Overwhelming TB

Roukaya Al Hammoud, MD

April 1, 2024

New Directions in TB
April 1 – 2, 2024
Houston, Texas

Roukaya Al Hammoud, MD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

Overwhelming TB

Roukaya Al Hammoud, MD
Assistant Professor
Pediatric Infectious Diseases
4/1/2024

I have no conflicts of interest to disclose

UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

History

- 14 year old Caucasian girl with history of “recurrent pneumonia” admitted for worsening cough and SOB
- **Between Dec 2020 & Nov 2021**

-Cough, green non-bloody sputum

-Diagnosed with pneumonia X4 and sinusitis X2

-Antibiotics received: amoxicillin, amoxicillin-clavulanate, azithromycin, ciprofloxacin and 1 cephalosporin.

-Seen by PCP, several urgent cares and an allergist. Received inhaled bronchodilators and prednisone.

-Evaluated for asthma. PFTs Non-obstructive

-Eventually stopped attending in-person school due to embarrassment by her persistent cough

-Weight loss (4 Kg)

-Unable to ride her bike due to shortness of breath

-CXR: “Mild lingular airspace disease concerning for pneumonia” (first month of symptoms)

- **Nov & Dec 2021:**

-Progressive weakness and respiratory symptoms (cough, shortness of breath with exertion)

-Right sided chest pain

UTHealth Houston McGovern Medical School

Children's Memorial Hermann Hospital

History

- **Past Medical History:** Eczema, “sinusitis” x2, multiple episodes of “pneumonia”
- **Birth Hx:** born full term via SVD. No complications during delivery or pregnancy
- **Past Surgical Hx:** none
- **Family history:** Mom has chronic fatigue syndrome. MGM has rheumatoid arthritis. No family history of chronic cough, TB, immune deficiencies, recurrent infections or asthma.
- **Immunizations:** up to date except for COVID and Flu
- **Home medications:** recently completed 7 days amoxicillin-clavulanate and 5 days of azithromycin

Exposure & Social Hx:

- Parents are separated. She lives with her mother, step-father, older brother (17 y), and younger brother (6 y). Multiple family members vape and smoke weed.
- Pt tried vaping for 4 months (8 months ago). Denied IVDU.
- She is in 8th grade (doing well), switched from in-person to online school because of cough.
- Traveled with father to Tennessee in Summer 2020 and for 1 week prior to admission to visit her grandma. Most of the trip was spent with family in-house. No international travel.
- Her father (reportedly not coughing) was recently incarcerated until about ~1.5 years ago. He lived in a halfway house for some time. CXR-NEG
- No known sick contacts or family members with chronic cough.
- Mother and step father works in a laboratory
- Not sexually active (premenarchal)
- Pets: 1 cat and 1 dog.

Review of System

- GENERAL: Denies fever, chills, **. +weight loss**
- EYES: Denies eye redness, or discharge
- EENT: Denies sore throat, rhinorrhea, congestion.
- RESP: Denies wheezing. **+ SOB, +cough, +sputum.** No hemoptysis
- CV: Denies palpitations, **+ chest pain, +lightheadedness & dizziness**
- GI: Denies vomiting, diarrhea, abdominal pain, **+ constipation, + decreased appetite, +nausea**
- GU: Denies change in UOP, dysuria, hematuria, urgency, frequency
- MSK: Denies joint swelling, **+left shoulder pain**
- HEME/LYMPH: Denies easy bruising, easy bleeding,
- NEURO: Denies AMS, seizure. **+Intermittent headache**
- PSYCH: Denies difficulty sleeping, **+ depressed mood**
- DERM: **+peeling and dry skin**

Physical Exam

Vitals: T: 100.9 °F (Axillary) **HR: 124 RR: 24 BP: 95/60 SpO2: 94% on RA**

WT: 40.5 kg (12.5 %tile), **Height:** 157 cm (31% tile), **BMI:** 16.4 (9.6%tile, Z score -1.3)

General Appearance: Pale, ill looking

Head and neck: Pupils equals and reactive, no eye erythema or discharge, no nasal discharge, no neck masses

Lungs: **Diminished breath sounds and + crackles in left, + intermittent tachypnea, no retractions or flaring**

Heart: Regular rate and regular rhythm, **tachycardic,** no murmur, 2+ radial pulses bilaterally

Abdomen: soft, **mild tenderness in epigastric region**, no guarding, non-distended, no organomegalies

Musculoskeletal: No joint swelling or limited ROM, no edema or cyanosis of extremities

Neurologic: Alert, appropriate answers, no focal deficits

Skin: **dry peeling skin**

Initial Labs

WBC: 9.6 K
Neutrophils: 74% (ANC 7100)
Lymphocytes: 18 % **(ALC 1800)**

Hgb: 8.1 g/dL
Hct: 26.1 %

MCV: 65
Platelet: 299 K

Sodium: 131 mEq/L
Potassium: 3.6 mEq/L
BUN: 7 mg/dL
Creatinine: 0.53 mg/dL
Glucose: 89 mg/dL
Calcium: 8.4 mg/dl
Alk Phos: 73 unit/L
ALT: 16 unit/L
AST: 12 unit/L
Bili Total: 0.2 mg/dL

Total CK: 23 unit/L
Procalcitonin: <0.05
Lactic Acid: 1.7 mMol/L
HIV 4th gen: Neg
SARS-CoV-2 PCR: Neg

Iron level: 11 mcg/dl (27-164)
Ferritin: 260 ng/ml (5-204)
PT, INR, PTT: Normal
Prealbumin 4.7 mg/dl (18-45)
Total Protein: 9.1 g/dL
Globulin: 6.8 g/dL
Albumin: 2.3 g/dL

- VBGs on RA:
  pH: 7.39
  O2 Sat: 44.5 %
  pO2: 25 mmHg
  pCO2: 44 mmHg
  HCO3: 27 mMol/L High

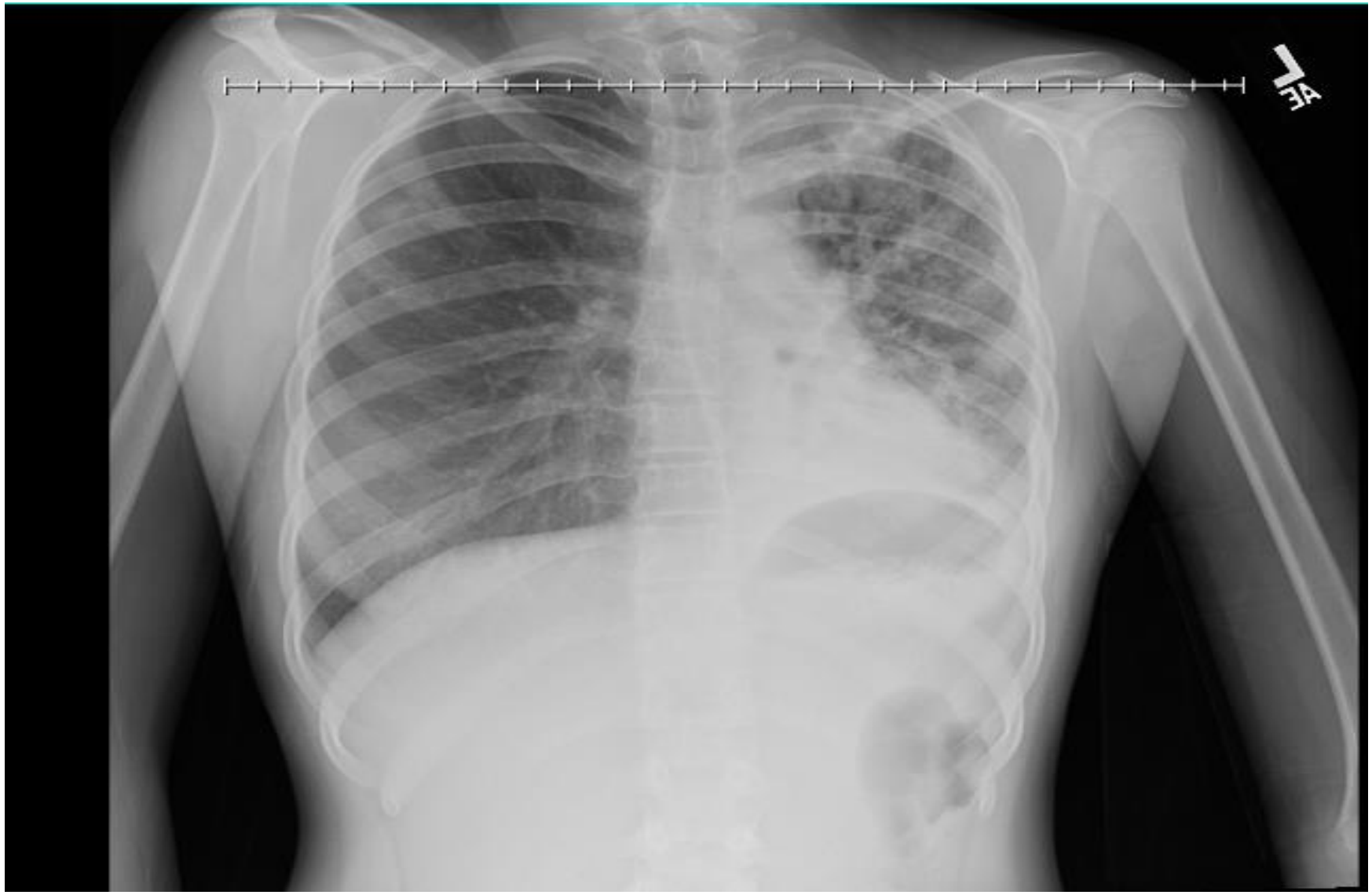
- **QuantiFERON TB Gold: Positive**
- BAL: **many AFB; AFB cx: positive**
  MTB PCR: Positive
  S to rifampin, isoniazid and ethambutol
  Bacterial and fungal cx: negative

- Fungal testing (Coccidiomycosis, histoplasmosis, Blastomycosis, Galactomannan, Fungitell): negative

UTHealth Houston McGovern Medical School

Children's Memorial Hermann Hospital

On Admission



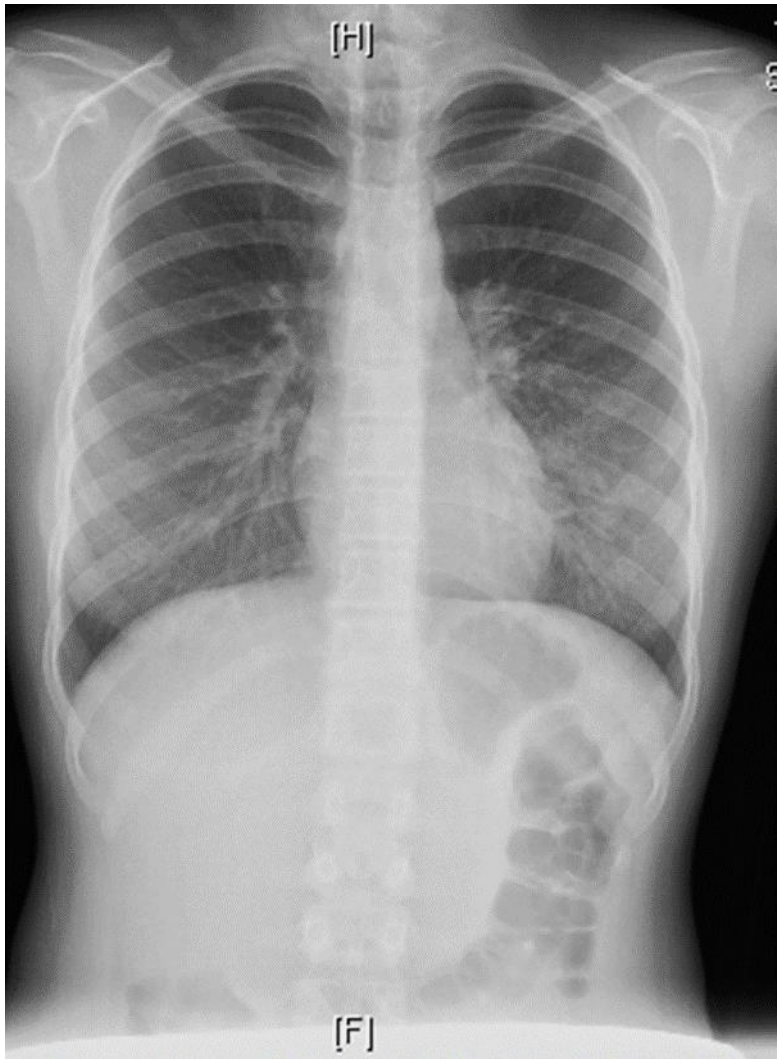
“Irregular airspace opacities throughout the left lung with dense consolidation of LLL.
Air bronchograms in LUL.
Mild hazy airspace opacities in RUL.
Possible small left pleural effusion.
No reported adenopathy.

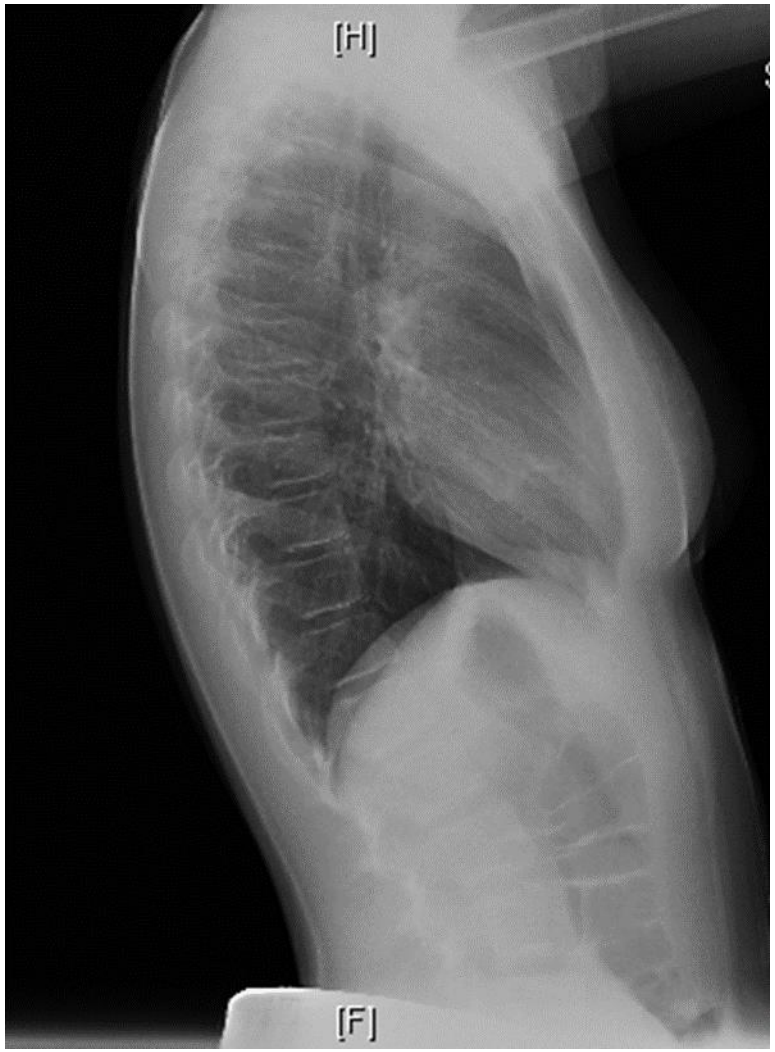
Conclusion: Multifocal airspace opacities compatible with pneumonia”

UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

One year prior to admission





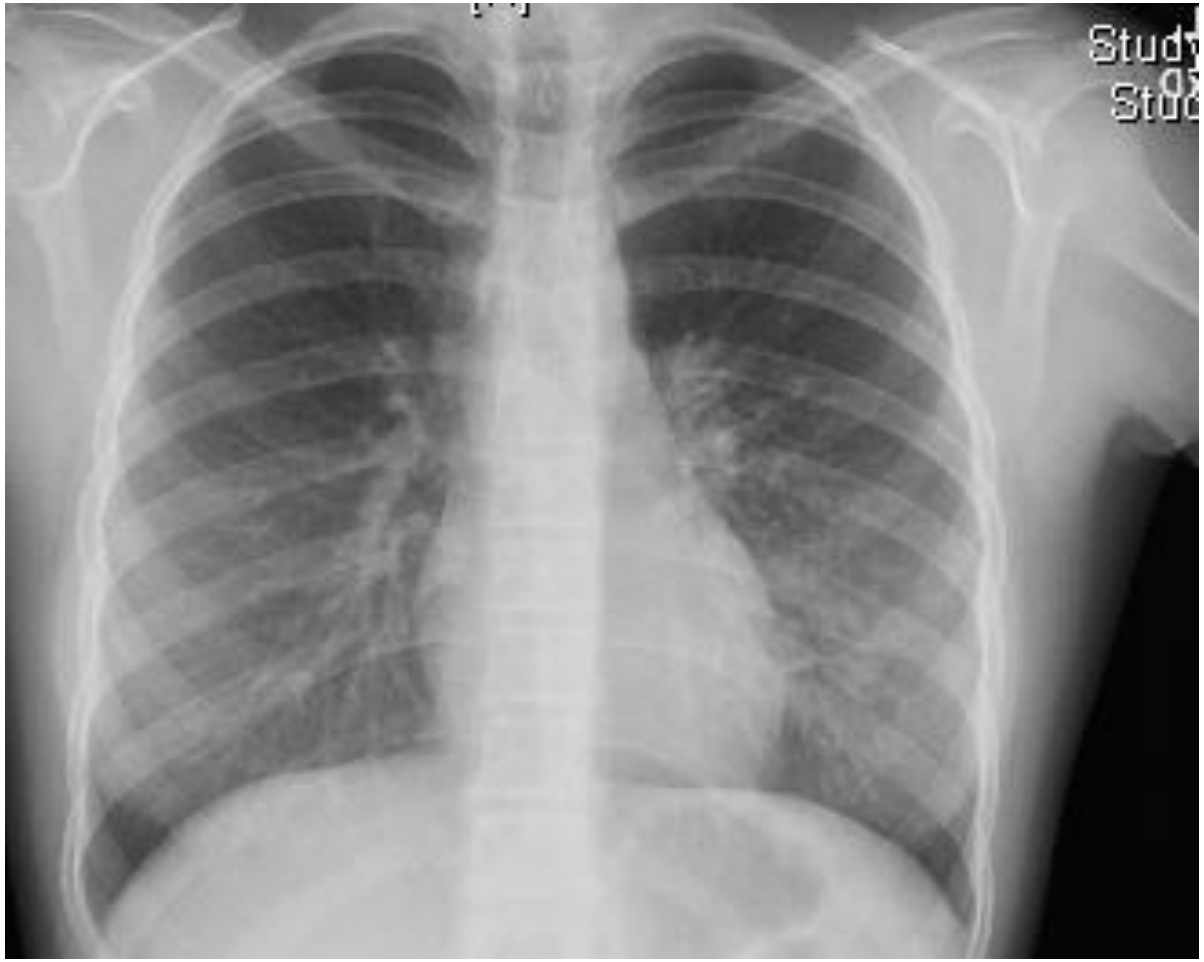
CXR report:

“Mild lingular airspace disease”

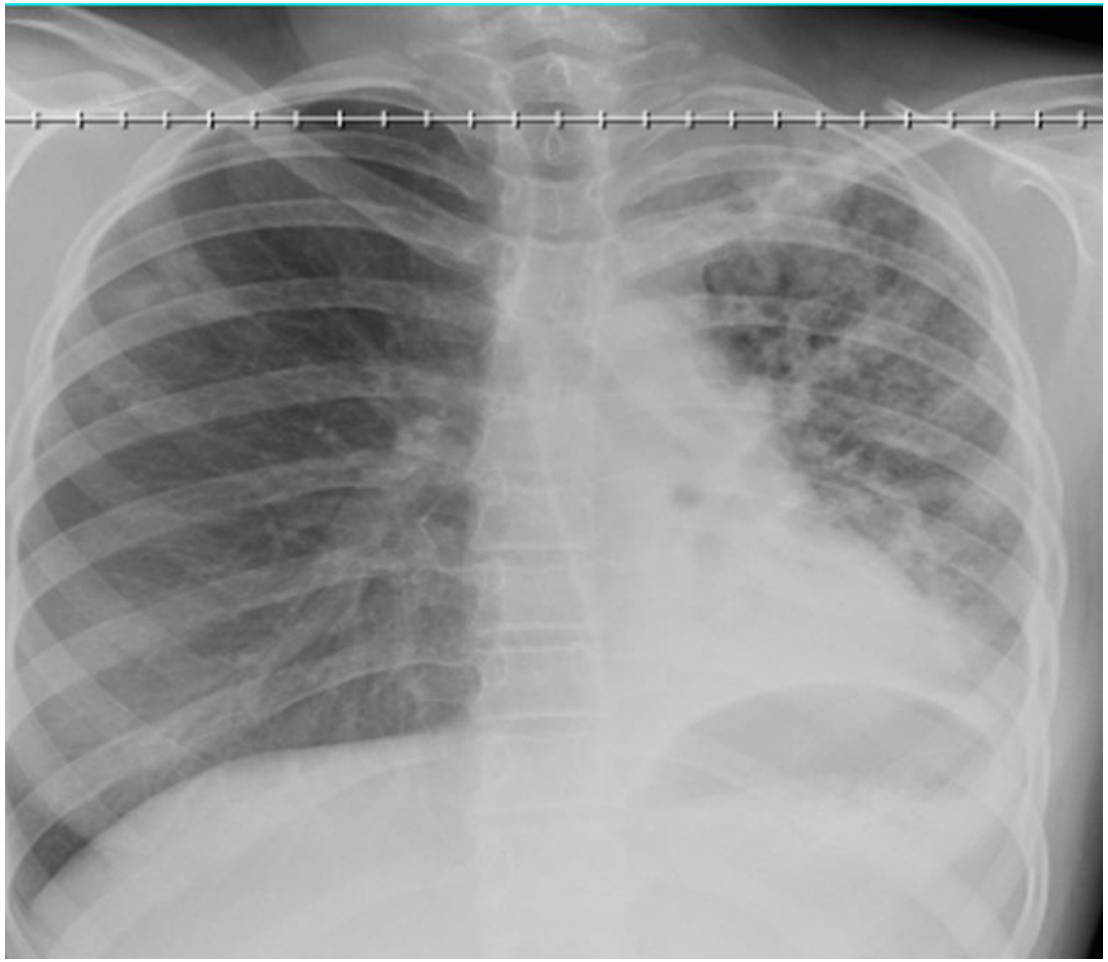
UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

1 year prior to admission



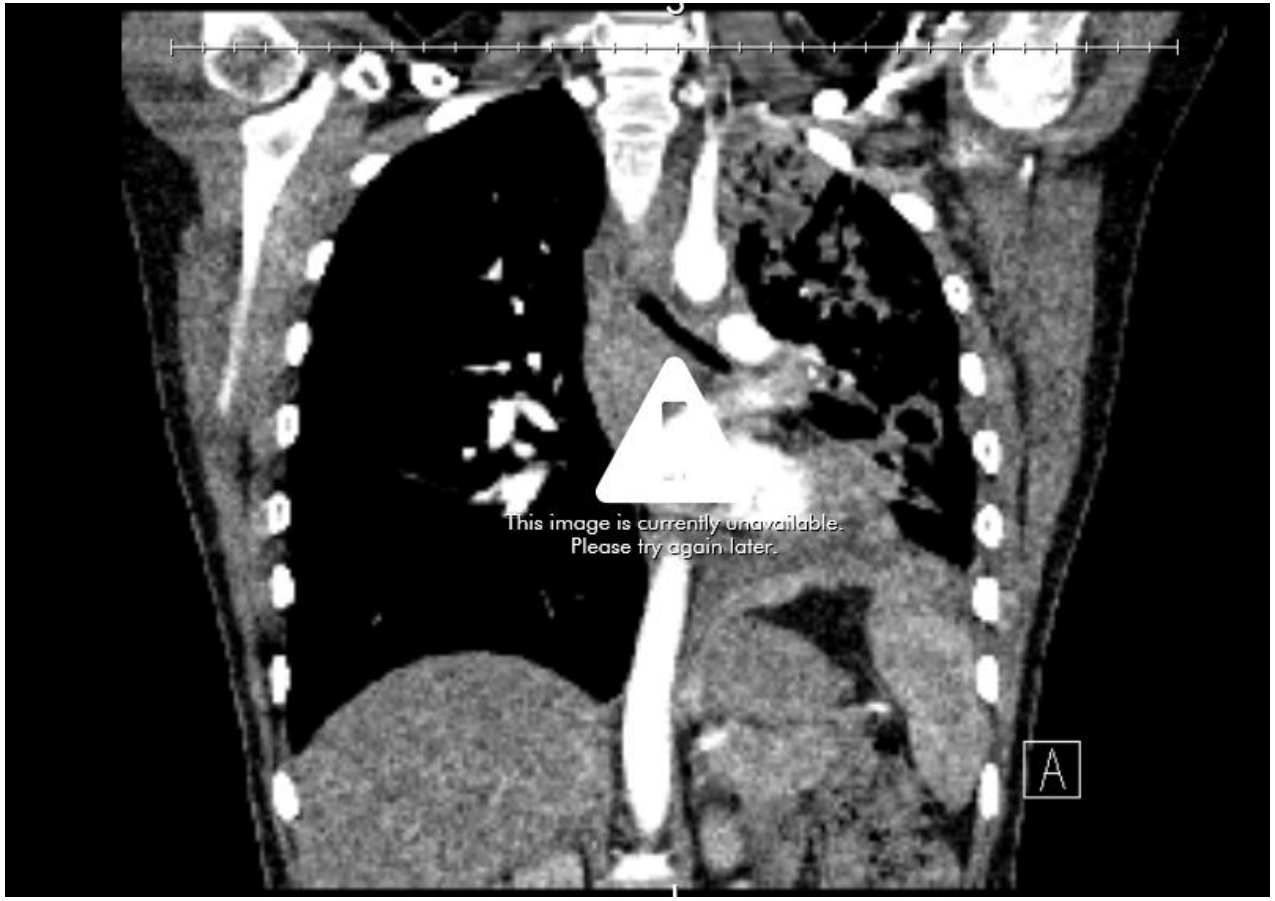
Admission



UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

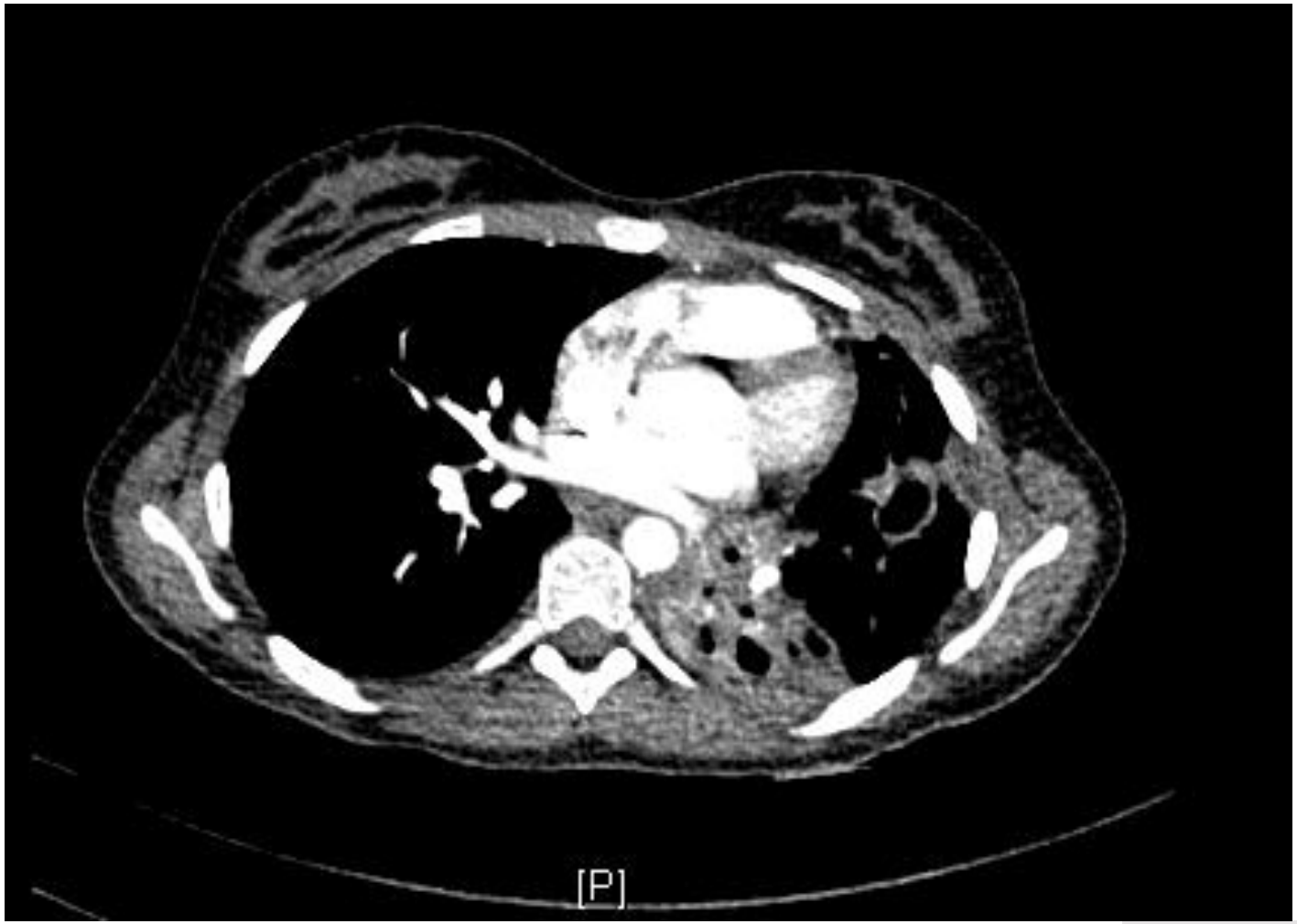
CT Chest



UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

CT Chest



Extensive abnormalities in the left lung with bronchial wall thickening, tree-in-bud opacities, and irregular areas of patchy consolidation.

A few scattered thick-walled cavities are also seen.

A large area of consolidation in the left lower lung is associated with volume loss and may represent atelectasis.

Mild abnormalities are seen in the right lung, including tree-in-bud opacities and a small airspace opacity in RUL.

No adenopathy.

Hospital Course

-HD#3: Bronchoscopy (copious greenish thick mucoid secretions from left lung, minimal secretions of right lung, friable mucosa, no bleeding)

-HD#4: RIPE started. Tachypneic, tachycardic, febrile. Started on NC 3 LPM. Broad spectrum antibiotics

-HD#5: Transferred to PICU: O2 requirement and hypotension →pressors. ECHO: small pericardial effusion

-HD#7: Intubated. RIPE changed to IV moxifloxacin, linezolid, rifampin and amikacin

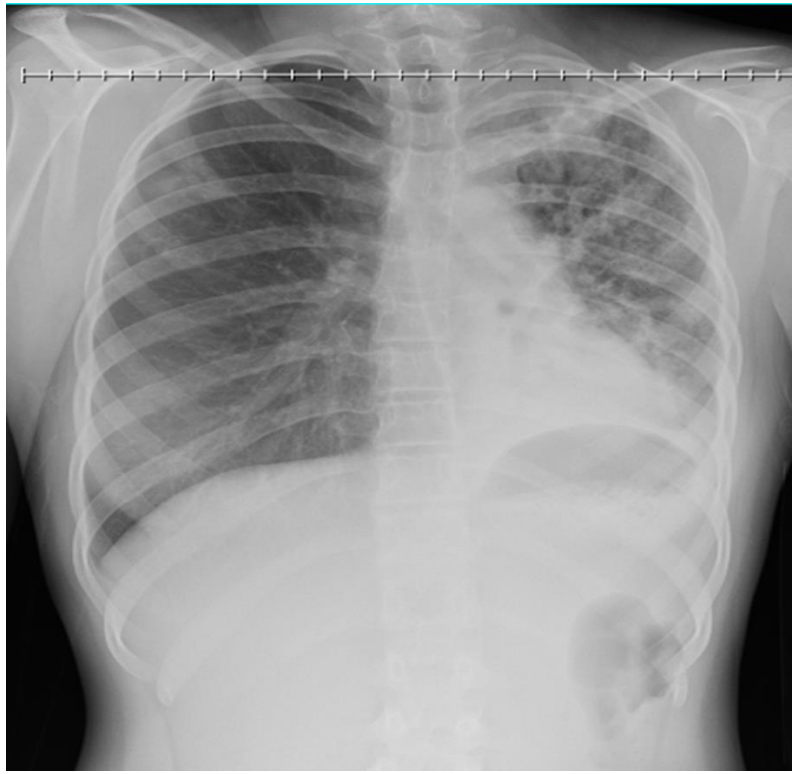
-HD#8: Dexamethasone started (10 mg IV Q12 hours ~0.3 mg/kg/day). Right leg DVT → enoxaparin

-HD#12&13: FiO2 100%. Hypotension. Right lung PE. CT with “increased pneumatocele/cavitation in left lung and progression of consolidation in right lung. Subcarinal and anterior mediastinal lymphadenopathy.” Pulmonary hypertension requiring iNO.

