female; HRCT, high-resolution computed tomography.

Efecto de la Azitromicina en la función pulmonar y exacerbaciones en pacientes con bronquiolitis obliterante postinfecciosa

Castaños, C; Salim, M; Pereyra, C; Aguerre, V; Lucero, B; Bauer, G; Zylbersztajn, B; Lelivedl L; Gonzalez Pena,H.

Servicio de Neumonología Hospital de Pediatría "Juan P. Garrahan". Buenos Aires, Argentina.

		Azithromycin	P Value*	Placebo	P Value*
		n 12		n 9	
Relative Change %	>	9	0,004	6	0,08
CVF	<	0		2	
1m – 6m	=	3		1	
Relative Change %	>	7	0,20	3	0,85
VEF1	<	4		3	
1m – 6m	=	1		3	
		n 12		n 6	
Relative Change %	>	9	0,07	3	0,40
CPT	<	2		3	
1m - 6m	=	1			
Relative Change %	>	6	0,93	5	0,07
VR	<	6		1	
1m - 6m	=				

POSIBLES TRATAMIENTOS

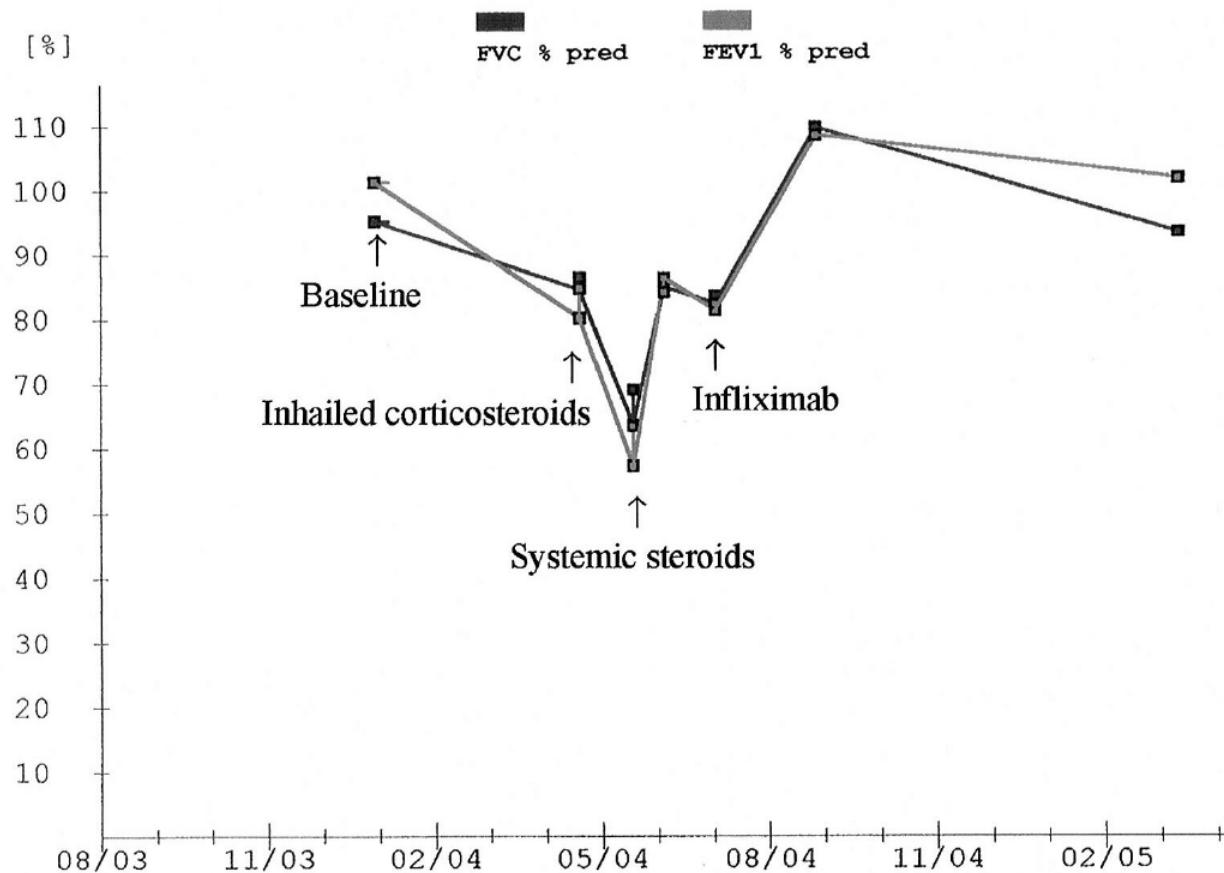
1. Corticoides
 2. Macrólidos
-

POSIBLES TRATAMIENTOS

1. Corticoides
 2. Macrólidos
 3. Anti - FNT- α
-

Successful Treatment of Bronchiolitis Obliterans in a Bone Marrow Transplant Patient With Tumor Necrosis Factor- α Blockade

Jason J. Fullmer, MD*; Leland L. Fan, MD*; Megan K. Dishop, MD‡; Cheryl Rodgers, RNPS; and Robert Krance, MD§



POSIBLES TRATAMIENTOS

1. Corticoides
 2. Macrólidos
 3. Anti - FNT- α
-

POSIBLES TRATAMIENTOS

1. Corticoides
 2. Macrólidos
 3. Anti - FNT- α
 4. Otras medicaciones...
-

Cuando medicar ???

Post-infectious bronchiolitis obliterans in children: CT features that predict responsiveness to pulse methylprednisolone

¹H M YOON, MD, ¹J S LEE, MD, ²J-Y HWANG, MD, ¹Y A CHO, MD, ¹H-K YOON, MD, ³J YU, MD, ³S-J HONG, MD and ¹C H YOON, MD

Objective: Intravenous pulse methylprednisolone therapy (IPMT) is an important treatment option for post-infectious obliterative bronchiolitis (OB), although it must be used carefully and only in selected patients because of its drawbacks. This study evaluated whether CT and clinical features of children with post-infectious OB can predict their responsiveness to IPMT.

Methods: We searched the medical records for patients (less than 18 years of age) who were diagnosed with post-infectious OB between January 2000 and December 2011. 17 children who received IPMT were included in this study. All underwent chest CT before and after IPMT. The radiological features seen on pre-treatment CT were recorded. The air-trapping area percentages on pre- and post-treatment CT images were determined. The nine patients who exhibited decreased air trapping on post-treatment CT scans relative to

pre-treatment scans were classed as responders. The patient ages and time from initial pneumonia to IPMT were recorded.

Results: All responders and only four non-responders had thickened bronchial walls before treatment ($p = 0.029$). The two groups did not differ significantly in terms of bronchiolitis, bronchiectasis or the extent of air trapping, although the responders had a significantly shorter median interval between initial pneumonia and IPMT (4 vs 50 months; $p = 0.005$) and were significantly younger (median, 2.0 vs 7.5 years; $p = 0.048$).

Conclusion: Immediate IPMT may improve the degree of air trapping in children with post-infectious OB if they show a thickened bronchial wall on CT.

Advances in knowledge: Children with post-infectious OB may respond favourably to IPMT when pre-treatment CT indicates bronchial-wall thickening.

