



Cross Canada Rounds

March 21, 2019

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- ▶ This presentation has been adapted from the original for online presentation.
- ▶ Figures have been removed with references for the sources of original figures noted.
- ▶ Timelines have been removed to ensure patient confidentiality.

14y M with Pancreatic Insufficient Cystic Fibrosis

► HPI:

- Cough x 3-4 weeks
- Green sputum, no hemoptysis
- Post-tussive emesis
- Chest pain on BiPAP
- Nasal congestion, rhinitis

14y M with Pancreatic Insufficient Cystic Fibrosis

- ▶ Decreased appetite
- ▶ Tolerating GT feeds
- ▶ No joint pain, myalgia or rash
- ▶ No sick contacts
- ▶ Started Cipro as an outpatient

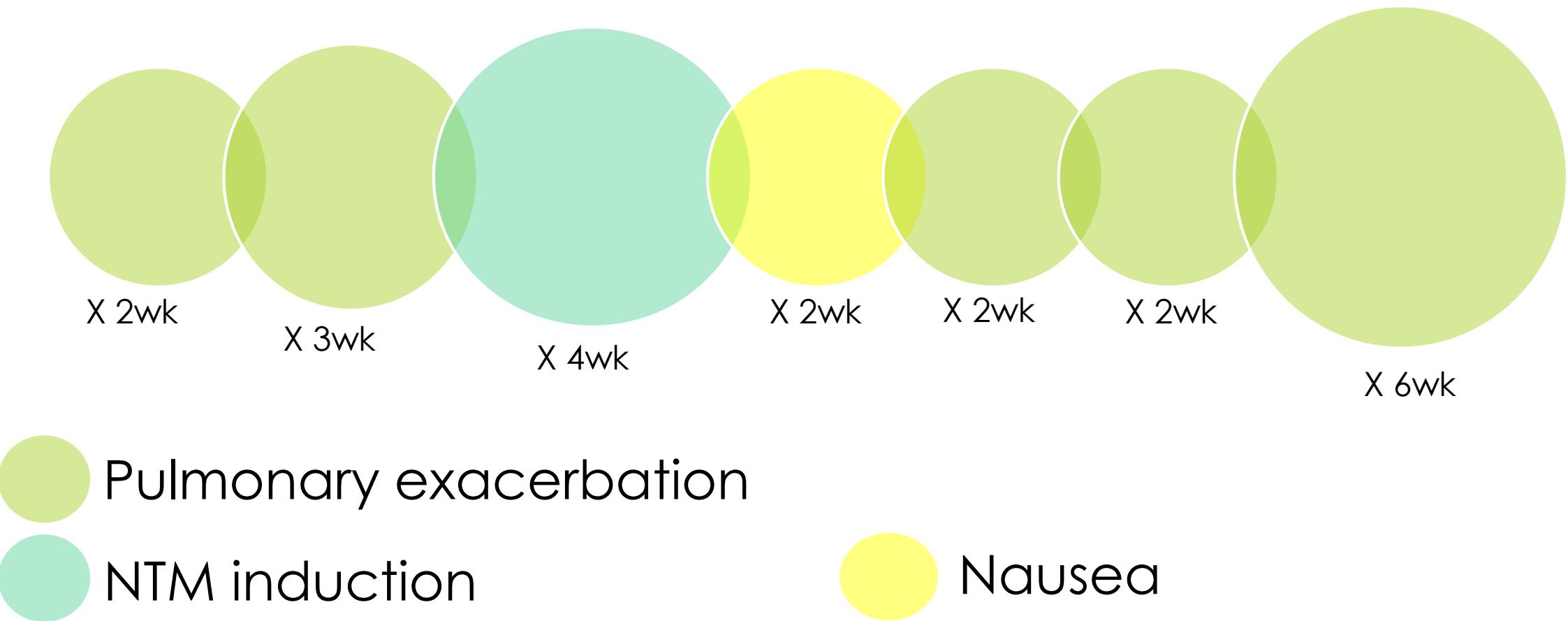
14y M with Pancreatic Insufficient Cystic Fibrosis

- ▶ Physiotherapy:
 - ▶ PEP mask BID
- ▶ Respiratory support:
 - ▶ Nocturnal BiPAP
- ▶ Nutrition:
 - ▶ Daytime high protein high calorie diet
 - ▶ Nocturnal G-tube feeds

Past Medical History

- ▶ Severe CF lung disease
- ▶ Chronic Pseudomonas
- ▶ M. abscessus
- ▶ Nocturnal G-tube feeding for failure to thrive
- ▶ Constipation
- ▶ CF-related liver disease

Admissions (last 5 years):