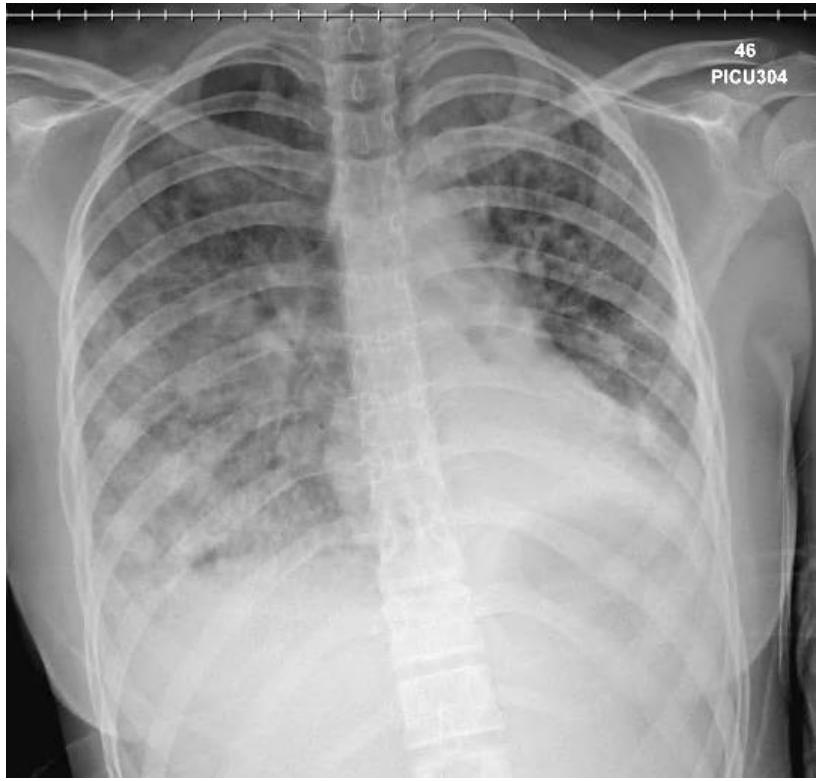
-HD#20-22: Left pneumothorax s/p chest tube. BAL AFB cx: Neg

-HD#26: Oscillator. Higher dose dexamethasone 10 mg IV every 6 hour~ 4mg/kg/day, planned for a slow wean.

-**HD#36:** Significant improvement: Oscillator → conventional ventilator



Admission

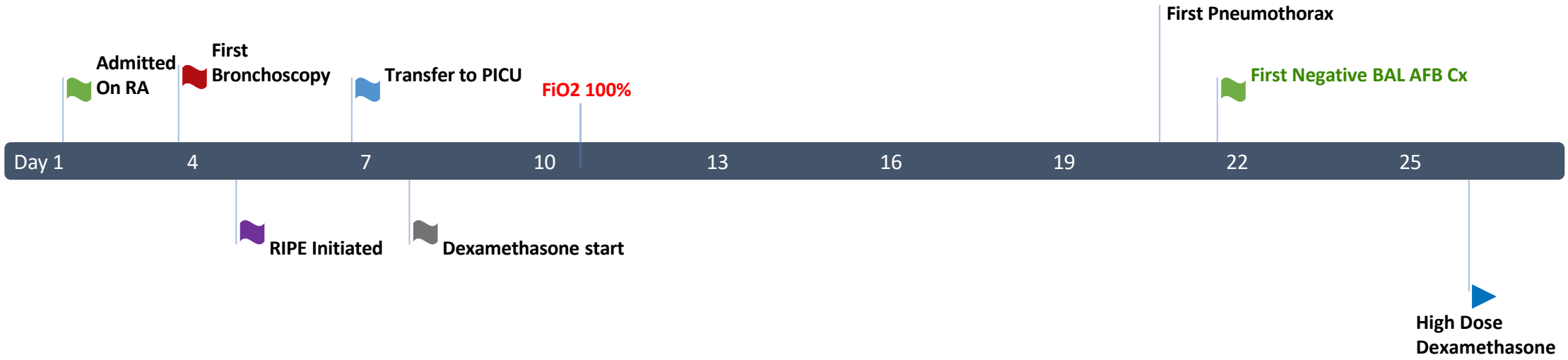


After 3 days of RIPE

UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

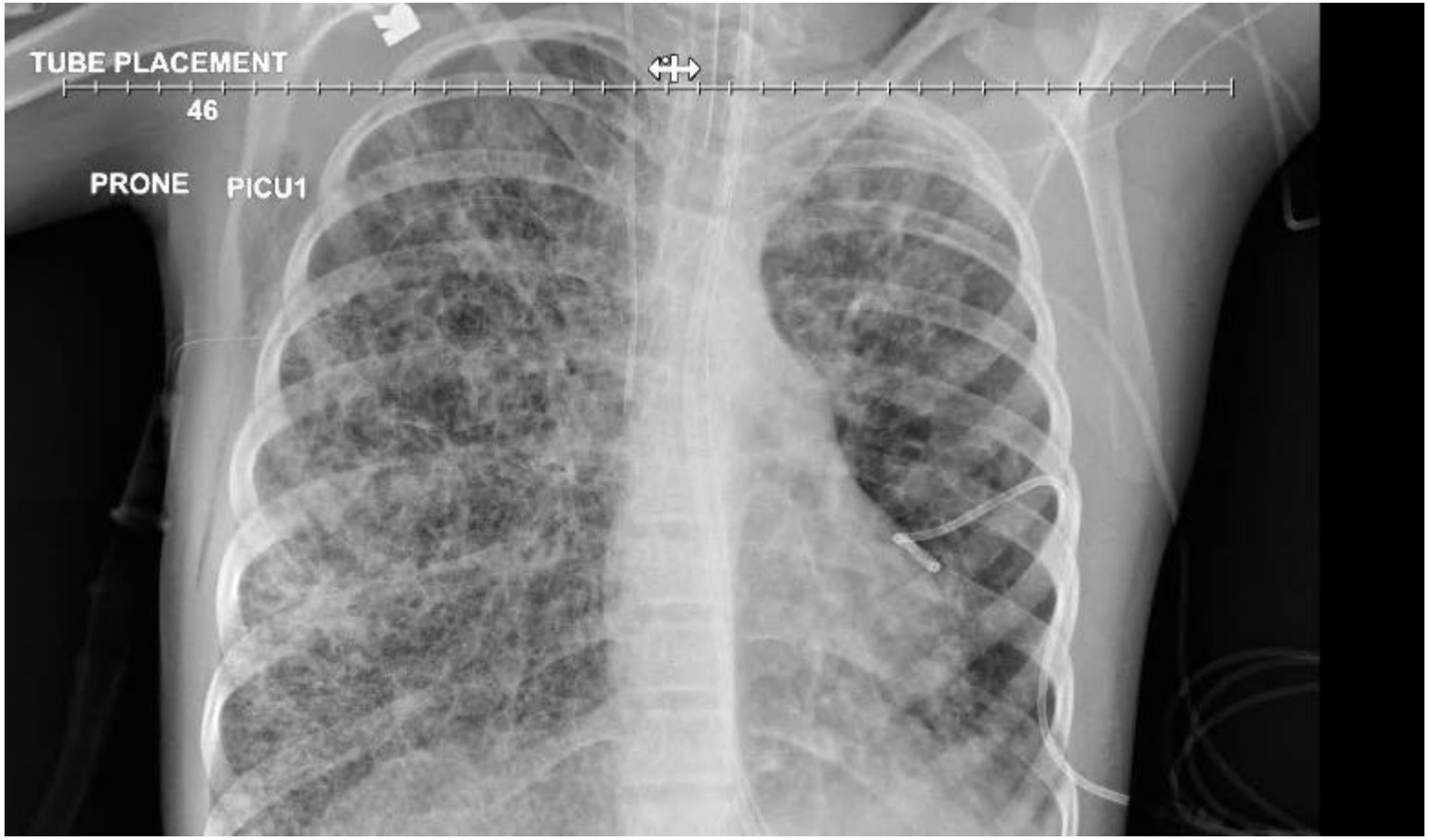
Month#1 Hospital Course



UTHealth Houston
McGovern Medical School

Children's
MEMORIAL
HERMANN
Hospital

1 month later



UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

Hospital Course

- **Month#2 of Hospitalization:**

-Oscillator → conventional ventilation → CPAP mode HD#50 (only for few days)→ ventilator

-ECMO team consulted

-Continued with pulmonary hypertension, iNO, sildenafil

-Weaning steroids very slowly in consideration of clinical status and CRP/IL6 levels.

-Continues to have extensive DVT in right leg. Found to have Factor V leiden mutation

-PJP and antifungal prophylaxis

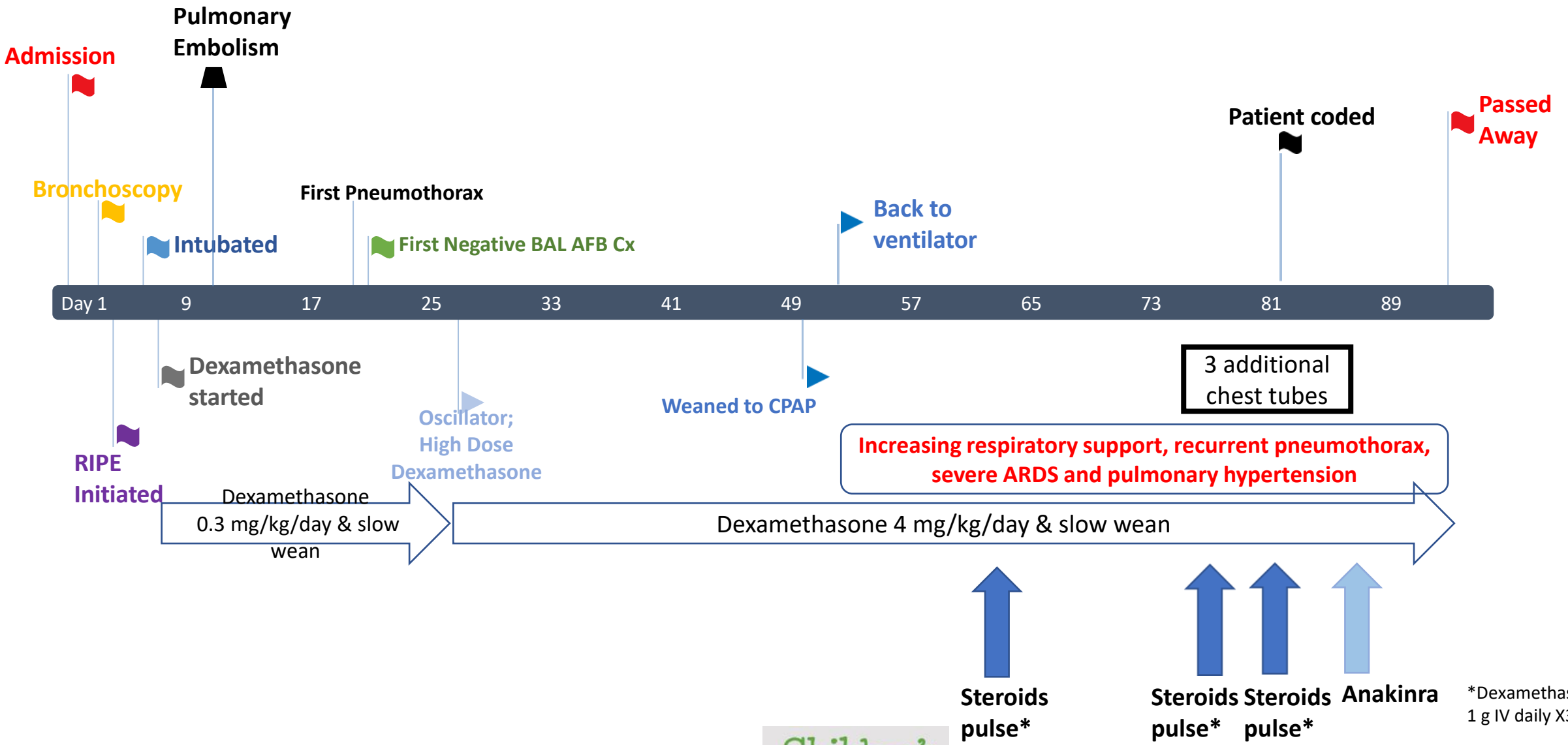
-Linezolid and rifampin were switched from IV to enteral. Serial TB drugs level monitoring

-Multiple sepsis evaluations (Neg. cultures)

Hospital Course

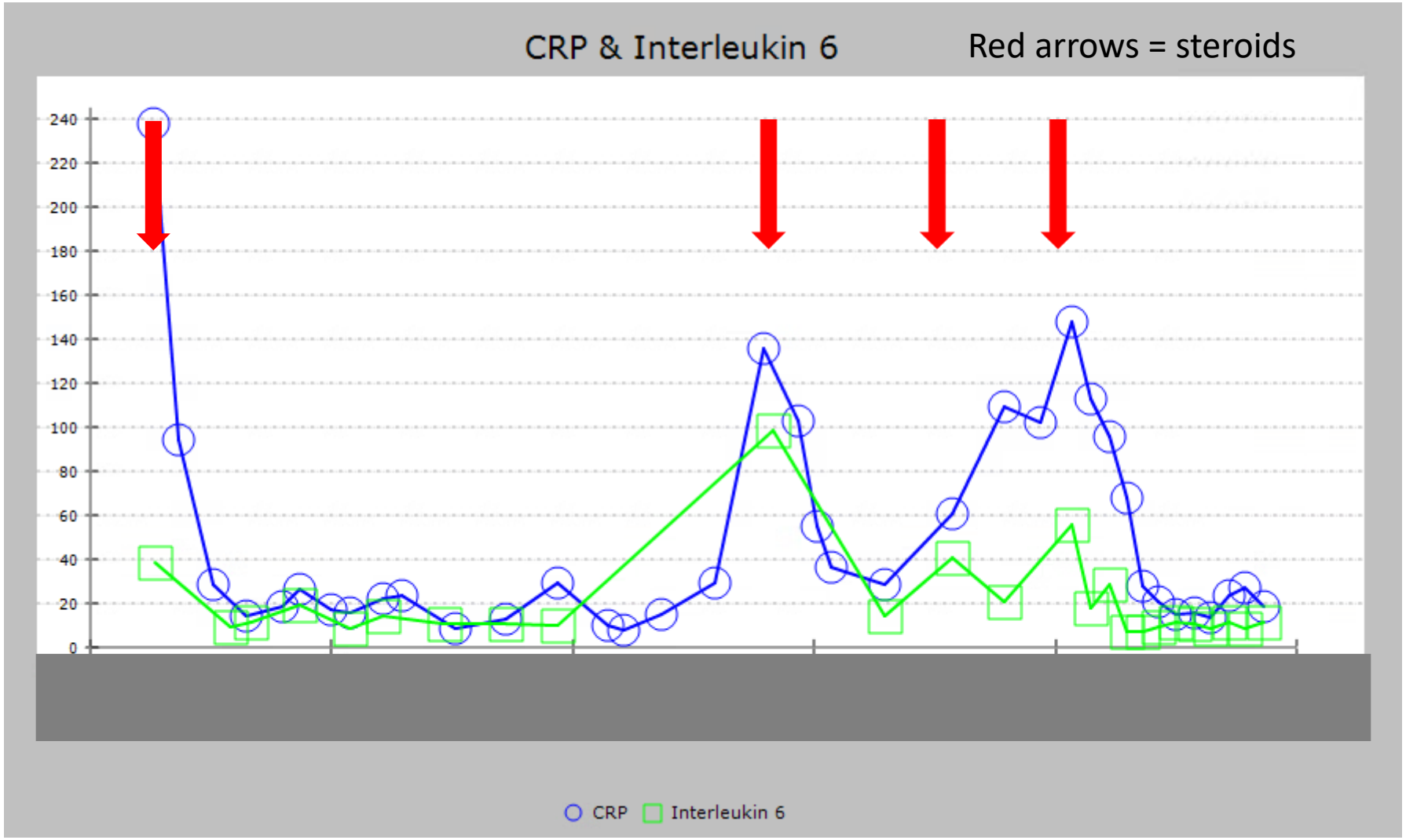
- **Month#3 of Hospitalization:**

-Increasing respiratory support, progressive ARDS and worsening pulmonary hypertension
-Recurrent pneumothorax; 5 chest tubes (3 left, 2 right)
-Dexamethasone for paradoxical reaction
-Required multiple steroids pulses
-Anakinra (IL1 receptor antagonist) started
-Systemic hypertension
-Multiple sepsis evaluations. Coded X2.
-Opportunistic infections evaluations-negative
-Tracheostomy.
-ECMO team re-involved (too sick to be eligible)
-Lung transplant considered, denied by multiple centers.



