Case Presentation: Disseminated Multidrug Resistant Tuberculosis in a Transplant Patient

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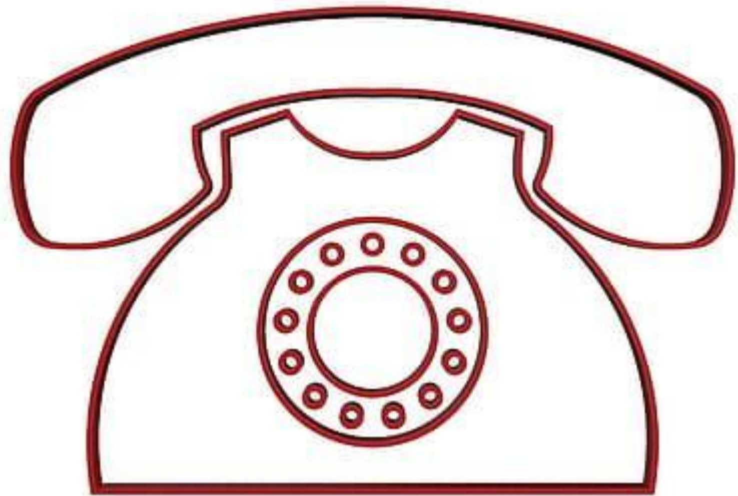
TB Program's Worst Fear

Ring! Ring!



2/2/24:

A Friday afternoon telephone call from an out of state hospital with a suspected Multidrug Resistant (MDR) tuberculosis (TB) case who is being released to our jurisdiction.

UGH!

Concerns

- Potentially, our program's first MDR patient
- Relatively new case managers in our program
- Already five (5) other new cases since 12/27/23
- No information from the Ohio Department of Health
- No patient records sent, only verbal report
- Unsure when the patient would arrive
- Patient not connected to any healthcare providers in our area
- Unsure of medical coverage as husband starting a new job
- Questionable absorption of medications
- What medication regimen? Do we have the meds? How quickly can we get them?

Patient Information

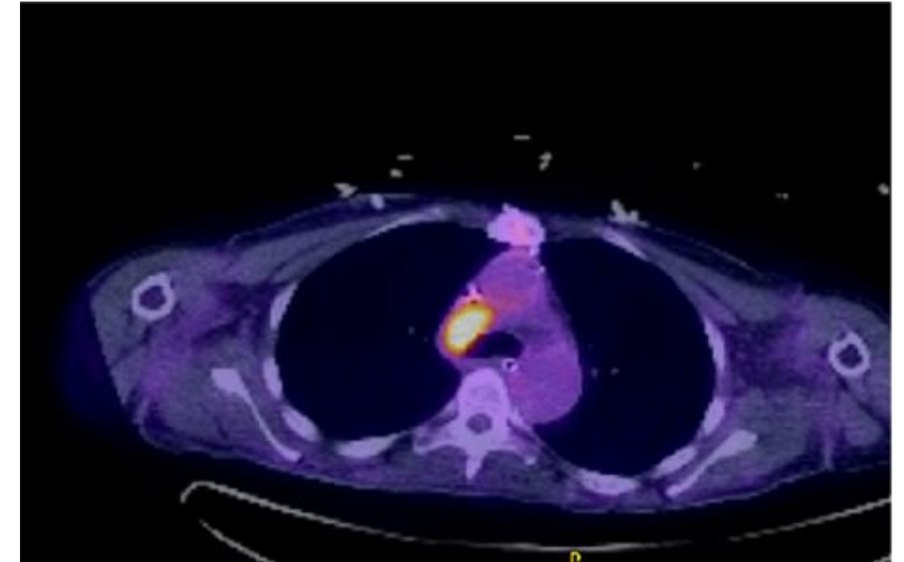
- 37yo female with disseminated TB
- Born in Cote d'Ivoire (Ivory Coast). Came to the United States in 2017. Residing in Dayton, Ohio.
- Risk factors for TB and other co-morbidities:
    - Takayasu arteritis (Dx in 2022)/aortic aneurysm
    - 5/23/22: Bentall procedure, aortic valve replacement, ascending aortic graft
    - 6/2022: Acute colonic perforation due to ischemic bowel leading to extensive small bowel/colon resection and short gut syndrome
    - 6/2022 to 10/2022: TLTBI with intravenous (IV) rifampin (IV due to concern for malabsorption)
    - 6/29/23: Small bowel transplant at Cleveland Clinic complicated by cellular rejection
    - 8/28/23: Post transplant infections related to abdominal wall bleed and enterocutaneous fistula (repaired)
    - 9/1/23: Septicemia with Klebsiella pneumoniae, acute hypoxemic respiratory failure
    - Immunosuppression ongoing with Tacrolimus, dexamethasone taper