Surgical History

- ▶ IVAD
- ▶ GT placement for FTT
- ▶ Endoscopic sinus surgery

Medications

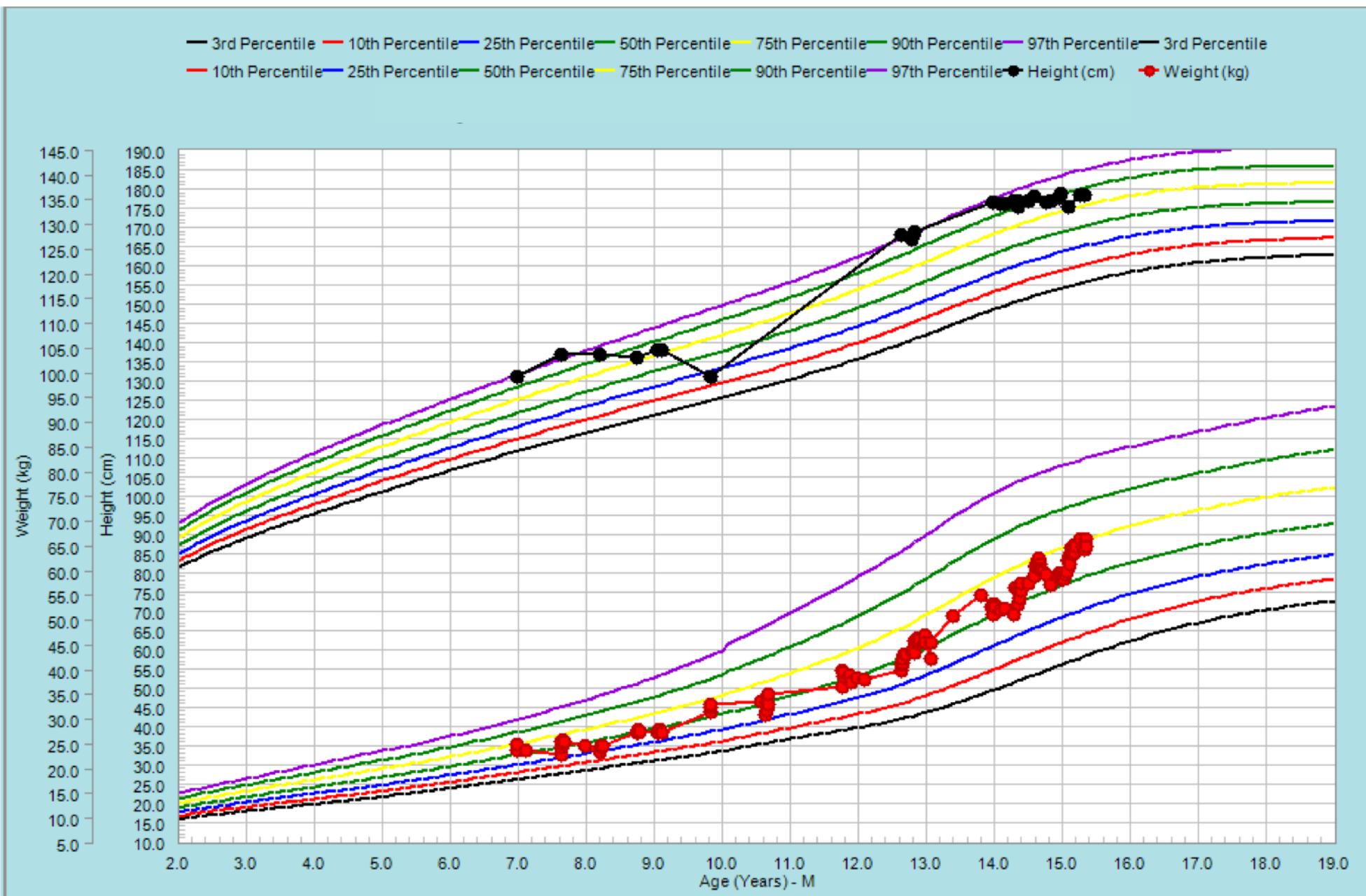
- ▶ Antibiotic for Pulmonary Exacerbation:
 - ▶ Ciprofloxacin 750mg po BID
- ▶ Maintenance NTM antibiotics:
 - ▶ Azithromycin 500 mg po daily
 - ▶ Clofazimine 100 mg po daily
 - ▶ Amikacin 500 mg inhaled BID
- ▶ Routine CF medications:
 - ▶ Pulmozyme 2.5 mg nebulized daily
 - ▶ Hypertonic saline 7% 4 mL nebulized daily
 - ▶ Advair 125 mcg 2 puffs BID
 - ▶ Ventolin 2 puffs inhaled q4h prn
 - ▶ Singulair 10 mg po daily
 - ▶ Nasonex 50mcg 1 spray in each nostril BID

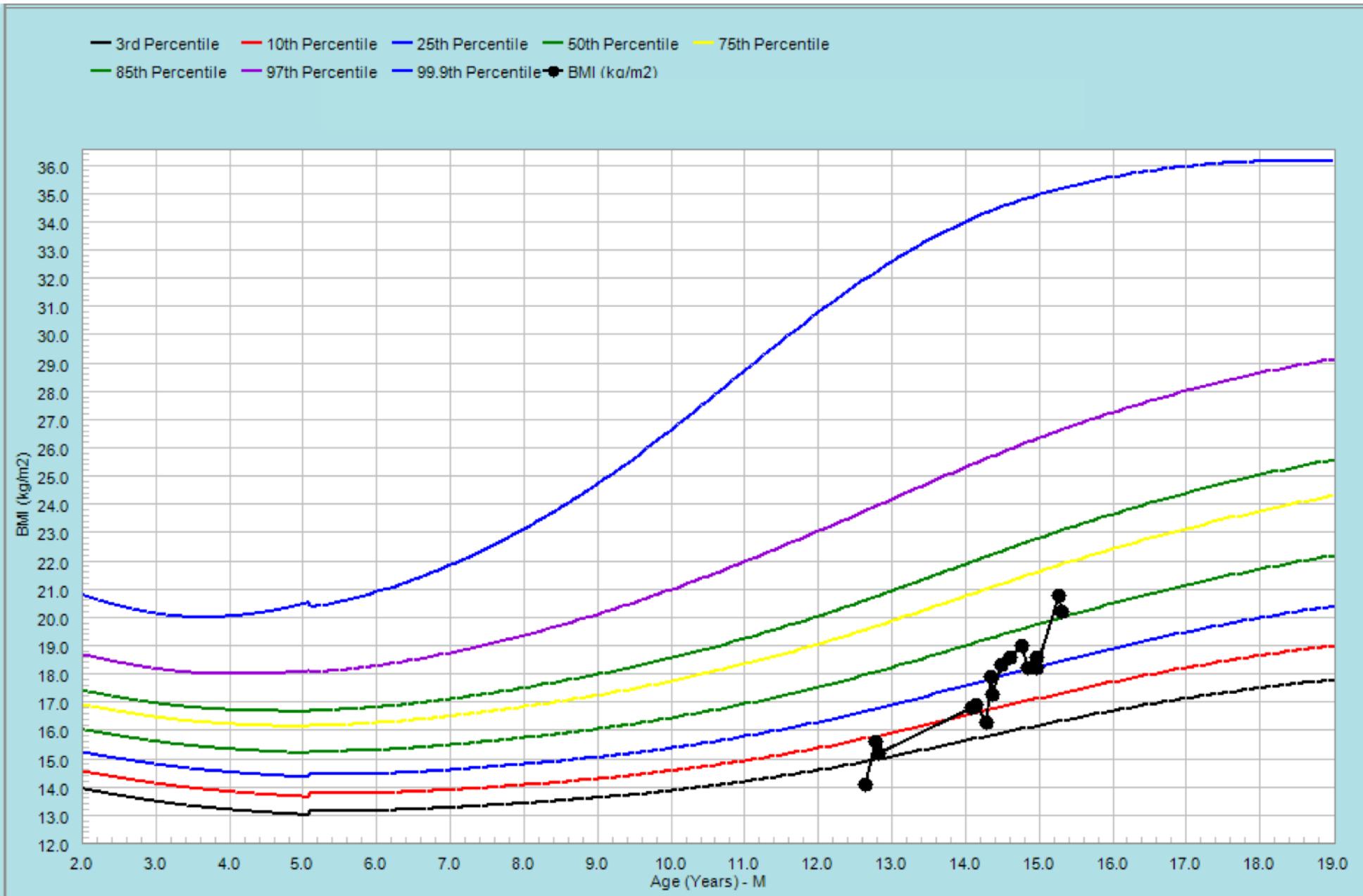
Medications

- ▶ Routine CF Medications:
 - ▶ Creon 25
 - ▶ MVW D3000
 - ▶ Cyproheptadine
 - ▶ Dexlansoprazole
 - ▶ Bisacodyl
 - ▶ Ursodiol
- ▶ Other medications:
 - ▶ Sertraline
 - ▶ Guanfacine
 - ▶ Melatonin