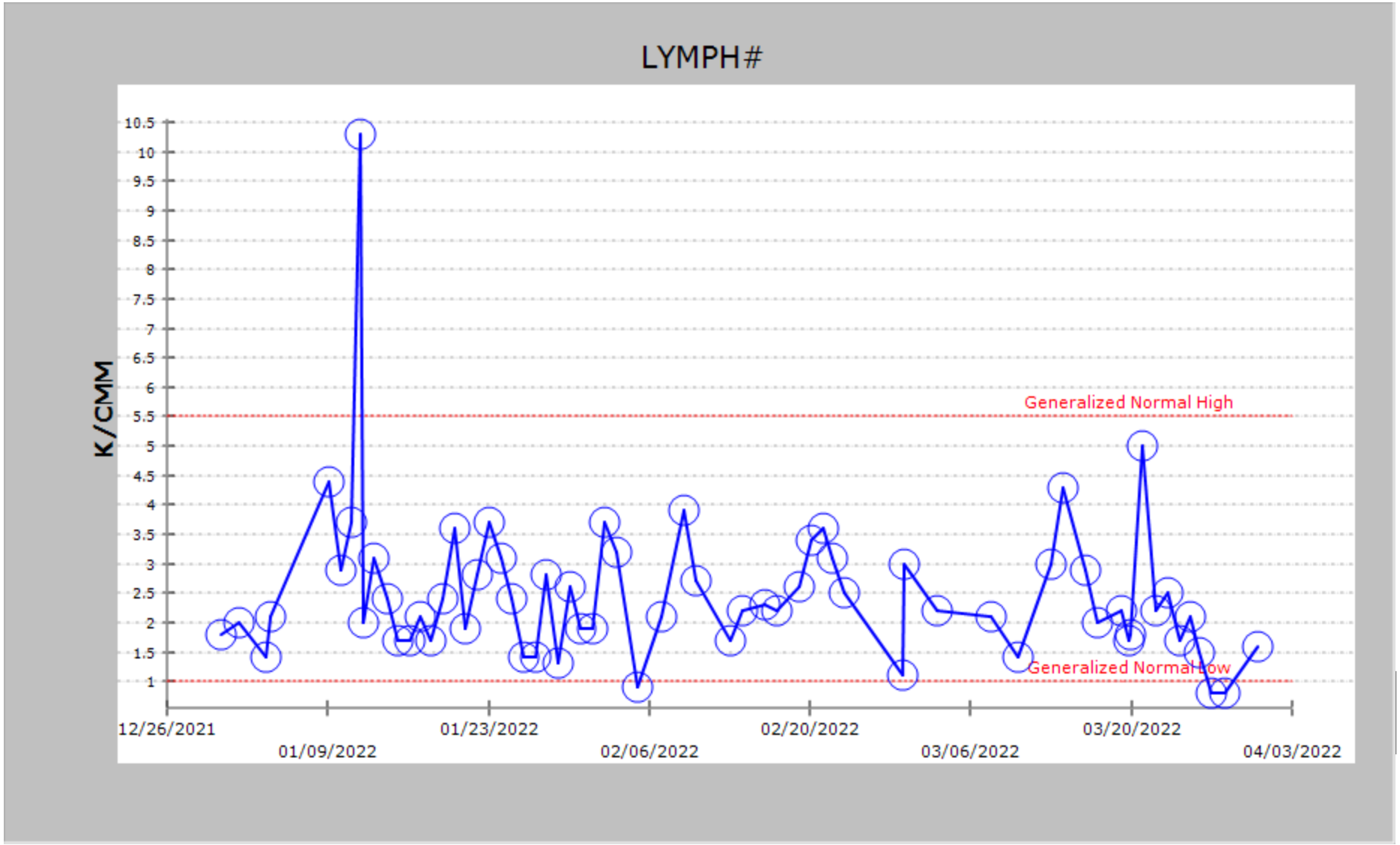
UTHealth Houston McGovern Medical School