Clinical Presentation and Hospitalization

- Symptom onset date and symptoms:
    - 11/15/23: Fever, headaches, altered mental status and worsening cytopenias
    - 11/17/23: Admitted to Cleveland Clinic from an outside hospital with abdominal pain and altered mental status
    - 11/18/23: Initially disoriented to place, not answering questions
    - 12/5/23: Agitated, paranoid, hallucinations
    - 12/13/23: Eyes closed, no communication, catatonia
    - 12/15/23: Recurrent fevers
    - 12/23/23: Nonverbal
- Hospitalization
    - Hospitalized at Cleveland Clinic from 11/17/23 to 2/7/24

Diagnostic Evaluation

- Imaging
  - CT Chest with IV Contrast
    - [Date]: Development of right paratracheal adenopathy, increase in size of small pleural effusions and improving of dependent and basilar atelectasis
  - MRI Brain
    - 12/05/23: Numerous punctate areas of susceptibility and punctate T2 hyperintensity
    - 12/20/23: Interval development of multiple infratentorial and supratentorial enhancing foci, associated parenchymal edema
    - 1/13/24: Resolution of punctate areas of parenchymal enhancement, interval development leptomeningeal enhancement



Labs and Microbiology

- AFB smear, culture, and pathology
  - 12/20/23: Cerebrospinal fluid = AFB culture negative
  - 12/26/23: Transbronchial FNA = AFB smear negative, culture positive for MTBC on 1/11/24
  - 1/2/24: Paratracheal lymph node = AFB smear negative, culture positive for MTBC on 2/5/24
  - 1/10/24: Bone marrow biopsy = Pathology showed non-caseating granulomas and culture positive for MTBC
  - All respiratory specimens returned AFB smear and culture negative
- CSF
  - 12/20/23: Nucleated 0, RBC 2, 7% segs, Total Protein = 40, Glucose = 51
  - 12/22/23: Nucleated 2, RBC 10, 27% segs, Total Protein = 17, Glucose = 75

Treatment

Treatment started

1/6/2024: INH 300/RPT 1200/PZA 1500 mg/Moxifloxacin 400

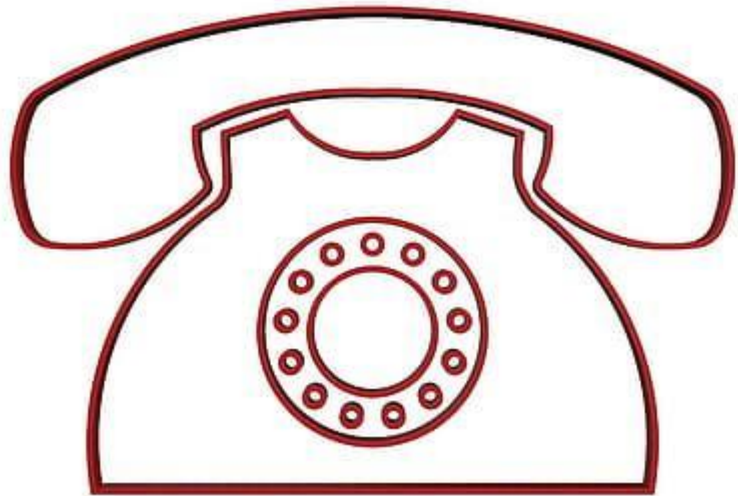
1/12/24: INH 300/RIF 600/PZA 1500/EMB 800/**LZD 600**/B6 100

Inpatient team reported fever curve improved with change of regimen 1/12

- Therapeutic drug monitoring
  - Not done

Second Call, Worse than the First

Ring! Ring!