Family and Social History

- ▶ Family History:
 - ▶ No history of CF
 - ▶ Healthy siblings
 - ▶ Otherwise non-contributory
- ▶ Social History
 - ▶ Stress with maintaining adherence to therapy, lack of improvement despite admissions and treatments



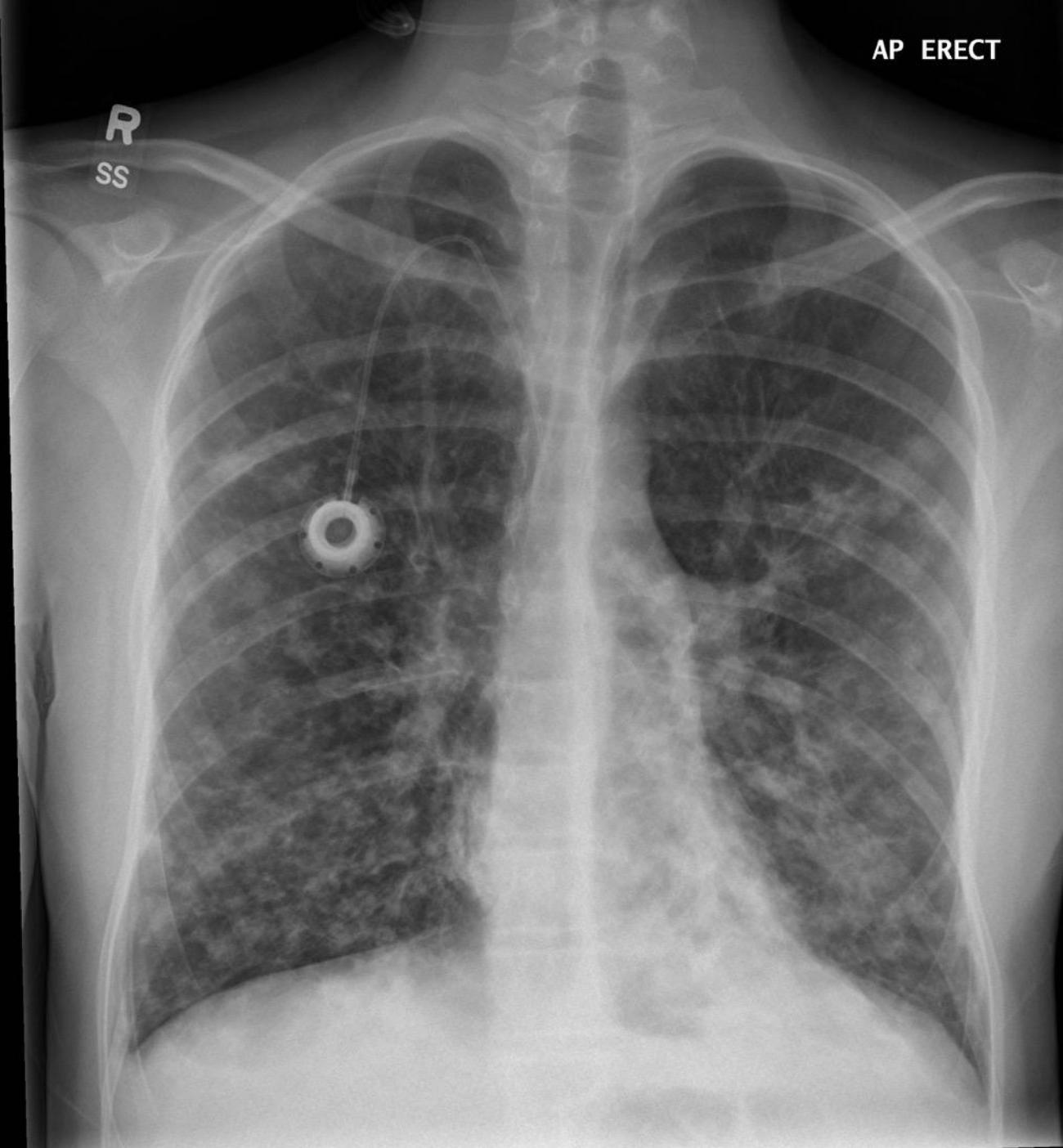


Physical Examination

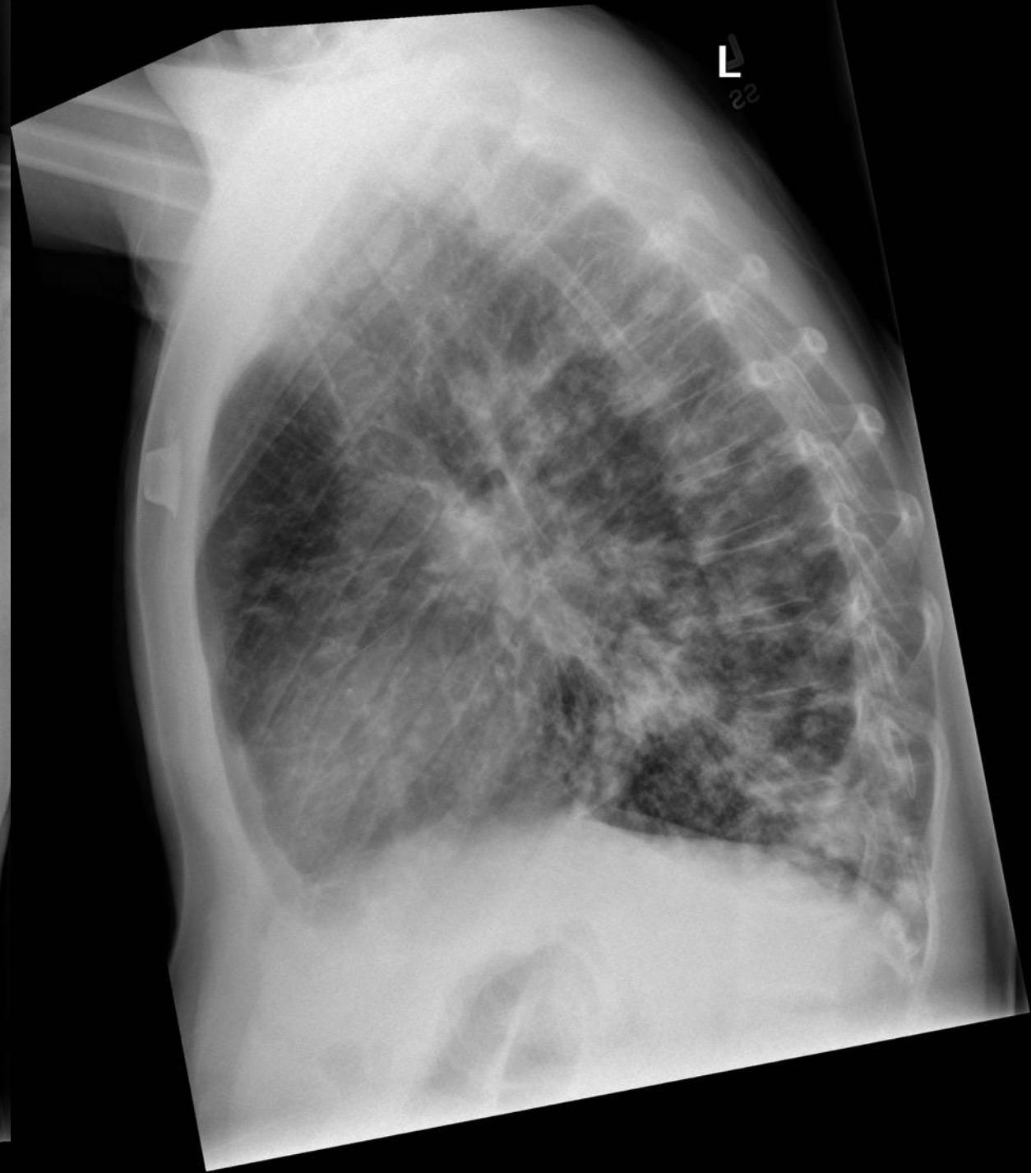
- ▶ Vitals T 37C, HR 116, RR 22, SpO₂ 93-94% on 2LPM NP
- ▶ No distress. Clubbed.
- ▶ HEENT: Erythematous nasal mucosa, clear rhinitis. No obstruction. Normal oropharynx. Few small cervical LNs.
- ▶ CVS: Well perfused. CR 2s. Normal S1 and S2, no murmur.
- ▶ RESP: GAEB, fine crackles diffusely on L and R, more to bases. Expiratory wheeze in left anterior chest.
- ▶ ABD: Soft, no HSM or mass. GT in situ.