Children's Memorial Hermann Hospital



UTHealth Houston
McGovern Medical School

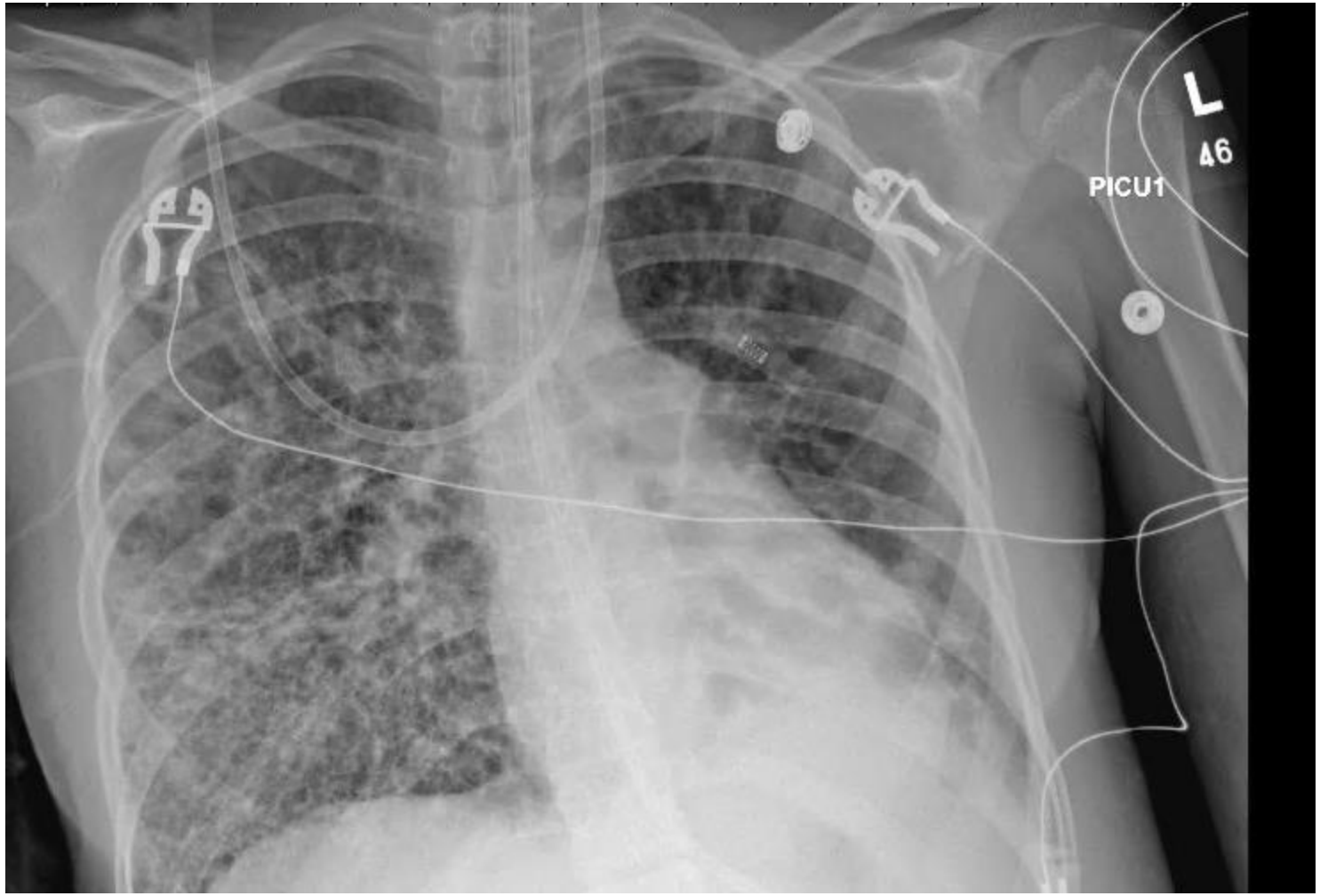
Children's Memorial Hermann Hospital



UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

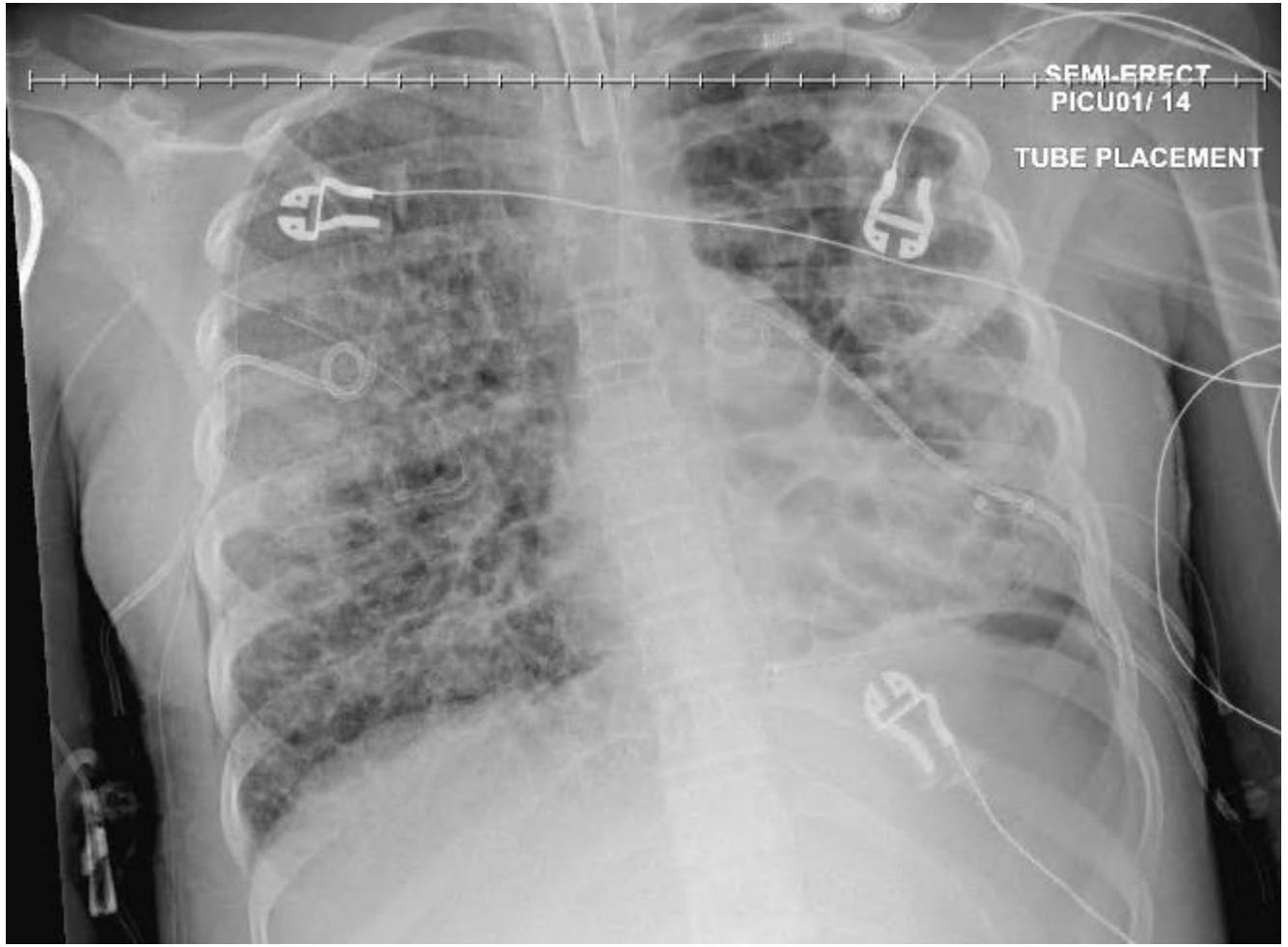
2 months later



UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

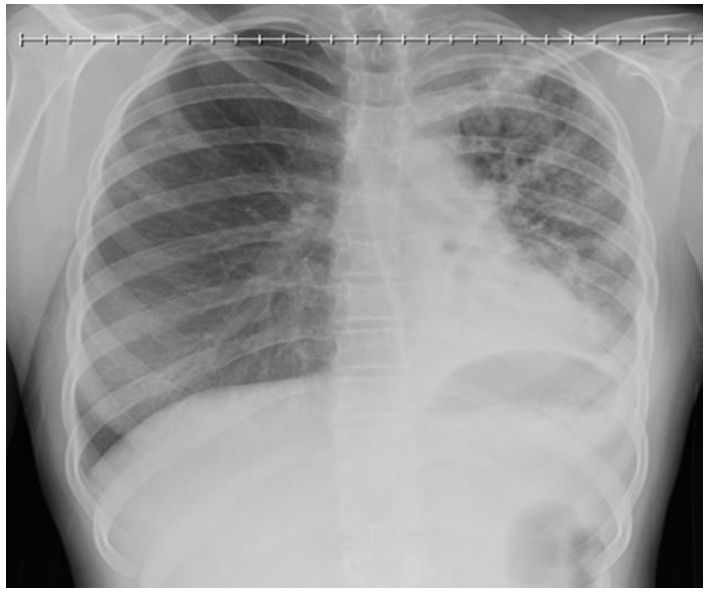
3 months later

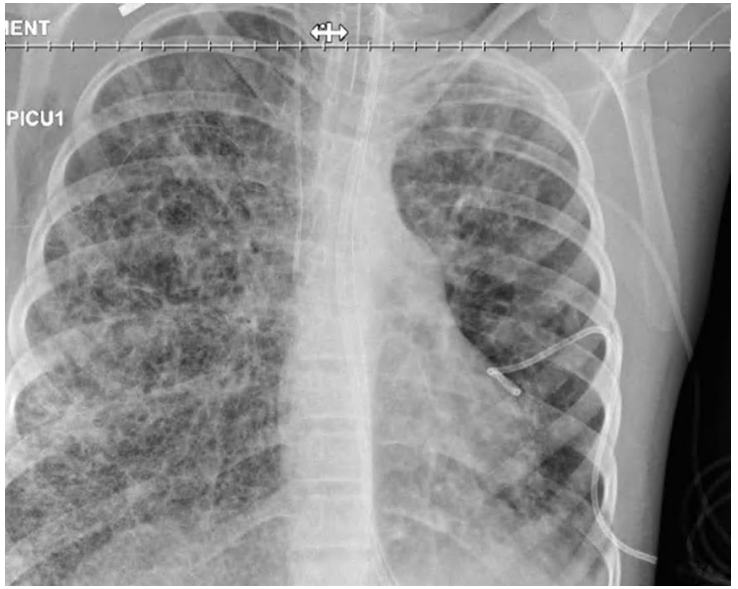


UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

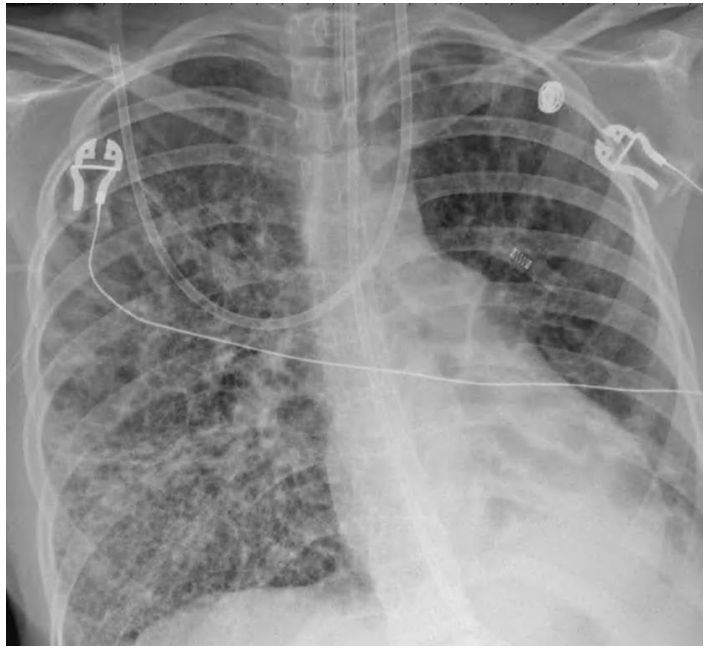
Admission

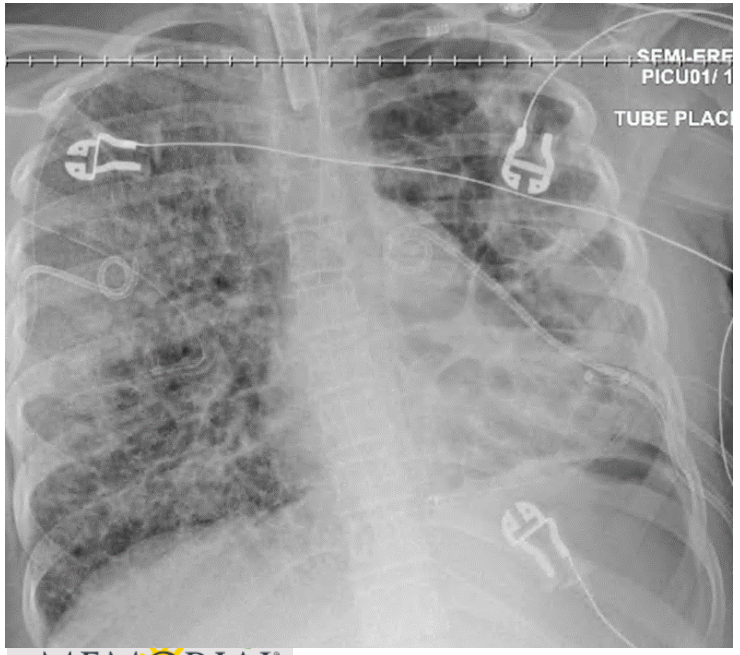




1 month later

2 months later





3 months later

UTHealth Houston
McGovern Medical School

MEMORIAL HERMANN
Hospital

Further Work up

- Extensive work up for co-infections infections: All negative
- Immune work up:

-IgG: 961 md/dL (500-1590)

IgA: 201 md/dL (ref 36-220)

IgM: 61 md/dL (ref 41-160)

-C3: 219 md/dL (ref 82-173)

C4: 51 md/dL (ref 13-46)

-Abs CD4: 261 (18%)

-Abs CD8: 361 (25%)

Cytokines	
TNF alpha	1.8 *
IL2	<2.1
IL2 Receptor Soluble	**1413.2** (ref 185-858)
IL12	<1.9
INF gamma	<4.2
IL4	<2.2
IL5	<2.1
IL10	3.6 ref < 2.8)
IL13	<1.7
IL1 beta	<6.5
IL6	2.1 H (ref <2) (Max 99)
IL8	<3.0
IL17	<1.4

UTHealth Houston McGovern Medical School

Children's Memorial Hermann Hospital

Further Work up

Flow Panel	
Absolute Total Lymphocytes	1434
CD3 T-cell %	**43 * L**
CD3 T cell absolute	**611 L**
CD4 T-Helper %	**18 L**
CD4 T-Helper absolute	**261 L**
CD8 T-Suppressor %	25
CD8 T-Suppressor absolute	361
Helper/Suppressor ratio	**0.72 L**
CD16 56 NK %	**2 L**
CD16 56 NK absolute	**22 L**
CD19 B cell %	**56 H**
CD19 B cell absolute	**806 H**

UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

Outcome

- Family withdrew care after progressive recurrent pneumothorax and hypotension.
- Patient passed away after ~ 3 months of hospitalization

Autopsy

- **Lungs:**

Microscopic examination of both lungs shows diffuse microscopic thrombi, congestion with hemosiderin laden macrophages, pulmonary hemorrhage, and mucus plugs. There are areas of acute, subacute, and chronic aspiration pneumonia. The lungs reveal a picture of severe necrotizing bacterial pneumonia. They exhibit areas of pneumonia with deposition of hyaline membrane in the alveolar walls. There are tissues with interstitial hemorrhage and calcifications. Some alveolar spaces show fibrin deposition and macrophages with engulfed proteinaceous material within. Bronchial cells show features of hyperplasia and dysplasia. Pulmonary alveoli exhibit congested capillaries, hyaline membranes, increased numbers of mononuclear cells, activated type II pneumocytes indicative of diffuse alveolar damage. Other findings are fibrotic thin irregular walled cavities with adjacent infarcted lung , irregularly shaped scattered scars, sloughed alveolar lining, and hemorrhagic infarcts. Special stains for bacteria, fungi, and acid fast organisms are negative.

- **CVS and GI**: no specific pathological alterations.
- **Kidneys:** ATN due to shock

Autopsy

- **Reticuloendothelial system:**

Microscopic examination of the shocked spleen shows no germinal centers and no reactive T-cells underdeveloped periarteriolar regions. LNs show no germinal centers or deep cortex

- Liver: diffuse areas of fibrosis, mild cholestasis, and focal necrosis
- **Bone Marrow**
- Hypercellular bone marrow with myeloid hyperplasia.
- **Neuropathology:**
- Acute hemorrhages, left parietal and temporal lobe.
- Diffuse metabolic gliosis, gray matter.
- No focal lesion in the midbrain, pons, medulla, or cerebellum

Autopsy

- **Major Anatomic Diagnoses:**
- Diffuse microscopic thrombi of both lungs, with congestion and hemorrhagic infarctions.
- Bilateral severe necrotizing bacterial pneumonia.
- Diffuse alveolar damage with congested capillaries, hyaline membranes, activated type II pneumocytes.
- Spleen with no germinal centers and no reactive T-cells with underdeveloped peri-arteriolar regions.
- Lymph nodes with no germinal centers or deep cortex

Autopsy

Cause of Death:

Primary cause of death: Primary immunodeficiency, Chronic pneumonia, Bronchiectasis

Immediate cause of death: Immune reconstitution inflammatory syndrome, and Respiratory failure

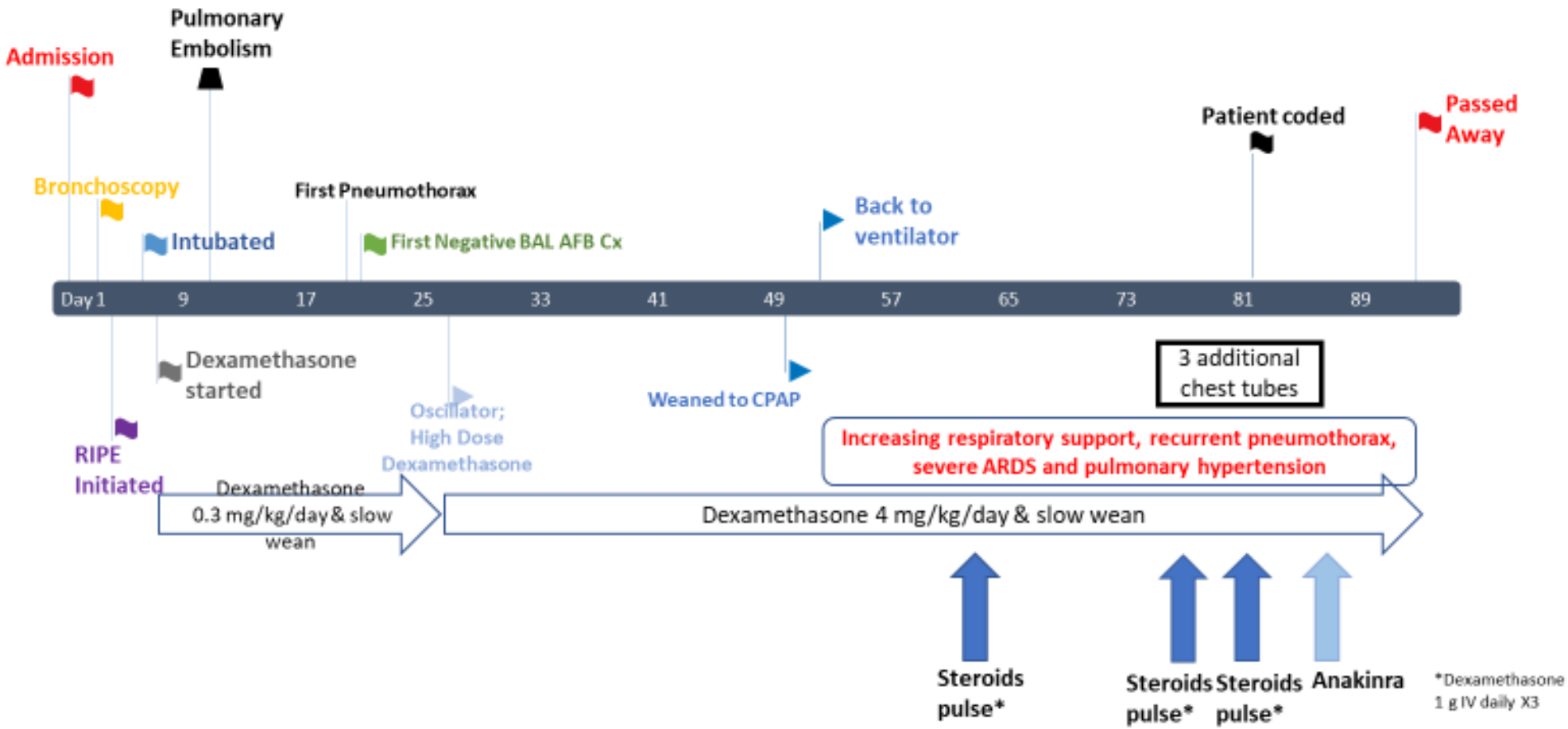
Genetics were consulted to run studies on paraffin fixed blocks.

