A 17 YEAR OLD FEMALE WITH PROGRESSIVE DYSPNEA AND PULMONARY NODULES

Andrea Parra Buitrago
Sarah Pulido Fentanes
Fellow, Pediatric Pulmonary Medicine
Pediatric Pulmonologist

Alicia Casey, M.D.
Pediatric Pulmonologist
Co-Director, Interstitial Lung Disease Program

CHIEF COMPLAINT

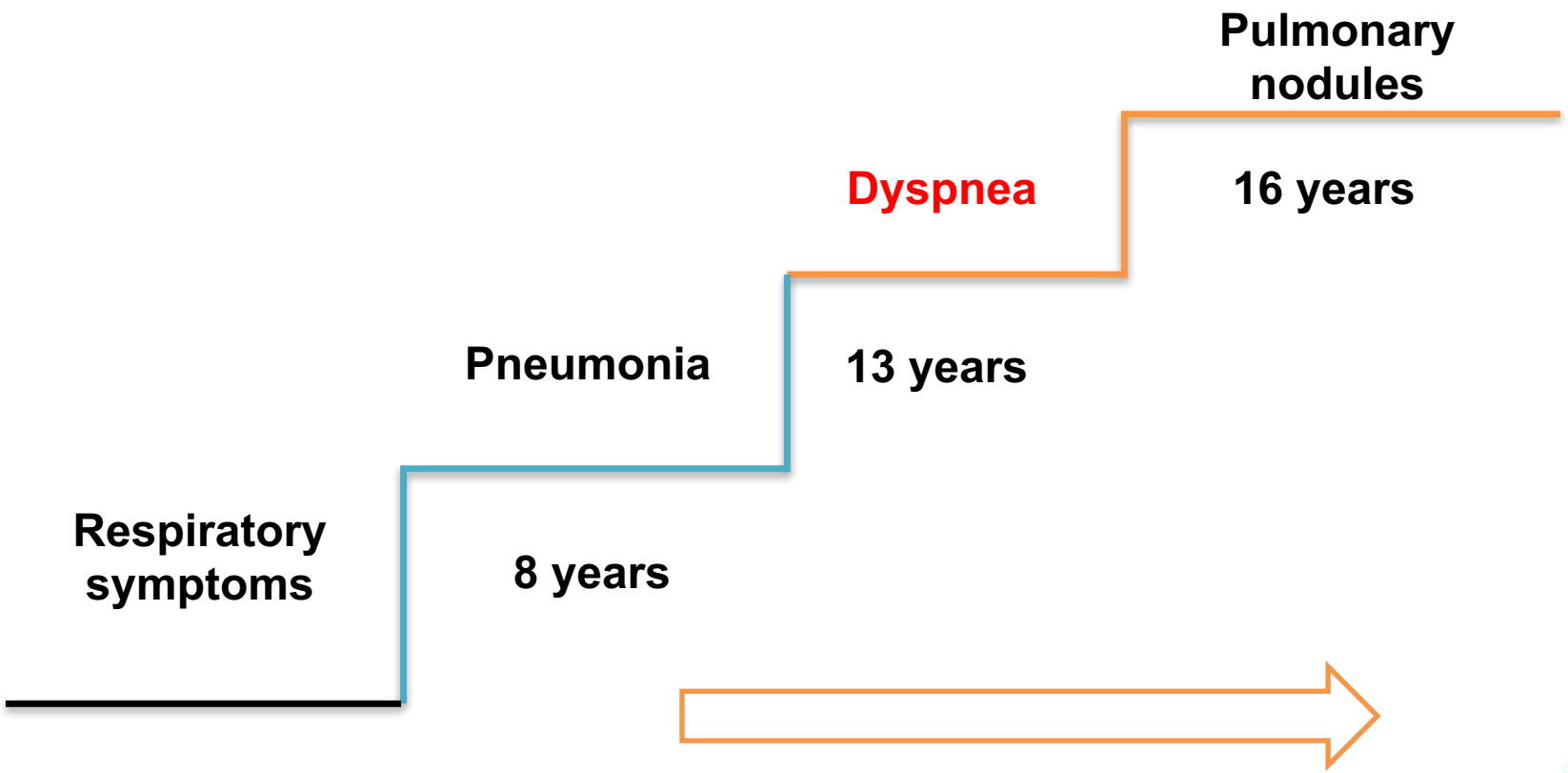
Fever and Dyspnea

HISTORY OF PRESENT ILLNESS

17 y/o female presented to the ER with fever, dyspnea, and shortness of breath for 2 days, associated with diarrhea and abdominal pain

History of dyspnea with exertion for the last 3 years, with progression over the previous two months

HPI



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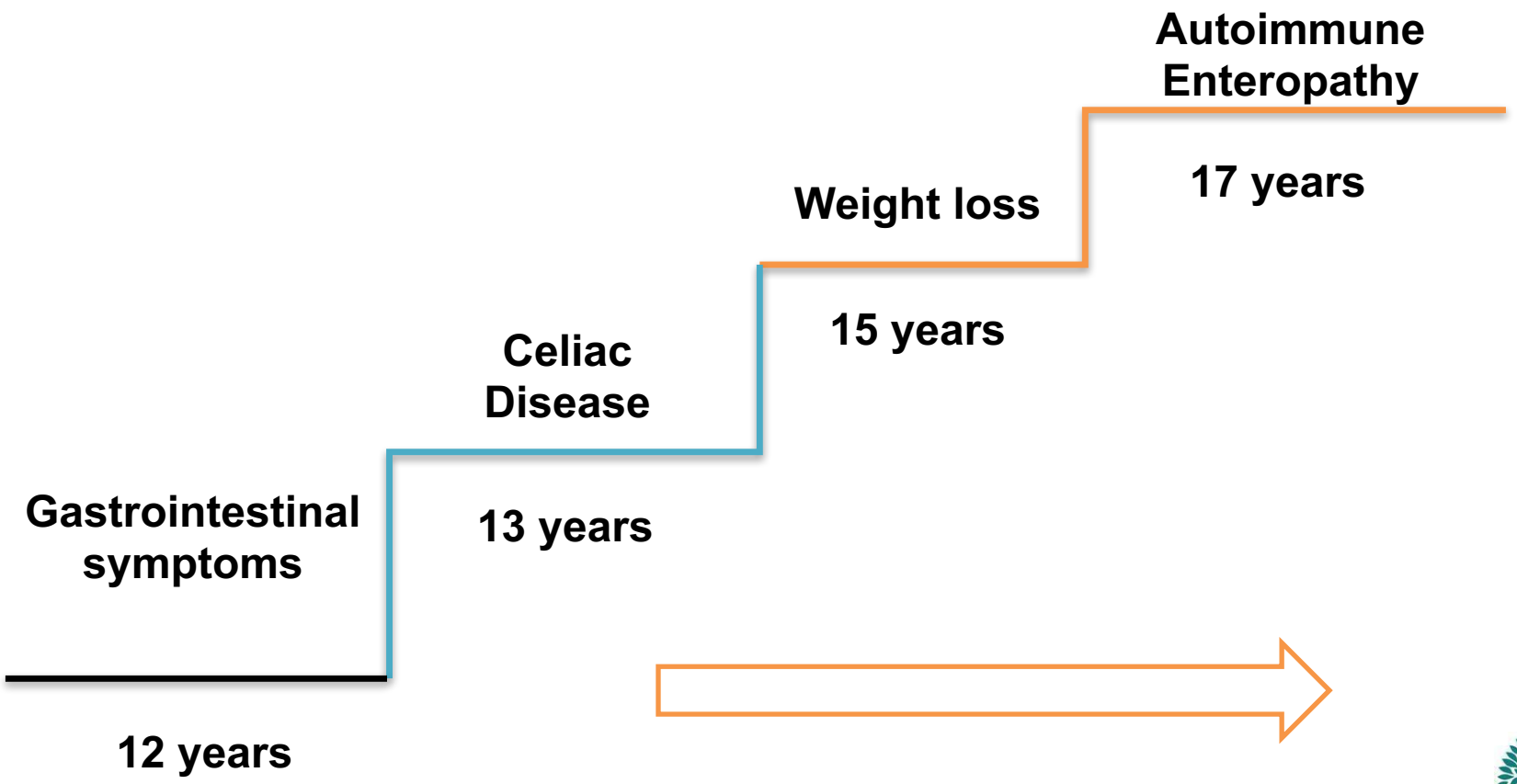
HPI



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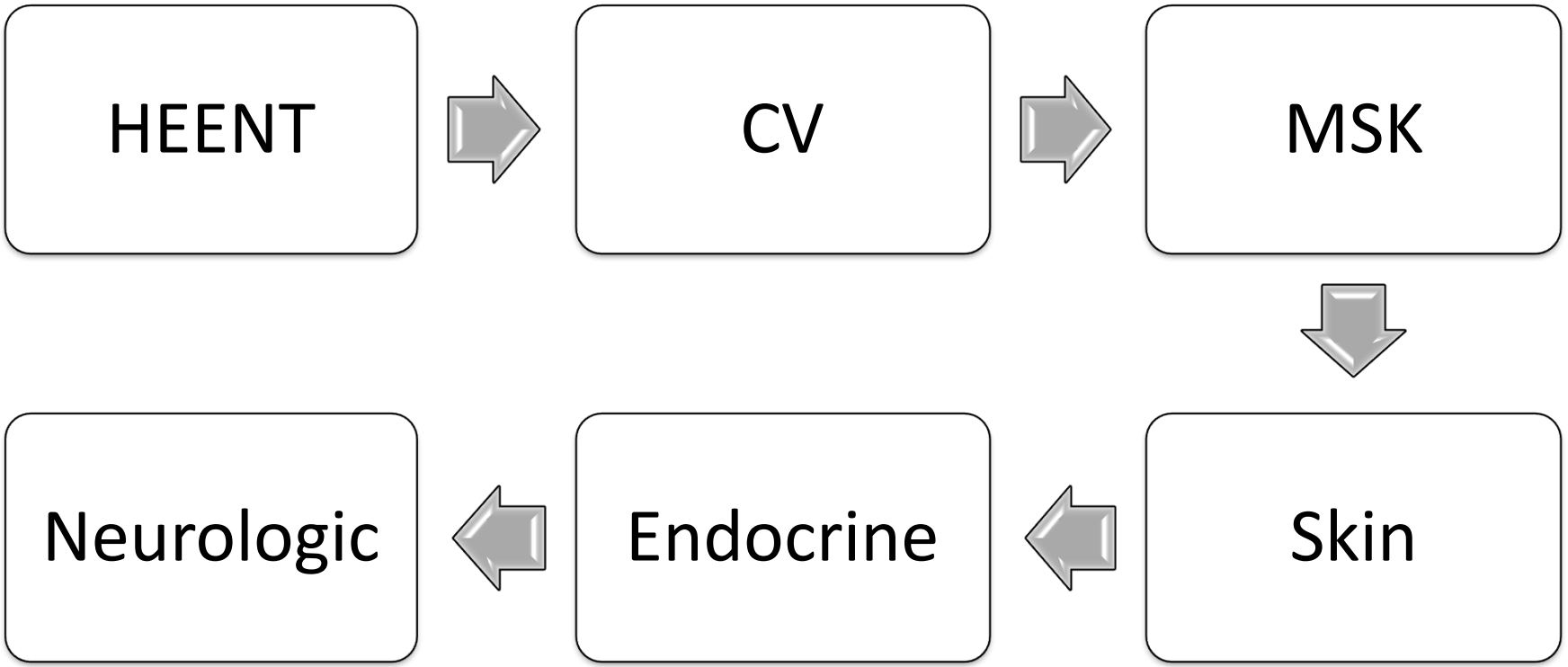
REVIEW OF SYSTEMS (ROS)