2/13/24:

The patient was discharged from the Cleveland Clinic on 2/7 and arrived in Maryland on 2/10. She has RIPE + Linezolid.

Oh, BTW… CDC called to confirm that patient has **INH and RIF resistance**. However, there is no written report available yet.

Testing Information

- Drug susceptibility
  - Phenotypic drug susceptibility:

Specimen Type : Isolate (Aspirate_Lymph Node) **Date Received :** 01/26/2024

Requisition # : R24013515

Submitter Specimen : MC23-360MC01195

Test	Result	Reference Value	Reported Date
Mycobacterium tuberculosis Molecular Detection (Isolate)	**Detected**	Not Detected	01/31/2024
Test Comment : The performance characteristics of MTBC Nucleic Acid Amplification were determined by the Ohio Department of Health Laboratory. It has not been cleared or approved by the FDA.			
Sent to Reference Lab	**Results to follow**		02/02/2024
Pyrazinamide (100 µg/ml)	Test Not Perfomed	Sensitive	02/09/2024
Reference Lab Results	**See Attached Prelim Report 1**		02/09/2024
Ethambutol (5.0 µg/ml)	Sensitive	Sensitive	02/12/2024
Isoniazid (0.1 µg/ml)	**Resistant**	Sensitive	02/12/2024
Rifampin (1.0 µg/ml)	**Resistant**	Sensitive	02/12/2024
Streptomycin (1.0 µg/ml)	Pending		
Reference Lab Results	Pending		

Testing Information

- Molecular Detection of Drug Resistance (MDDR):

Rifampin (RIF)	**Result**	**Interpretation**
RIF interpretation		RIF resistant
rpoB*	Asp435Val	

Comments and Disclaimers

* DTBE Reference Laboratory has transitioned from the E. coli to the M. tuberculosis numbering system for reporting rpoB gene mutations.

Isoniazid (INH)	**Result**	**Interpretation**
INH interpretation		INH resistant
inhA	No mutation	
fabG1	Leu203Leu	
katG	Ser315Thr	

Ethambutol (EMB)	**Result**	**Interpretation**
EMB interpretation		Likely EMB resistant
embB	Met306Ile	

Pyrazinamide (PZA)	**Result**	**Interpretation**
PZA interpretation		PZA resistant
pncA	Tyr103STOP	

Fluoroquinolones (FQ)	**Result**	**Interpretation**
FQ interpretation		Cannot rule out FQ resistance.
gyrA	No mutation	
gyrB	No mutation	

Testing Information

- Molecular Detection of Drug Resistance (MDDR):

Amikacin, Capreomycin, and Kanamycin (AMK, CAP, and KAN)	Result	Interpretation
AMK CAP and KAN interpretation		Cannot rule out resistance to AMK, CAP, and KAN.
rrs	No mutation	
eis	No mutation	

Bedaquiline (BDQ)	Result	Interpretation
BDQ interpretation		Cannot rule out BDQ resistance.
atpE	No mutation	
rv0678	No mutation	
pepQ	No mutation	

Clofazimine (CFZ)	Result	Interpretation
CFZ interpretation		Cannot rule out CFZ resistance.
pepQ	No mutation	
rv0678	No mutation	

Linezolid (LZD)	Result	Interpretation
LZD interpretation		Cannot rule out LZD resistance.
rplC	No mutation	
rrl	No mutation	