AP ERECT

R
SS



L
22



SPIROMETRY

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg	Flow	PRE POST
FVC	Liters	4.22	2.09	49	2.15	51	3		
FEV1	Liters	3.90	1.31	34	1.37	35	5		
FEV1/FVC %		86	63		64				
FEF25-75% L/sec		4.27	0.64	15	0.68	16	8		
FEF25% L/sec		5.94	3.62	61	3.57	60	-1		
FEF50% L/sec		3.93	0.86	22	0.89	23	3		
FEF75% L/sec		2.10	0.26	12	0.26	12	0		
PEF	L/sec	8.07	4.04	50	4.02	50	-0		
FIVC	Liters	4.22	1.61	38	1.26	30	-22		
PIF	L/sec	9.61	2.50	26	2.95	31	18		

COMMENTS

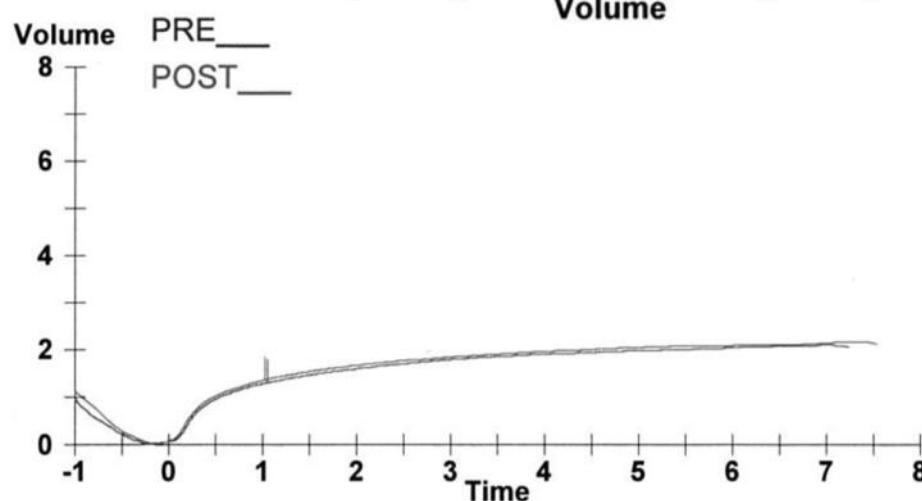
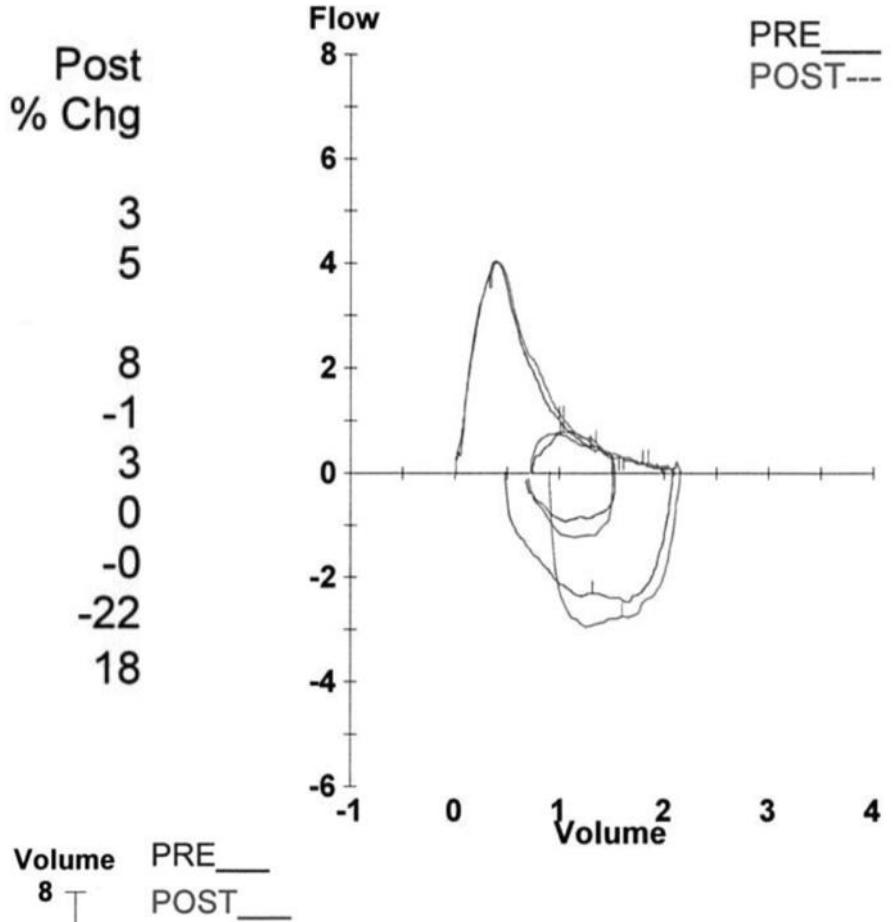
ATS criteria NOT met. Unable to exhale to full FVC

Excellent effort with PF tests.