OTHER PAST MEDICAL HISTORY

IMMUNIZATIONS: Complete

EXPOSURES: None

SURGICAL: Appendectomy at age 5

SOCIAL HISTORY : Lives with parents and sister

UNREMARKABLE

Adequate

contributory

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VITAL SIGNS AND MEASUREMENTS

BP: 100/51 mmHg
MAP: 75 mmHg
HR: 84-103
RR: 19-22
T: 97.7-98.6 Fº
SpO_2:92-98% (2600 Mt above sea level)

Weight 29,6 Kg/66 lb (-4 z score)
Height 147 cm/57 inch (-3 z score)
BMI: 14.08 (-4 z score)

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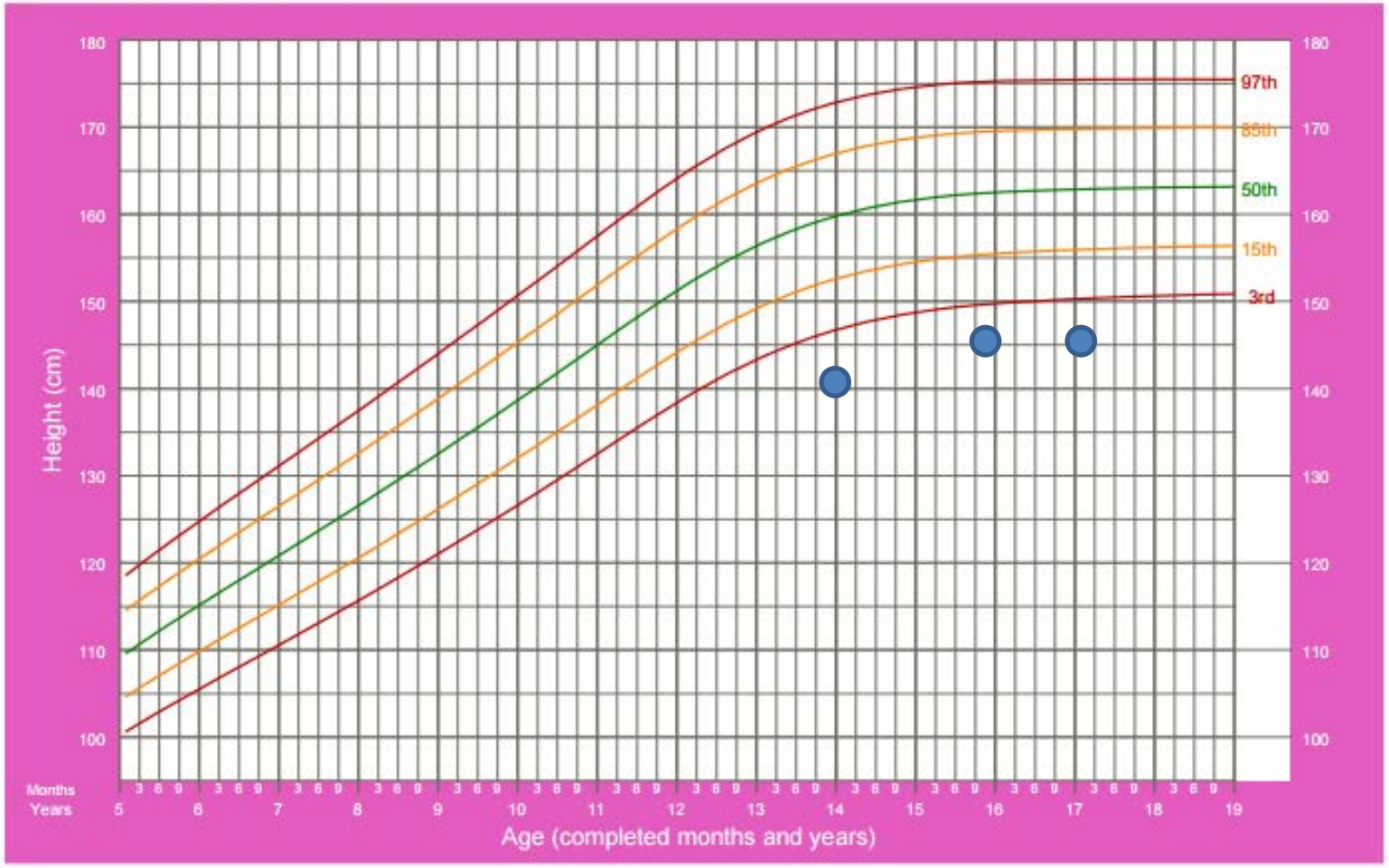
Height-for-age GIRLS

5 to 19 years (percentiles)

World Health Organization



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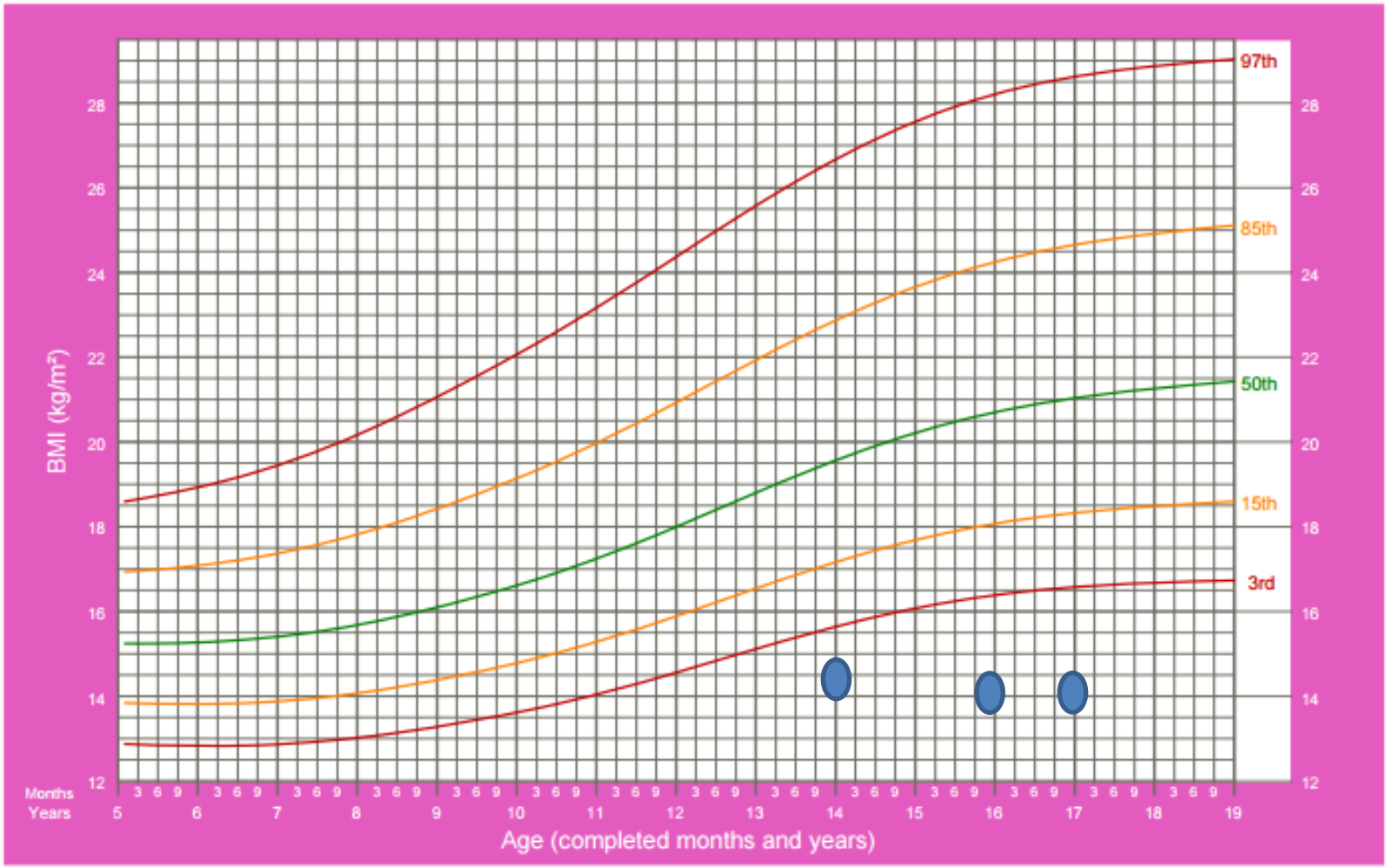
BMI-for-age GIRLS

5 to 19 years (percentiles)

World Health Organization



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PHYSICAL EXAM

- Alert and oriented, NAD, good color, very thin
- HEENT: Non-icteric sclera, dry oral mucosa
- Chest: Normal to palpation and percussion with clear lung sounds. Normal heart sounds without murmurs.
- Abdomen: Non-tender, non-distended without organomegaly
- EXTREMITIES: **Clubbing**

INITIAL CLINICAL APPROACH

Teenage Patient

Chronic dyspnea, increasing with exertion

Pulmonary nodules

History of gastrointestinal symptoms

Autoinmmune enteropathy

Chronic malnutrition

Multi-systemic disease with respiratory and GI involvement

DYSPNEA

Is the dyspnea:

- A new problem?
- An exacerbation of a chronic problem?
- A combination of the two?

