Drug Resistance

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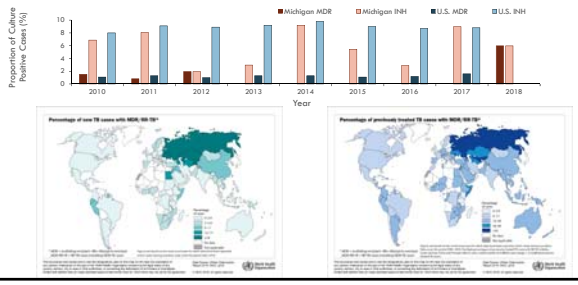
Drug – Resistant Tuberculosis

Global, U.S, and Michigan, 2010-2018



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Thank you!

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- Local Health Jurisdiction, Tuberculosis/Communicable Disease Nurses and Staff
- MDHHS, Tuberculosis Control Unit
- CDC, Division of Tuberculosis Elimination (DTBE)

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References:

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Global Tuberculosis Institute
NEW JERSEY MEDICAL SCHOOL

Nurse Case Management Techniques for the Treatment and Management of Multi-drug Resistant (MDR) TB

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What is Case Management?

- Case management has been defined in a variety of ways.

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Components of TB Nurse Case Management (NCM)

- Situated within the framework of public health, the nursing process and the case management approach
- Assignments of responsibility and accountability for individual patient outcomes including adherence to therapy, completion of treatment and cure
- Developed in response to identified program deficiencies
  - Poor adherence rates resulting in lengthy, interrupted treatment regimens

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Eight Elements of NCM

- Case finding
- Assessment
- Problem identification
- Plan development
- Implementation
- Outcome identification
- Evaluation
- Documentation

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Goals of TB NCM

- All hospitalized individuals diagnosed with or suspected of having TB disease receive uninterrupted care during transition from hospital to the outpatient setting
- Disease progression and drug resistance are prevented
- Each patient receives TB care and treatment according to published standards of care (ATS/CDC/IDSA, 2016)
- An integrated, coordinated system of health care allows patients to experience TB care along a continuum rather than in fragments

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Goals of TB NCM (2)

- TB treatment within appropriate time frames and with minimal interruption in lifestyle or work
- Transmission of TB is prevented through effective contact investigations
- Identification and treatment of latent TB infection (LTBI)
- The patient/family/community is educated about TB infection, disease, and treatment
- TB cases, contacts and B immigrants are reported according to State regulations

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Management, including Infection Control

- Teaching the patient and family about preventing transmission, especially etiquette and hygiene, use of masks where indicated, and handwashing
- Isolation precautions are usually needed until there have been 3 negative sputum cultures
- Ascertaining likelihood of adherence and using measures to enhance adherence
- Promptly isolate persons suspected or known to have TB
- Use appropriate infection control

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How does drug resistance develop?

- Resistance to anti-TB drugs can occur when these drugs are misused or mismanaged
  - Patients do not complete their full course of treatment
  - Health-care providers prescribe the wrong treatment, the wrong dose, or length of time for taking the drugs
  - The supply of drugs is not always available; or when the drugs are of poor quality

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How can MDR TB be Prevented?

- Health care providers can help prevent MDR TB by quickly diagnosing cases, following recommended treatment guidelines, monitoring patients' response to treatment, and making sure therapy is completed (within the recommended time frame)
- Providers should work with patients to avoid **any** missed doses, treatment interruptions, or stopping treatment early
- Patients should inform their provider if they are having trouble taking the medications
- If patients plan to travel, they should talk to their providers to ensure they have enough medicine to last while away
- Another way to prevent MDR TB is to avoid exposure to known MDR TB patients in closed or crowded places such as hospitals, prisons, or homeless shelters

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Challenges of MDR

- Managing second-line medication side effects or adverse reactions
- Medications are expensive
- Need additional assessments
  - Audiometry
  - EKG for some of the medications
  - Vision testing
  - PICC line or daily IM injections
  - Mental health
  - Additional labs
- Adherence for lengthy treatment (18 to 24 months)

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Education Is Key

- Always use a venue that guarantees confidentiality in communication
- Back up education sessions with written material (preferably culturally and linguistically appropriate materials)

