

CROSS CANADA ROUNDS - Long Case

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BC Children's Hospital

21 June, 2018

Long Case

History

- 10 Y, Boy

Feb 8th

- Fever- low-moderate grade, rhinorrhea, cough (dry), mild sore throat
- Nausea, non bilious vomiting

Day 5- worsening cough -dry, sleep disturbance.

- Walk in clinic- no wheeze. Prescribed ventolin. Minimal improvement

Day 8- redness eyes, purulent discharge, blisters on lips, ulcers on tongue & buccal mucosa. Difficulty to swallow solids.

History- cont

- No headache, abnormal movements, visual or hearing loss
- No chest pain/stridor/
- No diarrhoea. Vomiting stopped after D3
- No hematuria/dysuria.

Feb 17 (D10)- BCCH ED :

- concerns for extensive oral mucositis, new onset skin rash.

Past Hx

- Healthy pregnancy. No complications.
- Born by SVD, no neonatal resuscitation/NICU stay.
- Recurrent OM- evaluated by ENT-not required myringotomy tubes.
- Mild eczema.

Development - milestones normal

Immunization- upto date

Allergies- no known

Treatment Hx- Tylenol/benadryl/Ventolin. No antibiotics/NSAIDS

FHx- Caucasian descent. unremarkable.

Social Hx- active in sports. No exposure to pets/smoke

Physical exam

- Weight- 37.9kg(77centile)
- HR-96/min, RR-30/min ,
- SPO2 94% RA, T-39.2°C, BP115/64
- HEENT-
- B/L conjunctival injection, purulent discharge
- Lips, buccal mucosa , soft & hard palate-scattered vesicles & superficial erosions. No crusting (serous/hemorrhagic)
- B/L ears-normal
- No clubbing/lymphadenopathy

Skin-

- pink papules, 2-3mm, central erosion, about 15-20 on trunk, upper & lower extremities. Sparing palms & soles.
- MSK-no arthritis
- Perianal skin, glans- normal

Systemic Examination

- **Respiratory** - tachypnea. No retractions/indrawing. B/L air entry decreased. No wheeze/crackles.
- **CVS**-S1 S2 normal. no murmur
- **PA**- no HSM
- **Neurological** - conscious. Well oriented. No cranial nerve/cerebellar involvement. Tone normal

Investigations: Blood Work

- **WBC 16.8, N13.8, L1.72, M1.10, E0.06**
- Hb 126, Plt 257
- **CRP 55**
- Glu- 5.2
- Liver transaminases-normal
- Lytes/Urea/Creat-normal

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PA 92/1

LEP

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Differential Diagnosis?

Infectious causes

- Viral
- Atypical organisms-*Mycoplasma pneumoniae*

Non-Infectious

- Stevens-Johnson Syndrome (drug/infection triggered)
- ?Kawasaki Syndrome
- ?Behçet's

Investigations

Blood work

- WBC 16.8
- Hb 126
- Plt 257
- N13.8, L
- CRP 55
- Glu- 5.2
- Liver transaminases-normal
- Lytes/Urea/Creat-normal
- NPW
- Viral panel –neg
- Nasopharyngeal FLOQ swab-
Mycoplasma pneumoniae PCR- positive
- Oral swab- HSV 1 & 2- negative
- Blood /Urine Cx- no growth

Dermatology consultation

DDX

- *Mycoplasma pneumoniae* induced rash mucositis syndrome
- Stevens–Johnson syndrome (secondary to *Mycoplasma*)
 - Mostly mucositis
 - Skin- no typical target lesions (EM) or bullae
 - No H/o drug intake
 - Less likely

Skin Biopsy

- Patchy lichenoid inflammation with basal & suprabasal dyskeratotic Keratinocytes, suggestive of **erythema multiforme**.
- No eosinophils/viral cytopathic effects. Negative fungal stain.
- Histological differentials
 - Drug induced
 - Viral exanthem
 - *Mycoplasma* induced rash & mucositis (MIRM)

Diagnosis

Mycoplasma pneumoniae pneumonia with mycoplasma induced rash and mucositis.

