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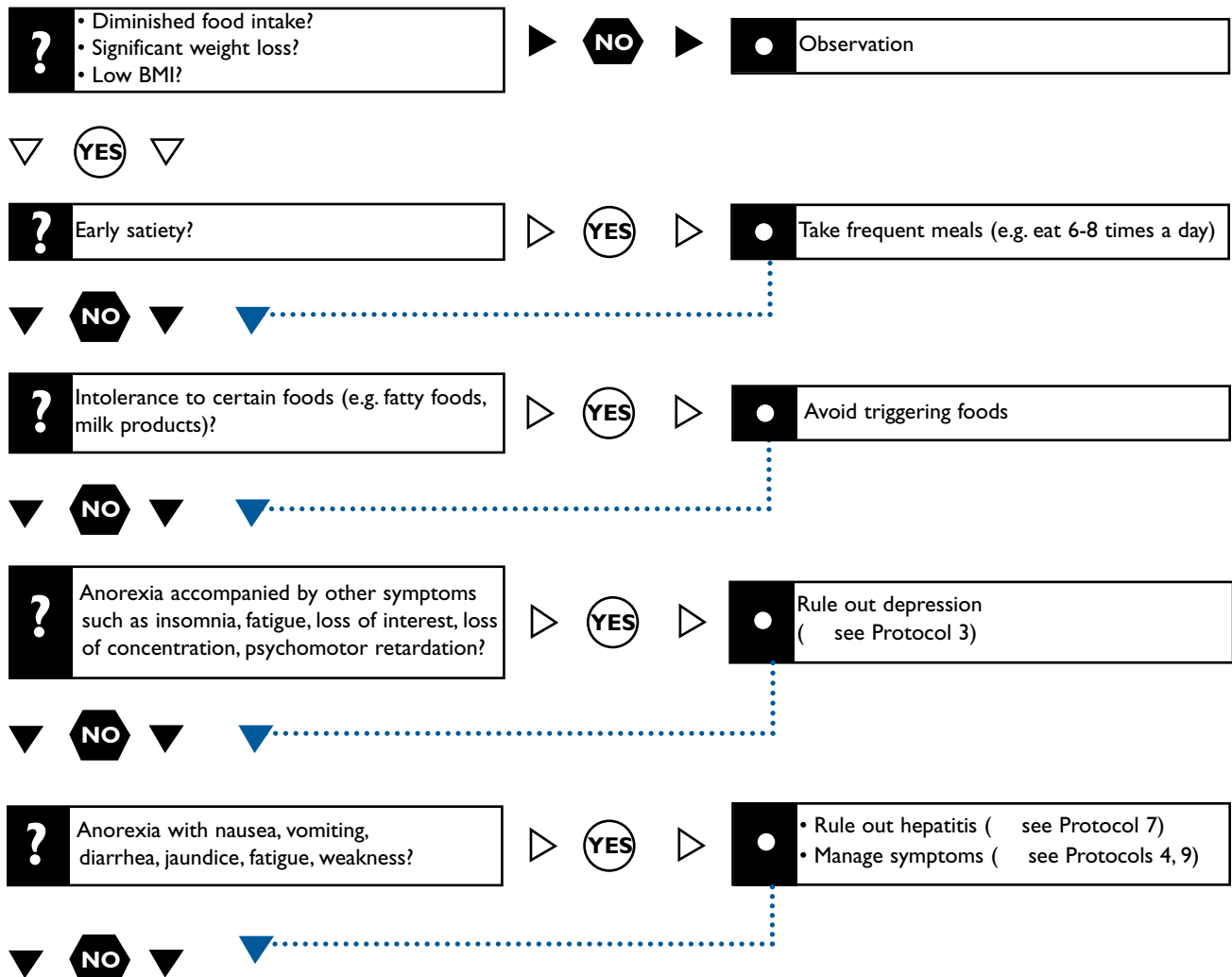
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Protocol I: Nutritional Surveillance Protocol

Anorexia is defined as the lack of appetite or the loss of the desire to eat. It is important to evaluate the duration of anorexia, the amount and tempo of weight loss, and any symptoms which may suggest an etiology (e.g. nausea, vomiting, diarrhea, jaundice). Monthly weights provide one of the most important indicators of clinical response to antituberculous therapy. Although many patients lose weight during the first few weeks of therapy with second-line drugs, failure to regain weight or continued weight loss during therapy must be considered an urgent management issue. Both BMI (body mass index) and chronological weight curves provide useful data. The following approach should be adopted in treating patients with a low BMI or poor growth curve.