Lands Larry C.Dyspnea in Children: What is driving it and how to approach it.Paediatric Respiratory Reviews http://dx.doi.org/10.1016/j.prrv.2017.03.013

DYSPNEA

Table 3 Laboratory Testing for Dyspnea

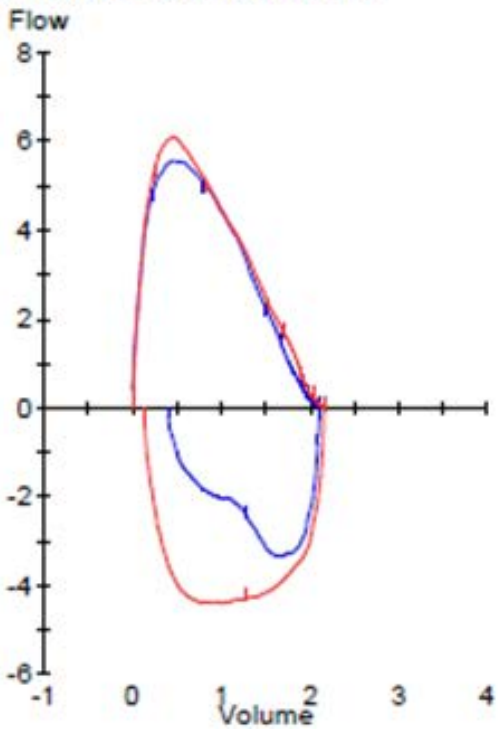
Pulmonary Function: spirometry pre- and post-bronchodilators, lung volumes, diffusing capacity, respiratory muscle strength
Oxygen saturation by pulse oximeter
Chest radiograph
Complete Blood Count and differential
Capillary blood gas
Electrolytes, urea nitrogen, creatinine, Thyroid Stimulating Hormone
Formal exercise testing
Provocation testing
(Cardiology: ECG and echo)

Lands Larry C.Dyspnea in Children: What is driving it and how to approach it.Paediatric Respiratory Reviews
http://dx.doi.org/10.1016/j.prrv.2017.03.013

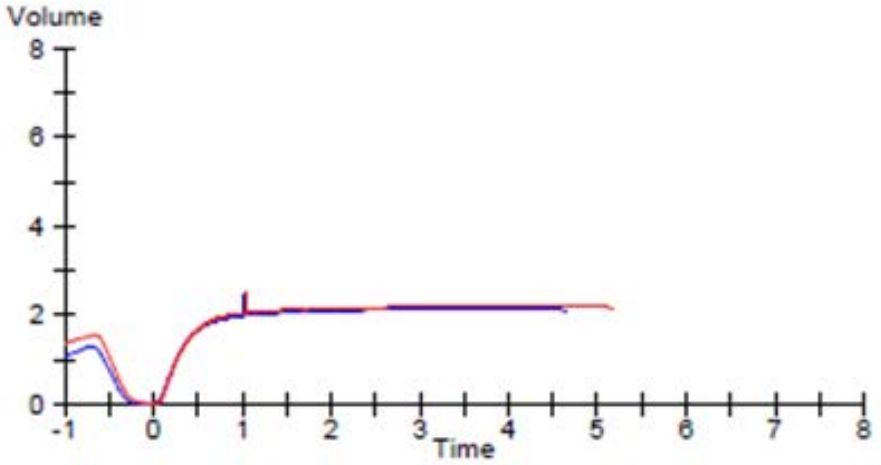
SPIROMETRY

		Ref	Pre Meas	Pre % Ref	CI	Post Meas	Post % Ref	Post % Chg
FVC	Liters	2.50	2.12	85		2.17	87	2
FEV1	Liters	2.35	1.99	85		2.04	87	3
FEV1/FVC	%	86	94	109		94	110	0
FEV.5	Liters		1.74			1.79		3
FEF25-75%	L/sec	2.74	3.66	134		3.66	133	-0
PEF	L/sec	5.24	5.80	111		6.14	117	6
FET100%	Sec		4.65			5.14		10

IC = Intervalo de Confianza



prebroncodilatador
postbroncodiltador



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BRONCHOPROVOCATION TEST

	Ref	Pre Meas	Level 1 Meas	Level 2 Meas	Level 3 Meas	Level 4 Meas	Level 5 Meas	Post Meas
Dose			0.0625	0.250	1.000	4.000	16.000	
FVC Liters	2.45	2.48	2.47	2.48	2.48	2.43	2.40	2.50
	mg/ml							
% Ref		101	101	101	101	99	98	102
% Chg			-0	0	-0	-2	-3	1
FEV1 Liters	2.31	2.17	2.15	2.16	2.15	2.07	2.03	2.23
% Ref		94	93	94	93	90	88	97
% Chg			-1	-0	-1	-5	-6	3
FEV1/FVC %	86	87	87	87	87	85	84	89
FEF25-75%	2.70	2.62	2.63	2.51	2.56	2.25	2.22	3.00
% Ref		97	97	93	95	83	82	111
% Chg			0	-4	-2	-14	-15	14

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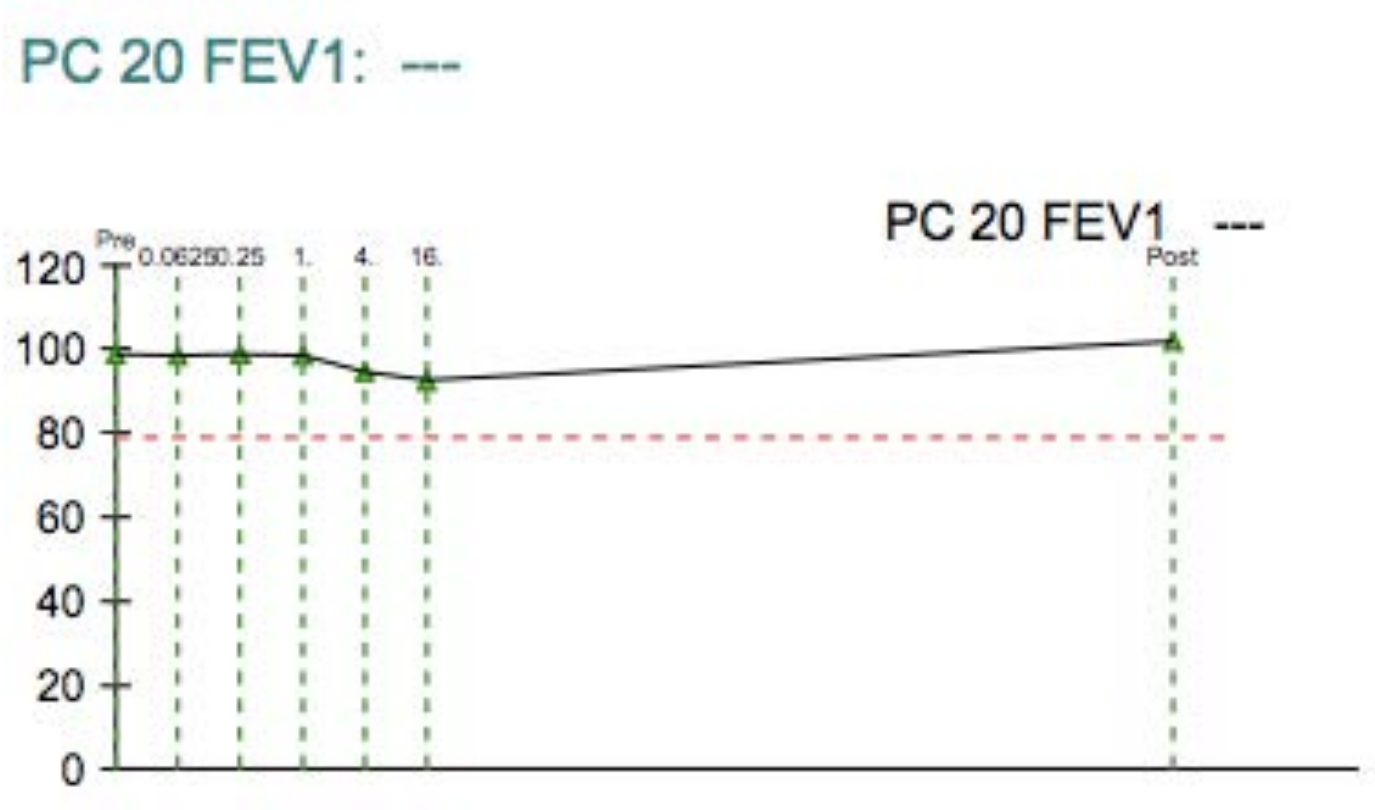
BRONCHOPROVOCATION TEST



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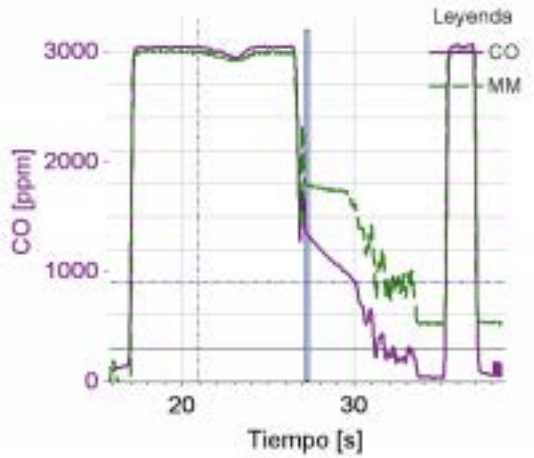
DIFFUSING CAPACITY OF CARBON MONOXIDE IN THE LUNG (DL,CO)

CAPACIDAD DE DIFUSION MONOXIDO DE CARBONO (DLCO)

Parámetro	Pred	LLN	Result.	%Pred
DLCO [ml/min/mmHg]	17,6	14,1	15,3	87
DLadj [ml/min/mmHg]	17,6	14,1	13,4*	76
VA sb [L]	3,15	2,87	3,02	96
DLadj/VA [ml/min/mmHg/L]	5,58	4,87	4,42*	79
VI [L]	-	-	2,35	-

* Indica valor situado fuera del rango normal o cambio posterior significativo.