Mycoplasma pneumoniae—induced rash and mucositis as a syndrome distinct from Stevens-Johnson syndrome and erythema multiforme: A systematic review

- “Atypical SJS”, “incomplete SJS”, “Fuchs syndrome”,
- Characterized by severe & painful oral, ocular and urogenital mucositis
- Less prominent or scattered skin lesions- vesiculo-bullous, macular, papular, morbilliform eruptions
- Target lesion **NOT SEEN**--hallmark of SJS/TEN and Erythema multiforme
- Younger age- Children 2-20 yrs; males (66%)
- MIRM has milder disease course, infrequent hepatic/renal involvement, no reported encephalopathy, in comparison to SJS
- Treatment options- antibiotics, systemic steroids, supportive, IVIG
- Prognosis better than SJS

Management

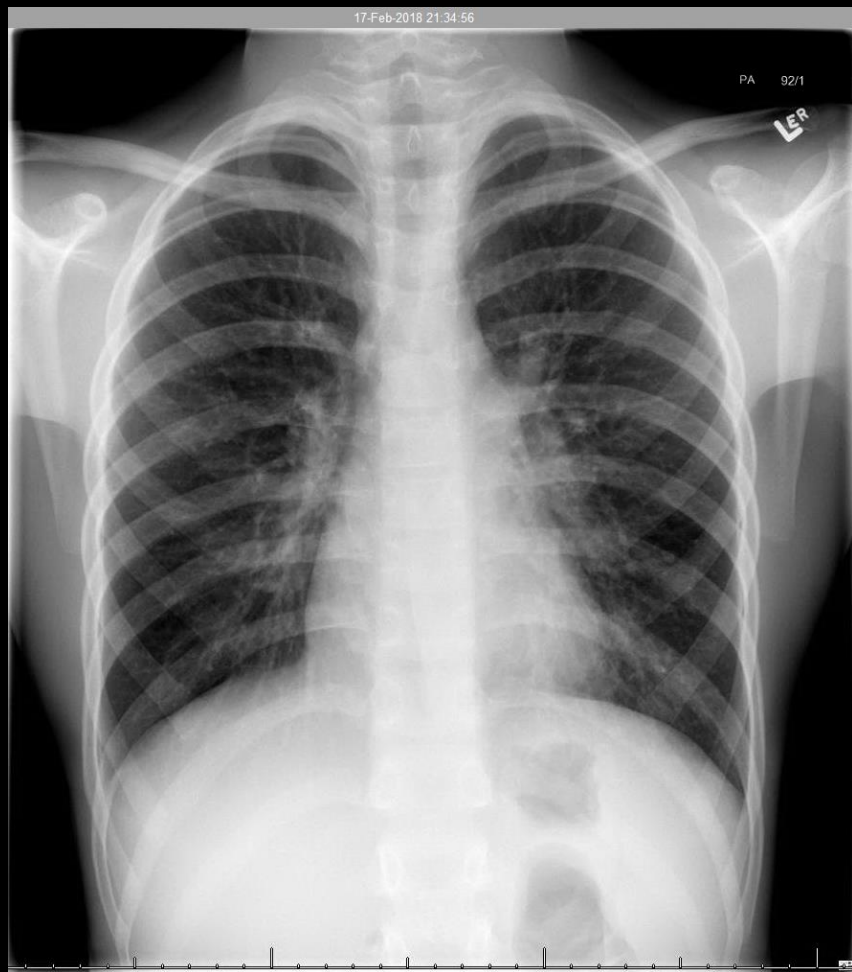
- 5 day course oral Azithromycin
- IV fluids
- Oral mucositis- Aquaphor lubrication for lips, Analgesic mouthwashes
- Ophthalmology consultation- erythromycin eye drops, artificial tears
- Pain- Tylenol , Advil. Morphine *prn*.

Course In Hospital

- Continued to spike fever (temp 38.6-39.5) till D5 of admission.
- Resp- tachypneic (RR 18-30), SPO2-97-99% RA
- Required NP oxygen one night for desats early AM, 92% lowest, 1L/minNP
- Oral mucositis persisting. Ocular inflammation improved.
- Gradually tolerating oral fluids, yogurt.
- Discharged on D8

Post Discharge FU- Gen Pediatrics (D3, D5, D10)

- Afebrile
- Appetite improved. Difficulty tolerating solids due to pain. Mostly on oral fluids
- Looked frail. Weight 33.7kg (Lost 4.5 kg since illness onset)
- Dry cough. Woke up at night with coughing,
- ? Dad felt wheezing at night
- Exam- chest clear. Mucositis (oral, ocular) improving.
- CxR done D10.
- No PFTs



During admission



Post discharge D10

Readmitted 10 April, 2018- (2 mo later) indication- worsening cough, WOB

- At presentation in ED at BCCH
- RR 44/min, HR 110/min, SPO2-96% RA, Afebrile
- Chest- B/L crackles & wheeze
- PRAM-8, treated as moderate asthma
- Ventolin + Atrovent
- IV methylpred 1mg/kg q 6 hr, MgSO4x1
- Persistent symptoms-
- shifted to PICU for BiPAP 14/6, FiO2 30%

Respiratory Consultation

Since discharge from previous hospitalization, persistent respiratory symptoms

Cough

- Intermittently wet, whitish mucoid
- Non spasmodic
- No diurnal variation but coughing at night also