Ventolin 400 mcg taken via MDI/light air.

DLCO adjusted for VA: 14.6 mL/mmHg/min = 50 %.

Inspired VC < 90% of Vital Capacity; DLCO maybe underestimated.



LUNG VOLUMES

		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
TLC	Liters	5.39	6.42	119			
VC	Liters	4.22	2.09	50			
IC	Liters	3.74	1.51	40			
FRC N2	Liters	2.55					
FRC PL	Liters	2.55	4.91	193			
ERV	Liters	1.87	0.55	29			
RV	Liters	1.10	4.33	393			
RV/TLC	%	20	67				

DIFFUSION

	Hb: gm/dL	Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
DLCO	mL/mmHg/min	29.5	11.5	39			
DLCO (Adj for VA)			14.6				
VA	Liters	5.39	2.63	49			
DLCO/VA	mL/mHg/min/L	5.37	4.36	81			
IVC	Liters		1.72	83			

COMMENTS

ATS criteria NOT met. Unable to exhale to full

FVC

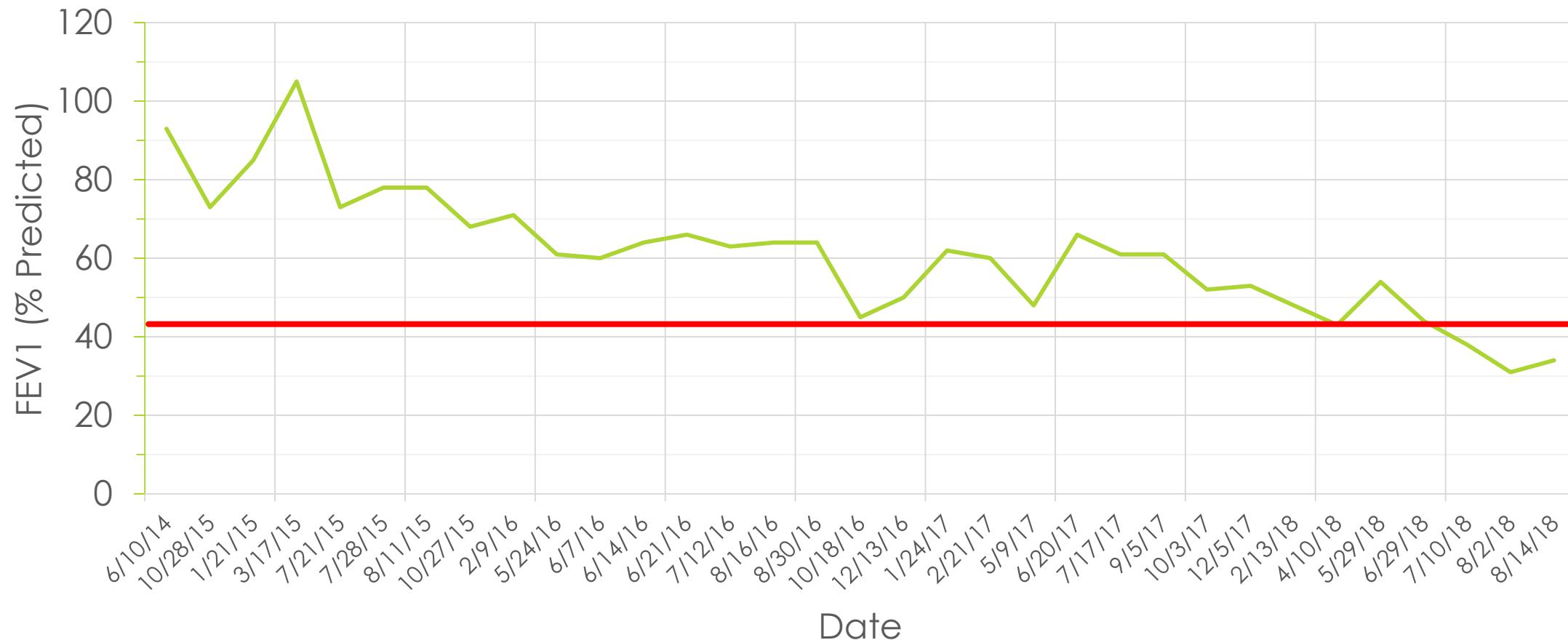
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Ventolin 400 mcg taken via MDI/light air.

DLCO adjusted for VA: 14.6 mL/mmHg/min = 50%.

Inspired VC < 90% of Vital Capacity; DLCO maybe underestimated.

Trend in FEV₁



Differential Diagnosis

- ▶ What is your differential diagnosis for this patient's declining lung function and what further investigations would you recommend at this time?

Differential Diagnosis

- ▶ Bacterial infection
 - ▶ *P. aeruginosa*
 - ▶ *B. cepacia*
 - ▶ *S. aureus*
 - ▶ MRSA
 - ▶ *H. influenza*
 - ▶ *M. catarrhalis*
 - ▶ *A. xylosoxidans*
 - ▶ *S. maltophilia*
 - ▶ Other
- ▶ Mycobacterial infection
 - ▶ *M. avium complex*
 - ▶ *M. abscessus*
- ▶ Fungal infection
 - ▶ *A. fumigatus*
 - ▶ Other
- ▶ Allergic Bronchopulmonary Aspergillosis
- ▶ Poor Nutrition
- ▶ Cystic Fibrosis Related Diabetes

Bloodwork

- ▶ Hgb 130, Platelet 310, WBC 13.2
 - ▶ Neut 10.1, Lymph 2.3, Mono 1.4, Eos 0.2
- ▶ CRP 25.8
- ▶ Electrolytes, Cr, urea, Ca, Mg, Phos normal
- ▶ Liver enzymes, bilirubin normal
- ▶ Albumin 30, total protein normal
- ▶ INR 1.3, PTT 37.4
- ▶ Vitamin A 0.7, 25-OHD and Vitamin E normal
- ▶ Lipase normal

Bloodwork

- ▶ Hgb A1C 5.7
- ▶ OGTT
 - ▶ Abnormal fasting glucose 8.5
 - ▶ Glucose monitoring normal
- ▶ IgE 65, IgE to Aspergillus fumigatus 0.83
- ▶ CBG pH 7.44, pCO₂ 51, HCO₃ 25