Help patients (and their families) understand

- He/she may feel worse before they feel better
- Toxicity symptoms will diminish over time as the patient's body adjusts to the treatment
- Steps can be taken to minimize the side-effects if and when they occur
- In the long run, the treatment will cure the disease, save the patient's life, and prevent transmission to loved ones

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Red Flags to Recognize Drug Resistance

- A history of previously treated TB in a person presenting with active TB
- High community rates of drug-resistant TB
- Positive HIV status
- High likelihood of exposure to healthcare associated, prison or community sources of MDR-TB
- The infected person is from a country with a high MDR-TB rates
- Contacts with persons who have confirmed MDR-TB
- Infected person has received inadequate treatment regimens for >2 weeks
- Smears or cultures remain positive despite 2 months of treatment for TB

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Molecular Tests for Rapid Identification of Drug Resistance

- Xpert MTB/RIF®
- Other NAAT that evaluates for rifampin (RIF) and/or isoniazid (INH) resistance
- CDC MDDR service

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Initial Evaluation

The important task of case managing and monitoring the patient with drug-resistant TB begins with a thorough and organized initial evaluation.

- The objective of the initial evaluation is to identify those patients at greater risk of adverse effects and to establish a baseline for monitoring
  - Confirm demographics
  - Medical history and physical exam
  - Review of systems
  - Baseline examinations
  - Past medical history
  - Full TB history
  - All symptoms of TB and onset
  - Social history (include country of origin)

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Contacts

- Source case
  - Especially when there is TB in a child under 5
- Contact information including
  - Incarceration history
  - Previous residences
  - Household contacts
  - Visitors
  - Work or school

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Regular Monitoring

- Patients with drug-resistant TB will require regular monitoring throughout treatment to document sputum culture conversion and to watch for the development of adverse reactions
- Patients should also be monitored closely for signs of treatment failure. The case manager is responsible for ensuring that all necessary monitoring for both toxicity and clinical response occurs and that abnormal results are brought to the attention of the treating clinician
- Monitoring response to treatment is done through regular evaluation of microbiology results, symptoms, weight, and radiography and other imaging

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Regular Monitoring (2)

- Patient centered care
  - Patient needs to be part on the plan
- Directly observed therapy (DOT) should be used for all MDR patients
- Adherence rate monitored weekly
  - Address missed doses as soon as they start to occur
  - Overcome barriers to DOT
    - Electronic
    - Reach out to other healthcare providers
      - School nurse
      - Occupational health

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Labs

- Laboratory exams should include:
  - HIV test
  - CBC
  - TSH
  - Pregnancy test for women of childbearing age
  - Comprehensive metabolic panel (CMP)
  - Obtain 24-hour creatinine clearance for any elevation of creatinine or question of renal insufficiency
- Additional labs may be needed
  - Vitamin D level
  - Magnesium
  - Electrolytes
  - Drug serum levels for therapeutic drug monitoring (TDM)

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Laboratory Flow Sheet

May be helpful in summarizing bloodwork results that will be assessed at baseline and throughout treatment

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Audiometry

- Second-line anti-TB injectables (SLIs) drugs are known for causing adverse reactions that may have lasting effects, such as hearing loss
- Audiometry is recommended as a baseline test for all patients starting DR-TB treatment, and as a follow-up test while on the SLI

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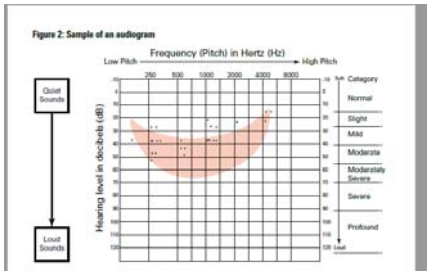
Audiogram



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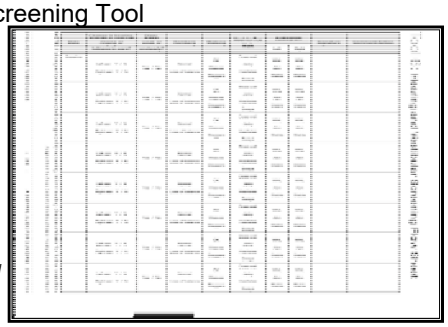
Hearing Screening Tool