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TRANSTHORACIC ECHO

22/04/16

- Normal LV dimension
- Normal cardiac valves
- Normal LV systolic function
- Normal PAP
- No pericardial effusion
- Absence of pulmonary hypertension

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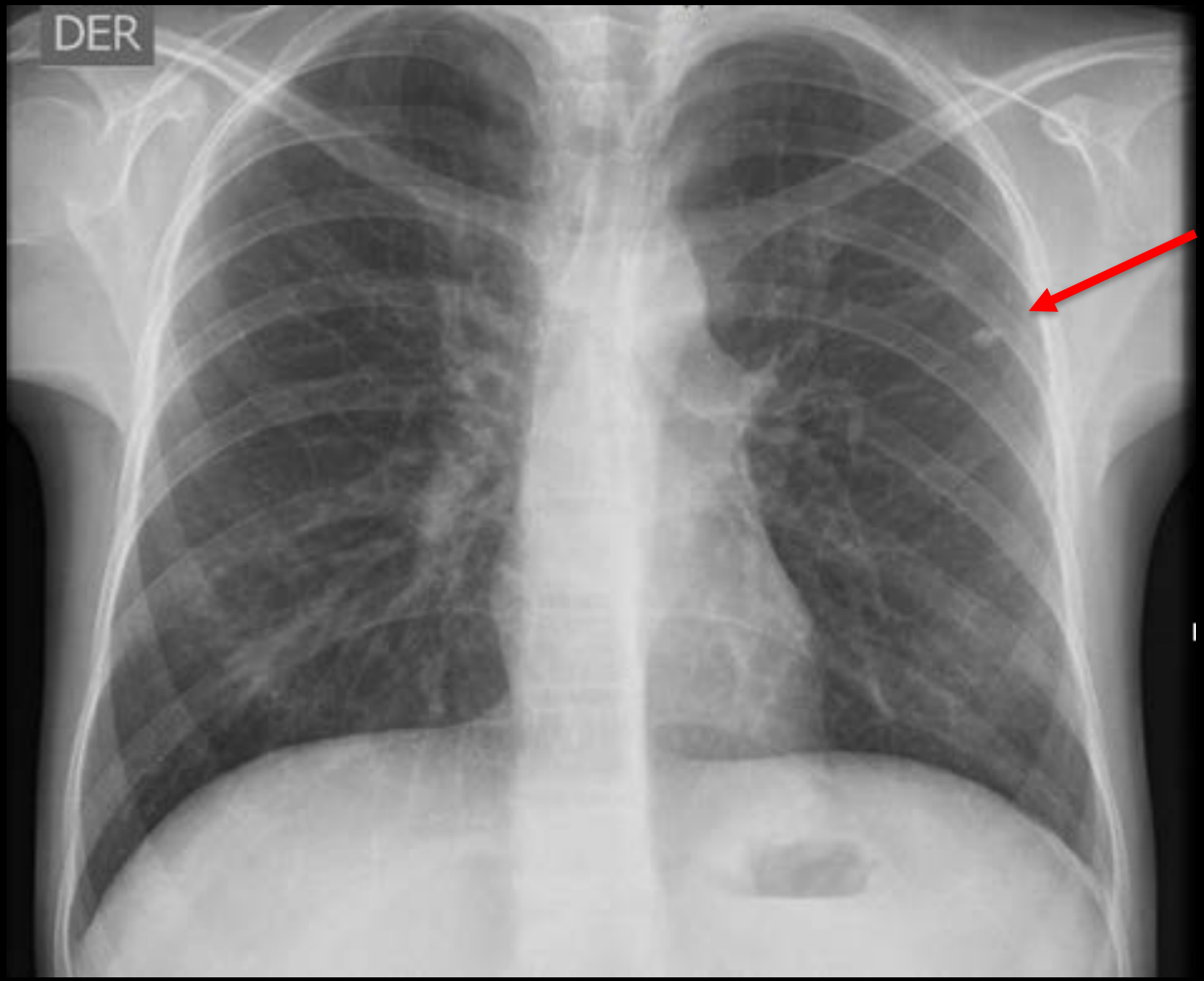
DER

ADDITIONAL TESTING

Chest X Ray

High-resolution CT

Blood work

Bronchoscopy with bronchoalveolar lavage

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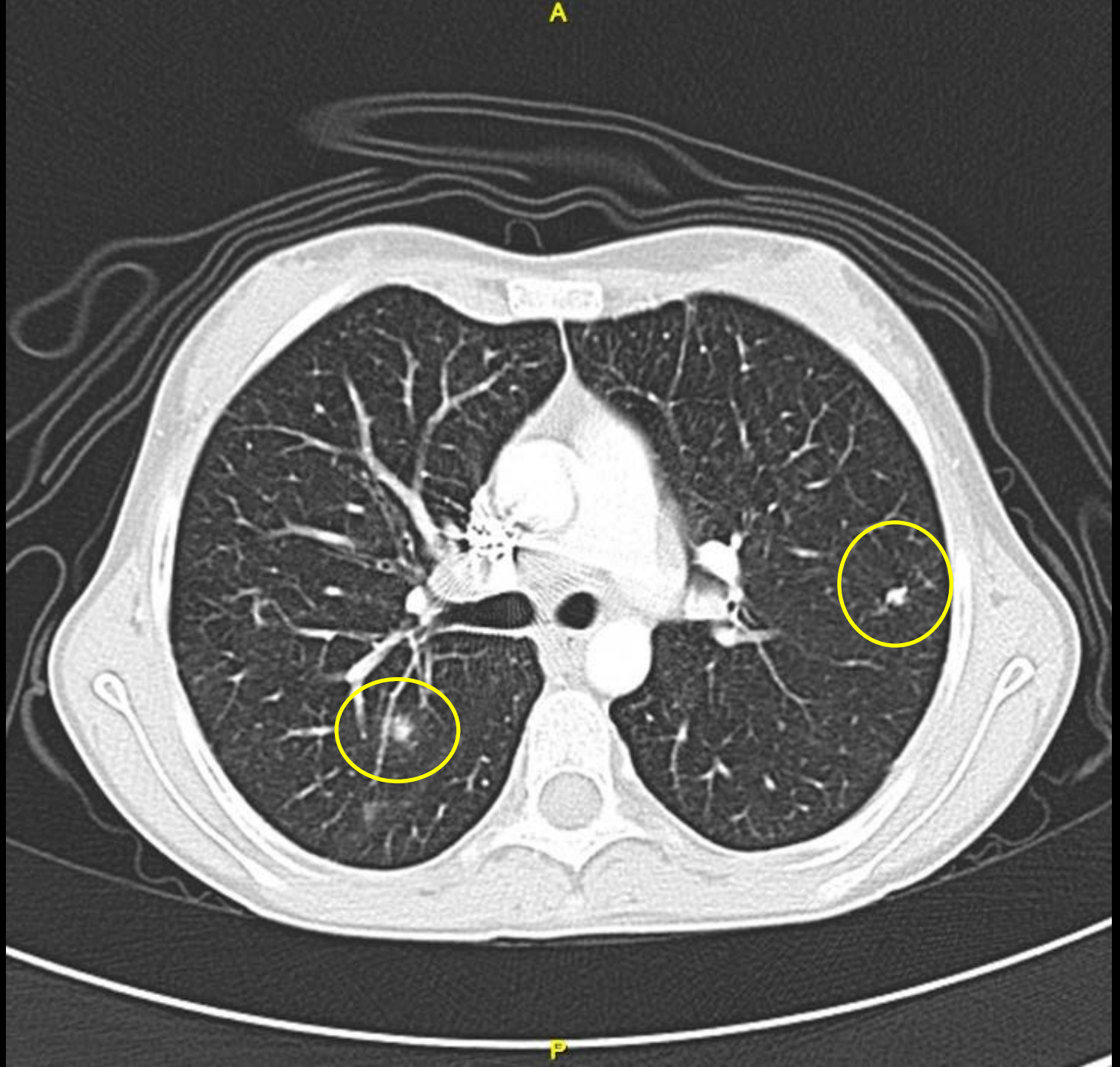
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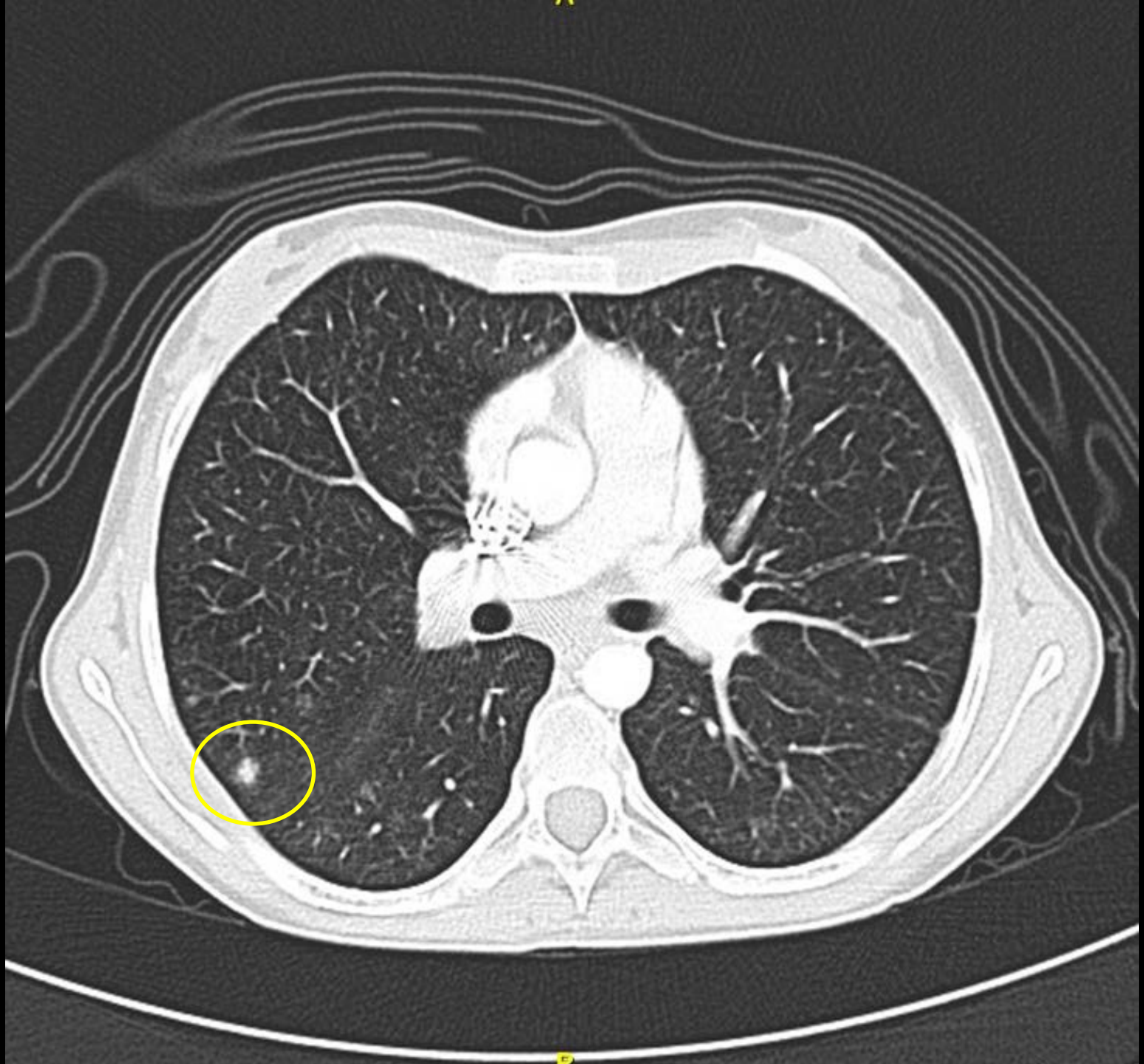
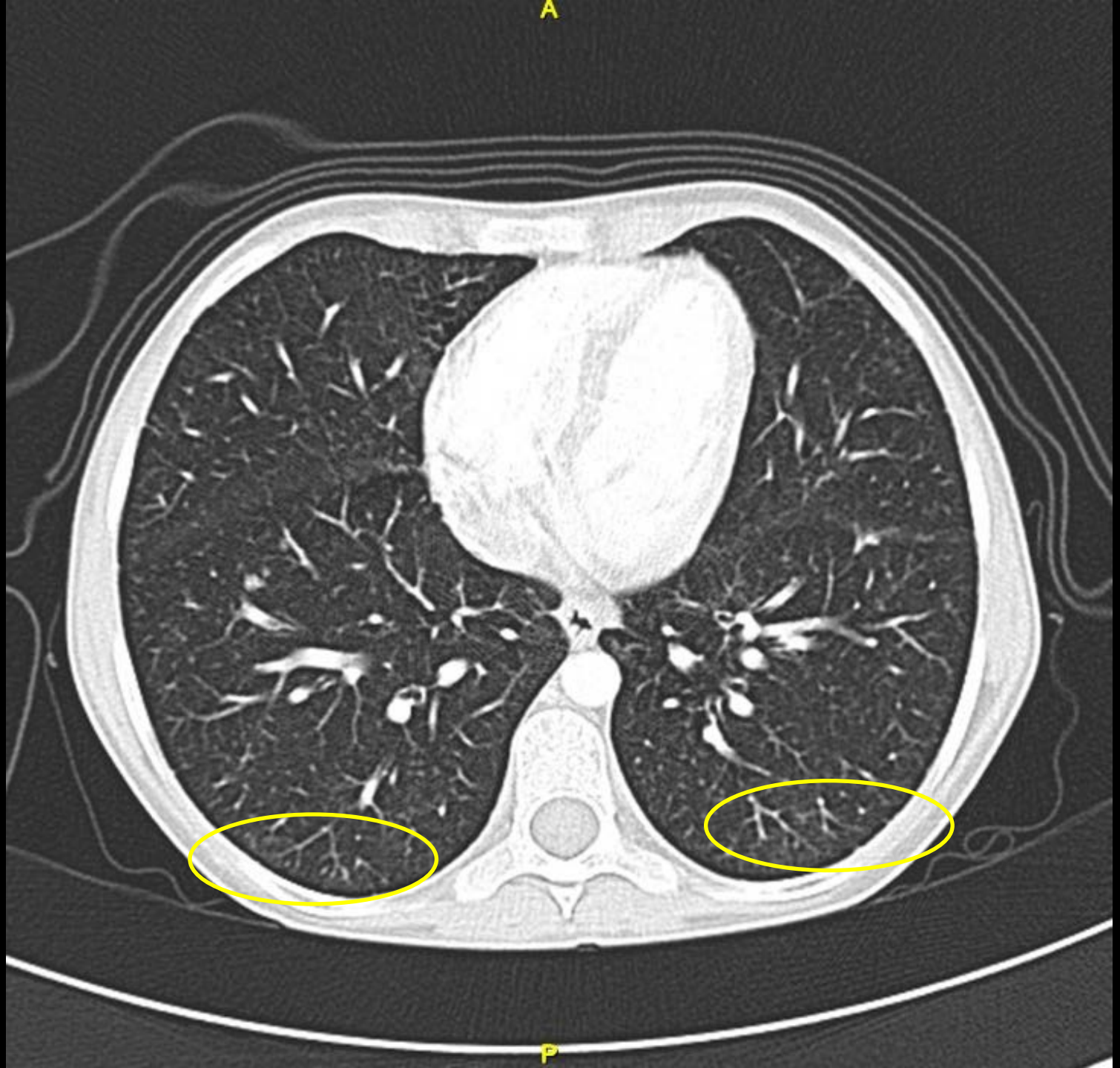