Post-infectious bronchiolitis obliterans in children: CT features that predict responsiveness to pulse methylprednisolone

¹H M YOON, MD, ¹J S LEE, MD, ²J-Y HWANG, MD, ¹Y A CHO, MD, ¹H-K YOON, MD, ³J YU, MD, ³S-J HONG, MD and ¹C H YOON, MD

Table 1. Clinical and radiological features of 17 patients with post-infectious obliterative bronchiolitis

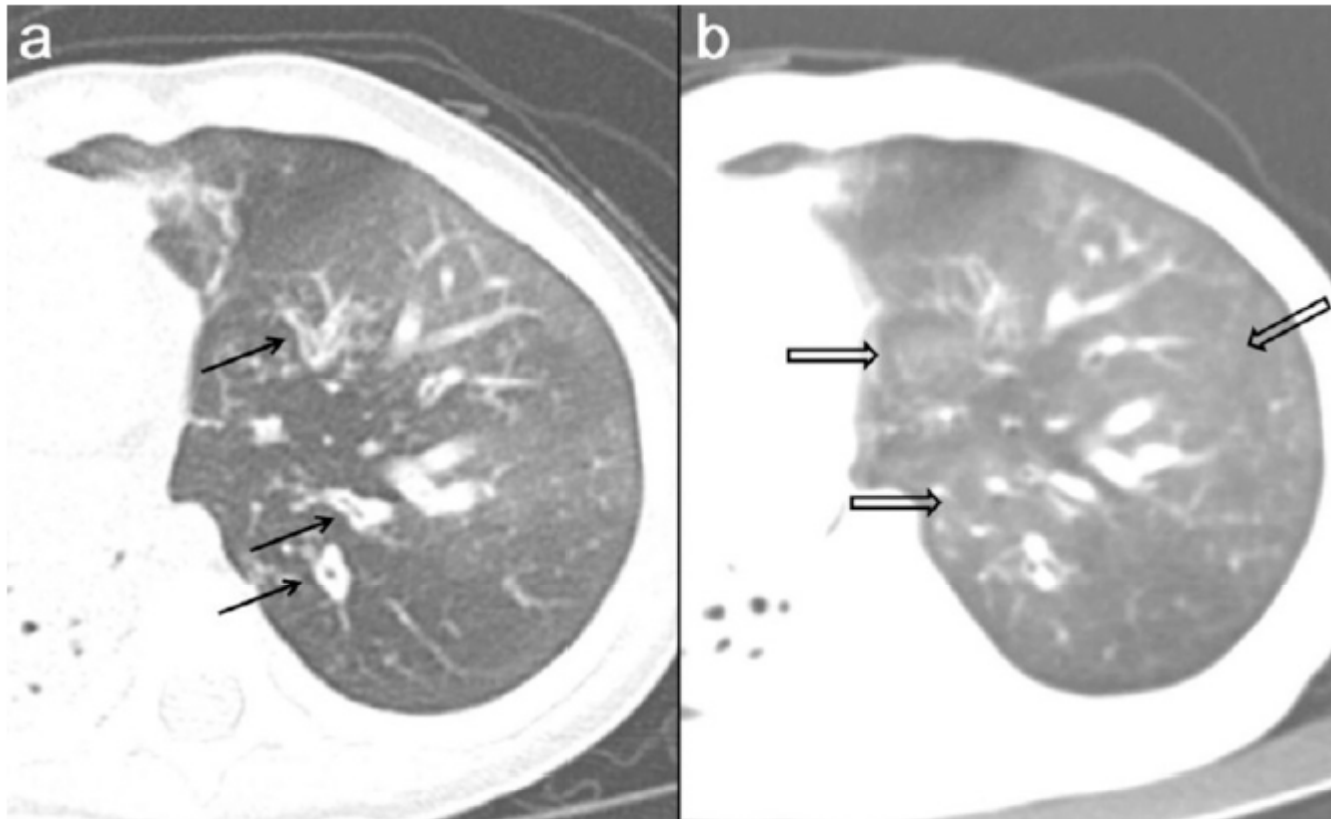
Clinical and radiological features	Responder	Non-responder	<i>p</i> -value
Bronchial wall thickening	9 (100%)	4 (50%)	<0.05
Inflammatory bronchiolitis	6 (66.7%)	2 (25%)	>0.05
Bronchiectasis	6 (66.7%)	3 (37.5%)	>0.05
Mean CT attenuation value (HU)	-868.8 (43.6)	-888.4 (42.0)	>0.05
Interval between the initial pneumonia episode and the start of IPMT (months)	4 (2-7)	50 (31.3-74.8)	<0.05
Interval between post-infectious obliterative bronchiolitis diagnosis and the start of IPMT (months)	1 (1-2)	5.5 (1-14.5)	>0.05
Median patient age at the start of IPMT (years)	2 (1-5)	7.5 (4.5-9.3)	<0.05

IPMT, intravenous methylprednisolone therapy.

The data are expressed as number (%), mean (standard deviation) or months/year (quartiles).

Post-infectious bronchiolitis obliterans in children: CT features that predict responsiveness to pulse methylprednisolone

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BO por inhalación de gases tóxicos

(SO₂, NH₃, NO₂, phosgene)

Exposición a
gases tóxicos

Leve	Sin síntomas		
Moderado	Bronquitis Horas - días	Recuperación Días - horas	
severo	Edema pulmonar (SDRA) 3 – 30 horas	Recuperación Días - semanas	

BO por inhalación de gases tóxicos

(SO₂, NH₃, NO₂, phosgene)

Exposición a
gases tóxicos

Leve	Sin síntomas		BO 2 – 8 semanas
Moderado	Bronquitis Horas - días	Recuperación Días - horas	BO 2 – 8 semanas
severo	Edema pulmonar (SDRA) 3 – 30 horas	Recuperación Días - semanas	BO 2 – 8 semanas

Que podemos esperar a largo
plazo...