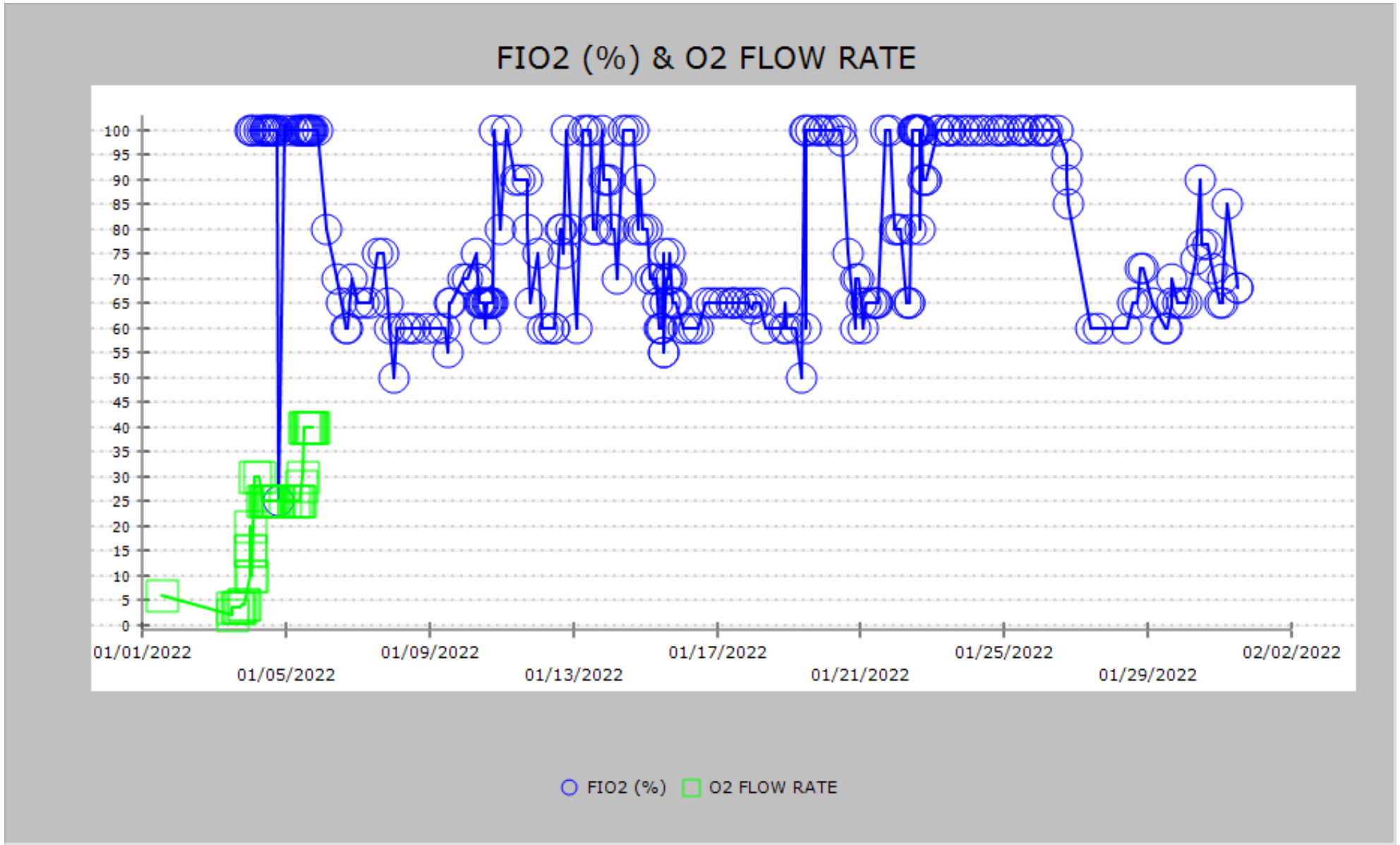
Thank you

UTHealth Houston
McGovern Medical School

Children's Memorial Hermann Hospital

End of Presendation

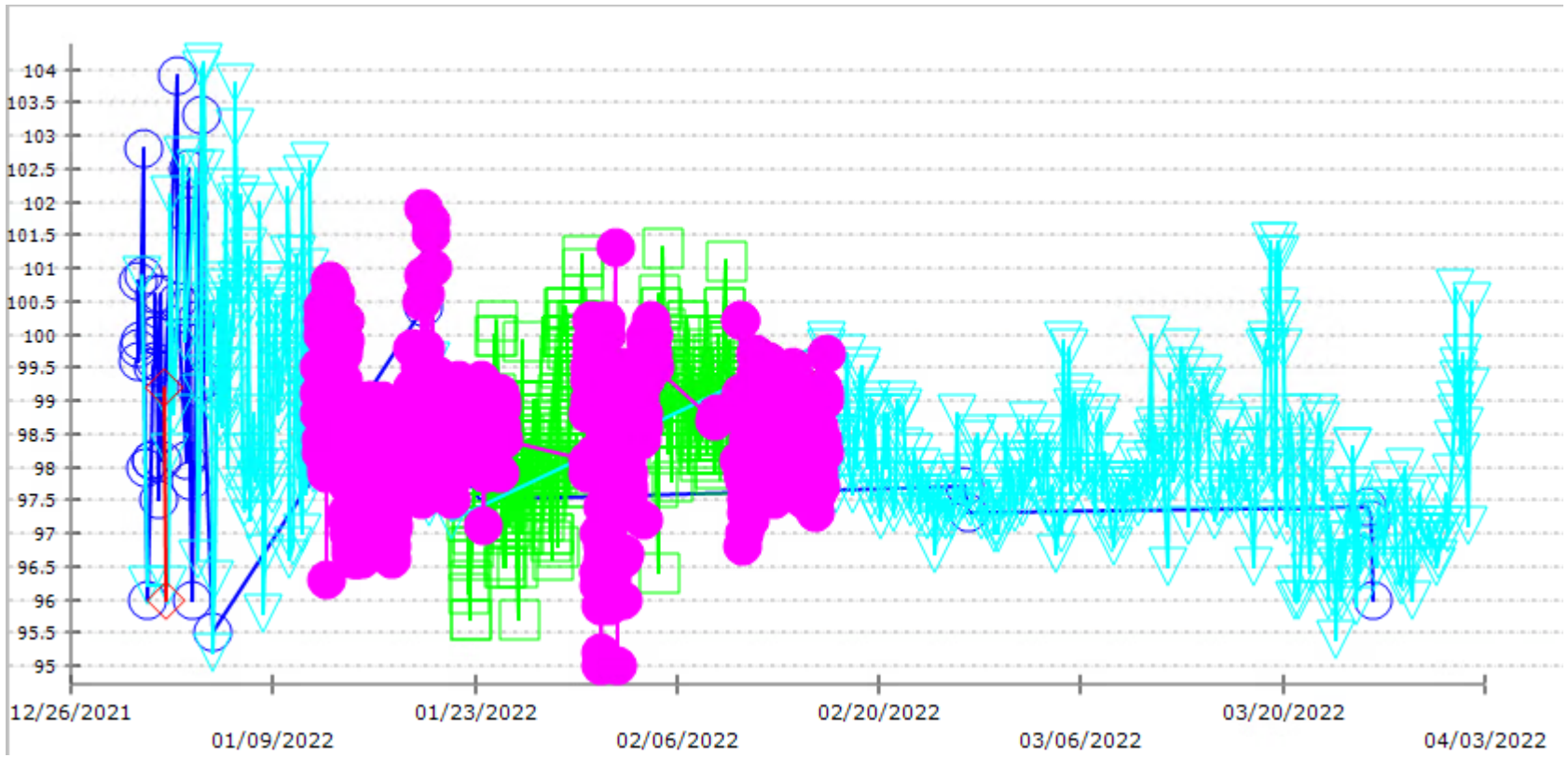

Admission
Pulmonary Embolism
Bronchoscopy
Intubated
First Pneumothorax
First Negative BAL AFB Cx
Back to ventilator
Patient coded
Passed Away
Day 1
9
17
25
33
41
49
57
65
73
81
89
Dexamethasone started
RIPE Initiated
Oscillator; High Dose Dexamethasone
Weaned to CPAP
3 additional chest tubes
Increasing respiratory support, recurrent pneumothorax, severe ARDS and pulmonary hypertension
Dexamethasone 0.3 mg/kg/day & slow wean
Dexamethasone 4 mg/kg/day & slow wean
Steroids pulse*
Steroids pulse*
Steroids pulse*
Anakinra
*Dexamethasone 1 g IV daily X3

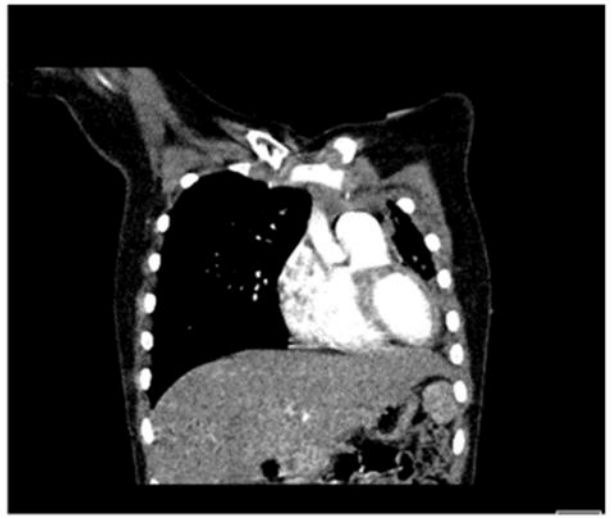

FIO2 (%) & O2 FLOW RATE
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
01/01/2022
01/05/2022
01/09/2022
01/13/2022
01/17/2022
01/21/2022
01/25/2022
01/29/2022
02/02/2022
FIO2 (%)
O2 FLOW RATE

History

- **Exposure / Social Hx:** She traveled with her dad to Tennessee in Summer 2020 and December 12/21-12/27 to visit her grandma. She spends most of her time inside during both trips. Her dad was recently incarcerated until about ~1.5 years ago. She lives with her mom, step dad, older brother (17), and younger brother (6). Her mom and brother vape (tobacco) at home. No known sick contacts. She has a cat and a dog

- **Birth Hx:** born full term via SVD. No complications during delivery or pregnancy
- **Past medical history**: “pneumonia”, eczema, sinusitis
- **Past Surgical Hx:** none
- **Family history:** Mom had history of chronic fatigue syndrome. Maternal grandmother has rheumatoid arthritis. No family history of skin infections, recurrent infections or asthma.
- **Immunizations:** up to date


104
103.5
103
102.5
102
101.5
101
100.5
100
99.5
99
98.5
98
97.5
97
96.5
96
95.5
95
12/26/2021
01/09/2022
01/23/2022
02/06/2022
02/20/2022
03/06/2022
03/20/2022
04/03/2022



UTHealth Houston
McGovern Medical School

Children's
MEMORIAL
HERMANN
Hospital

UTHealth Houston
McGovern Medical School

Children's
MEMORIAL
HERMANN
Hospital

UTHealth Houston
McGovern Medical School

Children's
MEMORIAL
HERMANN
Hospital

Differential diagnose?

- **Exposure / Social Hx:** She traveled with her dad to Tennessee in Summer 2020 and December 12/21-12/27 to visit her grandma. She spends most of her time inside during both trips. Her dad was recently incarcerated until about ~1.5 years ago. She lives with her mom, step dad, older brother (17), and younger brother (6). Her mom and brother vape (tobacco) at home. No known sick contacts. She has a cat and a dog
- **Birth Hx:** born full term via SVD. No complications during delivery or pregnancy
- **Past medical history**: pneumonia, eczema, sinusitis
- **Past Surgical Hx:** none
- **Family history:** Mom had history of chronic fatigue syndrome. Maternal grandmother has rheumatoid arthritis. No family history of skin infections, recurrent infections or asthma.
- **Immunizations:** up to date

- **T:** 100.9 °F (Axillary) **HR:** 133 (Apical) **RR:** 31 **BP:** 95/60 **SpO2:** 97% **WT:** 40.5 kg **BMI:** 16.02

- General Appearance: Well appearing, pale, and in no acute distress
  Head: Normocephalic atraumatic
  Eyes: Pupils equal/round/reactive to light, no scleral icterus, no erythema, no discharge
  Ears: Normal external shape, normal position
  Nose: Nares patent and no discharge
  Mouth: Moist mucous membranes, tongue normal, gingiva normal
  Lungs: crackles in LUL and LLL, diminished breath sound L > R, no retractions or nasal flaring
  Heart: Regular rate and regular rhythm, no murmur, 2+ radial pulses bilaterally
  Abdomen: soft, mild tenderness to palpation of epigastric region, no guarding, non-distended
  Musculoskeletal: No obvious deformity, no edema or cyanosis of extremities
  Neurologic: Alert/appropriate, good hand grip strength bilaterally
  Development: Appears normal for age
  Skin: dry peeling skin over lateral lower abdomen and suprapubic region

Hospital Course

- HD#1 bronchoscopy done. Findings: Normal airway anatomy, Copious thick mucoid airway secretions, greenish in color from left lung, minimal secretions in right lung, No frank bleeding observed, blood in mucous after suctioning, Friable mucosa.
- HD#2 BAL on 1/1/22 with positive AFB stain and PCR positive for Mycobacterium tuberculosis
- 1/2 started RIPE therapy. CT chest done
- 1/3 started on NC 3lt
- 1/4 transferred to PICU due concerns for septic shock given persistent desats despite escalation of support, hypotension and tachycardia. Started on pressors.
- 1/5 intubated due to persistent hypoxemia. Meds changed to IV due to poor tolerance.
- 1/6 unilateral right lower extremity swelling concerning for DVT. LE doppler positive for DVT in RLE from mid/distal femoral, popliteal and peroneal veins. Started on Lovenox.
- 1/11 pt became tachypneic, gasping for air, FiO2 increased, CTPE obtained showing R subseg PE and worsening ARDS with cystic areas in L lung


First Pneumothorax
First Bronchoscopy
Jan 2
RIPE Initiated
Jan 3
Admitted
Dec 31
First Negative BAL AFB Cx
Jan 20
Passed Away
Apr 4
Dec
Jan
Feb
Mar
Apr
2022
Jan 5
Transfer to PICU
Jan 6
Dexamethasone start
Jan 26
High Dose Dexamethasone, Wean

- **Pertinent Labs:**

Sodium Lvl: 131 mEq/L
Potassium Lvl: 3.6 mEq/L
BUN: 7 mg/dL
Creatinine Lvl: 0.53 mg/dL
Glucose Lvl: 89 mg/dL
Calcium Lvl: 8.4 mg/dl
Total Protein: 9.1 g/dL
Globulin: 6.8 g/dL
Albumin Lvl: 2.3 g/dL
Alk Phos: 73 unit/L
ALT: 16 unit/L
AST: 12 unit/L
Bili Total: 0.2 mg/dL

Coronavirus (COVID-19) NAA: Not Detected

pH Ven: 7.39
O2 Sat Ven: 44.5 %
pO2 Ven: 25 mmHg
pCO2 Ven: 44 mmHg
HCO3 Ven: 27 mMol/L High

Total CK: 23 unit/L
Procalcitonin Lvl: <0.05
Lactic Acid Lvl: 1.7 mMol/L

PT: 14.3 seconds
PTT: 32.1 seconds
INR: 1.12

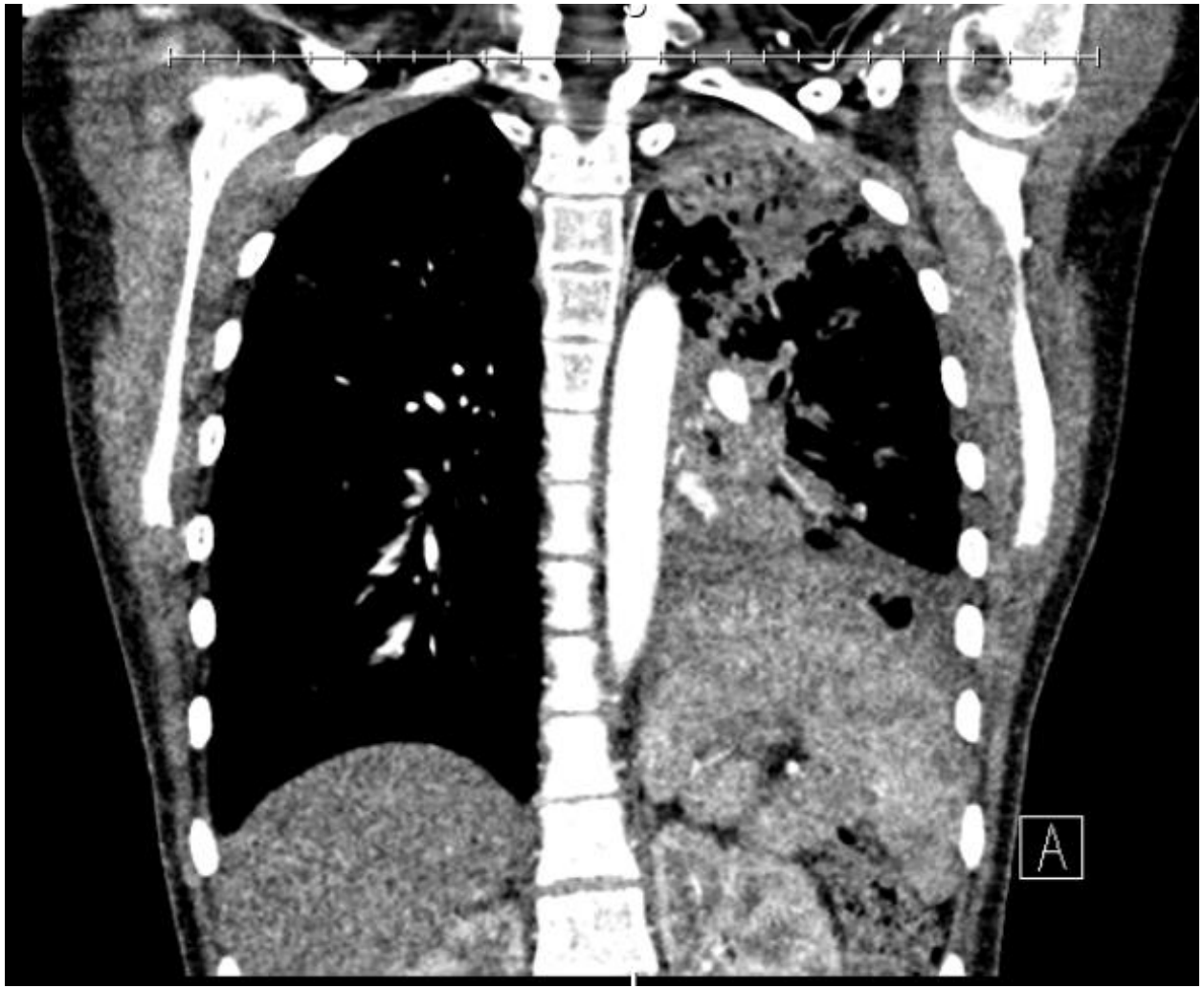
WBC: 9.6 K/CMM
Hgb: 8.1 g/dL
Hct: 26.1 %
Lymphocytes: 18.4 %
Segs: 74.2 %
Lymphocytes #: 1.8 K/CM
MCH: 20.2 pg
MCHC: 31.1 g/dl
MCV: 65 fL
RBC: 4.01 M/CMM
RDW: 17.8 %
Platelet: 299 K/CMM
MPV: 6.9 fL