A
P

What is the differential diagnosis of pulmonary nodules in children?

How does the differential diagnosis change given the clinical history of this patient?

Approach to Pulmonary Nodules in Children

- In comparison to adults there are not specific guidelines for the evaluation of pulmonary nodules
- Pulmonary nodules are **NOT** an incidental finding in a **symptomatic patient**
- Evaluation should be planned based on the clinical history
- Look for evidence of immunodeficiency, connective tissue disease, immune dysfunction, h/o malignancy, or h/o congenital pulmonary malformation

Westra S. et al. (2015) Pediatric Radiology.

Differential Diagnosis

Infection

Malignancy

Other

Inflammatory

WORK UP

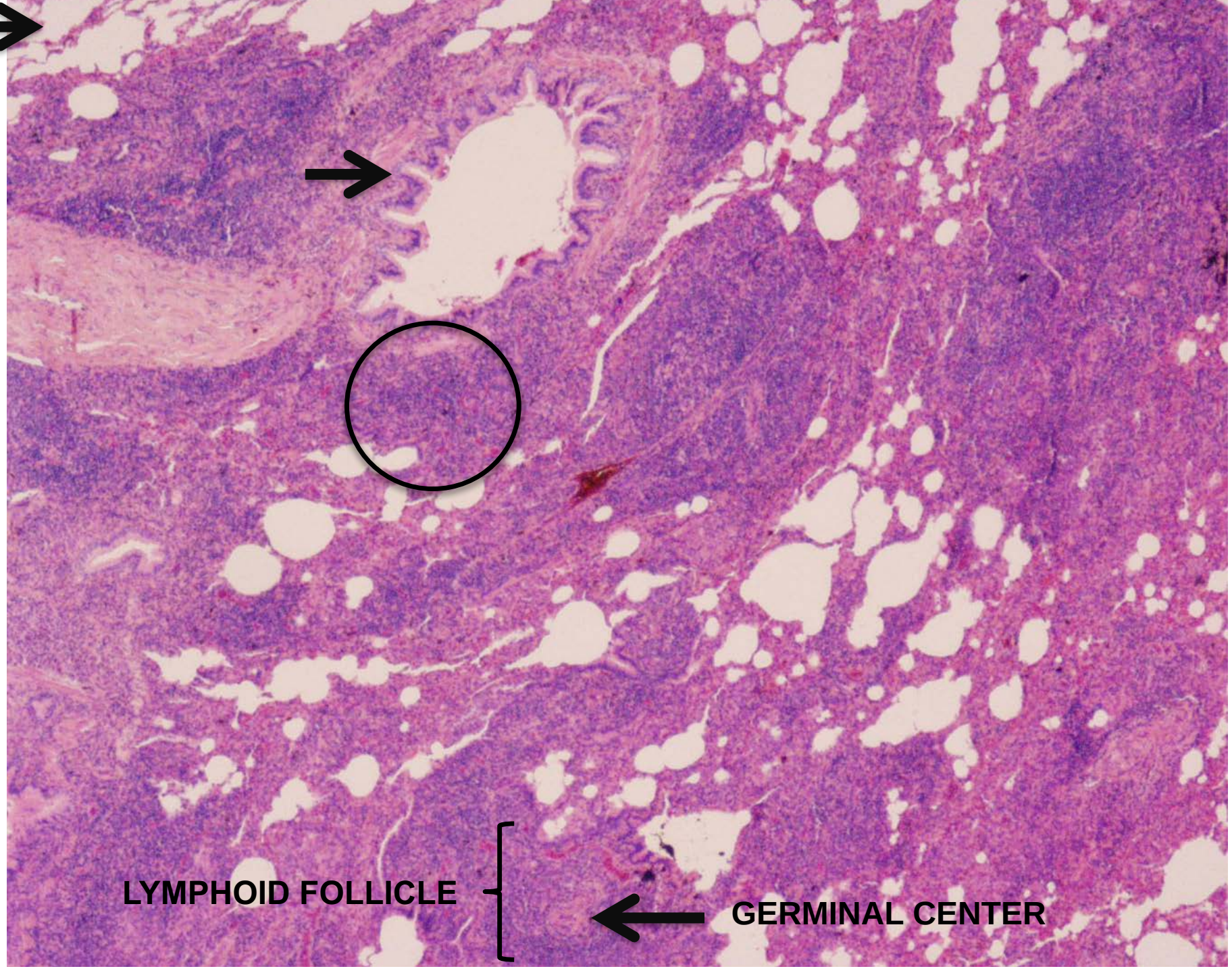
- Low complement levels
- Low vaccine titers
- Normal IgG,A,M,E
- T-cell lymphopenia
- Negative PPD and HIV testing

