Therapeutic Drug Monitoring in Practice: Two Clinical Scenarios

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Treatment Monitoring for Clients on RIPE TB Regimen

Spring 2024

Two Asian females aged 60-75 were diagnosed with pulmonary TB

Both females were of short stature and weighed less than 100 lbs at baseline

They started RIPE (rifampin, isoniazid, pyrazinamide, and ethambutol) treatment the same week

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Client #1

Client #1: Clinical Picture

Identified during the immigration process

- Required IGRA blood testing was positive for TB infection
- Marathon County Health Department (MCHD) notified by civil surgeon (testing provider)

Client reported having a cough two months prior and was treated for an acute COPD exacerbation; cough was "occasional" upon diagnosis

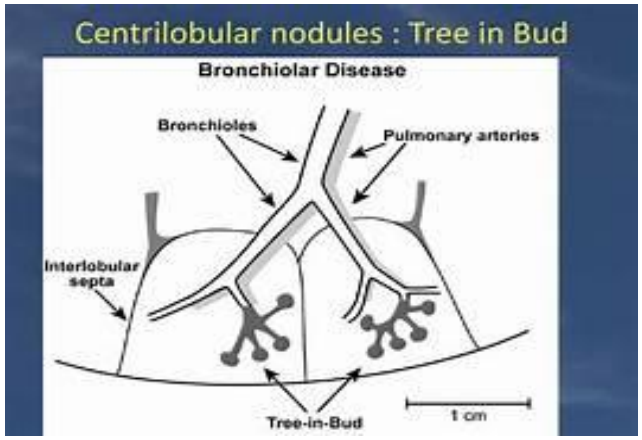
Client denied hemoptysis, weight loss, etc.

Baseline Hgb A1c: 5.8

Client #1: Imaging

Pre-treatment Chest CT:

"**Numerous tree-in-bud nodules throughout both lungs, multiple bilateral lower lobe dominant pulmonary nodules measuring up to 15 mm,** bronchial wall thickening (bronchitis), left lower lobe bronchiectasis."



Client #1: Cont'd

Sputum samples were smear negative

Culture positive for TB after 2 weeks

GeneXpert showed likely rifampin susceptibility

Client's baseline weight: 42.1 kg=92.6 lbs

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Client #1: Medication Dosages

Client started on weight-based RIPE (Rifampin, Isoniazid, Pyrazinamide, Ethambutol)

Medication	Standard Dose	Client Starting Dose
Rifampin	600 mg	450 mg
Isoniazid	300 mg	200 mg
Pyrazinamide	1000-2000 mg	1000 mg
Ethambutol	800-1600 mg	800 mg

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Client #1: Treatment Progress

Challenges with medication tolerance

- Client complained of nausea, weakness, itching, and poor appetite; weight decreased

Susceptibility testing showed that the client's TB was pan-susceptible to RIPE medications; ethambutol was stopped three weeks into treatment

- Some adverse effects continued and were managed by her case manager and provider

Client was released from isolation after two weeks of treatment

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Challenges of Completing Directly Observed Therapy (DOT)

Client initially refused to take all her medications together during intensive phase

After release from isolation, client began labor-intensive work during the day

Did not want to take TB medications until after work (after business hours)

Importance of consistent timing of daily TB medications made in-person DOT impractical

Client #1: Video DOT

Video DOT (VDOT) was implemented

Minimum 5 doses per week required between in-person DOT and VDOT

- Verification of doses is the primary, direct way to monitor treatment adherence; therapeutic drug monitoring is more useful when treatment can be verified

Success of Treatment

Based on the information provided, what concerns about treatment success would you have as a case manager?

A) Medication efficacy related to poor nutritional status
B) Lower efficacy of treatment after eliminating ethambutol
C) Abnormal A1C affecting treatment success
D) All of the above

Therapeutic Drug Monitoring (TDM) Process

The Wisconsin TB Program recommended TDM for RIF (rifampin) and INH (isoniazid), as they would be used in the continuation phase for client

Blood draws

- Completed at client's home
- Required morning dosing of medications (at least RIF and INH)
- Required a minimum of 8 mL blood for each draw (4 mL blood=2 mL serum each for INH and RIF)

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Blood Collection Process

PHN Process: Collect tubes from local lab, go to client's house to draw blood, label tubes appropriately, drop off filled tubes at lab