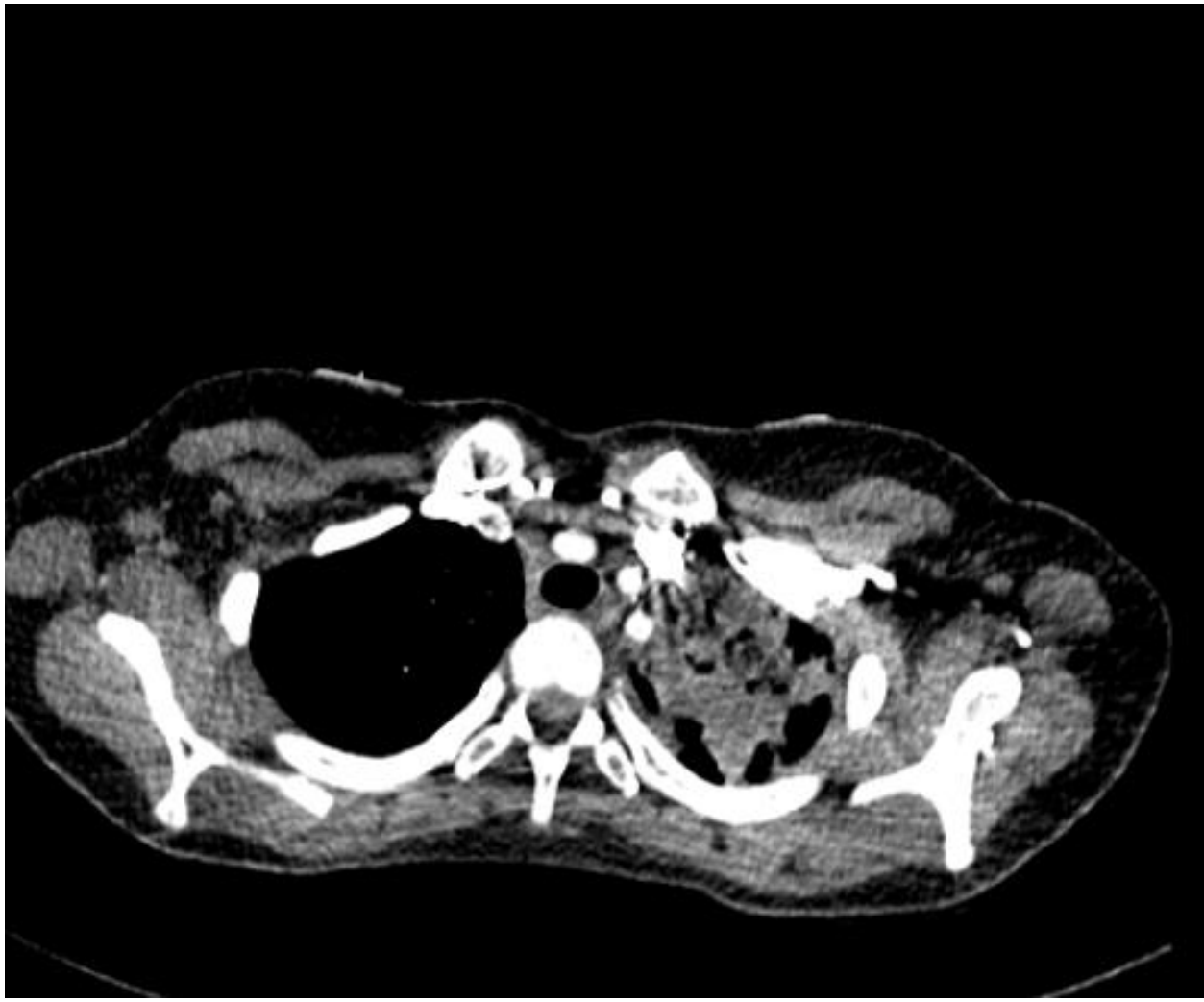
Further Work up

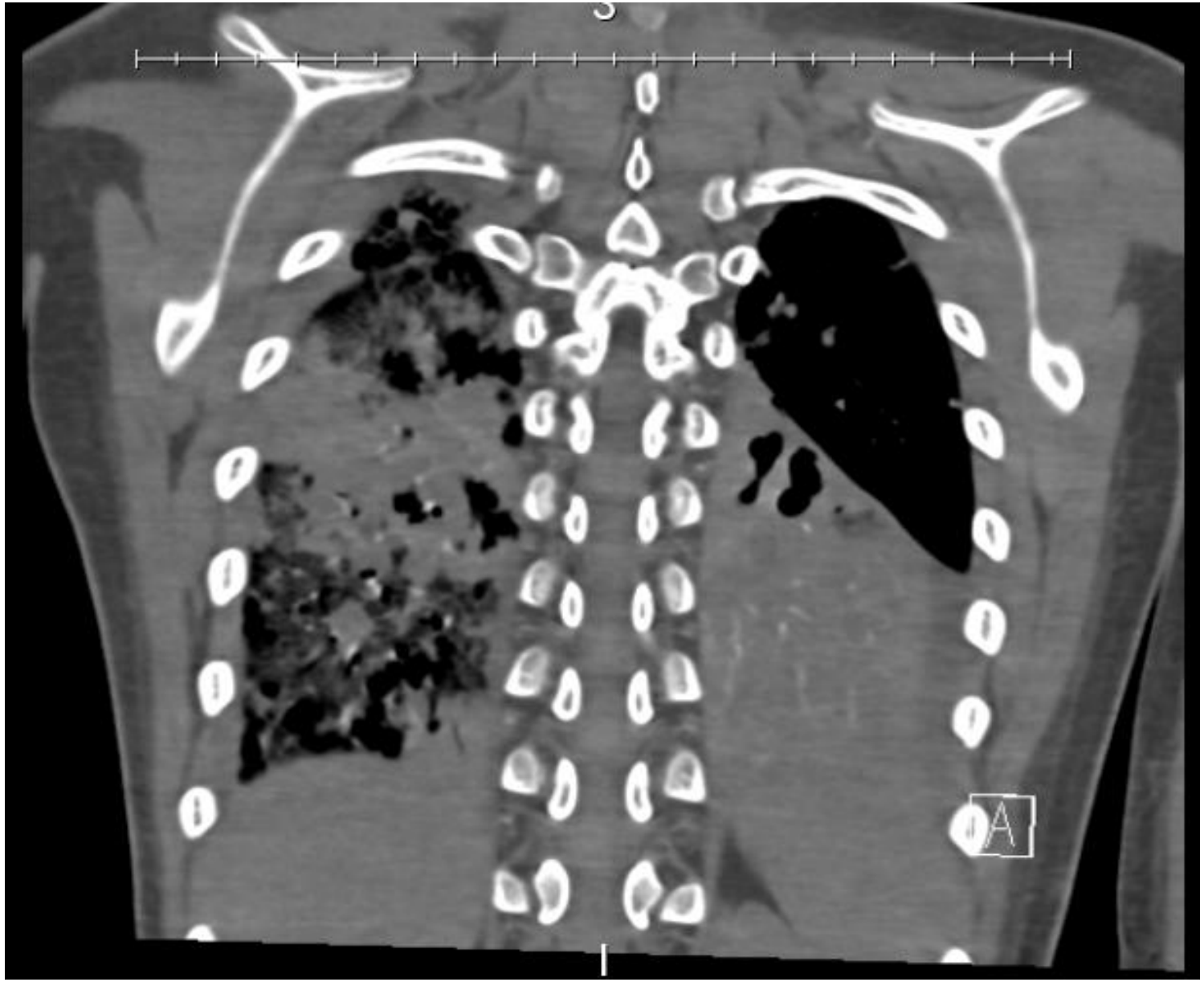
- **QuantiFERON TB Gold: Pos**

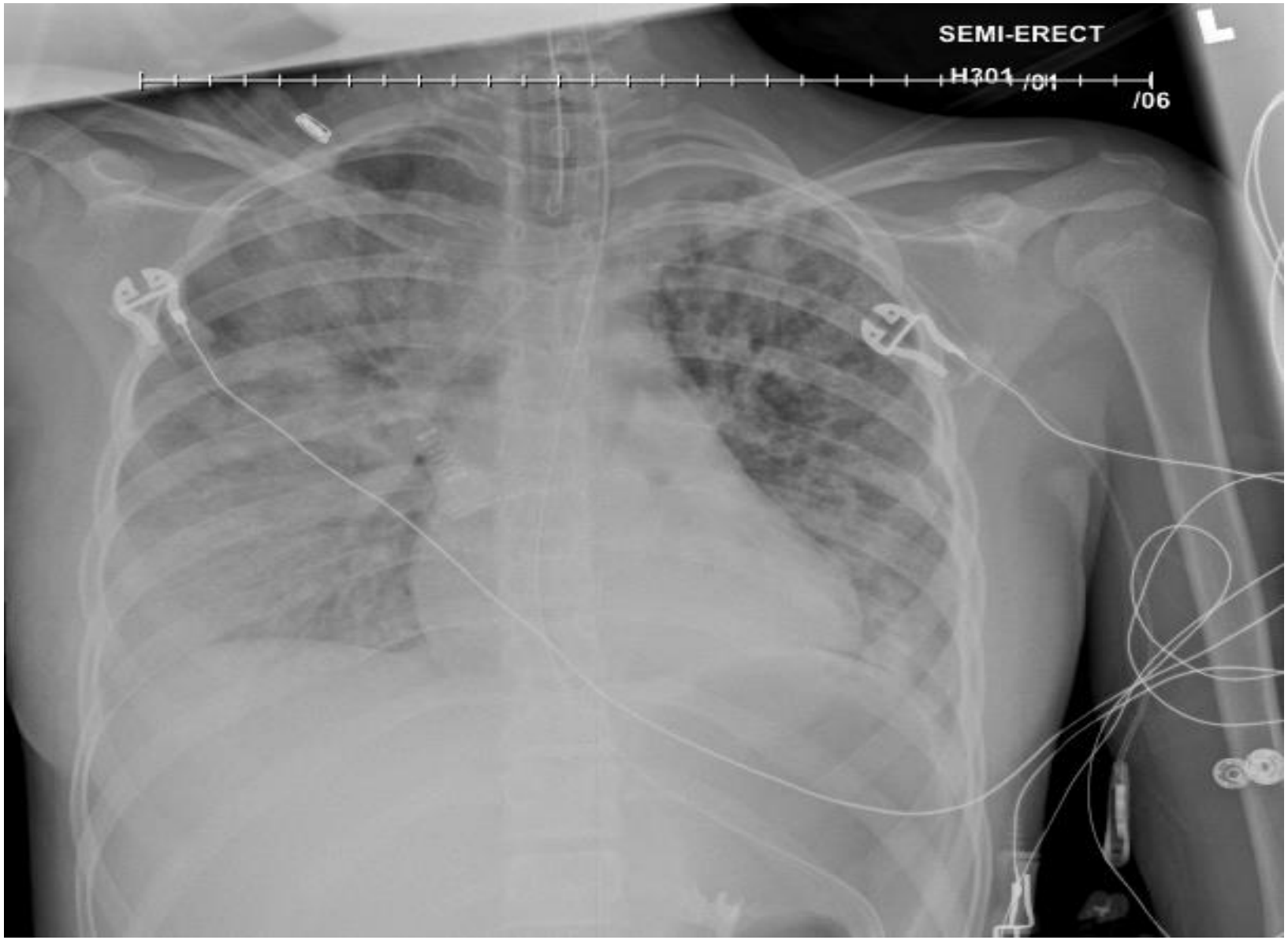
- BAL (HD#2)
  AFB stain: many AFB
  AFB cx: Pos
  BAL MTB PCR: Pos. Sensitive to rifampin, isoniazid and ethambutol
  Bacterial and fungal cx: Neg

- Fungal testing (Coccidiomycoses, histoplasmosis, Blastomycosis, Galactomannan, (1-3) Beta-D glucan): Neg


A




A


SEMI-ERECT
L

medications

Rifampin 600 mg IV q24h (1/2- current)
Moxifloxacin 400 mg IV q24h (1/5 - current)
Amikacin 10 mg/kg IV q24h (1/5 - held 1/10)
Linezolid 600 mg IV q24h (1/5 - current)
Dex D7/7

Discontinued
Vancomycin (01/04/2022 01/06/2022)
Cefepime (01/04/2022 - 01/06/2022)
Tamiflu (01/05/2022 - 01/06/2022)
Isoniazid 300 mg daily PO (1/2 – 1/5)
Pyrazinamide 1500 mg daily PO (1/2 – 1/5)
Ethambutol 800 mg daily PO (1/2 – 1/5

•

Work up

- **01/01 1245**
- Aspergillus galactoman 0.124
- Source HSV Bronchial Washin
- HSV 1 by PCR Negative
- HSV 2 by PCR Negative
- Aspergillus galactoman 0.070
- Source CMV Bronch Alv. Lavag
- CMV PCR Negative
- Fungitell 42
- Histoplasma Ag None Detected

12/31 1709
U Hist Ag Intrp NEGATIVE
12/31 0128
Aspergillus galactoman 0.039

Quantiferon - TB Gold POSITIVE
NIL 0.26
Mitogen - NIL 2.83
Quantiferon - TB1 Ag V 0.56
Quantiferon - TB2 Ag V 1.18

01/01 1244
Source MTB BAL
Mycobacterium tubercul Detected
Rifampin resistance Not Detected

micro

- BCx (12/30): NGTD x5
- Fungal Cx (1/1, BAL): no yeast or fungal elements
- AFB smear/Cx (1/1, BAL): + many acid fast bacilli x 2 samples,
  AFB culture: MT
  Culture BAL Quant (1/1): Neg x2
  Pneumocystis carinii DFA (1/1): negative
- BCx (1/4): Neg x 1
-

tb

- Pulmonary tuberculosis (TB) is defined as TB of the lung parenchyma and the tracheobronchial tree. The lungs are the major site for *Mycobacterium tuberculosis* primary infection and tuberculosis (TB) disease.

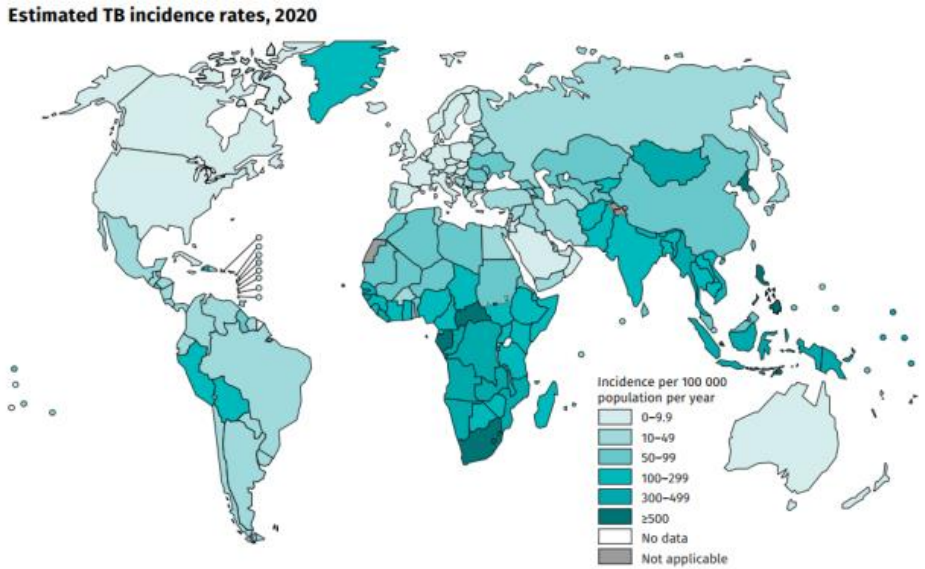
- Clinical manifestations of TB include primary TB, reactivation TB, laryngeal TB, endobronchial TB, lower lung field TB infection, and tuberculoma.

- After primary infection, 90 percent of individuals with intact immunity control further replication of the bacilli, which may then be cleared or enter a "latent" phase.

- The remaining 10 percent of individuals develop progressive primary disease with TB pneumonia and expansion of infiltrates.

https://www.uptodate.com/contents/tuberculosis-disease-in-children/abstract/1

Epidemiology



- A total of 1.5 million people died from TB in 2020
- In 2020, 1.1 million children fell ill with TB globally
- It has been estimated that, of nearly one million children who developed TB disease in 2014, 58,000 had isoniazid-monoresistant TB, 25,000 had multidrug-resistant (MDR)-TB, and 12,000 had extensively drug-resistant TB.

World Health Organization. Global tuberculosis report 2019. https://www.who.int/tb/publications/global_report/en/

Tb disease progression

- While intrathoracic lymphadenopathy is the commonest radiographic feature of primary pulmonary tuberculosis (PTB) in children, parenchymal abnormalities do occur in the form of alveolar consolidation and linear interstitial opacification.

- In primary pulmonary infection, a Ghon complex is formed with a primary parenchymal focus (Ghon focus) and lymphadenopathy occurs in the draining regional lymph nodes.

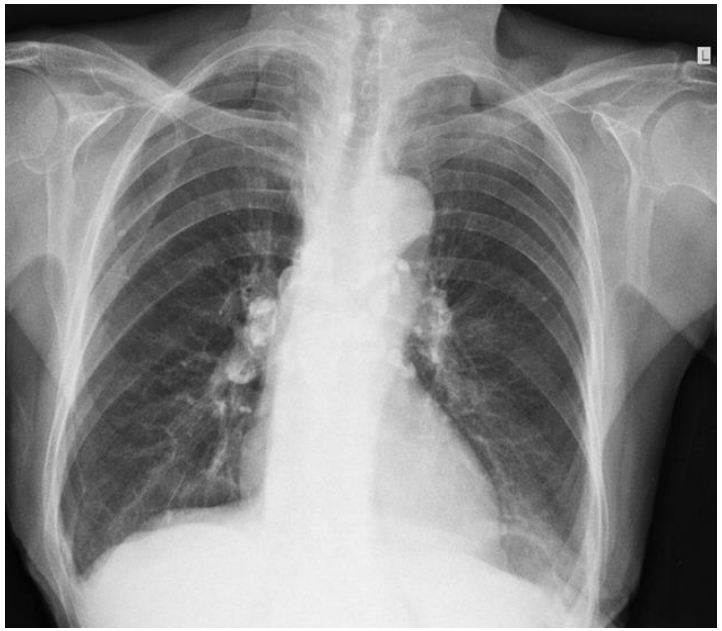
- In 5–10% of children with primary PTB, the primary focus can enlarge and undergo caseous necrosis; this is called progressive primary PTB.