Casos nuevos de BO desde 1986

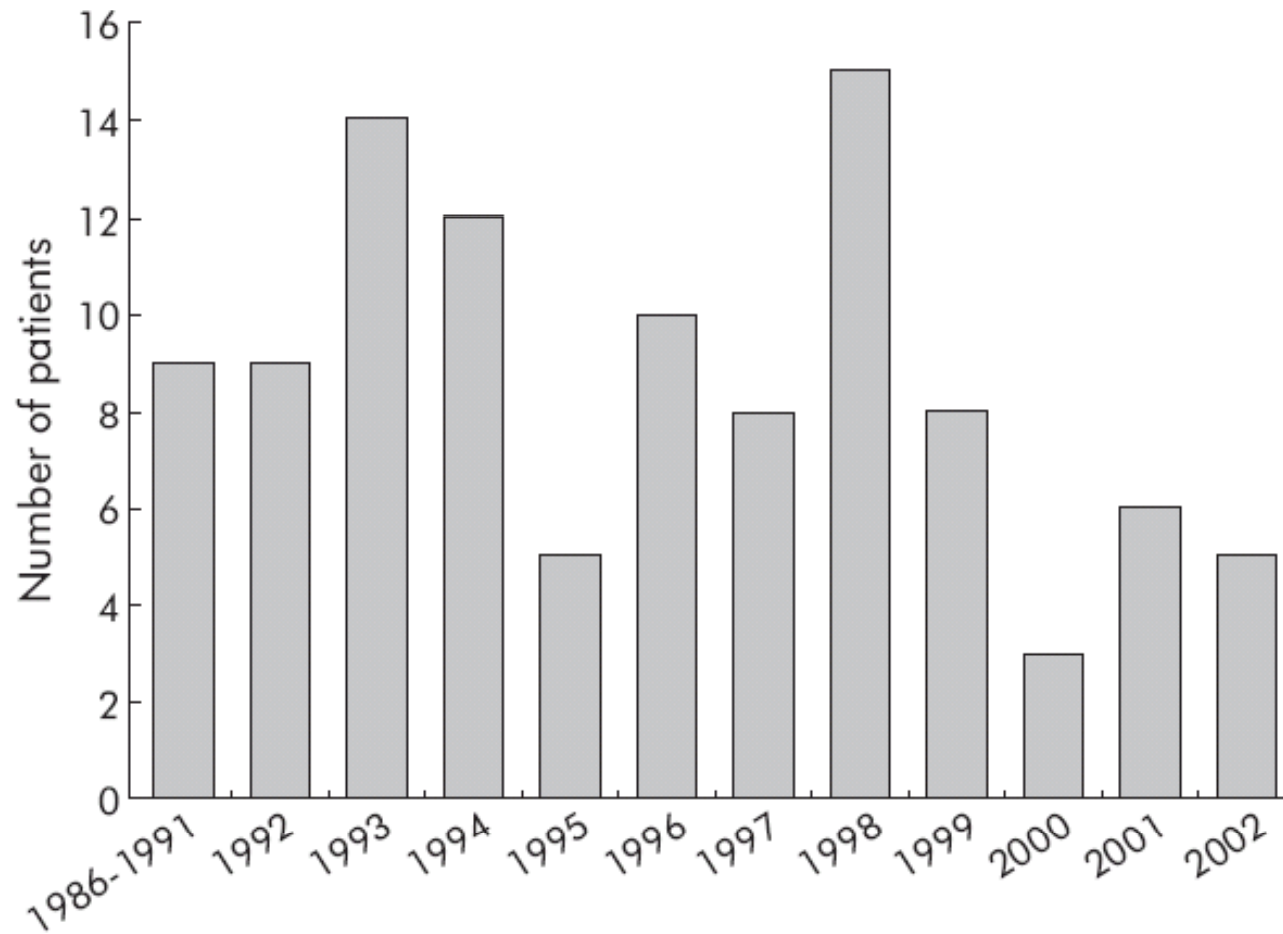


Figure 1 Cases of post-infectious BO by calendar year.

Pulmonary function of a paediatric cohort of patients with postinfectious bronchiolitis obliterans. A long term follow-up

Alejandro J Colom,¹ Alberto Maffey,¹ Facundo Garcia Bournissen,² Alejandro Teper¹

Objetivo

Determinar la evolución de la función pulmonar de niños con BO posinfecciosa.

Población

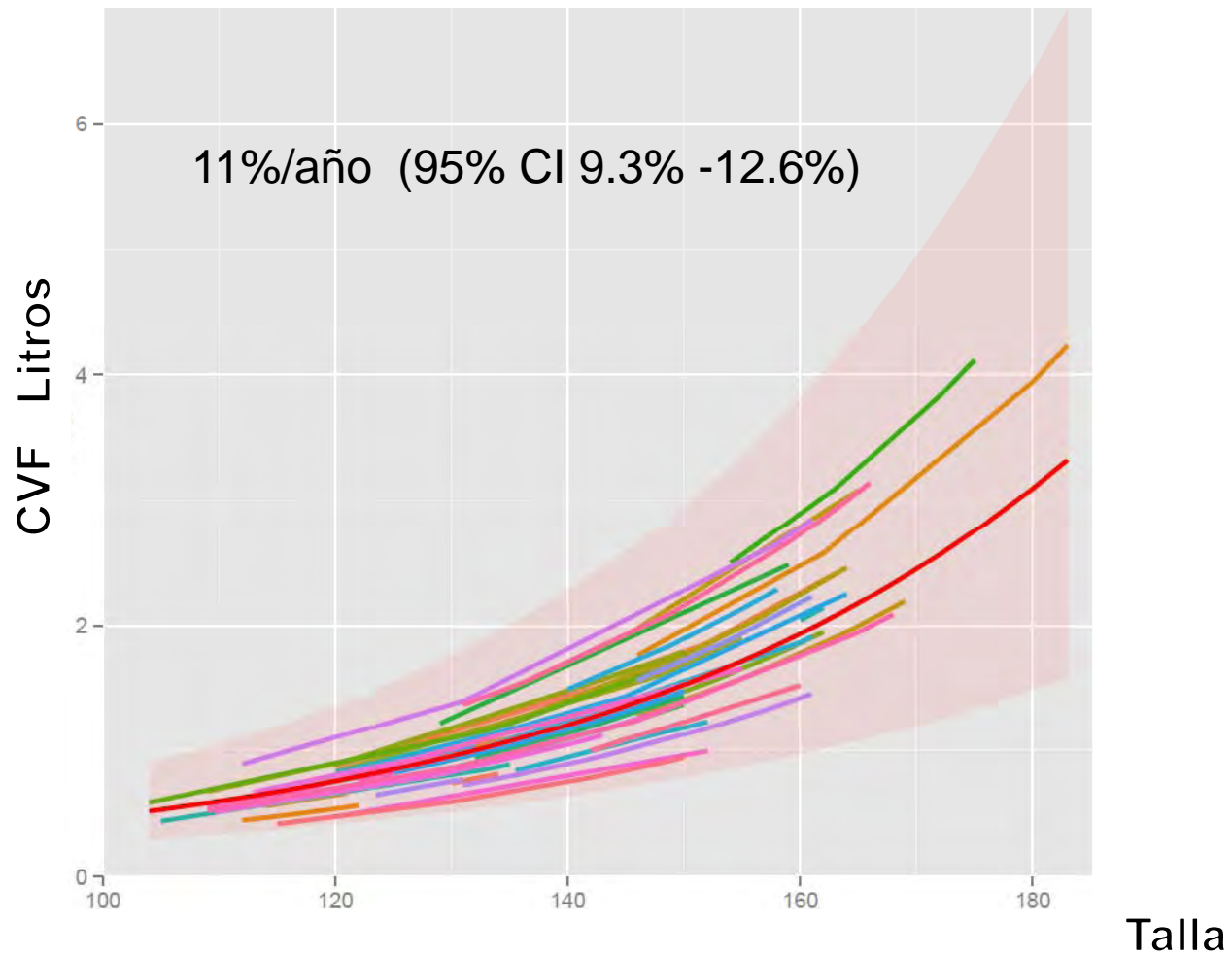
n	46
Edad al ingreso	9±3
Sexo masculino	54%
Años de seguimiento	12.5±3.5
Espirometrías	197
Pletismografías	41

Resultados

Z-score BMI	-0.5 ± 1.3
FVC (%)	55±16
FEV1 (%)	42±13
FEV1/FVC	68±12
FEF25-75 (%)	25±14
TLC (%)	120±26
RV (%)	309±108
RV/TLC	55±13