Sputum cultures

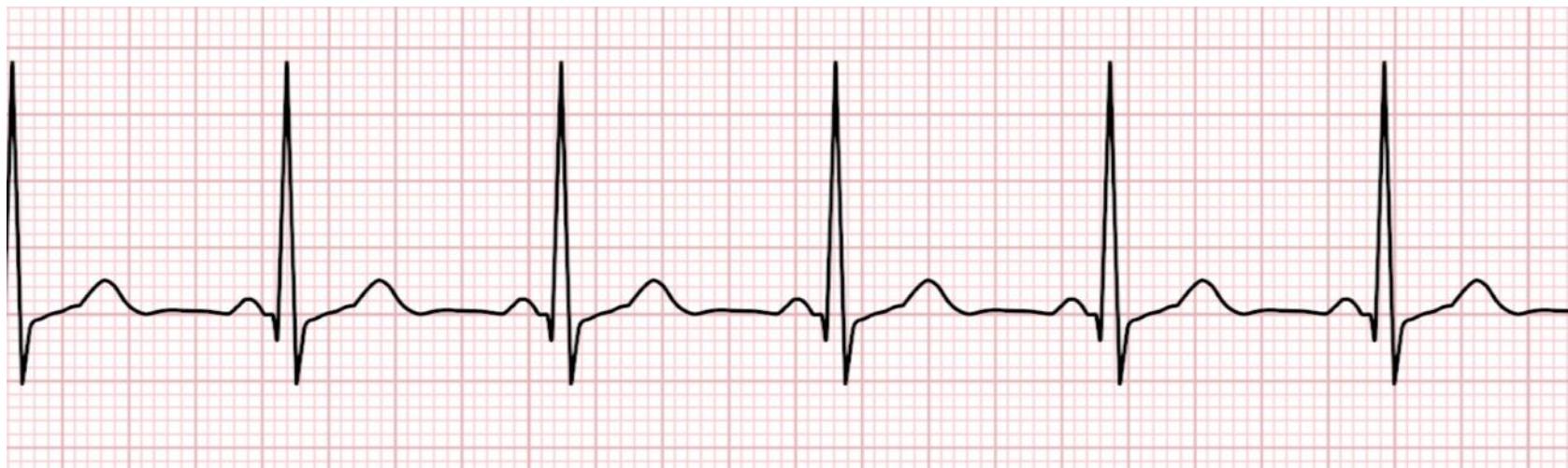
- ▶ Bacterial culture: oropharyngeal flora.
- ▶ Mycobacterial culture: No AFB, culture negative
- ▶ Viral respiratory panel negative
- ▶ Remote cultures:
 - ▶ *Pseudomonas aeruginosa*, *Klebsiella Oxytoca*,
Stenotrophomonas, *S. aureus*, *Enterobacter*

Previous Bronchoscopy and BAL

- ▶ BAL
 - ▶ Heavy neutrophils, no organisms
 - ▶ Bacterial culture -ve
 - ▶ Candida albicans
 - ▶ Rare, questionable AFB, culture negative
- ▶ Sputum - 1 colony M. abscessus growth at 36d

Other investigations

- ▶ Echo: normal function, RVSP 32mmHg + RAp
- ▶ ECG: sinus rhythm, normal QTc



Treatment: 3 week admission

- ▶ IV Ceftazidime + po Levofloxacin
- ▶ Continued M. abscessus maintenance therapy
- ▶ Airway clearance QID
- ▶ Optimization of nocturnal BiPAP tolerance
- ▶ Constipation management
- ▶ Discharged on supplemental daytime O₂

Readmission

- ▶ Increased cough productive of green sputum
- ▶ Work of breathing
- ▶ Decreased energy and appetite
- ▶ Increased O₂ requirement when assessed by home O₂ vendor, came to ED

Course in Hospital

- ▶ Daytime O₂ 4-8L
- ▶ BiPAP 14/5, O₂ 10L entrained overnight
- ▶ Airway clearance
- ▶ Ceftazidime IV, Levofloxacin po → IV
- ▶ Septra IV

Review of M. abscessus treatment

- BAL: M. abscessus bolletii
- Outpatient Rx Steno and Psa, discussion with family

- Admission for Pulmonary exacerbation

- Induction: Azithromycin po, Amikacin IV, Tigecycline IV, Linezolid po

- Maintenance: Azithromycin po, Amikacin inh, Minocycline po, Linezolid po (changed to Clofazamine)

*M. abscessus bolletii**M. abscessus massiliense*
(2 strains)

Sensitive	Amikacin	Amikacin Linezolid (1 species)
Intermediate		Imipenem Clofazimine (MIC ≤0.5mg/L)
	Tigecycline (MIC 2mg/L)	Tigecycline (MIC 0.25-0.5mg/L)
Resistant	Imipenem Cefoxitin Ciprofloxacin Clarithromycin Linezolid Moxifloxacin Septra	Cefoxitin Ciprofloxacin Clarithromycin Linezolid (1 species) Moxifloxacin Septra



Management

- ▶ Ongoing consultation with infectious disease
- ▶ Discussion with Respirology in Edmonton, Toronto
 - ▶ Not a candidate for transplantation while smear +
- ▶ Discussion with family
- ▶ Plan for re-induction therapy for *M. abscessus*
- ▶ Involvement of palliative team
- ▶ Support from physiotherapy for rehabilitation

Course in Hospital - Antibiotics

Week 1	2	3	4	5	6	7	8
Levofloxacin po		Levofloxacin IV					
Ceftazidime IV				Septra IV			
Amikacin inhaled		Amikacin IV					
Azithromycin po		Azithromycin IV				Azithro po	
Clofazamine po						Tigecycline IV	



Challenges of Treating *Mycobacterium abscessus* in Cystic Fibrosis

Objectives

- ▶ Overview of *M. abscessus* in CF
 - ▶ Epidemiology
 - ▶ Lung Disease
- ▶ Treatment of *M. abscessus* in CF
 - ▶ Guidelines
 - ▶ Emerging Therapies
- ▶ Transplant outcomes in *M. abscessus*

M. abscessus complex

M. abscessus
spp *abscessus*

M. Abscessus
spp *massiliense*

M. Abscessus
spp *bolletii*

Prevalence of respiratory infections of individuals with CF

- ▶ See Figure p. 31

Risk Factors for Acquisition of Non-tuberculous mycobacteria (NTM)

- ▶ Aspergillus fumigatus and ABPA
- ▶ Chronic therapies
- ▶ Geographic variation
 - ▶ Annual atmospheric water vapor
- ▶ Indoor swimming pool use