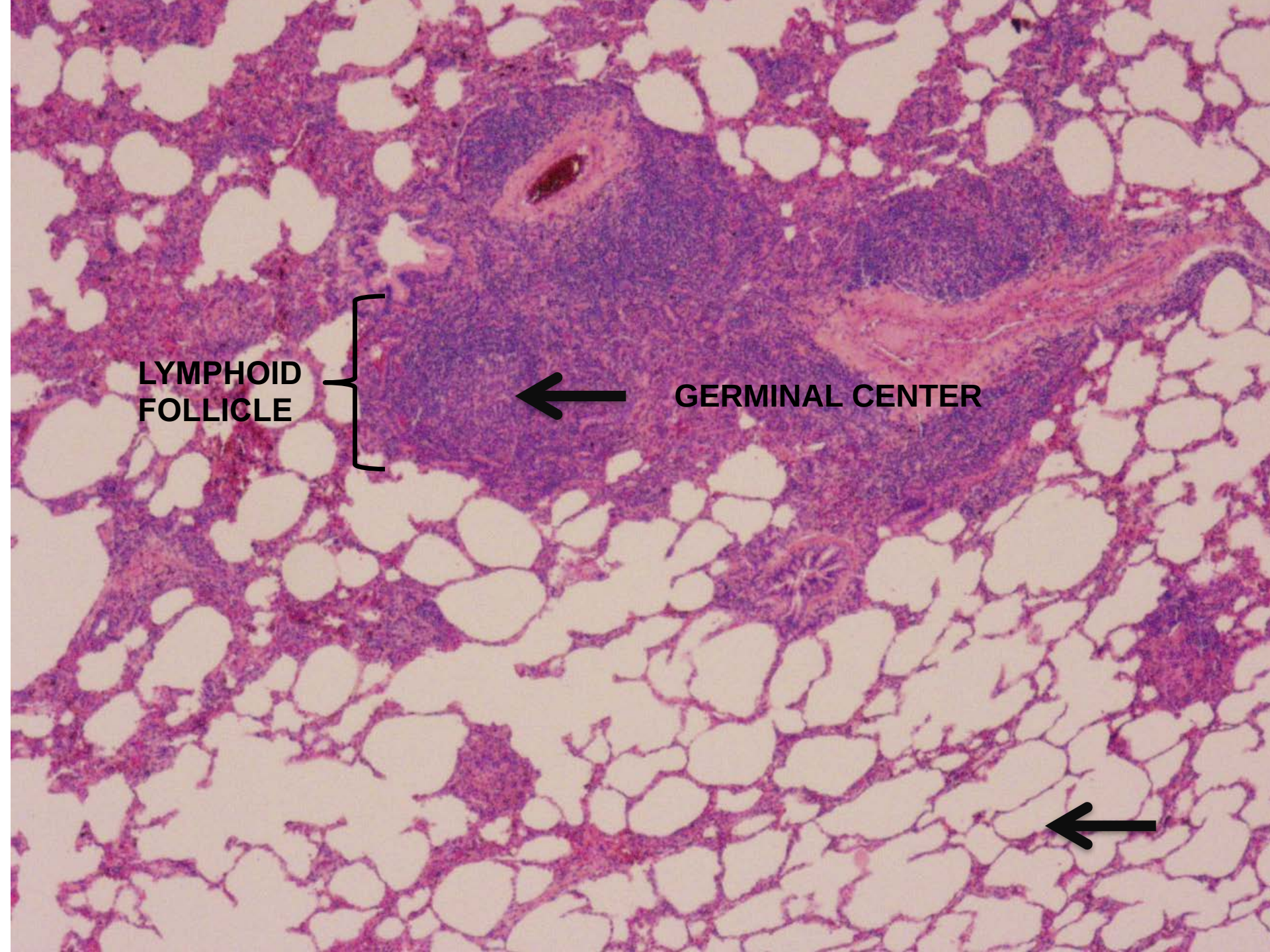
BRONCHOSCOPY AND BAL

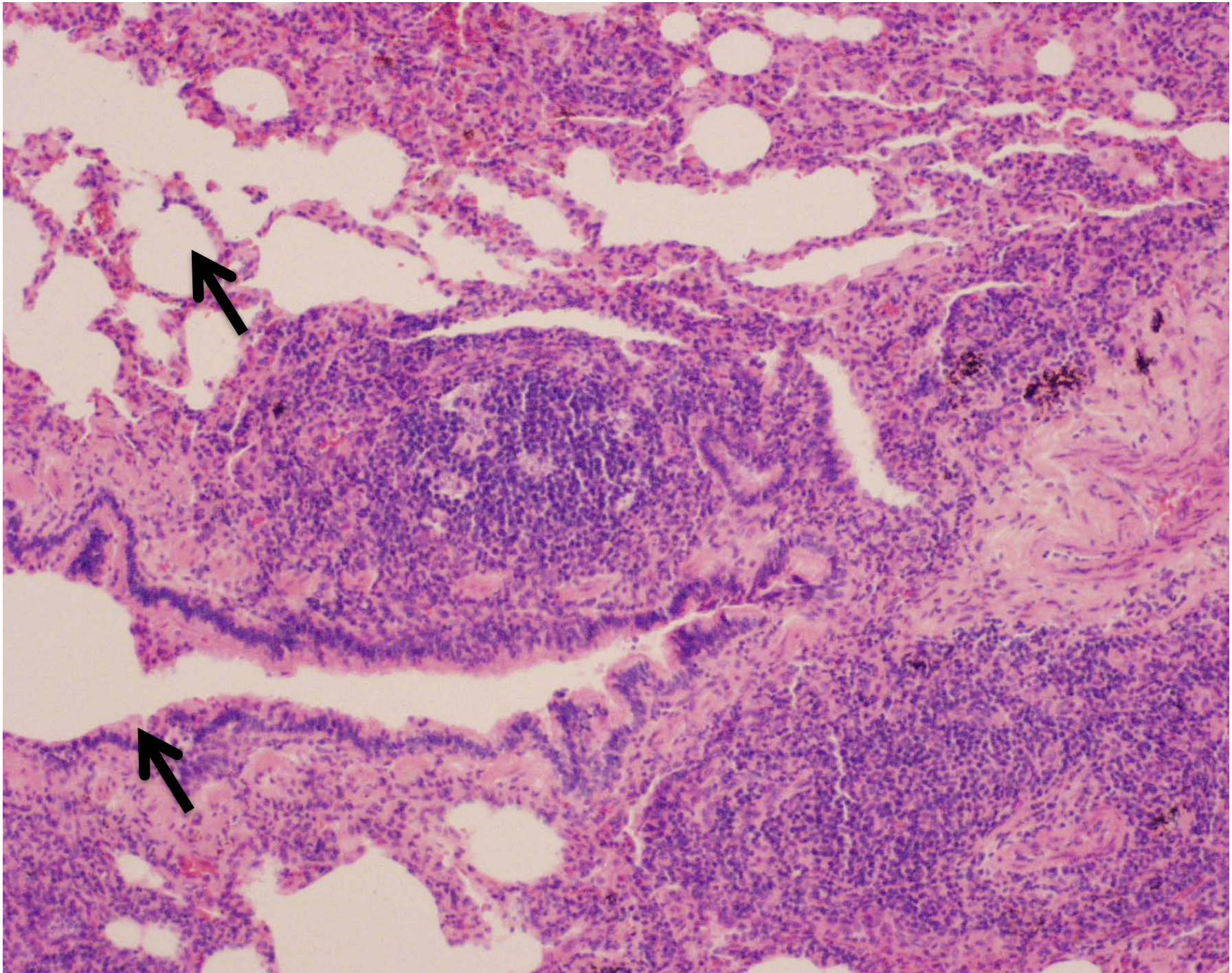
- Normal findings on inspection
- Bronchoalveolar lavage and brushings
  - Negative cultures
  - BAL cell differential: Ly-93%, N-5%, M-2%

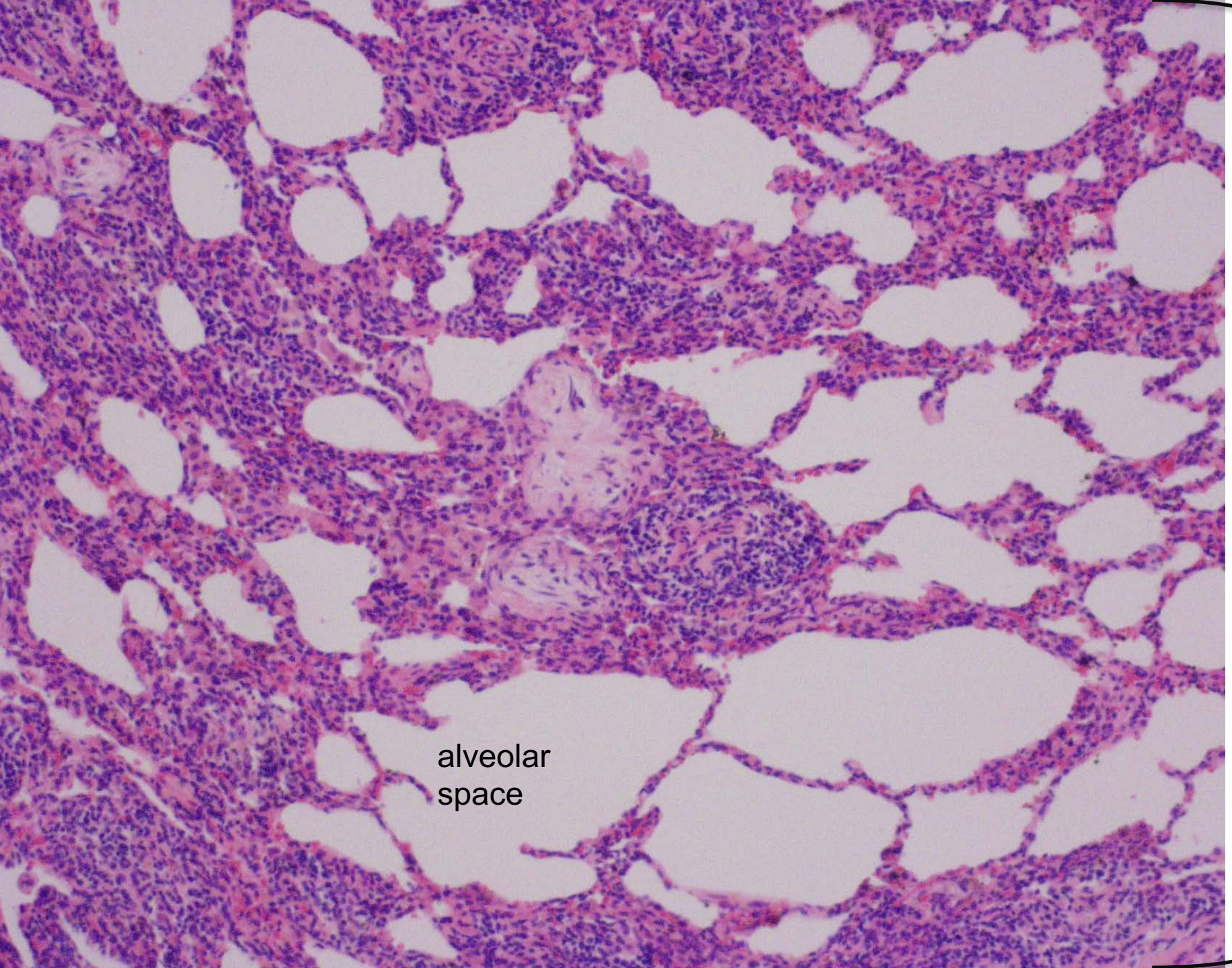
NEXT STEP

Open biopsy of pulmonary nodules


LYMPHOID FOLLICLE
GERMINAL CENTER


LYMPHOID
FOLLICLE
GERMINAL CENTER




alveolar
space

DIAGNOSIS: FOLLICULAR BRONCHIOLITIS (FB)

Follicular Bronchiolitis

- Rare, benign lymphoproliferative disorder
- Hyperplasia of bronchial associated lymphoid tissue
- More common in adults
- CT findings include
  - Peribronchial & centri-lobular nodules
  - Ground glass opacities
- Symptoms
  - Shortness of breath
  - Cough
  - Fever
  - Recurrent LRTI
- Most often associated with
  - Connective tissue disease
  - Immunodeficiency
  - Hypersensitivity
  - Infection

Carrillo J, et al. (2013) Seminars in Ultrasound, CT, and MRI.
Toprak Kanik E, et al. (2014) Turkish Archives of Pediatrics.
Nicholson A. (2001) Seminars in Respiratory and Critical Care Medicine.