Treatment Timeline in Maryland

- 2/13/24
    - Consulted with the Maryland Department of Health's Center for Tuberculosis Control and Prevention (CTBCP) and Dr. Saleeb about treat regimen
    - Recommended holding TB medications until we could obtain all medications needed for BPaL/M and possibly add clofazimine and/or cycloserine
- 2/14/24
    - Nurse visited the place of lodging
    - Collected list of all current medications (see next page)
    - Husband unwilling to stop TB meds
    - Patient has a port for weekly blood draws via home health agency
    - Cleveland Clinic transplant team plans to continue to manage her care
    - Patient with baseline QTc 494

Nursing Assessment and Concerns

- Social
  - Moved from Ohio with husband and 9yo son after discharge
  - Will be living in a hotel temporarily until permanent housing
  - Husband starting training for a new job. Not available by phone during the day (8am to 4pm)
  - No support system in the area to include child care
- Medical
  - Confirmed resistance to multiple drugs
  - Concern about absorption of medications
  - Has not been connected to medical providers in our area
  - Possible change in insurance due to husbands starting new job
- Emotional/Mental
  - Language barrier
  - Privacy of medical information
  - Uncomfortable speaking to us without her husband present

Patient's Current Medications

- Tacrolimus 8 mg BID
- Dexamethasone taper
- Prednisone 5 mg daily
- Bactrim 800 mg q Mon, Wed, Fri
- Acyclovir 400 mg BID
- Nystatin 500,000 units/5ml oral solution 4 x daily
- Protonix 40 mg BID
- Aspirin 81 mg daily
- Toprol XL 50 mg daily
- Nifedipine 30 mg daily
- Fludrocortisone acetate 0.1 mg daily
- Multivitamin daily
- MG Plus Protein 399 mg QID
- Sodium bicarbonate 650 mg TID
- K-Phos neutral 250 mg daily
- Ergocalciferol 50,000 units every Monday
- Senna-Lax 8.6 mg BID
- Colace 100 mg BID

Treatment Timeline in Maryland

- 2/21/24: BDQ arrived
  - Cleveland Clinic asked us to wait on changing the treatment regimen until a tacrolimus drug level could be drawn
- 2/22/24: All TB drugs stopped except rifampin
- 2/23/24: Lab result with hemoglobin of 6.9
  - Patient instructed by Cleveland Clinic and us to report to nearest Emergency Department (ED) for a blood transfusion
- 2/24/24: Patient presented to ED at Baltimore Washington Medical Center (BWMC) in Glen Burnie for anemia
  - Patient told that a repeat CBC was okay
  - Discharged and instructed to follow up with transitional care center at BWMC

Treatment Timeline in Maryland

- 2/25/24: Worsening cough and shortness of breath
  - Returned to ED at BWMC
  - Tested positive for COVID and was admitted
  - Inpatient pharmacy reported that the patient had not stopped taking the TB medications
  - BDQ and pretomanid delivered by Department of Health nurse to BWMC pharmacy
  - Discontinued the rifampin
  - Adjusted tacrolimus dose to 5mg BID
  - **Patient given first dose of BPaL/M**

Treatment Timeline in Maryland

- 2/26/24
    - Patient found to have lactic acidosis, profound hypoglycemia, hyperkalemia and prolonged QTc
    - Transferred to ICU and started on D5W
    - **All TB meds held, started on meropenem**
    - Patient and family refused to transfer back to Cleveland Clinic that was recommended by the inpatient team

Treatment Timeline in Maryland

- 3/3/24
  - Patient had acute onset tachypnea, tachycardia, CXR with pulmonary vascular congestion and right pleural effusion consistent with volume overload
  - Treated with lasix, started on bipap, mental status worsened, required emergent intubation
  - CT pulmonary angiogram ruled out a pulmonary embolism; found to have multifocal consolidations
  - Thoracentesis done
  - Transferred to Georgetown University Hospital (GUH) because they have an intestinal transplant team

Treatment Timeline in Maryland

- During her stay at Georgetown University Hospital:
  - Restarted the **linezolid**. Added **meropenem, amp/sulbactam and amikacin**
  - Planned to add cycloserine and clofazimine
  - Change moxifloxacin to levofloxacin for less risk of QTC prolongation
  - BDQ and pretomanid delivered to GUH restarted on March 5
  - Continued to have QTc > 500 and lactic acid >5.0
  - Patient started to have neuropathy in lower extremities (thought to be secondary to LZD)
  - 4/3/24: LZD discontinued
  - Ongoing tx with BDQ, pretomanid, levofloxacin, meropenem and amp/sulbactam