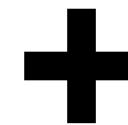
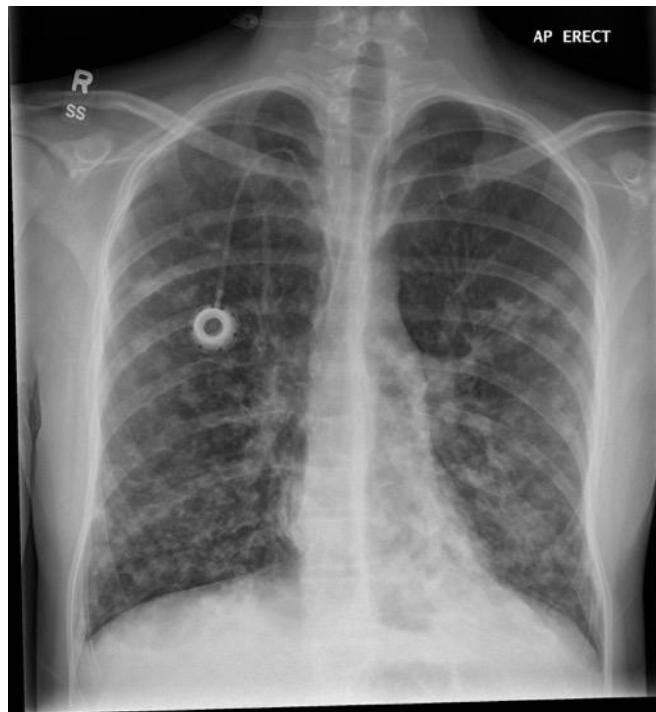
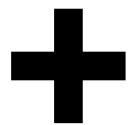
Furukawa et al. Semin Respir Crit Care Med 2018. 39:383-391.
Martiniano et al. Clin Chest Med 37 (2016): 83-86.

Epidemiology of NTM amongst individuals with CF

► See Table 3

Diagnosis of NTM

Pulmonary
Symptoms



Positive culture

Griffith et al. Am J Respir Crit Care Med 2007. 175: 367–416.
Floto et al. Thorax 2016. 71: 88-90.

Clinical Significance of a First Positive NTM Culture in CF

- ▶ 96 patients (pediatric and adult)
- ▶ 3 groups:
 - ▶ Transient infection (23%)
 - ▶ Persistent infection (38.5%)
 - ▶ Active NTM disease (38.5%)

Martiniano et al. Ann Am Thorac Soc 2014. 11 (1): 36–44
Ravnholz et al. APMIS 2018. 126: 885–891.

- See Figure 1

- See Figure 3

► See Figure 2

Development of Resistance

- ▶ Slow growth
- ▶ Waxy cell wall
- ▶ Biofilm
- ▶ Erythromycin ribosomal methylase gene (*erm*)
- ▶ Acquired mutational resistance
 - ▶ 16sRNA gene - amikacin
 - ▶ 23sRNA gene – clarithromycin

Griffith et al. Am J Respir Crit Care Med 2007. 175: 367–416.
Semin Respir Crit Care Med 2018. 39: 362-376.

Treatment

- ▶ Intensive Phase (3-12 weeks):
 - ▶ Daily macrolide po AND
 - ▶ Amikacin IV AND
 - ▶ ≥1 of Tigecycline, Imipenem, Cefoxitin IV

Thorax 2016. 71: 88-90.

Semin Respir Crit Care Med 2018. 39: 362-376.

Treatment

- ▶ Continuation Phase:
 - ▶ Daily macrolide po AND
 - ▶ Amikacin inhaled AND
 - ▶ 2-3 of Clofazimine, Linezolid, Moxifloxacin, Minocycline po
- ▶ Continue until 12 mos after culture conversion

Thorax 2016. 71: 88-90.
Semin Respir Crit Care Med 2018. 39:383–391.

Inhaled Liposomal Amikacin

- ▶ Liposomes taken up by lung macrophages, allows for intracellular delivery of high levels of Amikacin
- ▶ 32% culture conversion overall in NTM patients

American Journal of Respiratory and Critical Care Medicine 2017. 195 (6): 814-823.

Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease

- ▶ Diarylquinoline antibiotic
- ▶ Inhibits ATP synthase
- ▶ Possible clinical and microbiologic response
- ▶ Adverse effects nausea, hepatotoxicity, QTc prolongation

Transplantation in *M. abscessus*

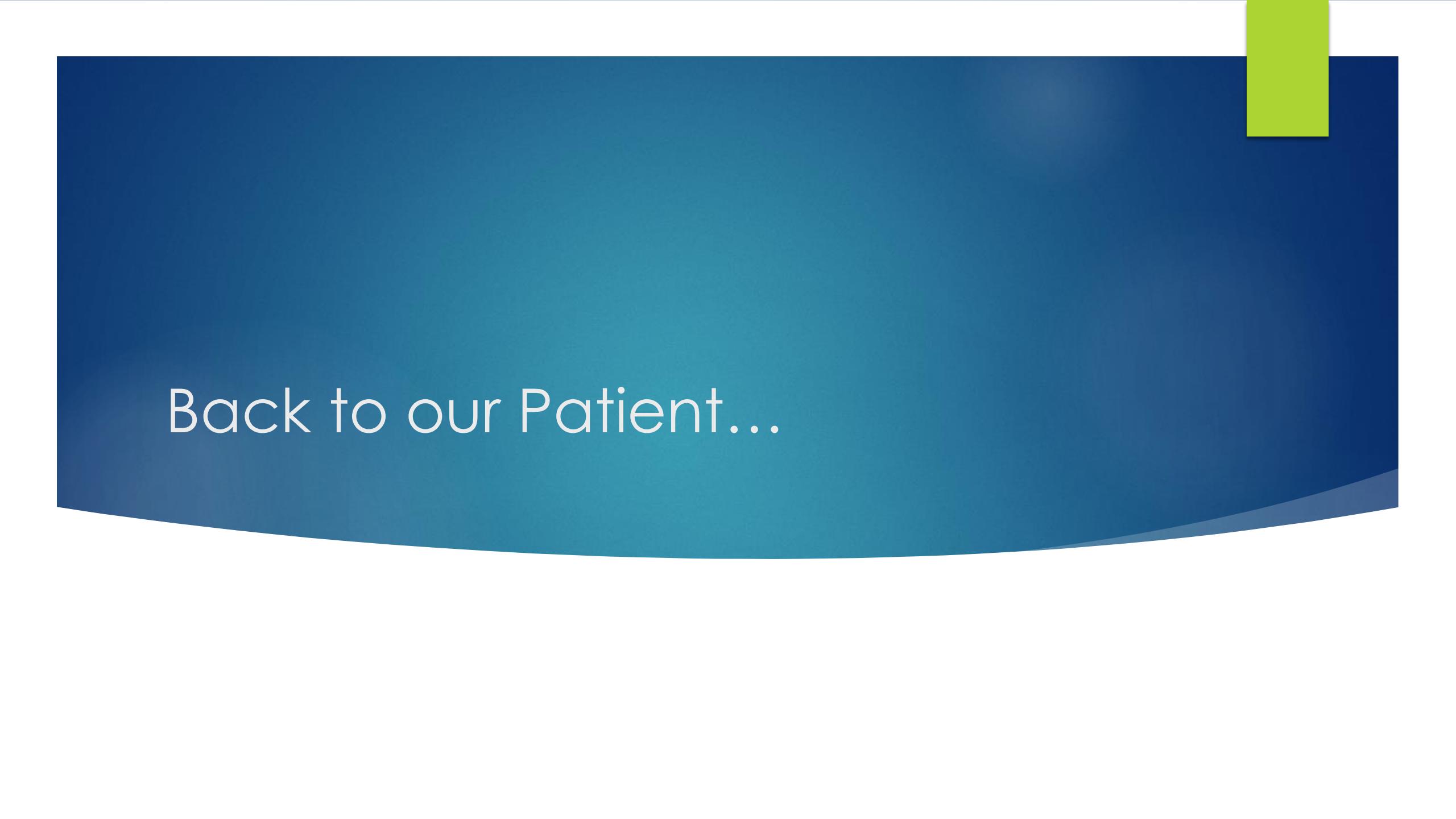
- ▶ 20% patients referred for transplant have NTM
- ▶ Pre-transplant NTM risk for:
 - ▶ post-transplant NTM
 - ▶ *M. abscessus* wound infection