TREATMENT

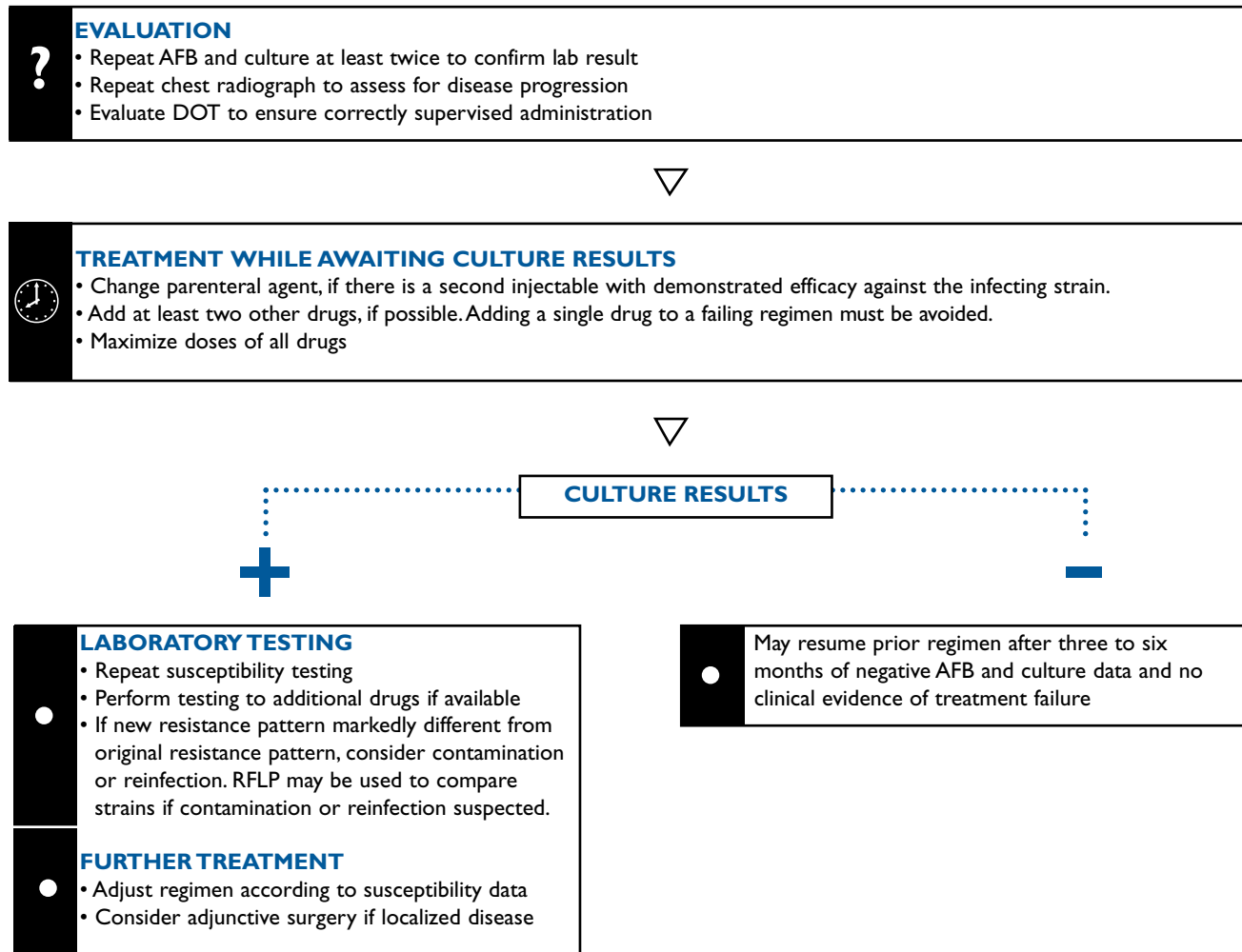
- Encourage high-protein, high-calorie diet
- Provide fortified milk (milk with additional milk powder)
- Exercise (e.g. walking) before and after eating
- Follow weight surveillance
- Offer nutritional evaluation and orientation (e.g. calorie counts, socioeconomic assessment, education on food groups and calorie goals)