Shortness of breath

- Able to just walk few steps in the house, felt tired & needed rest

- No respiratory noises/wheeze heard
- No chest pain/tightness/hemoptysis
- No recent travel outside north America
- No contact with TB patient

Rx by GP

- Azithromycin x5d,
- Amoxicillin x 5days
- Oral prednisone x 5 days-twice
- Ventolin PRN
- Some relief to symptoms

Exam

- High Flow 35L/min, FiO2 30%, SPO2 98%
- RR 25/min, HR 116/min
- No stridor/audible wheeze
- No retractions on High Flow
- Off High flow- tracheal tug, using sternocleidomastoid, mild ICR
- No clubbing/lymphadenopathy/rash
- No joint pain/tenderness/swelling
- Resp- B/L prolonged expiration
- No wheeze,
- B/L crackles posteriorly
- On Ventolin 10 puffs q one hour
- PA- No HSM
- CVS- no murmur
- Neuro- normal

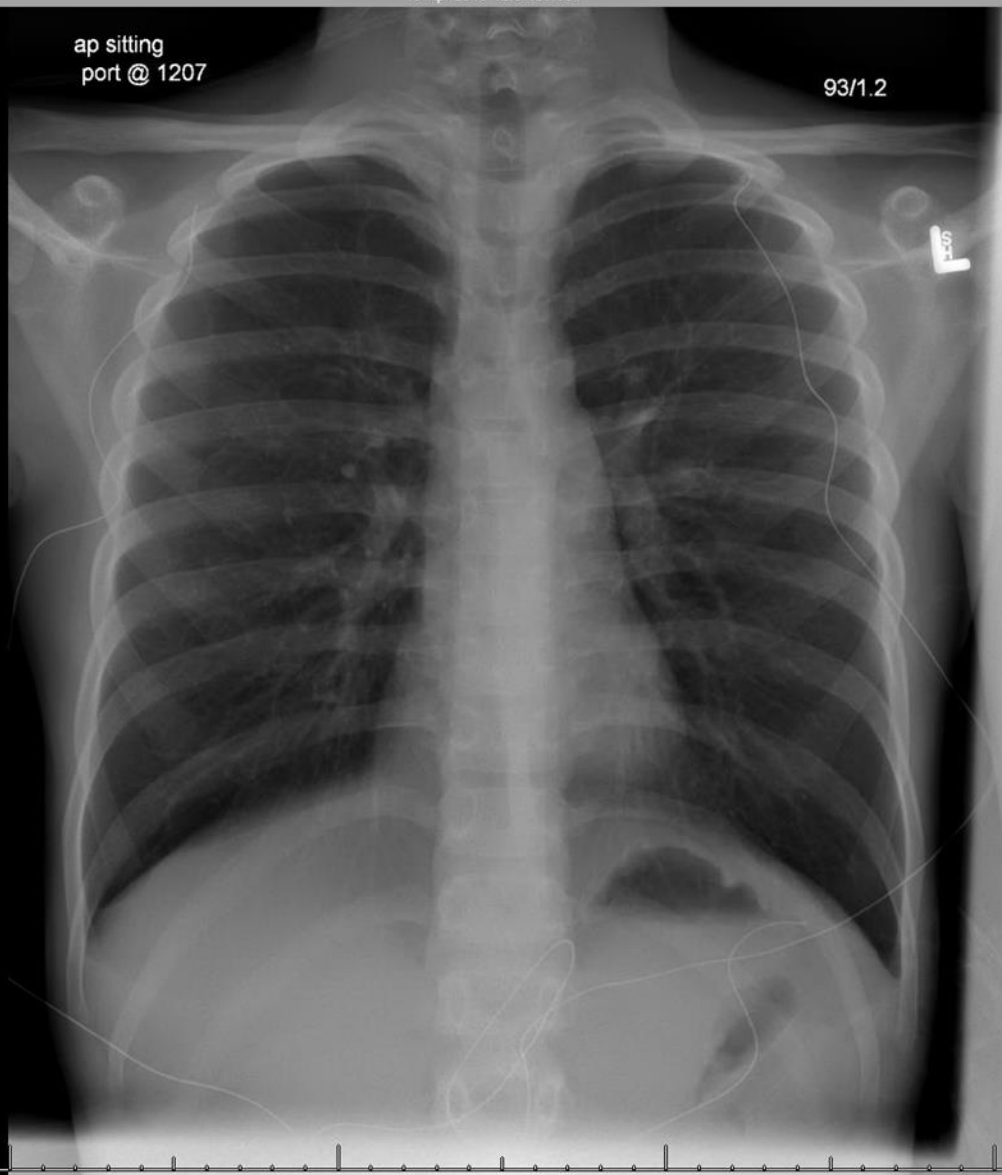
Investigations

- WBC-11.7 , N9.37, L1.8, M0.3, E0.
- Hb-141
- Plt-188
- Lytes/Urea/Creat- Normal
- LFT- normal
- Blood Cx- no growth
- Sputum Cx- normal flora, AFB neg
- Sputum-fungal Cx- no growth
- NPW- *Mycoplasma* negative
- NPW- *Streptococcus pneumoniae* +
- IgG, IgM, IgA, IgE-normal
- ANA, ANCA-negative
- ECHO-normal LV SF-69%
- Troponin I- <0.02 –normal
- Sweat chloride- 11mmol/L