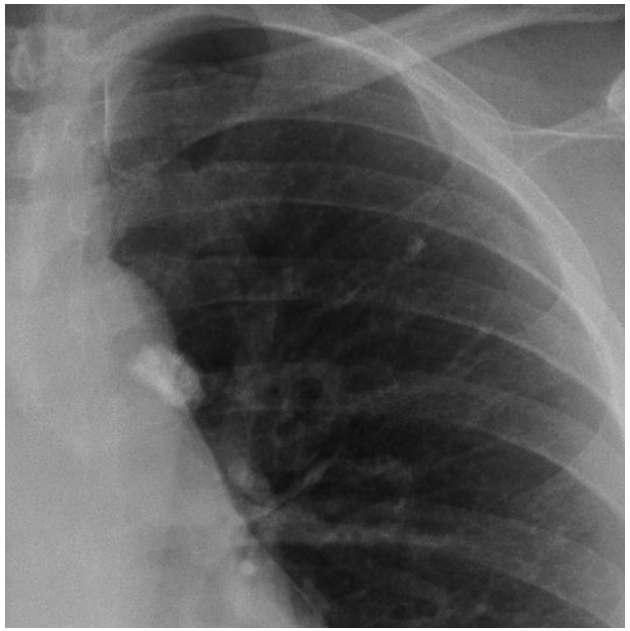
- This can lead to endobronchial spread and miliary dissemination. The lymph nodes themselves may undergo disease progression and the result is lymphobronchial TB.

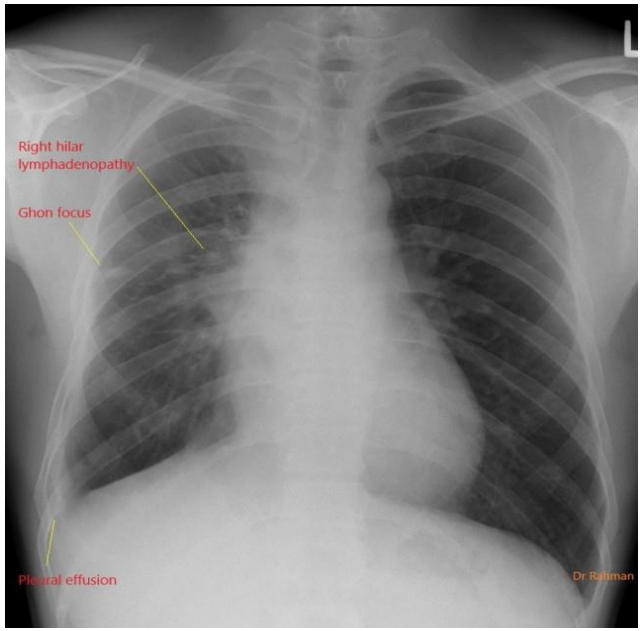
Lee, L.-N., Liu, J.-L., Chang, H.-C., Lin, C.-H., & Wang, J.-Y. (2010). Septic shock due to mycobacterium tuberculosis. *D24. TUBERCULOSIS TREATMENT AND OUTCOMES: ANIMAL AND HUMAN STUDIES*. https://doi.org/10.1164/ajrccm-conference.2010.181.1_meetingabstracts.a5454

Ghon complex

- Ghon lesion is the initial tuberculous granuloma formed during primary infection and is not radiologically visible unless it calcifies - this occurs in up to 15% of cases.
- A Ghon focus alongside ipsilateral mediastinal lymphadenopathy is known as a Ghon complex. A calcified Ghon complex is called a Ranke complex, which is radiologically detectable.







Kim, W. S., Choi, J.-I., Cheon, J.-E., Kim, I.-O., Yeon, K. M., & Lee, H. J. (2006). Pulmonary tuberculosis in infants: Radiographic and CT findings. *American Journal of Roentgenology*, *187*(4), 1024–1033. https://doi.org/10.2214/ajr.04.0751

tb

- Although TB disease often presents subacutely, it can also manifest as sepsis or septic shock. In some instances, TB sepsis is accompanied by acute lung

Classic Symptoms for Active TB	
Chest symptoms	Constitutional
• Cough • Sputum • Haemoptysis • Chest pain • Breathlessness	• Fevers • Night sweats • Weight loss • Lack of appetite • Malaise

Table 1. Selected acute and chronic TB related complications, by site

Anatomic site	Complication
Lung parenchyma	• Tuberculoma
	• Residual cavitation
	• Aspergilloma
	• Scarring or fibrosis
	• Obstructive or restrictive ventilatory deficits
Airways	• Bronchiectasis
	• Tracheobronchial stenosis
	• Broncholithiasis
Vascular	• Pulmonary or bronchial arteritis or thrombosis
	• Rasmussen pseudoaneurysm
Mediastinal or cardiac	• Lymph node calcification
	• Esophagobronchial fistula
	• Cardiac tamponade
Pleural	• Chronic empyema
	• Bronchopleural fistula
	• Pneumothorax
Central nervous system	• Tuberculomas–focal neurologic deficits or seizures
	• Vasculitis or stroke
	• Hydrocephalus
Eye	• Posterior or anterior uveitis
	• Choroiditis
	• Optic neuropathy
Genitourinary	• Renal TB
	• Ureteral stenosis
	• Hydronephrosis
	• Prostatic abscess
Endocrine or metabolic	• Adrenal insufficiency
	• Hypercalcemia
Lymph nodes	• Paradoxical worsening of lymphadenitis
	• Lymphocutaneous fistulas
Abdomen	• Tuberculous ascites
	• Peritoneal implants
	• Granulomatous colitis (may be mistaken for Crohn's disease)
	• Pelvic abscess
Bone	• Focal osteomyelitis
	• Spinal diskitis and osteomyelitis (Pott's disease)

Ethiop J Health Sci. 2018 Nov; 28(6): 683–690.
doi: 10.4314/ejhs.v28i6.2
PMCID: PMC6308747
PMID: 30607084

Tuberculosis Status and Coinfection of Pulmonary Fungal Infections in Patients Referred to Reference Laboratory of Health Centers Ghaemshahr City during 2007–2017

Mohammad Reza Jabbari Amiri,[1] Rora Siami,[2] and Azad Khaledi[3,4]

- From a total of 3577 patients with suspected TB during ten-years, 10731 smears were prepared.

- In total, 48/10731 smears (0.44%) were positive for fungi infections. Amongst the positive tuberculosis patients, 16/130 cases (12.3%) had the coinfection of *Mycobacterium tuberculosis* with fungi microorganisms such as *Candida albicans, Aspergillus fumigatus* and, *A. flavus.* Ten out of 16 cases (62.5%) had the coinfection *Aspergillus spp.*, with TB and 6 /12(37.5%) had the coinfection of *Candida spp.*, with TB.

tbss

- Tuberculosis sepsis shock is extremely rare and there are only sporadic cases reported to date
- TBSS is frequent to occur in those with low immunity, incidence is lower in children. TBSS can lead to such symptoms as fever, shortness of breath and multiple organ dysfunction to sepsis.
- TBSS can cause hyponatremia and anemia, it also triggered various similar symptoms to G-bacilli bloodstream infection, for example, thrombocytopenia, elevated procalcitonin, persistent high fever and septic cardiomyopathy.
- There have been a large number of studies substantiating that the tuberculosis sepsis patients needing ICU treatment are at increased risk of in-hospital mortality

Kethireddy, S., Light, R. B., Mirzanejad, Y., Maki, D., Arabi, Y., Lapinsky, S., Simon, D., Kumar, A., Parrillo, J. E., & Kumar, A. (2013). Mycobacterium tuberculosis septic shock. *Chest*, *144*(2), 474–482. https://doi.org/10.1378/chest.12-1286

tbss

- A late start of anti-tuberculosis therapy will lead to the poor clinical outcomes.
- One study suggested that the median time to appropriate antimicrobial therapy for MTB septic shock was 31.0 h (interquartile range, 18.9-71.9 h). Only 11 patients received anti-MTB therapy within 24 h of documentation of hypotension; six of these (54.5%) survived.
- Only one of 21 patients (4.8%) who started anti-MTB therapy after 24 h survived.
- Suboptimal drug absorption is a potential complication. Drug intolerance is functionally similar to drug resistance because both require alternative TB regimens.

Kethireddy, S., Light, R. B., Mirzanejad, Y., Maki, D., Arabi, Y., Lapinsky, S., Simon, D., Kumar, A., Parrillo, J. E., & Kumar, A. (2013). Mycobacterium tuberculosis septic shock. *Chest*, *144*(2), 474–482. https://doi.org/10.1378/chest.12-1286

Abstract: Poster Presentations | October 2005

MYCOBACTERIUM TUBERCULOSIS AN UNUSUAL YET HIGHLY FATAL CAUSE OF SEPTIC SHOCK

Raquel Nahra, MD*; Sergio L. Zanotti-Cavazzoni, MD; Anand Kumar, MD
Cooper University Hospital, Camden, NJ

Chest. 2005;128(4_MeetingAbstracts):380S.
doi:10.1378/chest.128.4_MeetingAbstracts.380S

McGee et al., Lung Dis Treat 2016, 2:4
DOI: 10.4172/2472-1018.1000115

Journal of Lung Diseases & Treatment

Case Report Open Access

Mycobacterium tuberculosis Presenting as Septic Shock with ARDS: Multiculturalism Promotes Early Therapy

- A immunocompetent patient developed septic shock from a pulmonary tubercular infection which necessitated vasopressor and ventilatory support
- ARDS is a relatively rare manifestation of miliary tuberculosis.
- Few old case reports exist of an entity called “sepsis tuberculosis gravissima”, an acute septic shock with ARDS and multiorgan failure from MTB
- Few cases of ARDS in military tuberculosis have been reported in patients started on antibiotic therapy which suggests that the cell lytic process may be an initiating factor

treatment

- The core aims of the treatment are to rapidly reduce bacterial load to achieve clinical improvement, to remove slow growing persistor organisms to prevent relapse, and to avoid the emergence of drug resistance.

- The rationale for multi-drug approaches is well described. Replicating *M. tuberculosis* organisms are prone to spontaneous genetic mutations which confer resistance to individual anti-tuberculosis drugs.

- The probability of incident resistance mutations is high in early treatment when bacillary loads and replication rates are high.

- The drugs employed in TB treatment have different activities, including early bactericidal activity to reduce bacterial load (INH and RIF) and sterilizing activities to remove persistor organisms (RIF and PZA), in part related to their ability to penetrate caseating tissue.

Global burden of drug-resistant tuberculosis in children: A mathematical modelling study. (2016). *Indian Journal of Tuberculosis*, *63*(4), 277–278. https://doi.org/10.1016/j.ijtb.2016.11.025

Treatment complications

- Paradoxical reactions consistent with IRIS (Immune Reconstitution Inflammatory Syndrome) can occur following the initiation of antituberculous therapy.

- In one study of 110 children, clinical or radiographic deterioration was observed in 14 percent of cases after initiating therapy. The most common complication was enlarging intrathoracic lymphadenopathy. Deterioration was more likely among children with weight-for-age ≤25th percentile and multiple sites of disease. Corticosteroids were administered in 60% of cases.

- In another study of 115 immunocompetent children, 12 developed paradoxical worsening within 15 to 75 days of starting TB therapy; The most common manifestation was worsening of preexisting pulmonary lesions, observed in 75 percent, while 25 percent had new disease present in new anatomic locations.

Sun, L., Yang, Z., Yang, F., Wang, Z., Li, H., Wang, H., & Sun, T. (2021). Diagnosis of mycobacterium tuberculosis septic shock in patients with anti-synthetase syndrome based on next-generation sequencing: A case report and literature review. *Frontiers in Medicine*, *8*. https://doi.org/10.3389/fmed.2021.675041

Clinical Infectious Diseases
MAJOR ARTICLE

Effects of Corticosteroids on Critically Ill Pulmonary Tuberculosis Patients With Acute Respiratory Failure: A Propensity Analysis of Mortality

Ji Young Yang,[1,a] Minkyu Han,[2,a] Younsuck Koh,[3] Woo-Sung Kim,[3] Jin-Woo Song,[3] Yeon-Mok Oh,[3] Sang-Do Lee,[3] Sei Won Lee,[3] Jae-Seung Lee,[3] Chae-Man Lim,[3] Chang-Min Choi,[3] Jin-Won Huh,[3] Sang-Bum Hong,[3] Tae Sun Shim,[3] and Kyung-Wook Jo[3]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Busan Paik Hospital, Inje University College of Medicine, Busan, [2]Department of Clinical Epidemiology and Biostatistics, and [3]Division of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

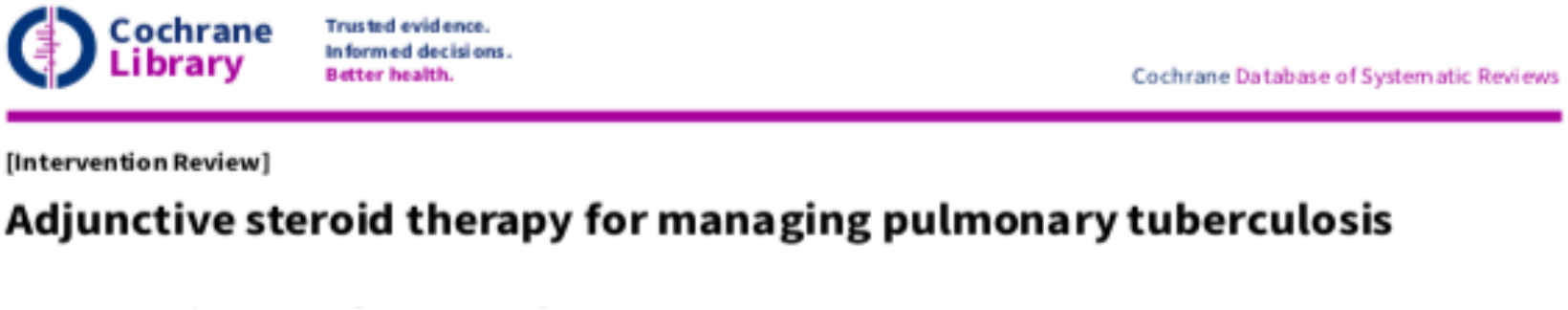
- Although rare, acute respiratory failure complicated by pulmonary tuberculosis is a predominantly fatal disease. We have previously reported an in-hospital mortality rate of 65.6% (59/ 90) in pulmonary tuberculosis patients with acute respiratory failure.

- In our present analysis, the most important finding was that adjuvant corticosteroid treatment could reduce the 90-day mortality rate in these patients.

- Although 7 of the 54 (13.0%) patients who did not receive corticosteroids were diagnosed with newly developed infectious complications 48 hours after ICU admission, 23 (32.9%) patients in steroid group suffered from superinfection—mostly pneumonia after initiating corticosteroids.

- These beneficial effects of adjuvant steroids in the treatment of tuberculosis can be explained in several ways. First, they can block excessively high concentrations of cytokines shortly after the initiation of antituberculosis medication, especially for patients with a high mycobacterial burden. Moreover, they can promote the penetration of antituberculosis drugs into granulomas by disrupting granuloma formation.

- Additionally, it should be noted that early administration of steroids has been reported to ameliorate pulmonary and extrapulmonary organ dysfunction in patients with ARDS.



- Corticosteroids did not reduce mortality from pulmonary tuberculosis (18 trials, 3816 participants, *low quality evidence*). When compared to taking placebo or no steroid, corticosteroid use was not shown to to reduce all-cause mortality, or result in higher sputum conversion at 2 months or at 6 months

- Significant, short term clinical benefits of corticosteroid use were not maintained in the long term. Failure or relapse rate were not found to differ amongst those taking corticosteroid compared to those taking no steroid or placebo.

- Corticosteroid use was found to reduce the duration of fever, increase weight gain during differing study specific time points, and to decrease length of hospital stay when compared with no steroid treatment or placebo.