IF NO IMPROVEMENT

- If no improvement, consider appetite stimulant (e.g. medroxyprogesterone)
- Many over-the-counter vitamin supplements are marketed as appetite stimulants, but have no proven efficacy as such and are often expensive
- Consider tube feeds in life-threatening situation

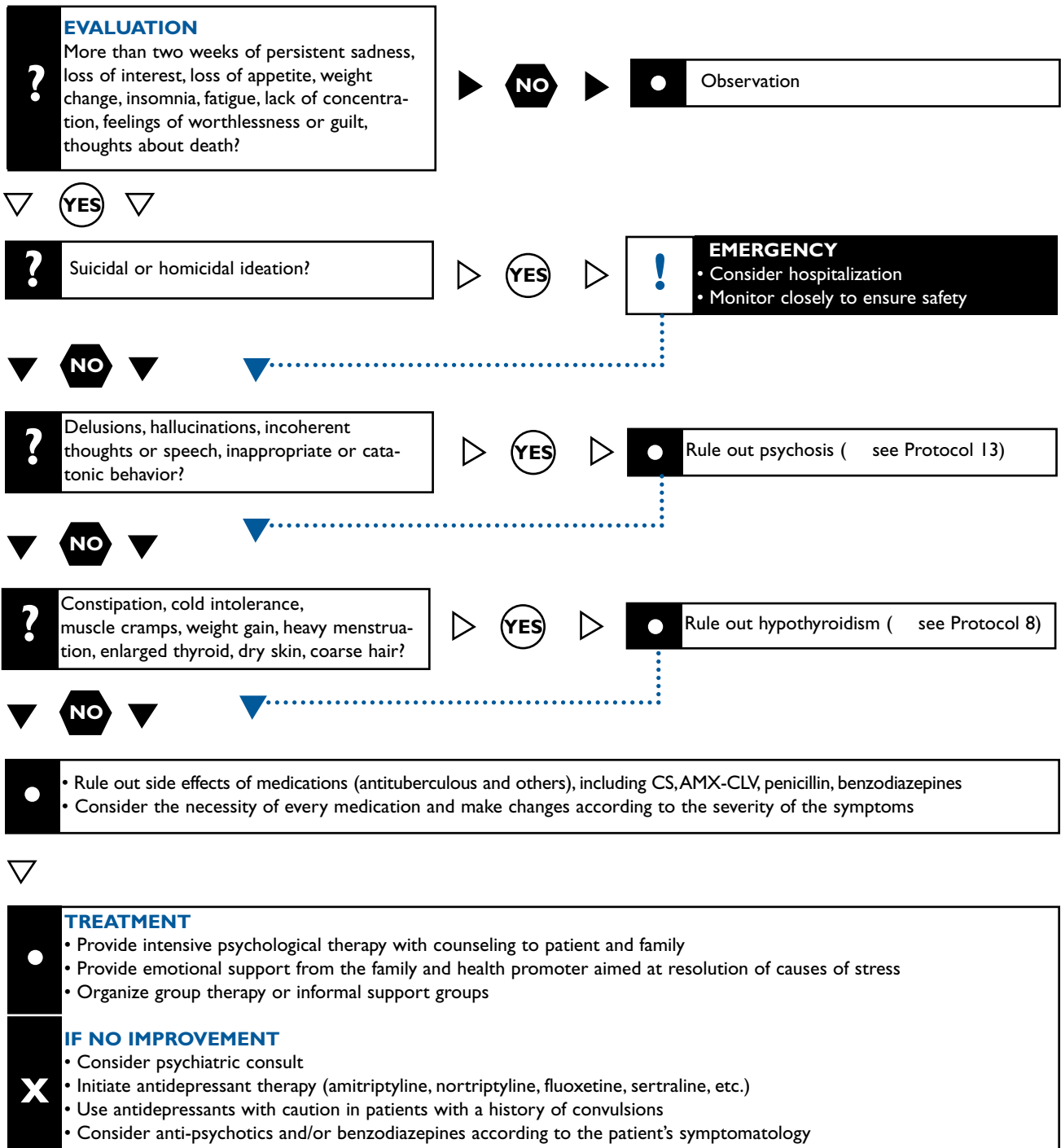
Protocol 2: Management of Positive Smear or Culture after Five or More Months of Treatment