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ap sitting
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Differential Diagnosis

Differential Diagnosis

- Post Infectious (*Mycoplasma*) Bronchiolitis Obliterans
- *Mycoplasma* induced asthma/wheezing
- Resistant *Mycoplasma* infection

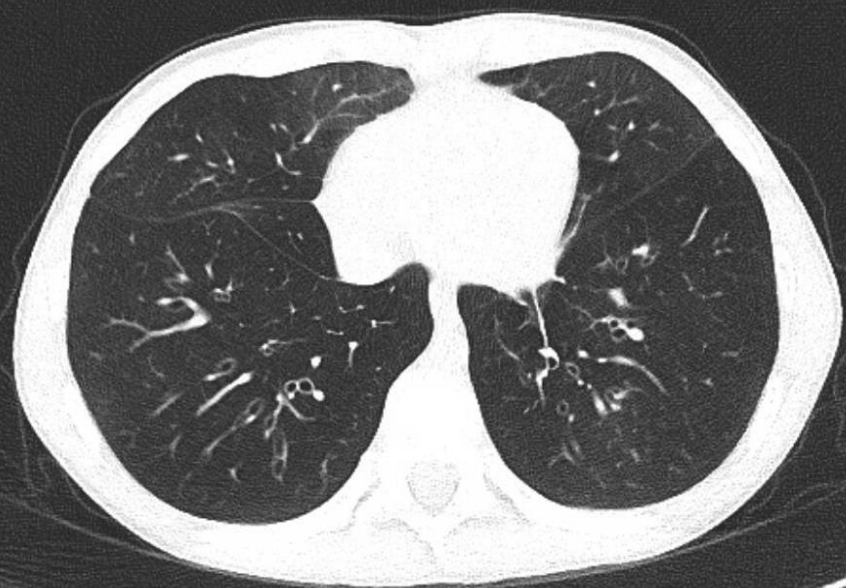
Table 2 - Differential diagnosis: postbronchiolitis recurrent wheezing and postinfectious BO

Postinfectious	Postbronchiolitis BO	Recurrent wheeze
Symptomatology	Persistent	Recurrent
Fine crackles	Persistent	Absent
Radiological alterations	Persistent	Recurrent
Pathophysiology	Obliteration of bronchioles	Bronchial hyperresponsiveness
Response to bronchodilator use	Unsatisfactory	Satisfactory
Prognosis	Unfavorable	Favorable