Resultados

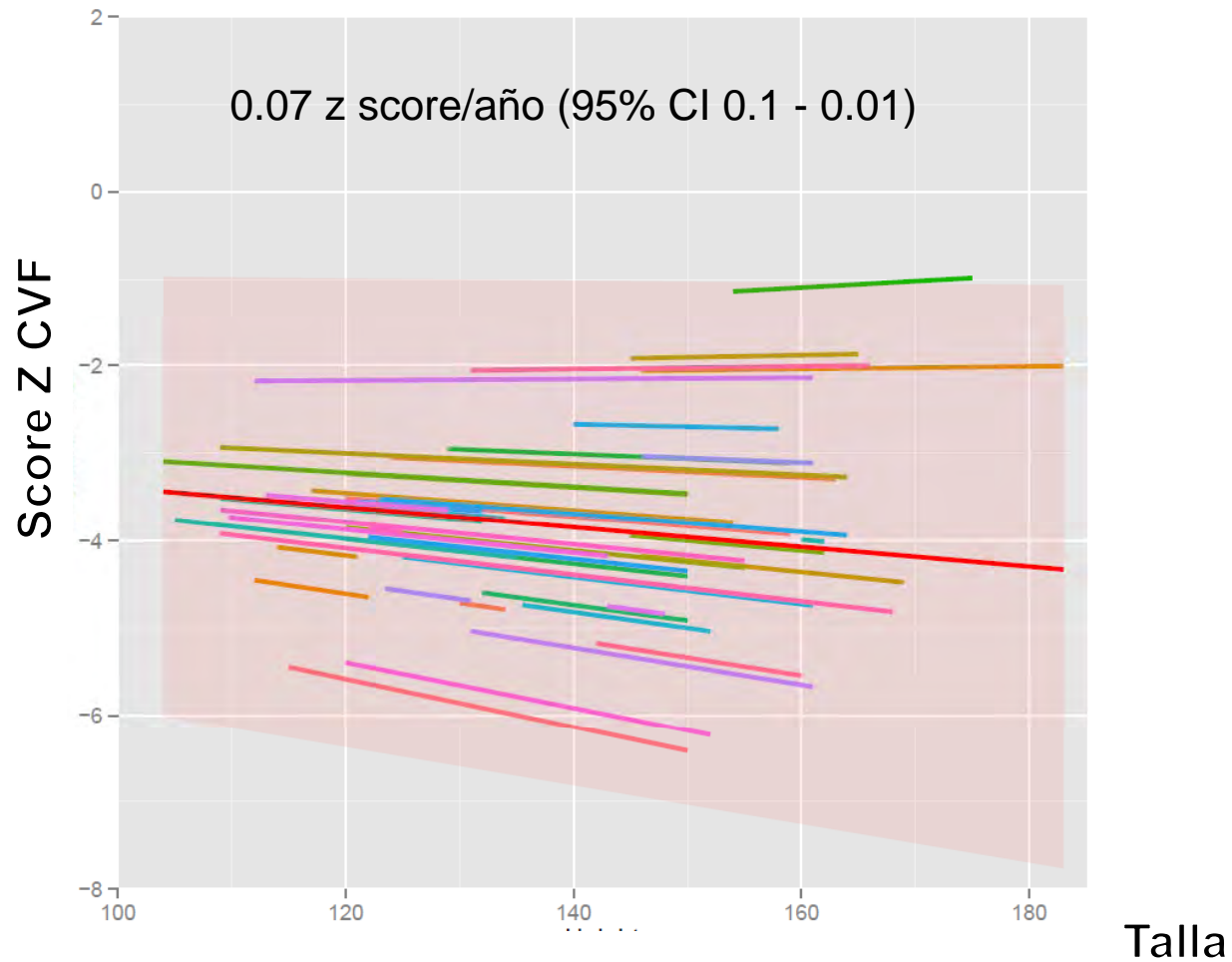
CVF Vs Talla



Colom AJ, et al. Thorax 2015;70:169–174.

Resultados

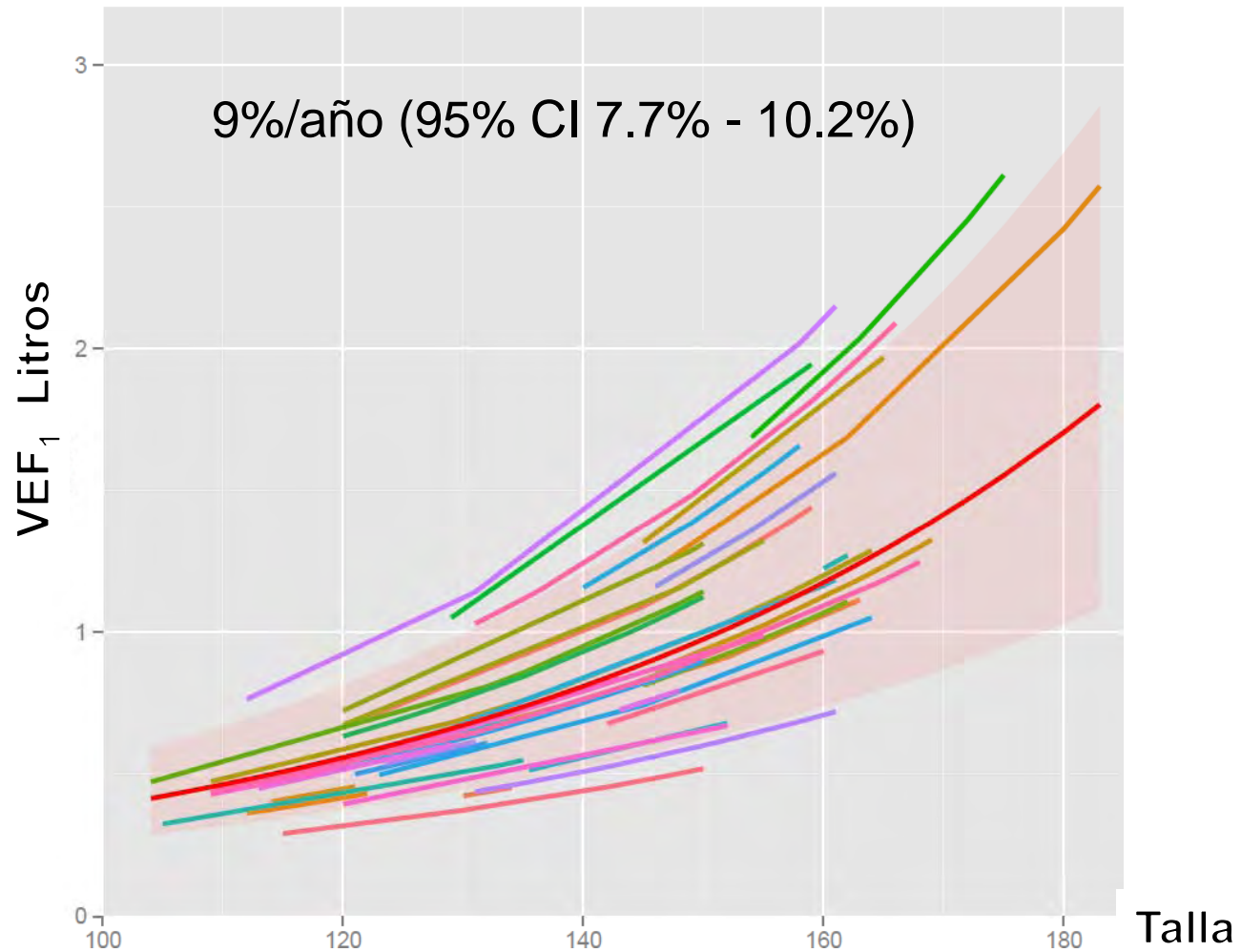
Score Z CVF Vs Talla



Colom AJ, et al. Thorax 2015;70:169–174.