Pulmonary Complications of Primary Immunodeficiencies (PID)

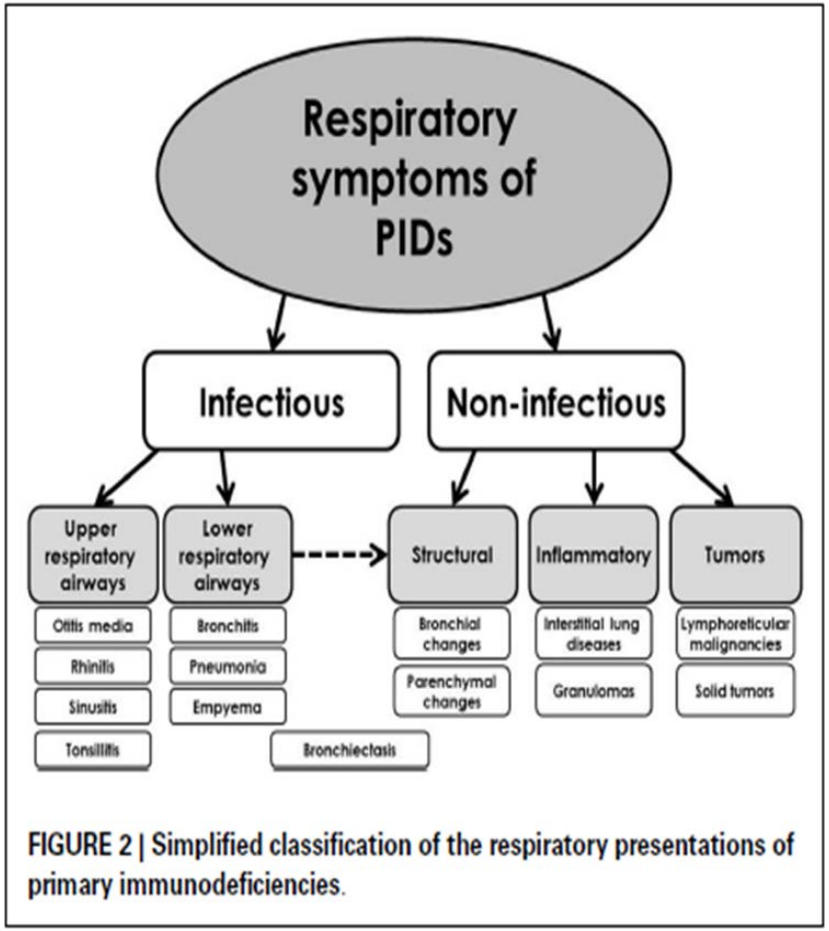


FIGURE 2 | Simplified classification of the respiratory presentations of primary immunodeficiencies.

Jesenak, et. al. Frontiers in Pediatrics (2014)

Common Variable Immunodeficiency & Lung Disease

- Most common symptomatic humoral PID
- Genetic defects found to cause in some cases
- Recurrent respiratory tract infections
- Inflammatory complications
- Autoimmune manifestations
  - Most common hemolytic anemia or thrombocytopenia

Given the diagnosis of FB and autoimmune enteropathy, what further evaluation is recommended in this patient?

PID Associated With Autoimmune Disease

PID	Defect	Autoimmune GI Disease	Other Features
Common Variable Immunodeficiency	Polygenetic	X	Lymphoproliferation, other autoimmunity
X-Linked Agammaglobulinemia	BTK	X	Neutropenia in setting of infection
Autoimmune Lymphoproliferative Syndrome (ALPS)	FAS, FASL, CASP 10	X	Lymphoproliferation, other autoimmunity
Partial DiGeorge	22q 11.2	X	Craniofacial anamolies, cardiac anamolies, hypocalcemia, other autoimmunity
Cytotoxic T-lymphocyte antigen 4	CTLA4	X	Lymphoproliferation, other autoimmunity
LPS- responsive vesicle trafficking, beach & anchor containing protein	LRBA	X	Growth retardation, eczema, lymphoproliferation, other Autoimmunity
Immune dysregulation polyendocrinopathy enteropathy X linked syndrome	FOXP3	X	Failure to thrive, dermatitis, lymphoproliferation, other autoimmunity
Signal transducer and activator of transcription 3	STAT3	X	Short stature, eczema, lymphoproliferation, other autoimmunity
Signal transducer and activator of transcription 1	STAT1	X	Aneuryms, eczema, carcinomas, other autoimmunity
Wiskott –Aldrich syndrome	WAS	X	Microthrombocytes with low count & poor function, eczema, mucosal bleeding, renal disease
Chronic granulomatous disease	CYBB, CYBA, NCF1, NCF2, NCF4	X	Lymphoproliferative pathology with severe multi-organ granulomatous disease

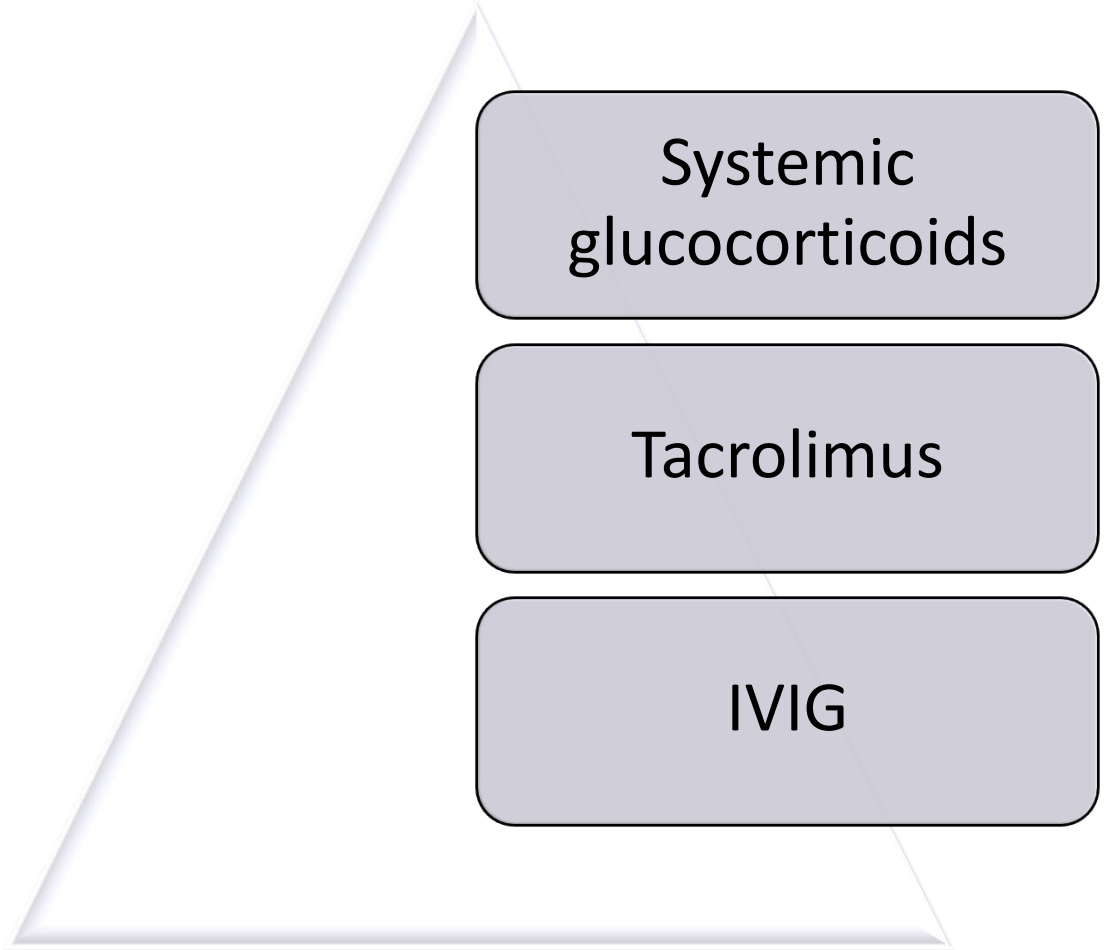
Adapted from Walter J. et al. (2016) J. Allergy Clinical Pract.

What would be the suggested treatment approach of FB in this patient?

Treatment Approach

- IVIG
- Preventative antibiotics
- Prevent & treat infections
- Consider airway clearance
- Nutritional therapy
- Anti-inflammatory therapies
  - No RTC
- Targeted therapies if underlying disorder found
- Monitor progression

TREATMENT



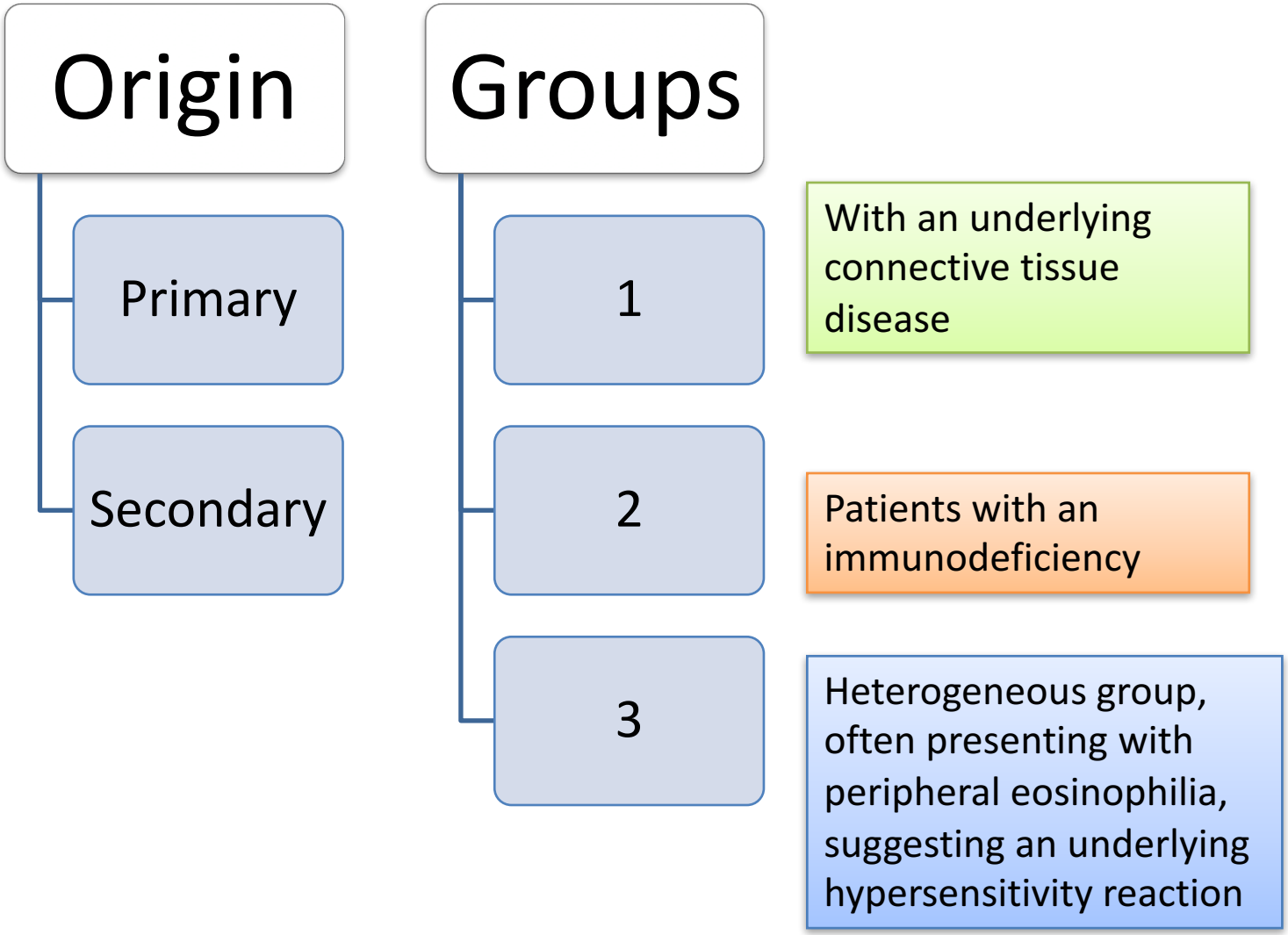
CONSIDER FOLLICULAR BRONCHIOLITIS IN PATIENTS WITH

- Chronic cough
- Recurrent upper respiratory tract infections
- Unexplained progressive dyspnea