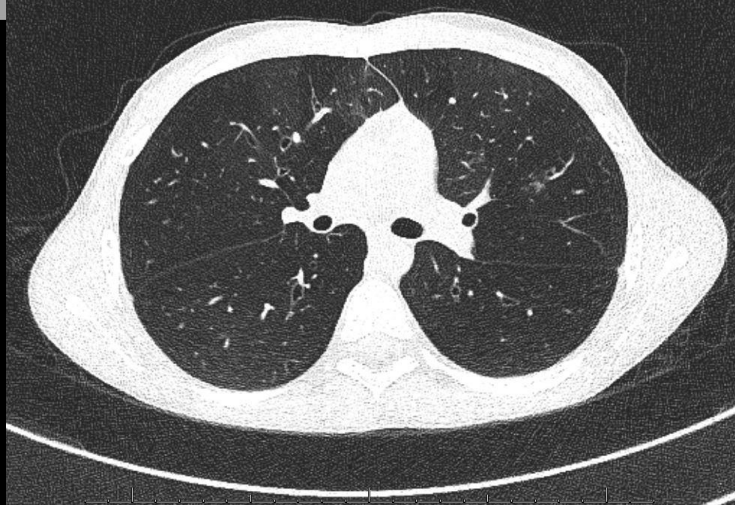
What next steps in evaluation

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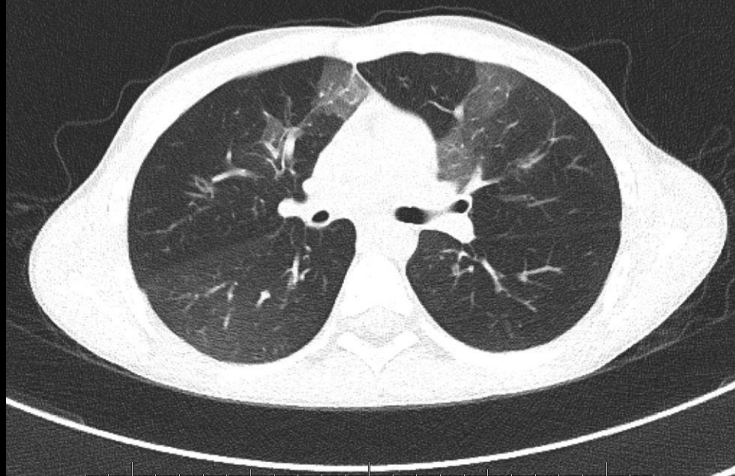


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Inspiratory

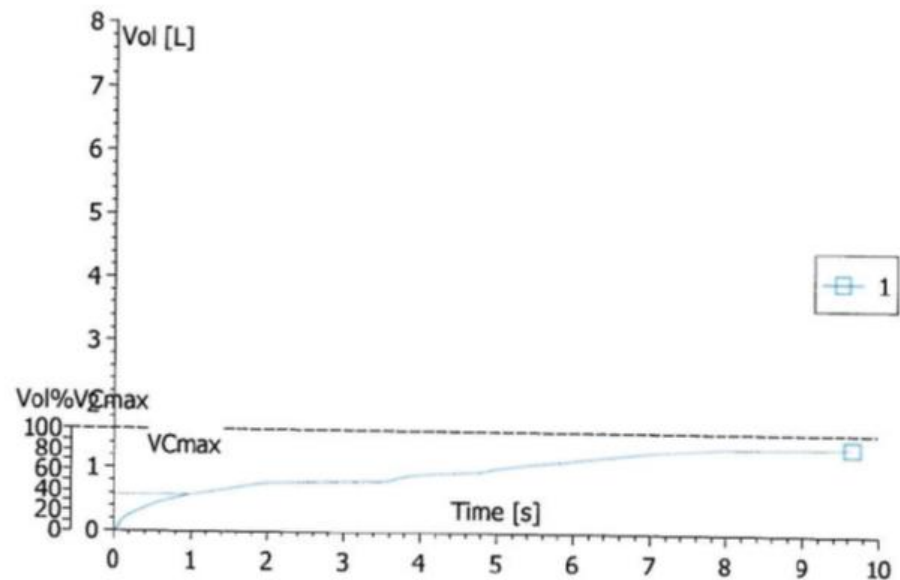
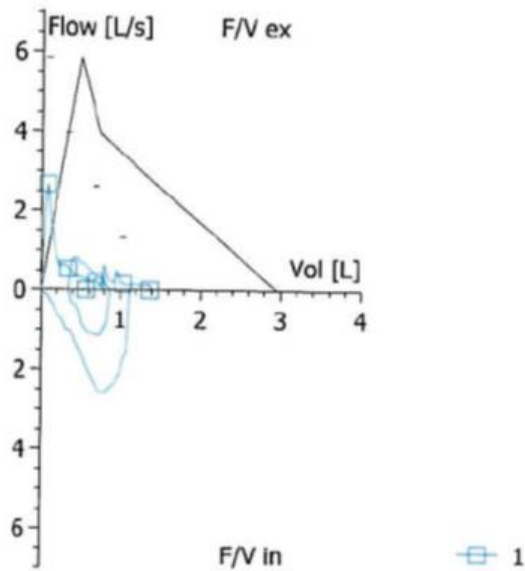
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Expiratory

PFT

	FVC	FeV1	FeV1 /FVC	FeF 25-75%	% Change FeV1	SPO2
13 Apr (D3 Adm)	1.05L(36%)	0.53L(21%)	50	0.28L(11%)	+7	96%
17 Apr	1.38L(47%)	0.56L(23%)	41	0.14L(5%)	-	94%



Summary

- 10 year old boy , previously healthy and developmentally normal
- Mycoplasma pneumoniae pneumonia with mucositis (MIRM or atypical SJS).
- Ongoing cough, exertional dyspnea x 2months, slowly resolving mucositis
- 2 mo later- Respiratory distress , B/L crackles +wheeze
- CxR- hyperinflation. No significant parenchymal changes
- CT chest- air trapping, mosaic attenuation, peribronchial thickening, bronchiectasis
- Spirometry- fixed, very severe airflow obstruction with restriction.
- **Current clinical diagnosis** - Post Mycoplasma bronchiolitis obliterans with mycoplasma induced rash & mucositis (MIRM)

Bronchiolitis Obliterans

- Bronchiolitis obliterans (BO) is characterized by chronic progressive airway obstruction.
- Inflammation & granulation tissue in small airways (terminal bronchiole & higher)
- progresses to fibrosis and scarring
- leading to partial or total occlusion of the airway lumen
- associated with large airway bronchiectasis.