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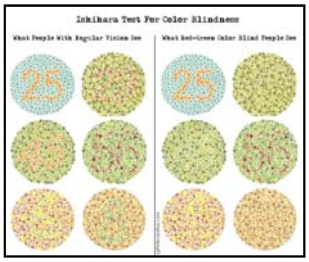
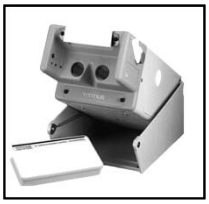
Vision Screening





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Vision Tool

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Radiography

- Obtained prior to treatment initiation
- Posteroanterior (PA) views (and lateral in children) of the chest for pulmonary disease are recommended
- Additional views and/or CT scan may be helpful in some instances
- At baseline, every 3 to 6 months during treatment, and at the end of treatment

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Sputum Collection

- Preferably three specimens collected at least 8 hours apart
- At least one of which is an early morning expectorated specimen
  - Expectorated preferably early morning (before brushing teeth)
  - Consider rinsing mouth with sterile or bottled water to reduce risk of contamination with non-tuberculous mycobacteria
  - Volume of 5-10mL ideal; should be >2mL
- Sputum induced with nebulized
  - hypertonic (3-10%) saline
  - Hypotonic .9% saline
- Ultrasonic nebulizer

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Sputum

- Acid-fast bacilli (AFB) smear
- Culture and
- Drug-susceptibility testing (DST)
- Monitor for culture conversion
- At the start of treatment, obtain 3 sputa for AFB smear and culture
  - Repeat sputum collection every 2 weeks until smear conversion
  - Collect monthly until the end of treatment

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Delay in Sputum Conversion

When AFB smear or culture positivity persists or recurs, address and consider:

- Adherence to therapy
- Accurate dose calculation and administration
- Drug absorption
- Adequacy of the drug regimen
- Development of acquired resistance
- Respiratory and constitutional symptoms
- Radiographic findings
- Possible poor penetration of drugs into a localized area (e.g., empyema, thick-walled cavity in poorly vascularized lung)
- Presence of conditions that may delay culture conversion (e.g., uncontrolled diabetes, malabsorption, extensive disease)

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Bacteriology Flow Sheet

Helpful for summarizing the important microbacteriology, molecular tests, and DST results

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Tool 3: Bacteriology Flow Sheet

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EKG

- Bedaquiline (BDQ
- Patients have a known QT prolongation
- Hypokalemia (low potassium)
- Considered for other drugs that prolong the QT interval (e.g., moxifloxacin (MFX) and/or clofazimine (CFZ)

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Mental health

- Psychosocial assessment
- Assess for existing mental health and social conditions that may impact treatment
- Assess routinely while on cycloserine

- See section: Psychosocial Support

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Depression


Appendix B: PHQ-9 Depression Screening Tool

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Review of Injection - Heartland National TB Center (COE)


ADMINISTRATION OF CAPREOMYCIN INJECTION

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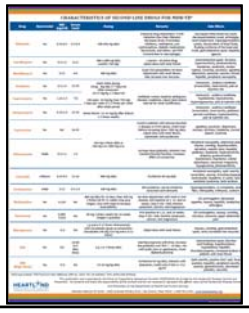
Second Line Drugs for MDR - Heartland National TB Center



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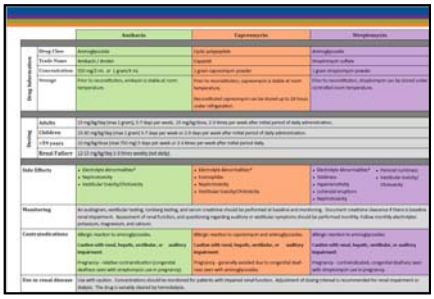
Injectable



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Monitoring for Drug Toxicity

- Screening and close monitoring for drug toxicity and adverse effects is an important part of MDR-TB treatment
- Counsel every patient beginning any TB therapy to anticipate toxicity
- Monitor patients for general toxicities and drug-specific toxicity at every healthcare visit (including during DOT encounters)
- Patients with drug-resistant TB may experience more toxicity than patients treated for drug-susceptible disease
  - Most of the second-line TB drugs are associated with significant side effects
- Take measures to minimize toxicity and to help patients tolerate the toxicity rather than losing the drug in the regimen