Although a positive smear or culture after five or more months of therapy may reflect a slow but favorable response to treatment, several other possibilities must be explored. First, the possibility of contamination needs to be ruled out. This can be done by obtaining two more samples and examining them for the presence of acid-fast bacilli or growth in culture, comparing resistance pattern of the new or continued positive specimen with the pattern at treatment initiation, and by using RFLP data to compare the genomes. Second, direct observation of therapy should be confirmed and any irregular therapy promptly corrected. Third, the presence of a positive smear or culture may indicate failure of therapy. Regimen changes and possible surgical intervention should be considered at this time as outlined below.



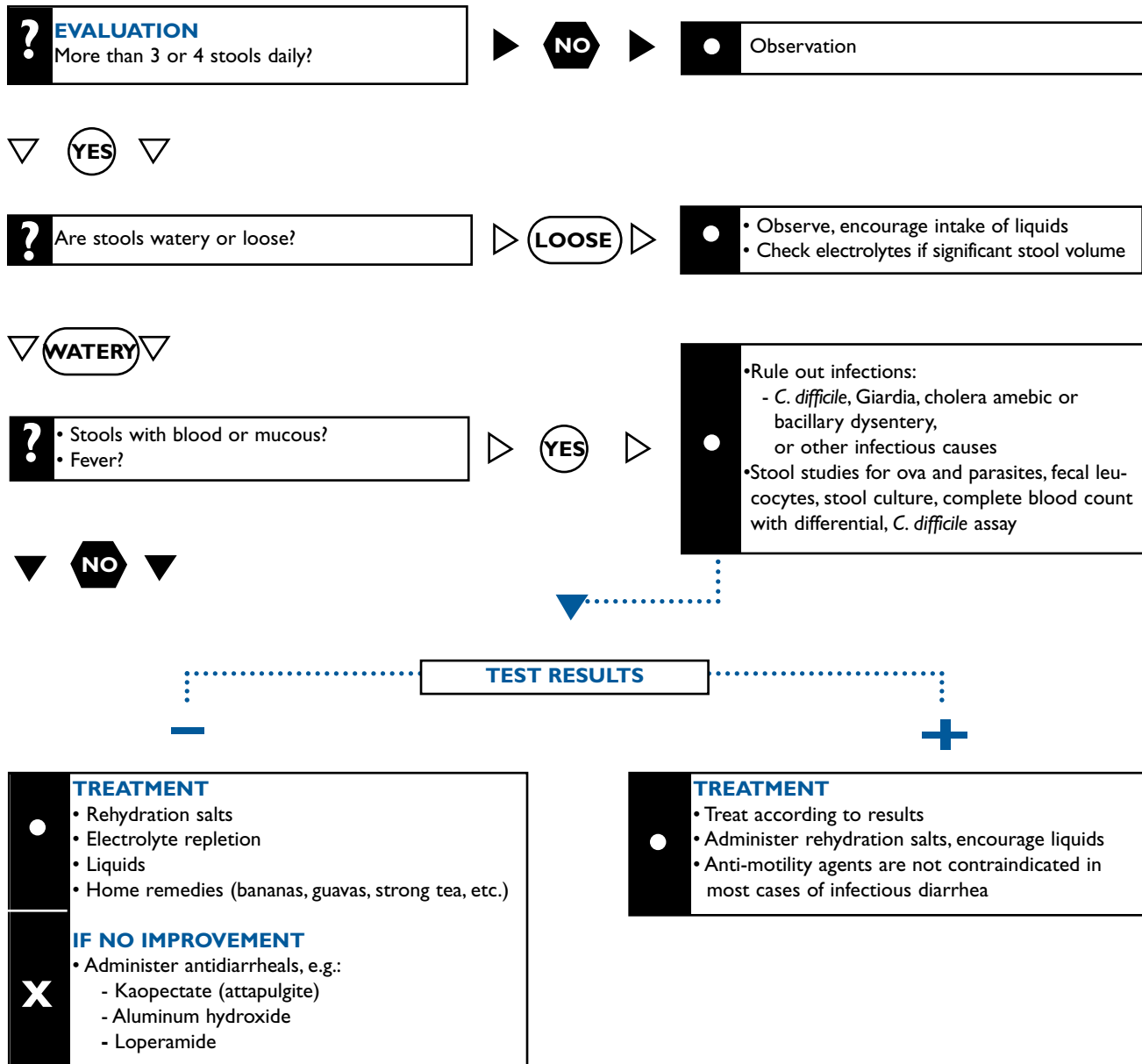
Protocol 3: Management of Depression

Although the word “depressed” is often used to describe sadness, clinical depression refers to a specific psychiatric diagnosis. Symptoms of major depressive disorder can