Lab sent tubes to an outside contracted lab for processing and analysis (total process from blood draw to receiving results=at least one week)

Cost of TDM was covered by WI TB Program

Blood Collection (Cont'd)

2-hour and 6-hour blood draws were ordered to check for peak concentration and potential delayed absorption

Client allowed 2-hour blood draw but refused 6-hour blood draw, citing concerns for her health with too much blood loss in one day

6-hour blood draw was completed on another day

Client #1: TDM Results and Outcomes

TDM showed therapeutic peak and 6-hour levels of RIF and INH in client's blood

No dosage adjustments were made per WI TB Program staff; treatment continued as ordered

There was no specific concern about response to treatment

Client culture converted after 2 weeks

Client #2

Client #2: Clinical Picture

Symptomatic for TB for 5 months when diagnosed

- Coughing, hemoptysis, shortness of breath, weakness

Diagnosed multiple times with pneumonia. Imaging did not improve following use of antibiotics

HgbA1c: 13.6

Abnormal IGRA received by health department prompted investigation

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Client #2: Imaging

2 Months After Symptom Onset

"Prominent, abnormal, partially consolidated opacity in the mid-superior aspect of left upper lobe is suspect for pneumonia"

4 Months After Symptom Onset

"Mild interval worsening of prominent, patchy and consolidated, opacity in the left mid and upper lung zones, consistent with the reported history of pneumonia"

Client #2: TB Diagnosis

Client had smear moderate-smear many sputum smears

Cultures grew out TB in six days

Baseline weight: 44.5 kg=98 lbs

RIPE was also prescribed for client #2 after her GeneXpert showed rifampin susceptibility

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Client #2: TDM

Wisconsin TB Program also recommended TDM for this client due to lower RIPE dosages based on weight

Medication	Standard Dose	Client Starting Dose
Rifampin	600 mg	450 mg
Isoniazid	300 mg	200 mg
Pyrazinamide	1000-2000 mg	1000 mg
Ethambutol	800-1600 mg	800 mg

Client Infectiousness

Based on the information provided, which client was more infectious at diagnosis?

A) Client 1
B) Client 2
C) Not enough information

Client #2: Treatment and Progress

Continued all RIPE medications for 2 months due to lack of smear conversion and continued culture growth

Sputum continued to grow out TB despite consistent treatment via DOT and VDOT

Client #2: Treatment Monitoring

What factors of client #2 could delay response to treatment?

A) Normal kidney function
B) Weight gain of 5-10 pounds
C) Elevated A1C
D) Limited mobility

Client #2 Concerns: Response to Treatment

What are indicators of delayed treatment response/treatment failure?

A) Delayed smear conversion

B) Delayed culture conversion

C) Both A & B

D) Neither A nor B

Client #2: TDM Process and Results

2-hour and 6-hour RIF and INH levels were drawn on client

Both levels were sub-therapeutic

Client's dosages were increased 7 weeks into treatment based on recommendations from E. Ann Misch, MD Medical Consultant to the Wisconsin TB Program:

- RIF: Increase from 450 mg to 600 mg
- INH: Increase from 200 mg to 450 mg

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Why was culture conversion delayed?

What factors could have contributed to delayed culture conversion in client #2?

A) Acuity of illness

B) Poor blood sugar control

C) Use of insulin

D) A & B

E) All of the above

Considerations with Dosage Increases

What would you want to monitor when increasing dosages of rifampin and isoniazid?

A) Side effects
B) Insulin needs
C) Liver function
D) A & C

Client #2: Outcomes

Last positive culture grew from sample produced 7.5 weeks into treatment

Client culture converted one week after increasing RIF and INH dosages

Client reported increased nausea but tolerated treatment

Liver function remained within normal limits

Client was able to complete treatment in 6 months due to her culture conversion occurring at 2 months

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Summary

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Challenges of TDM

Logistics of specimen collection and processing

- Coordination of dosing and blood draw times
- Obtaining necessary tubes from the lab
- Communicating with lab to ensure necessary protocols are followed to obtain accurate results
- Time involved for transportation to client homes and blood draws themselves
- Cost for lab processing

Interpretation of lab results and recommendations for adjusted dosages

- Relied on Mayo and the WI TB Program for guidance

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Benefits of TDM

Client #1: Reassuring

Client #2: Helped to guide dosage increases and prevented treatment failure/prolongation