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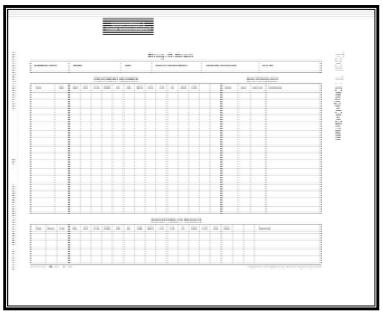
Drug-o-gram



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PICC line or daily injections

- Who will administer
- Who will maintain the PICC line
- Amikacin (AK) may be a better option than capreomycim (CM) for home infusion. Pharmacies typically provide premixed solutions of AK as it remains stable at room temperature for at least 3 weeks.
- Patients receiving CM may need to learn to reconstitute the powder as it is not considered stable after 24 hours upon refrigeration (refer to package insert for full instructions)

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Prospective Monitoring for ADRs

- Collaboration between patient and the TB program
- Patient education
  - Make sure they are educated about potential serious ADRs from their regimen
  - Make sure that they understand need to report them
- Staff education
  - Make sure they are aware of potential serious ADRs from the different TB medications
  - Make sure they assess for symptoms of ADRs from the patient at each interaction AND document them
- Interactions: Monthly medication pick ups, daily or twice weekly DOT visits, phone calls, any other interactions

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Minor Drug Reactions

- Mild reactions
- No lasting effects
- Usually do not require change in the TB regimen
- May often respond to simple interventions e.g. taking pills with food, use of an antihistamine

- Some Examples
  - Discoloration of body fluids
  - Gas, bloating, mild nausea
  - Itching and mild rash
  - Photosensitivity
  - Sleep disturbance
  - Headaches

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Serious Adverse Drug Reactions

- More "severe"
- Require more intensive monitoring
- Potentially life threatening if ignored
- May require change in therapy
- May require hospitalization

- Severe N/V/diarrhea
- Liver toxicity
- Electrolyte abnormalities
- Allergic reactions
- Severe skin reactions
- Vision loss
- Neurologic damage
- Kidney damage
- Hearing loss
- Death

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Consequences of Severe ADRs

- Worst case scenario: severe morbidity and even death for example: fatal hepatitis
- Need for more intensive clinical and laboratory monitoring
- Need for alterative, usually more protracted and potentially less effective treatment regimen
- Potential impact on compliance and treatment outcome

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Most Common Types of Drug Toxicity

- Gastrointestinal toxicity
- Hepatotoxicity
- Hypersensitivity (allergic) reactions
- Other dermatologic reactions
- Joint symptoms
- Neuropathy
- Visual symptoms
- Drug fever
- Other

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ADRs to First Line Agents (and FQ)

Reaction	INH	RIF	EMB	PZA	FQ
Gastrointestinal	X	X	X	X	X
Hepatotoxicity	X	X		X	X
Cutaneous	X	X	X	X	X
Peripheral Neuropathy	X		X (rare)		
Optic Neuritis	X (rare)		X		
Arthralgias	X			X	X
Gout			X (rare)	X	
Tendonitis					X
Flu-Like Syndromes		X			
Thrombocytopenia		X			
CNS	X				X

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ADRs to Second Line Agents

Reaction	Eto/Pto	Bdq	PAS	LZD	Am/Km S/Cm
Gastrointestinal	X		X		
Hepatotoxicity	x	x	X		
Fatigue	x	x	x	x	x
Periph. Neuropathy				x	
Optic Neuritis				x	
Musculoskeletal	x	x	x		
Neurological/Vestibular/Ototoxicity					x
hypothyroidism	x		x		
Cardiac		x			
Thrombocytopenia				x	
CNS					

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Gastrointestinal Toxicity

- Nausea
- Vomiting
- Diarrhea
- Bloating
- Anorexia
- Abdominal pain
- Overlap of gastrointestinal symptoms and symptoms of hepatic toxicity- need to check LFTs (ALT, AST and bilirubin)

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Management of GI Symptoms

Initial options after excluding hepatotoxicity:

- Change the timing of the dose
- Give the meds with food
- Daily dosing with fewer pills rather than intermittent therapy
- Antacids 2hr before or after
- Anxiolytic if the nausea occurs prior to swallowing the pills
- Antiemetics