Causes

Postinfectious

Posttransplant

Chronic rejection of lung or heart/lung transplantation
Graft-versus-host disease associated with bone marrow transplantation

Connective tissue disease

Rheumatoid arthritis
Sjogren's syndrome
Systemic lupus erythematosus

Toxic fume inhalation

NO₂
NH₃

Chronic hypersensitivity pneumonitis

Avian antigens
Mold

Aspiration

Stomach contents: gastroesophageal reflux

Drugs

Foreign bodies
Penicillamine
Cocaine

Stevens–Johnson syndrome

Idiopathic
Drug-induced
Infection-related

Post Infectious Bronchiolitis Obliterans (PIBO)

- Exact incidence not known
- Most common form of BO reported in children
- Most reported from South America (Argentina, Brazil, Chile), East & west Europe, Asia (Korea, Taiwan, India), Australia& NZ
- Studies from Chile & Argentina- among infants hospitalized with adenoviral LRTI, PIBO developed in 40%.
- Most common organisms- Adenovirus, Mycoplasma

Many faces of Bronchiolitis terminologies

Cellular bronchiolitis

Bronchiolitis obliterans

Obliterative bronchiolitis

Organising pneumonia

Bronchiolitis obliterans syndrome

Bronchiolitis obliterans organising pneumonia (BOOP)



Cellular bronchiolitis	Bronchiolar wall is infiltrated with inflammatory cells
Bronchiolitis obliterans (pathologist prefer)	Lumen of bronchiole narrows due to inflammation and/ fibrosis/granulation tissue
Obliterative bronchiolitis (clinicians prefer)	Synonymous; designates clinical condition with airflow obstruction at PFT & characteristic features on HRCT.
Bronchiolitis obliterans syndrome (BOS)	Delayed allograft dysfunction after lung transplantation/HSCT, airflow obstruction
Organising Pneumonia/ cryptogenic OP (formerly BOOP)	When inflammation/granulation extends to involve alveoli (masson body)

Small Airway Disease

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

Sputum cell counts in induced sputum of BO patients and healthy controls.

	Controls (n = 23)	BO (n = 20)	p-Value
Total cells ×10 ⁴ /ml	22.5 (6.6–153.0)	115.0 (20.0–818.0)	<0.0001
Macrophages ×10 ⁴ /ml	384.0 (191.0–400.0)	91.0 (29.0–256.0)	<0.0001
Macrophages (%)	97 (63–100)	28.3 (7–64)	<0.0001
Neutrophils ×10 ⁴ /ml	5.0 (0.0 – 128.0)	275.5 (47.0–371.0)	<0.0001
Neutrophils (%)	2 (0–32)	68.9 (30–93)	<0.0001
Lymphocytes ×10 ⁴ /ml	3.0 (0.0–36.0)	7.0 (0.0–28.0)	0.01
Lymphocytes (%)	1 (0–9)	2 (0–7)	0.01
Eosinophils ×10 ⁴ /ml	0.0 (0.0–42.0)	0.0 (0.0–4.0)	n.s.
Eosinophils (%)	0 (0–8)	0 (0–1)	n.s.

Cytokines measured by CBA in the induced sputum supernatant of controls and patients with BO.

Cytokines		Controls (n = 23)	BO (n = 20)	p-Value
IL1-β	pg/ml	147.5 (56–3511)	923.7 (82–99,313)	<0.001
IL-6	pg/ml	0 (0–604)	324.7 (0–3541)	<0.001
IL-8	pg/ml	1742 (529–49,658)	21110 (579–49,658)	<0.001
TNF-α	pg/ml	0 (0–0)	0.0 (0–2314)	<0.001
IL-5	pg/ml	0 (0–99)	0.0 (0–122)	n.s.
IFN-γ	pg/ml	116 (0–174)	26.5 (0–325)	n.s.

Histology of Childhood Bronchiolitis Obliterans

Thais Mauad, MD, PhD^{1*} and Marisa Dolhnikoff, MD, PhD,¹ and the São Paulo Bronchiolitis Obliterans Study Group²

34 children with BO- 30 OLB, 2 lobectomy, 2 autopsy

All non-transplant patients, Adeno-3, RSV-1, Measles-1, No viral-15, reflux-9

Airway inflammation- Patchy, multifocal

- terminal bronchioles (50-600µm): mild(wall)-63%, moderate (peribronchiolar)-38%, severe (alveoli)-19%