Not an easy diagnosis

Toprak E. , Follicular bronchiolitis: a rare disease in children, Tu̇rk Ped Ars̨ 2014; 49: 344-7

CLASSIFICATION



Toprak, E, **Follicular bronchiolitis: a rare disease in children,** Türk Ped Arş 2014; 49: 344-7

Connective tissue disease
Sjögren's syndrome [13,14] Rheumatoid arthritis [15,16] Systemic lupus erythematosis [17,18]
Other immunological disorders
Evans Syndrome (Autoimmune haemolytic anaemia and immune thrombocytopenia) [19,20] Pernicious anaemia [21]
Immunodeficiency
AIDS, particularly in children [22] Common variable immunodeficiency (CVID) [23,24]
Infections
Pneumocystis Jirovicci pneumonia [25] *Legionella pneumonia* [26] Active hepatitis [27]
Interstitial lung diseases [24, 28-30]
LIP Respiratory bronchiolitis-ILD (RB-ILD) Desquamative interstitial pneumonia (DIP) Hypersensitivity pneumonitis (HP) Cryptogenic organizing pneumonia (COP) Granulomatous lymphocytic-ILD (GLILD)
Airway inflammatory diseases [10,11]
Bronchiectasis Asthma COPD
Familial [31,32]
Idiopathic (primary)

[Table/Fig-2]: Diseases associated with follicular bronchiolitis

Table 1: Clinical, radiological, and pathological findings in the common small airways diseases [1, 3, 4, 6, 11, 15].

Histologic classification [6]	Clinical features	High resolution CT scan findings	Common causes
Cellular bronchiolitis	Mild dyspnea ± cough in adults; acute onset in infants; obstructive and/or restrictive pattern; good prognosis	Linear opacities or small centrilobular nodules	Infection, collagen vascular diseases, immune disorders
Nonspecific chronic bronchiolitis	Obstructive and/or restrictive pattern; variable prognosis	Linear opacities or centrilobular nodules	Infection, collage vascular diseases, posttransplantation graft versus host disease, IBD
Follicular bronchiolitis	Progressive dyspnea, chronic cough, recurrent URTI; obstructive and/or restrictive; generally good prognosis	Peribronchial nodules ± ground-glass opacities	RA, Sjogren syndrome, CVID, AIDS, hypersensitivity pneumonitis
Diffuse panbronchiolitis	Chronic productive cough, dyspnea, sinusitis; progressive airflow obstruction	Tree-in-bud appearance and centrilobular nodules	Idiopathic
Constrictive bronchiolitis obliterans	Chronic cough, dyspnea, wheeze; irreversible airflow obstruction on pulmonary function tests	Tree-in-bud pattern; low attenuation/mosaic perfusion	Lung transplant rejection, mineral dust disease, toxin/fume exposure, IBD, collagen vascular diseases
Respiratory (smoker's) bronchiolitis	Usually asymptomatic/incidental; excellent prognosis	Normal, ground-glass opacities and micronodules	Heavy smoking

IBD, inflammatory bowel disease; RA, rheumatoid arthritis; CVID, common variable immunodeficiency syndrome; AIDS, acquired immunodeficiency syndrome.

PROGNOSIS

- More progressive disease and higher mortality in patients:
  - Under 30
  - With underlying immunodeficiency

Shipe R, Lawrence J, Green J, Enfield K.Am J Respir Crit Care Med. 2013;188(4):510-1
Camarasa Escrig A, Amat Humaran B, Sapia S, León Ramírez JM. Follicular bronchiolitis associated with common variable immunode ciency. *Arch Bronconeumol*. 2013;49(4):166-68.
Costa-Carvalho BT, Wandalsen GF, Pulici G, Aranda CS, Solé D. Pulmonary complications in patients with antibody de ciency. *Allergol Immunopathol*. 2011;39:128-32.

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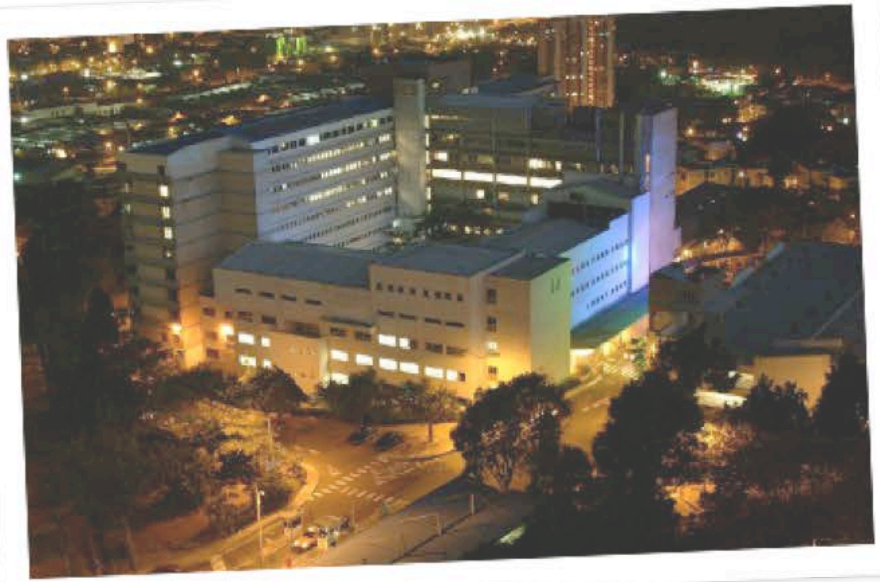
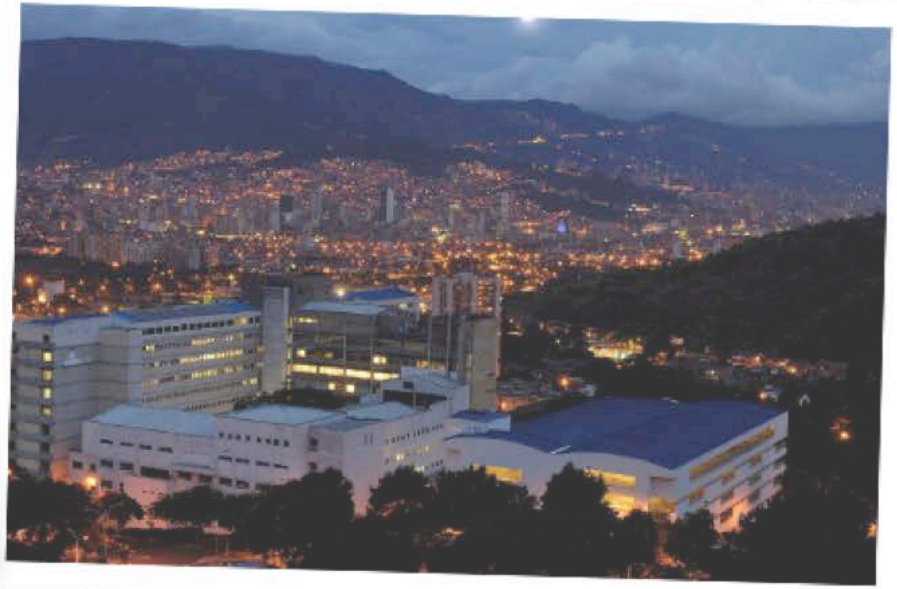
EL HOSPITAL CON ALMA

Pablo Tobón Uribe





Thank you!

CHEST RADIOGRAPHY IS MOST OFTEN NORMAL IN PATIENTS WITH FOLLICULAR BRONCHIOLITIS, BUT HIGH RESOLUTION CHEST COMPUTED TOMOGRAPHY (HRCT) SCAN CAN BE USEFUL

WHICH OF THE FOLLOWING ARE THE MOST COMMON HRCT FINDINGS NOTED IN CHILDREN WITH FOLLICULAR BRONCHIOLITIS

A Small centrilobular nodules associated with bilateral patchy ground glass opacities

B Peripheral sub-pleural small nodules associated with cysts

C Bronchial wall thickening and mild interlobular septal thickening

D Bronchiectasis associated with mosaic attenuation pattern

E Honeycombing and peribronchovascular consolidation

IN A 8 YEAR OLD GIRL PRESENTS WITH CHILDREN'S INTERSTITIAL LUNG DISEASE (CHILD) SYNDROME AND IS FOUND TO HAVE AN HISTOPATHOLOGIC DIAGNOSIS OF FOLLICULAR BRONCHIOLITIS ON LUNG BIOPSY. WHICH OF THE NEXT OPTIONS, WOULD BE THE LEAST HELPFUL IN FINDING A SECONDARY CAUSE FOR THE DISEASE

A Autoimnume profile.

B Immunoglobulin levels and lymphocyte subsets

C HIV testing

D Testing for adenovirus ,Legionella, mycoplasma pneumonia, and hepatitis

E Eosinophil count

WHICH OF THE FOLLOWING IS A MAIN CHARACTERISTIC OF THE BIOPSY FOR THE DIAGNOSIS OF FOLLICULAR BRONCHIOLITIS?

A. Chronic pleuritis overlying cellular non-specific interstitial pneumonia pattern.
B Fibrotic non-specific interstitial pneumonia pattern
C. Peribronchovascular cysts
D. Presence of well formed lymphoid follicles in the walls of bronchioles and narrowing or complete obliteration of the bronchiolar lumen.
E. Uniform thickening of all of the alveolar walls and scant chronic inflammation