Resultados

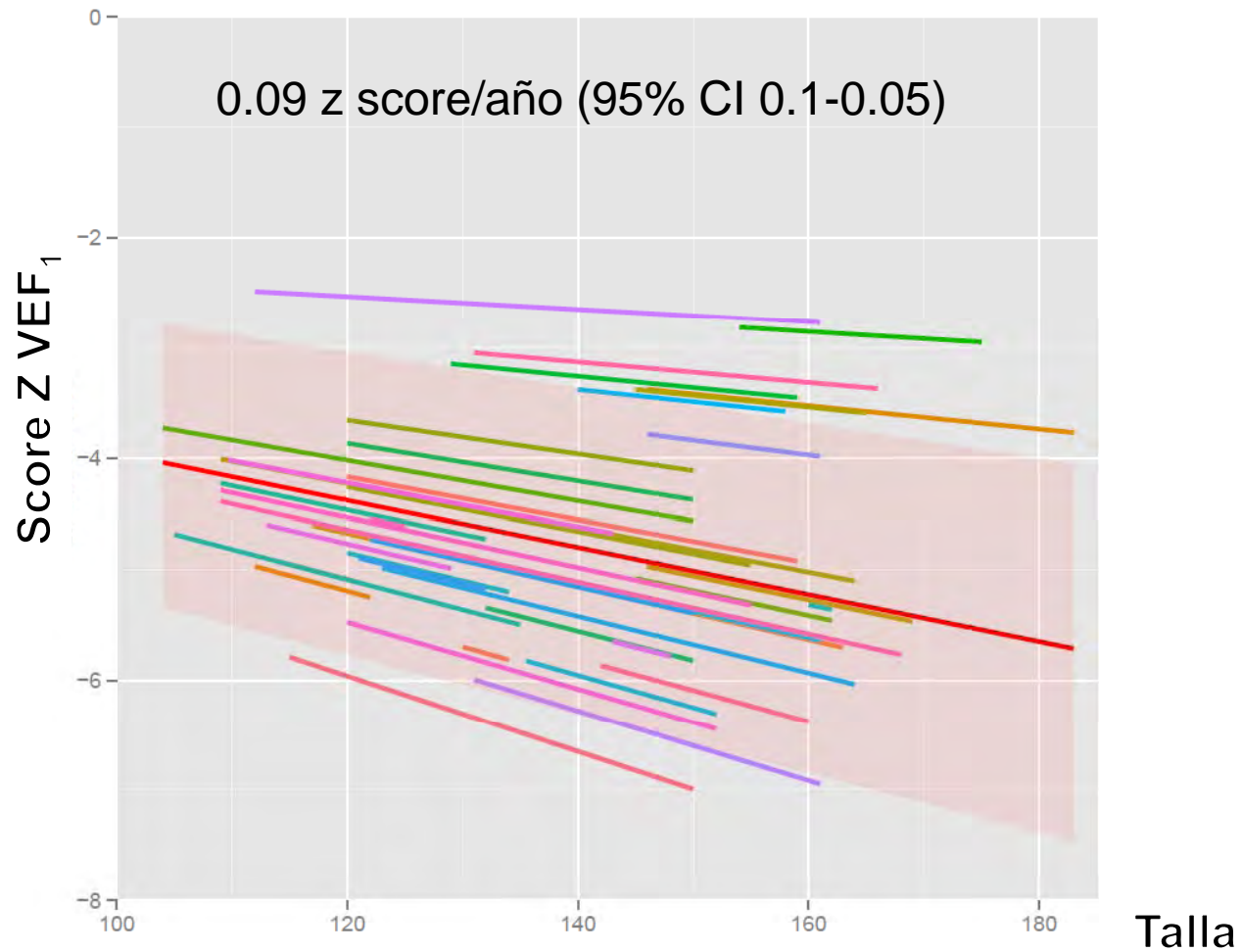
VEF₁ Vs Talla



Colom AJ, et al. Thorax 2015;70:169–174.

Resultados

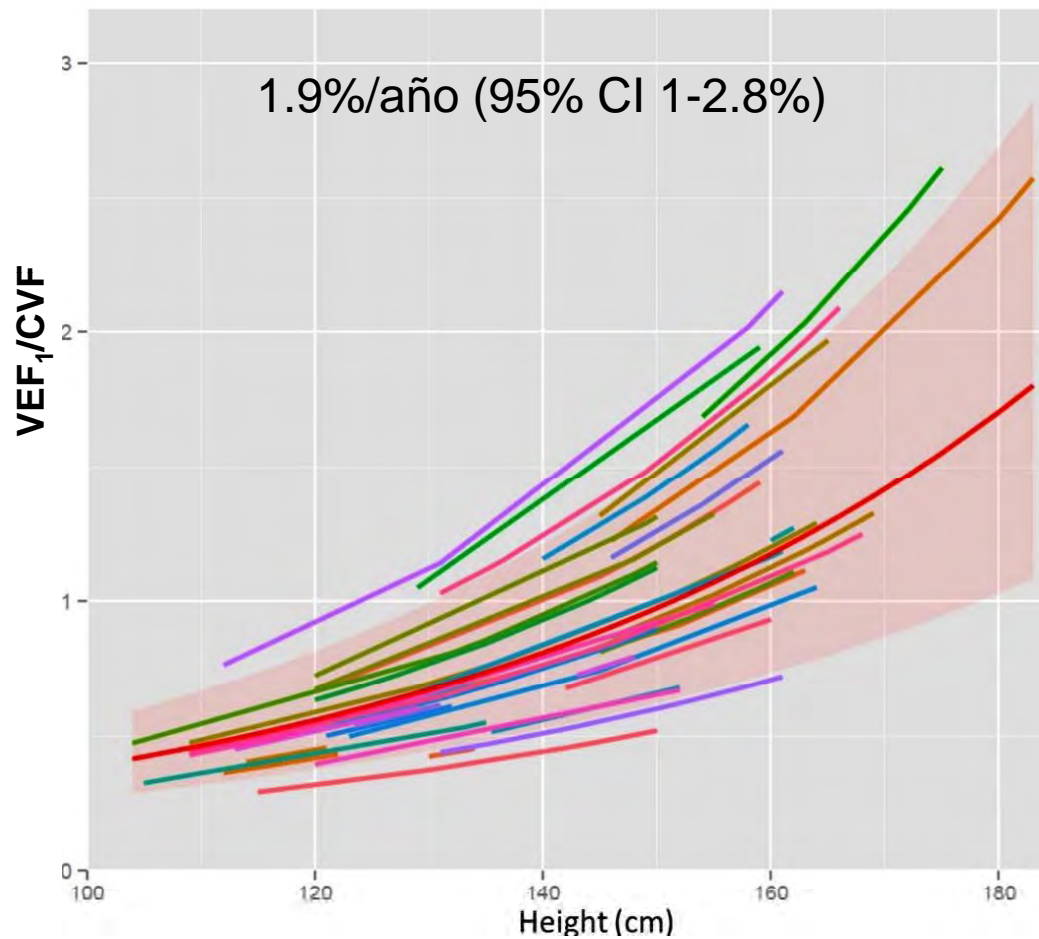
Score Z VEF₁ Vs Talla



Colom AJ, et al. Thorax 2015;70:169–174.