► See Figure 1

► See Figure 2

Contraindication to Transplantation

- ▶ Relative : MDR Mycobacterium abscessus
 - ▶ Sufficient treatment pre-op
 - ▶ Center with experience in this infection
- ▶ “Progressive pulmonary or extrapulmonary disease secondary to NTM despite optimal therapy or an inability to tolerate optimal therapy is a contraindication for transplant listing.”



Back to our Patient...

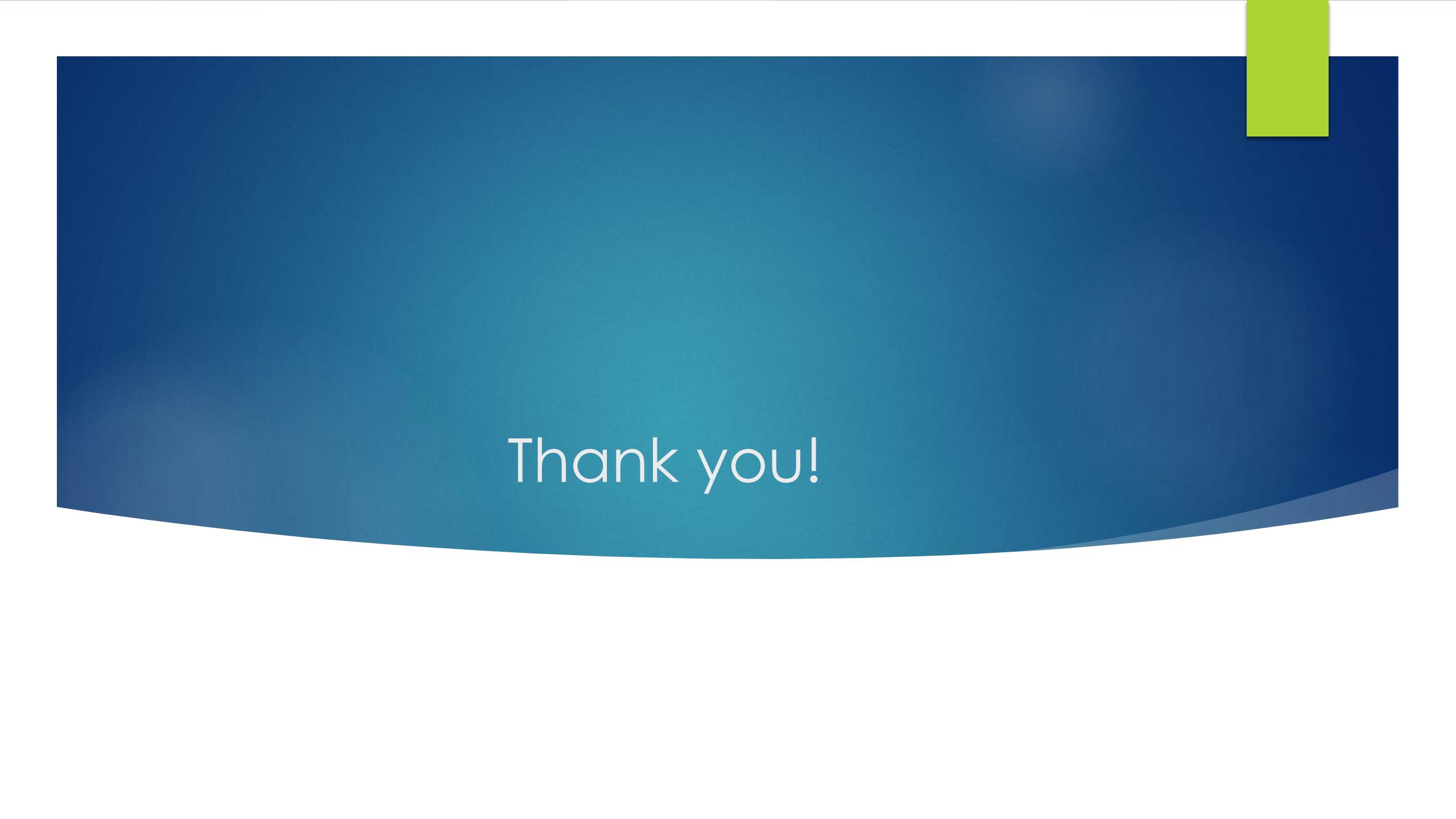
M. Abscessus at 21d

M. Abscessus at 34d

Sensitive	Imipenem Linezolid	Linezolid
Intermediate	Cefoxitin	
Resistant	Amikacin Ciprofloxacin Clarithromycin Doxycycline Moxifloxacin Septra Tobramycin	Cefoxitin Ciprofloxacin Doxycycline Moxifloxacin Septra

Follow up

- ▶ Continuing close follow up with CF and ID clinic
- ▶ No further hospitalization
- ▶ Respite admissions
- ▶ Slight improvement in cough
- ▶ Stable O2 requirement
- ▶ Nausea and vomiting improved with ondansetron



Thank you!



Experience in other centres?

- ▶ Screening and Diagnosis:
 - ▶ Frequency of cultures?
 - ▶ Sputum vs BAL?
- ▶ Management:
 - ▶ Per CFF 2016 guidelines?
 - ▶ Preferred agents?
 - ▶ Availability and use of alternative agents in treatment failure?
- ▶ Contraindication to transplantation?

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