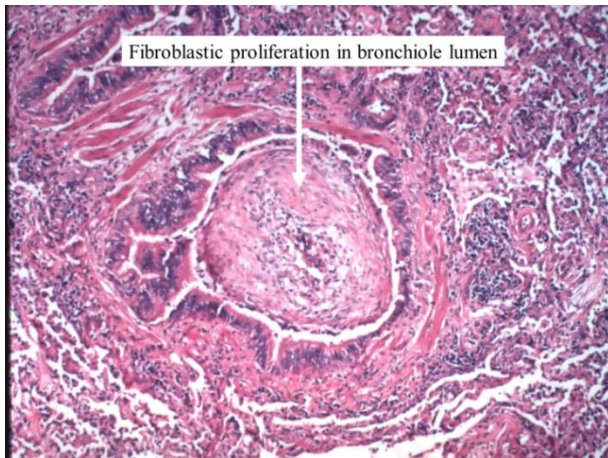
Airway obstruction- mucostasis, foamy macrophages, hyperinflation

Airway architecture- hyperinflation-40%, collapse-24%

Myers & Colby pathological classification

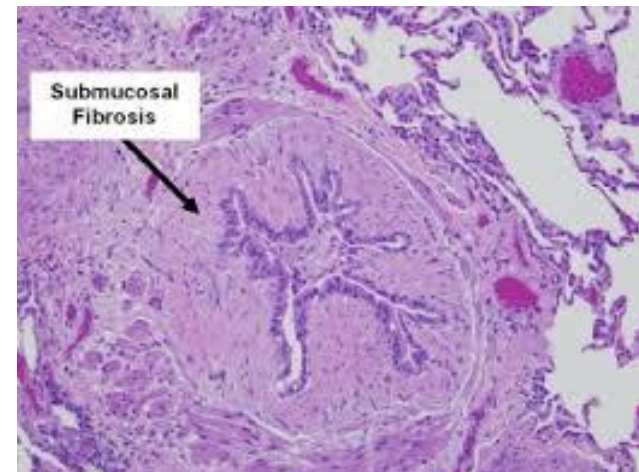
Proliferative BO

- Classical type
- Polyps of granulation tissue in bronchiolar lumen



Constrictive BO

- Most common childhood BO
- Submucosal fibrosis leading to luminal narrowing
- Poor response to steroids



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

A J Colom, A M Teper, W M Vollmer, G B Diette



Thorax 2006;**61**:503–506. doi: 10.1136/thx.2005.044909

Argentina; Case- control study: 109 cases, 99 controls, Children < 3 years

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.

Other Risk factors for PIBO

- Hospitalization >30 days
- Admission in ICU
- Need for supplemental O2
- Multifocal pneumonia
- Hypercapnea
- Those prescribed systemic steroids

Castro-Rodriguez et al. Pediatr Pulmonol 2006

Murtagh P et al. Pediatr Pulmonol 2009

Clinical Presentation

Acute Bronchiolitis/pneumonia stage

Cough, fever, dyspnea, wheezing, crackles
O2 requirement/mechanical ventilation

1-8months



Bronchiolitis Obliterans stage

Persistent wet cough, wheezing, crackles
Dyspnea at rest or exertion
O2 supplementation- median period 30 mo
Symptoms persist for several months

Severe cases PIBO

Recurrent pneumonia/atelectasis
Wheezing exacerbations
Reduced exercise capacity
Bronchiectasis, clubbing, Thoracic wall deformity
Pulmonary hypertension

Diagnosis- PIBO

1. Chest Xray- hyperinflation, peribronchial thickening, atelectasis, bronchiectasis
2. Pulmonary function-
 - Fixed airflow obstruction
 - Reduced FVC –may reflect severe obstruction
 - Some patients may show significant bronchodilator response
3. Plethysmography
 - TLC normal, RV increased, RV/TLC increased reflecting air trapping & obstruction.

Diagnosis- CT/HRCT chest

Post-infectious Bronchiolitis Obliterans

Abnormalities in the CT of the Lungs of 250 Children and Adolescents [*]		
	n	%
Mosaic perfusion	220	88
Air trapping	230	92
Bronchial Wall Thickening	195	78
Bronchiectasis	240	96
Atelectasis	165	66
Mucus Plugging	145	58

G.B. Fischer et al. / Paediatric Respiratory Reviews 11 (2010) 233–239

Role of Lung Biopsy

- Gold standard of diagnosis of BO
- Patchy, multifocal involvement- yield not always informative
- Suggestive history, imaging, lung function may be sufficient for diagnosis
- Lung biopsy may be indicated- if dilemma/ rule out other differentials