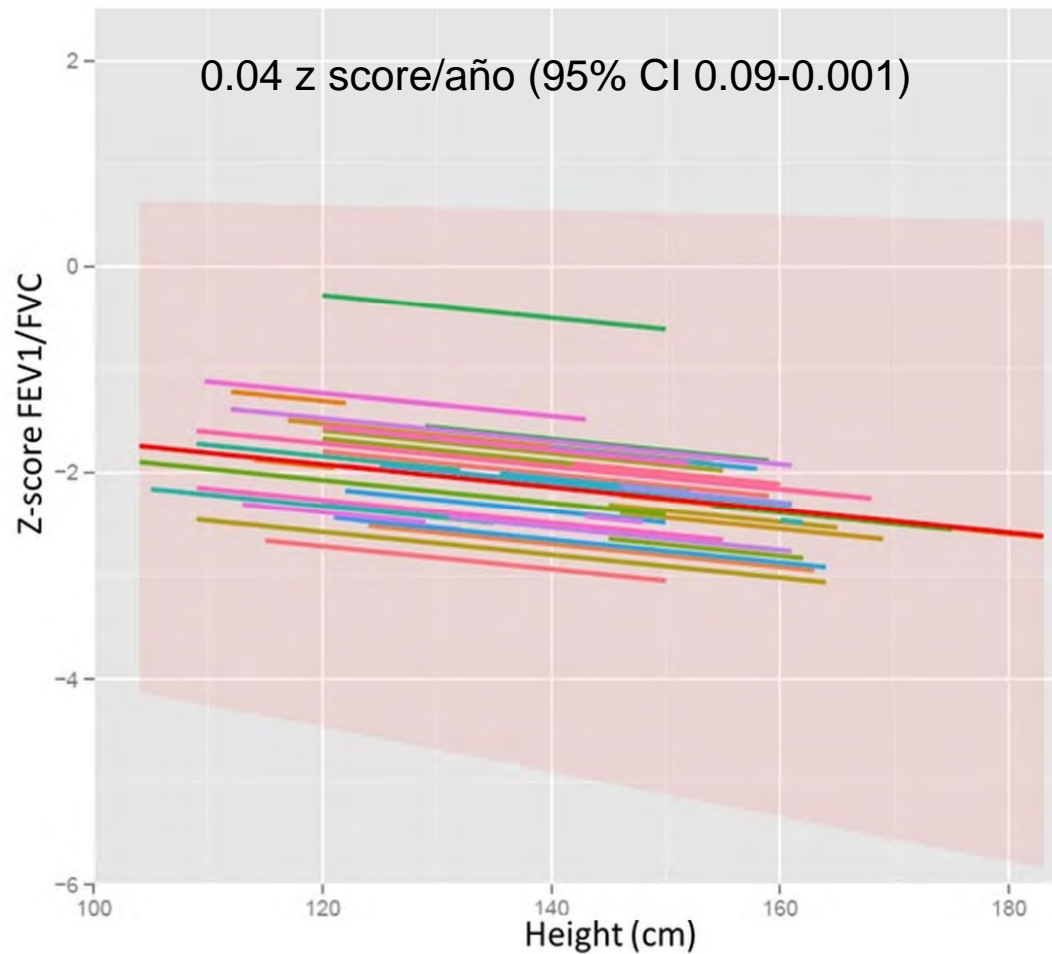
Resultados

VEF₁/CVF Vs Talla



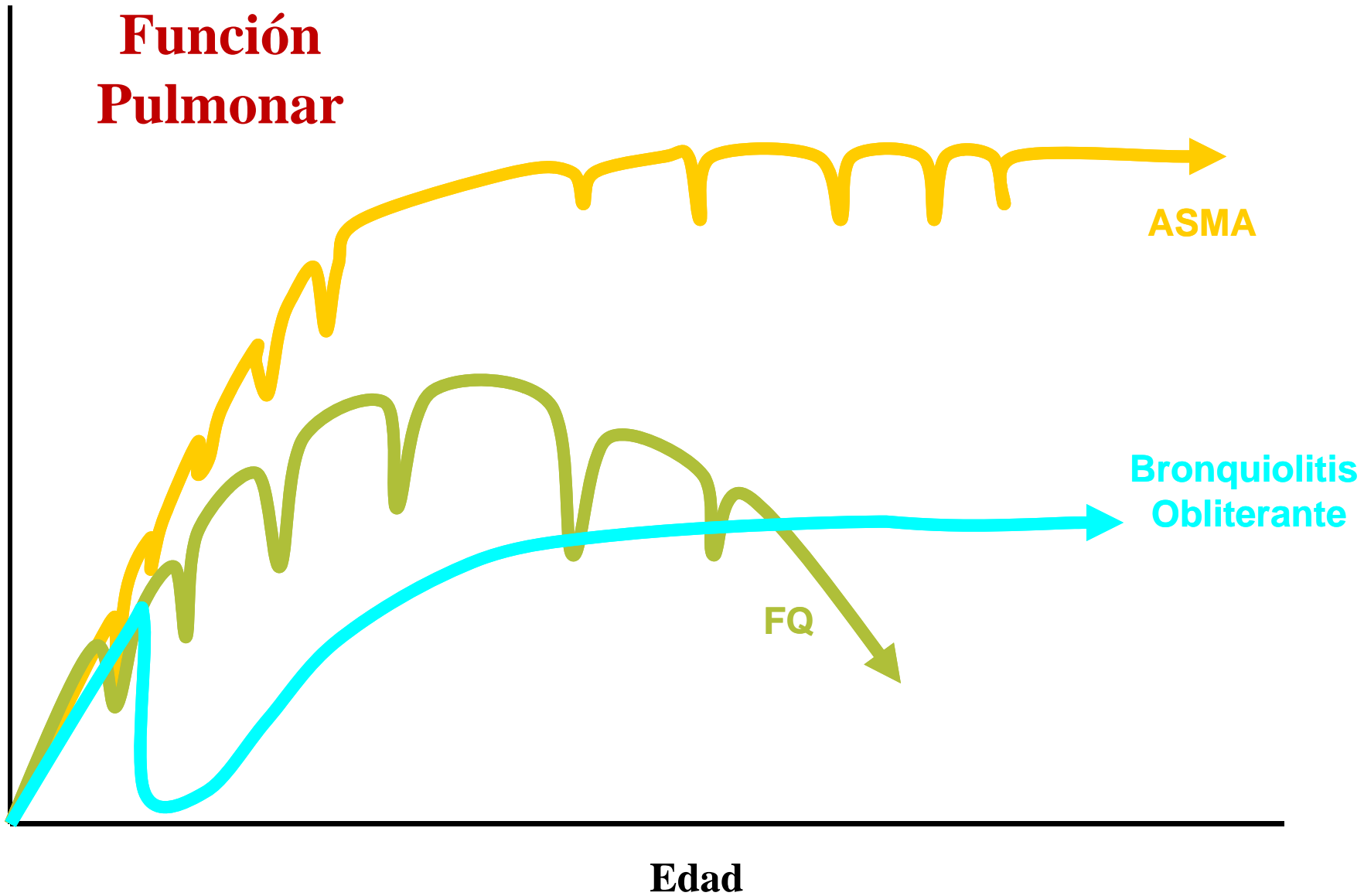
Resultados

Score Z VEF₁/CVF Vs Talla



Colom AJ, et al. Thorax 2015;70:169–174.