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Hepatotoxcity

- Symptoms
  - Nausea, vomiting + PLUS Abdominal pain, fatigue, and loss of appetite
  - Later stage symptoms may include: Fever, rash, jaundice (yellowing of the eyes and skin)
- Assessment
  - Same observations and questions for assessing nausea and vomiting PLUS:
    - Observe for signs of jaundice (yellowing of the skin and whites of the eyes)
    - Ask the patient: Do you drink alcohol? If yes, how much, how often and when was your last drink?
  - Check:
    - Latest liver function test (LFT), total bilirubin, serum albumin and electrolytes, viral hepatitis panel results, urine and stool color, patient's nutritional status (weight and BMI) and nutritional intake

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Proposed Risk Factors for Hepatotoxicity from Anti-tuberculous Therapy

- Increasing age
- Malnutrition or hypoalbuminemia
- PZA in regimen
- Other hepatotoxic agents
- Alcohol
- Pregnancy or post-partum
- Elevated baseline ALT
- HIV infection
- Multiple medical problems
- Pre-existing chronic liver disease
- Chronic Hepatitis B and C

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Hepatotoxicity

- Elevation in liver enzymes: ALT more specific for liver than AST
- Confounders:
  - Other drugs/supplements, alcohol, viral hepatitis, other liver/biliary tract disease
- Spectrum of hepatotoxicity
  - Symptomatic or asymptomatic disease
  - ATS symptom related threshold for stopping therapy: ALT 3x upper limit of normal
  - ATS asymptomatic threshold for stopping therapy: ALT 5x upper limit of normal

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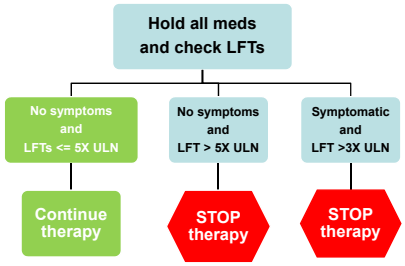
Management of Hepatotoxicity



Note: Patients with underlying cirrhosis may not demonstrate typical elevations in ALT and AST, must rely on other clues

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Nausea and Vomiting

- Observe for signs of:
  - Hepatitis (fatigue, abdominal pain, yellowing of eyes and skin)
  - GI bleeding (vomit with red blood or "coffee ground" appearance, abdominal pain, dizziness)
  - Dehydration (dry/tenting of skin, sunken eyes, decreased urination, confusion)
- Ask the patient:
  - What medicines are you taking?
  - When does the nausea or vomiting start?
  - How often do you experience the nausea and/or vomiting and how long does it last?
  - What makes it better or worse?
  - How is your appetite?
  - What have you had to eat/drink today?
  - If vomiting, describe color and consistency

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Diarrhea

- Observe for signs of:
  - Hepatitis (fatigue, abdominal pain, yellowing of eyes and skin)
  - GI bleeding (blood in vomit or stool)
- Ask the patient:
  - What medicines are you taking?
  - When do the symptoms occur?
  - How long does it last?
  - What makes it better or worse?
  - How is your appetite?
  - What have you had to eat/drink today?
- Check for symptoms of gastritis (epigastric burning, sour taste in mouth, abdominal distention or bloating)

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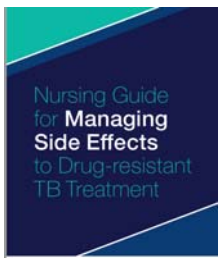
Resources



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Resources

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Sample MDR Care Plan

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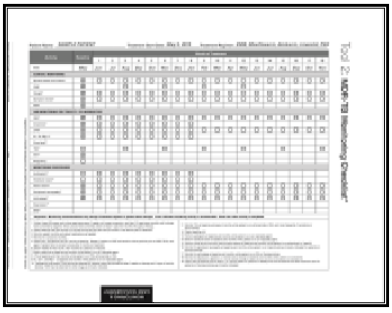
MDR Checklist



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Post-Treatment Monitoring

At the end of treatment:

- A sputum culture and chest radiograph (CXR) should be obtained.
- The patient should undergo post-treatment monitoring for a minimum of 2 years to monitor for relapse. At 6, 12 and 24 months post-treatment (or as clinically indicated), the patient should be monitored with:
  - Symptom review
  - Medical evaluation
  - Sputum for AFB smear and culture
  - Chest radiograph

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Questions

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