Treatment Timeline in Maryland

- Complications at GUH
  - Severe anemia; concern for bleed vs hemolysis
  - Severe aortic stenosis, heart failure (EF < 20 %)
  - Extensive discussions regarding timing of aortic valve replacement (inpatient versus outpatient procedure)
  - Continued to have pulmonary edema
  - Acute kidney injury

Treatment Timeline in Maryland

- 4/10/24
  - Department of Health physician and nurse case manager met the patient for the first time via virtual visit while patient at GUH
  - Discussion with patient and her husband about the risks of clofazimine including discoloration of the skin, GI symptoms, bowel obstruction, GI bleeding, splenic infarction, discoloration of body fluids, risk of cardiac arrhythmias and sudden death
  - Consent had to be signed by patient, husband and the provider
- Current regimen:
  - **BPa (3/25) + levofloxacin (3/25) + cycloserine (4/5)**
  - LZD on hold by inpatient team due to lactic acidosis, neuropathy

Treatment Timeline in Maryland

- 4/12/24
  - **Given first dose of clofazimine**
  - Intubated due to volume overload
  - Then coded requiring CPR with ROSC after 4 min
  - **Clofazimine discontinued** since unable to be given via OG tube
  - BPa + levofloxacin + cycloserine continued
  - Blood cxs grew Candida
- 4/17/24
  - GUH informed us that the patient would be transferred to Cleveland Clinic within 24 hours; arranged to have the BDQ and clofazimine transported with a chain of custody

Treatment Timeline in Maryland

- 4/18/24
  - ID pharmacist informed inpatient team that pretomanid and cycloserine cannot be administered via OG tube; therefore, both discontinued
  - **Regimen changed to BDQ + meropenem + unasyn + levofloxacin**
  - Inpatient team hesitant to restart the LZD due to concern of neuropathy and low platelet count (30K)
  - No LZD levels had been drawn prior to discontinuation of the drug on 4/3/24
  - Patient's husband decided against a transfer to Cleveland Clinic at this time
- 4/19/24
  - TEE showed vegetation on prosthetic valve, concerning for candida endocarditis
- 4/23/24
  - Patient coded and passed away

Additional Information

- Contact investigation
    - 2 household contacts (husband and son)
    - The husband declined testing for himself and the son
    - Shortly after the case died, the son went to stay with family in Ivory Coast

Challenges

- Challenges
  - Difficult to establish a therapeutic relationship with the patient and family (language, culture, severity of illness, husband’s new job)
  - Coordinating care with transplant team in Ohio
  - Coordinating care with local hospitals
  - Comorbidities and drug interactions
  - Keeping track of drugs and drug changes
    - Obtaining insurance information from the family
    - Working with CTBCP to obtain the clofazimine, BDQ, pretomanid and cycloserine that we don’t keep in stock
    - Obtaining informed consent when patient hospitalized
    - Delivering these medications to the hospitals and keeping track of each dose

Lessons Learned

- Lessons Learned
    - Don’t assume that all states run their TB program like ours
    - Frequent communication with not only the ID team, but also the primary team is necessary
    - There is a large network of TB experts willing to help guide treatment

Acknowledgments

- Anne Arundel County TB team: Denise Dreyer, Cheryl Murphy, Darlene Dittrich, Gina Moreno, Kristy Frashure and Jennifer Schneider
- MDH CTBCP staff including Medical Consultants, Dr. Paul Saleeb and Dr. Mohan Amlani
- Cleveland Clinic: Dr. Christine Koval
- Georgetown University Hospital: The ID team of Dr. Gayle Balba, Dr. Rebecca Kumar, and Dr. Joseph Timpone as well as the Pharmacy team
- Johns Hopkins University: Dr. Maunank Shah and Dr. Sanjay Jain

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