Función Pulmonar

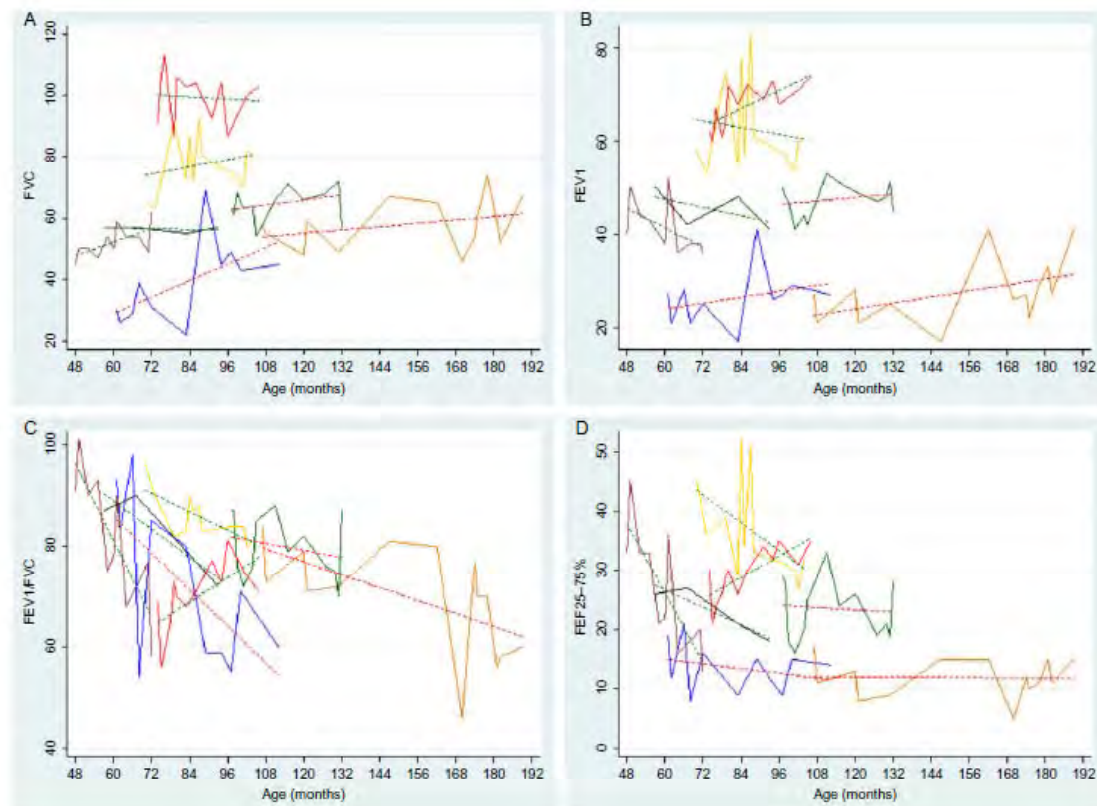


Dysanaptic growth of lung and airway in children with post-infectious bronchiolitis obliterans

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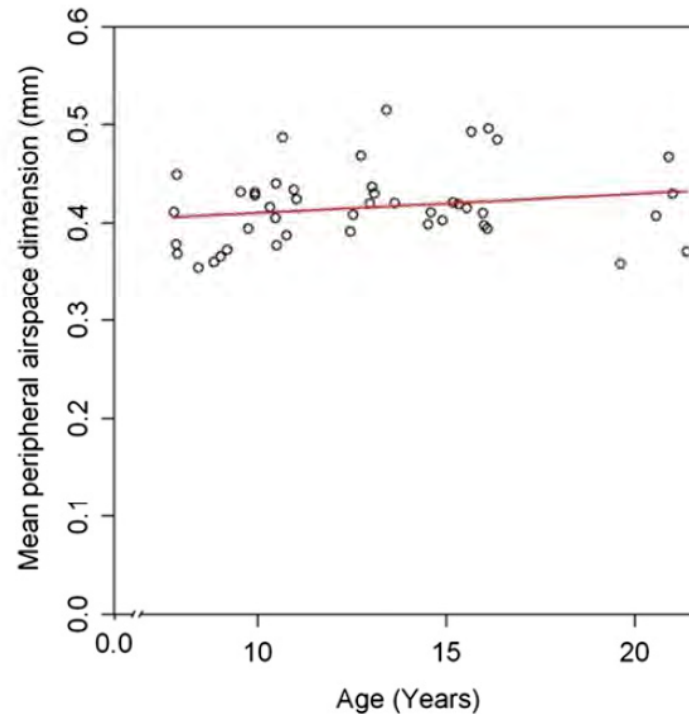
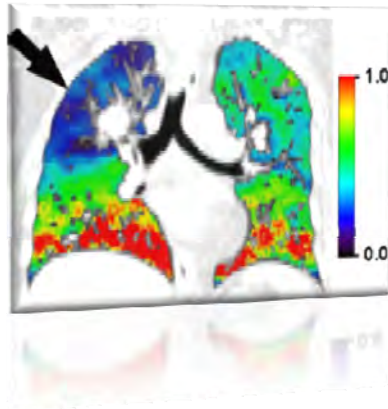


Alveolarization Continues during Childhood and Adolescence

New Evidence from Helium-3 Magnetic Resonance

Manjith Narayanan¹, John Owers-Bradley², Caroline S. Beardsmore¹, Marius Mada², Iain Ball², Ruslan Garipov², Kuldeep S. Panesar², Claudia E. Kuehni³, Ben D. Spycher³, Sian E. Williams¹, and Michael Silverman¹

¹Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, United Kingdom; ²School of Physics and Astronomy, University of Nottingham, Nottingham, United Kingdom; and ³Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