Treatment & Outcome - PIBO

- No RCT available to guide therapy
- Supportive care
 - Supplemental oxygen, maintain sats >94%
 - Respiratory physiotherapy in bronchiectasis
 - Respiratory muscle strength training
 - Nutritional care
 - Vaccination- respiratory pathogens
- Corticosteroids-
 - Oral prednisone/ pulse methylprednisolone- several months
 - Inhaled steroids
- Bronchodilators-
 - some may have bronchodilator reversibility- inhaled LABA
- Macrolides-
 - Azithromycin- anti-inflammatory & immunomodulatory
- Antibiotics- pulmonary exacerbations if bronchiectasis
- Lung transplantation- severely impaired pulmonary function, oxygen dependency

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

Brazil, 1996-2007, retrospective follow up
40 children (5mo-13Y); 37 post infectious
Pulse methylprednisolone dose-30mg/kg/day x 3 days

Characteristics of the clinical follow-up of patients with BO

Characteristics (n = 40)

Age at beginning of follow-up	mean 40.9, median 25 (6-186 months)
Follow-up period	mean 51.6, median 49.2 (<u>23-93 months</u>)
Age at beginning of pulse therapy	mean 50.5, median 31.5 (6-180 months)
Onset of disease/pulse therapy interval	mean 32.1, median 18.5 (2-142 months)
Pulse therapy cycles	mean 20.2, median 18.5 (<u>6-40 cycles</u>)
Pulse therapy period	mean 26.2, median 24 (6-48 months)

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

- Reduced frequency of **wheezing** exacerbations at 24 mo ($p=0.0042$)
- Reduced frequency of **hospitalization** after 18mo ($p<0.0001$)
- Improvement in **O2 sats** in 1st year ($p=0.0002$) & 2nd year ($p=0.0005$) after pulse.
- 19 (83%) out of 23 patients were able to **discontinue oral steroids** at an average of 12.4months($p<0.001$)

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

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

Argentina, total cohort 155, PIBO(BO score, HRCT, PFT)
46 children FU ; Mean Age at diagnosis- 14mo±3
Mean Length of FU- 12.5Y±3.5

	Initial Lung Function	Annual Change in Z scores
FVC(z score)	-3.8±1	↓0.07
FeV1(z)	-4.3±1	↓0.09
FeV1/FVC(z)	-2.2±1	↓0.04
FeF 25-75	-3.7±1	
TLC %	120±26	
RV%	309±108	
RV/TLC	55±13	

Mycoplasma pneumoniae– Associated Bronchiolitis Obliterans Following Acute Bronchiolitis

Scientific Reports 2017

Chengsong Zhao¹, Jinrong Liu¹, Haiming Yang¹, Li Xiang² & Shunying Zhao¹

17 patients, PIBO developed 1.5-8 mo after initial infection. Diagnosis on HRCT
Follow Up 1-6 years

	Mild- moderate (n=11)	Severe (n=6)
Symptomatic changes	Improved -11 (100%)	Improved 2 (33%) Worsened- 3 (50%) Unchanged-1
Lung function changes		
Improved	9 (82%)	0
worsened	0	3 (50%)
unchanged	2 (18%)	1
HRCT changes	0	0

Back to Case.....

Management

- O2 Supplement- NP, max 2L/min, weaned after 6 days
- Pulse IV Methy Prednisolone- 30mg/kg x 3 days, f/b monthly pulses.
- Oral Prednisone- 2mg/kg/day x 1 week weaned over 2 weeks to 10mg alternate day
- Azithromycin Oral- 175 mg/day x 2 weeks f/b 500mg three times/week
- Advair MDI (125)- 1 puff BID

Post discharge FU

- 2 weeks- Tachypneic (RR 25/min), no retractions, B/L expiratory wheeze, no crackles.
- 2nd pulse-18th May: RR24/min, no retractions. Occasional wheeze. No crackles. Able to walk up stairs at home without rest.

	FVC %	FeV1%	FeV1 /FVC	FeF 25-75%	% Change FeV1	FRC	TLC	RV	SPO2%	6MWT
13 Apr (D3 Adm)	36	21	50	11	+7	-	-	-	96	-
17 th before 1 st Pulse	47	23	41	5	-	-	-	-	94	221m
7May (2wks post Ds)	61	24	33	8	+6	-	-	-	96	333m
18May (2 nd Pulse)	47	23	41	8	+2	-	-	-	94	-
14 June (3 rd pulse)	49	22	37	6	+11	3.9L 205%	4.9L 127%	3.4L 411%	96	-

Take home Message

- Suspect post infectious BO after LRTI if wheezing/crackles/hypoxemia/dyspnea persist >3-4 weeks.
- Chest X-ray changes may be minimal.
- Diagnosis- A typical history, exam, obstructive airflow defect on spirometry, CT features(mosaic attenuation/air trapping/bronchiectasis).
- Lung Biopsy not always warranted.
- Treatment of Post infectious BO is not standardized but may warrant several months of systemic steroids