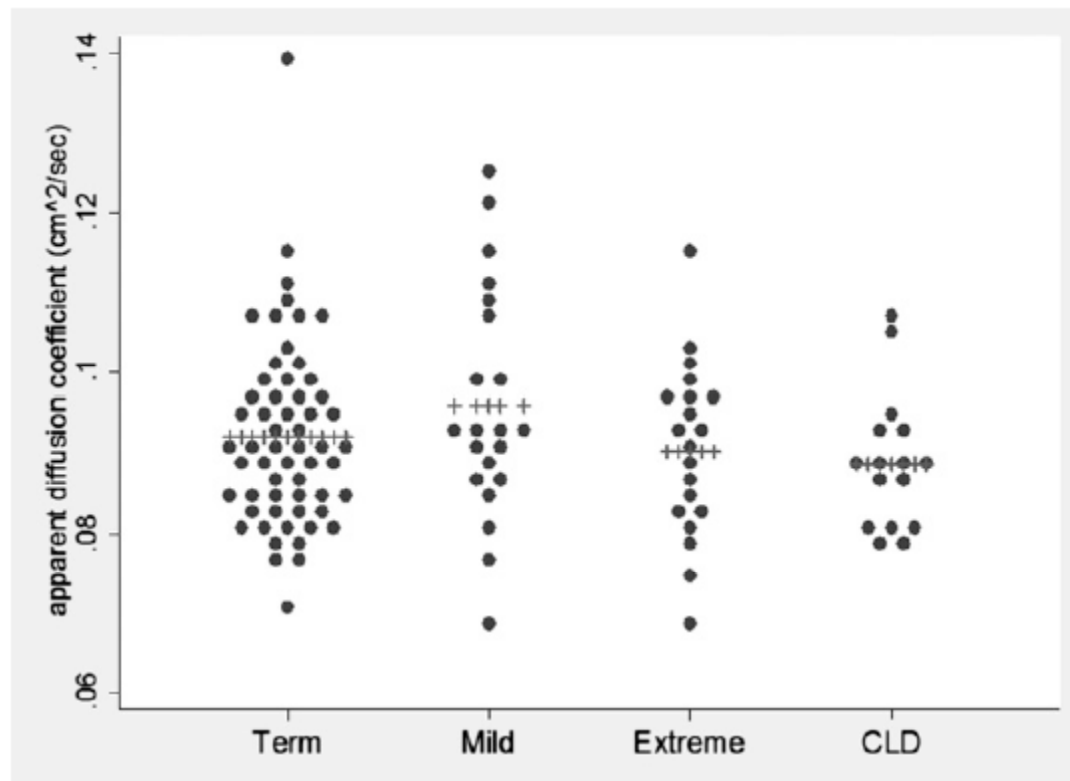


Catch-up Alveolarization in Ex-Preterm Children

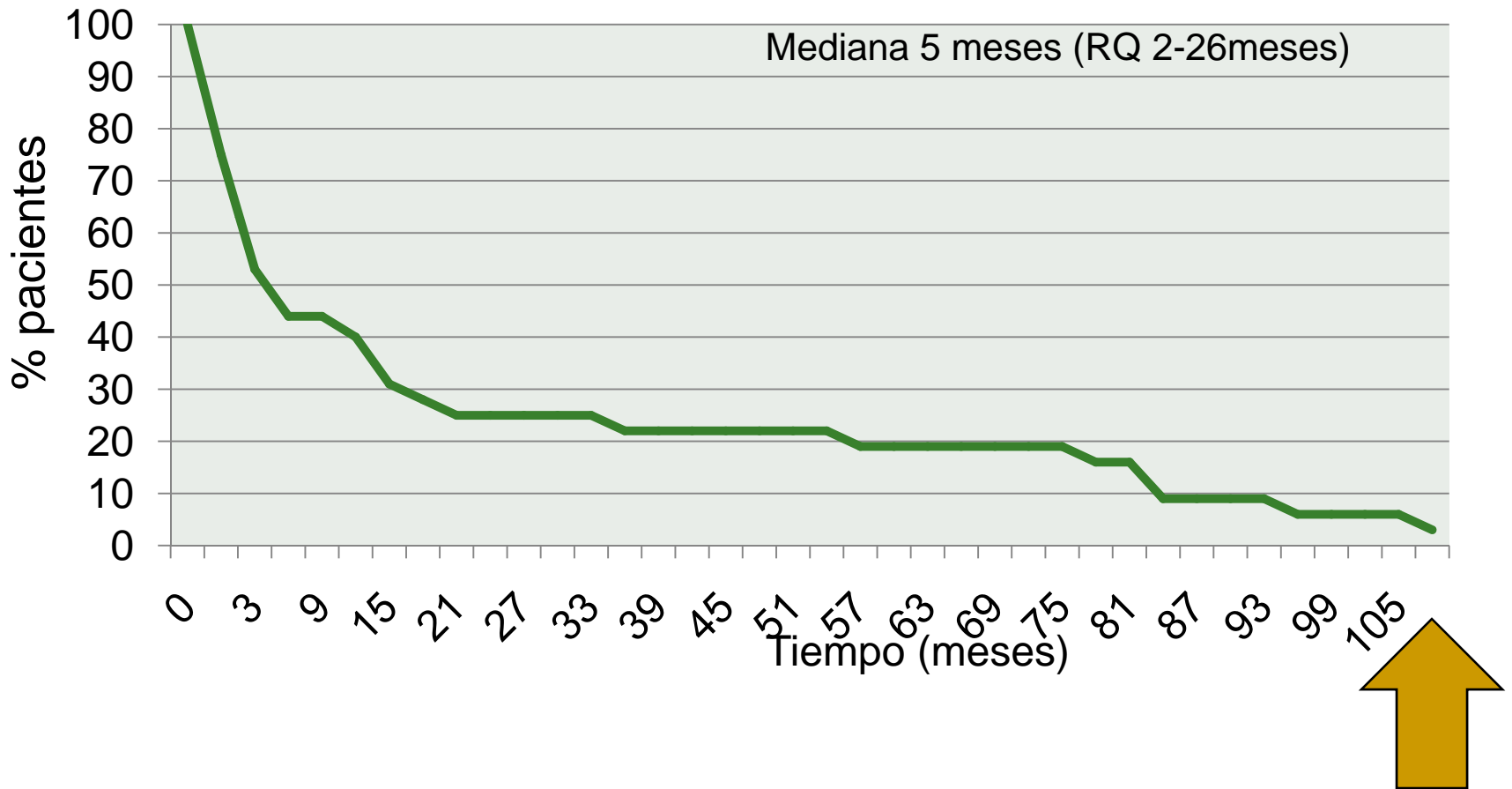
Evidence from ^3He Magnetic Resonance

Manjith Narayanan¹, Caroline S. Beardsmore¹, John Owers-Bradley², Cristian M. Dogaru³, Marius Mada², Iain Ball², Ruslan R. Garipov², Claudia E. Kuehni³, Ben D. Spycher³, and Michael Silverman¹

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Requerimientos de oxígeno



Colom AJ, et al. Thorax 2015;70:169–174.

OXIGENACIÓN NOCTURNA Y FUNCIÓN PULMONAR EN NIÑOS CON BRONQUIOLITIS OBLITERANTE POSINFECCIOSA

Colom, Alejandro; Selvino Verónica, Kuhar, Florencia; Teper, Alejandro.

n	40
Edad (años)	12 (4-19)
Masculinos	22
SapO2	98 ± 1

Test de marcha

Variable	
Distancia recorrida	459 ± 107m.
% de la distancia esperada*	63 ± 8
SapO2 reposo	97 ± 1
SapO2 al finalizar estudio	93 ± 3
Indice de fatiga Borg	0 (0-2)

* GUTIÉRREZ M, RIOSECO F, ROJAS A, CASANOVA D. Determinación de valores espirométricos en una población chilena normal mayor de 5 años, a nivel del mar. Rev Méd Chile 1996; 124: 1295-306.

Oximetría nocturna

Variable	
Tiempo de estudio libre de artefactos	518 ± 102
Episodios de hipoxia nocturna *	0
SapO2_ (x±DS)	96 ± 2
SapO2 inferior_(x±DS)	90 ± 3
Tiempo con SapO2 <90%	0.56% (20 segundos)

* Hipoxia nocturna: SapO2<90% por >5% del tiempo de estudio.

Functional capacity assessment during exercise in children and adolescents with post-infectious bronchiolitis obliterans

Rita Mattiello,¹ Edgar E. Sarria,² Ricardo Stein,³ Gilberto Bueno Fischer,⁴
 Helena Teresinha Mocelin,⁵ Sergio Saldanha Menna Barreto,⁴
 João Antônio Bonfadini Lima,⁶ Diego Brandenburg⁷

Table 2 - Comparison of variables for the 6-minute walk test and the cardiopulmonary exercise test

	6-minute walk test	Cardiopulmonary exercise test	p
	Mean ± SD	Mean ± SD	
Respiratory rate (PE)	30.0±3.7	57.4±9.0	0.000*
Heart rate (PE)	124.6±8.7	182.5±11.6	0.000*
Heart rate (MP)	62.5±9.4	91.6±5.8	0.000*
Minimum SaO ₂	94.1±3.2	90.2±4.6	0.001*
Borg (PE)	Median (quartiles)	Median (quartiles)	
Fatigue in legs	0 (0-3)	3 (1-7)	0.005*
Dyspnea	1 (0-3)	2 (1-6)	0.047*

MP = predicted maximum heart rate; PE = post-exercise; SaO₂ min = lowest oxygen saturation during exercise; SD = standard deviation.
 * p < 0.05

Nuevos Desafíos.....



21 años

Mas aún....

Mas aún.....



Para finalizar...

- En el daño pulmonar que se produce en la bronquiolitis obliterante postinfecciosa la reacción inflamatoria innata cumple un rol destacado.
 - El tratamiento para evitar su desarrollo debería contemplar esta reacción inflamatoria.
 - La evolución a largo plazo de los pacientes con bronquiolitis obliterante postinfecciosa es de lenta y progresiva mejoría.
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Muchas gracias !