include changes in sleep pattern, loss of interest in usual activities, feelings of guilt, diminished energy, decreased concentration, lack of appetite, psychomotor retardation (slowed movement and thought), and suicidal ideation. Depression can be considered a normal reaction for a patient with a chronic illness such as TB; however, additional factors (including antituberculous drug side effects) may exacerbate this condition. If a patient presents with significant changes in behavior or mood that affect his or her daily activities, he or she should be evaluated for depression.



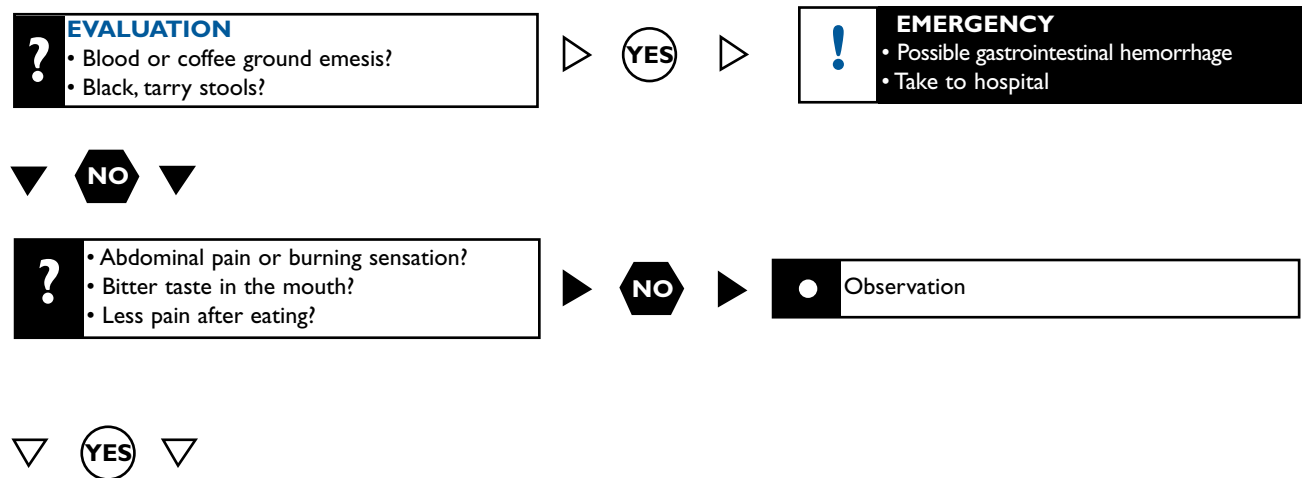
Protocol 4: Management of Diarrhea

Diarrhea is characterized by frequent watery bowel movements. Since many patients use the term diarrhea to describe bowel movements that are more frequent or loose than normal, it is important to note whether the stool is truly watery and more than three or four times a day. Both loose stool and diarrhea are frequent side effects of many antituberculous medications.



Protocol 5: Management of Gastritis

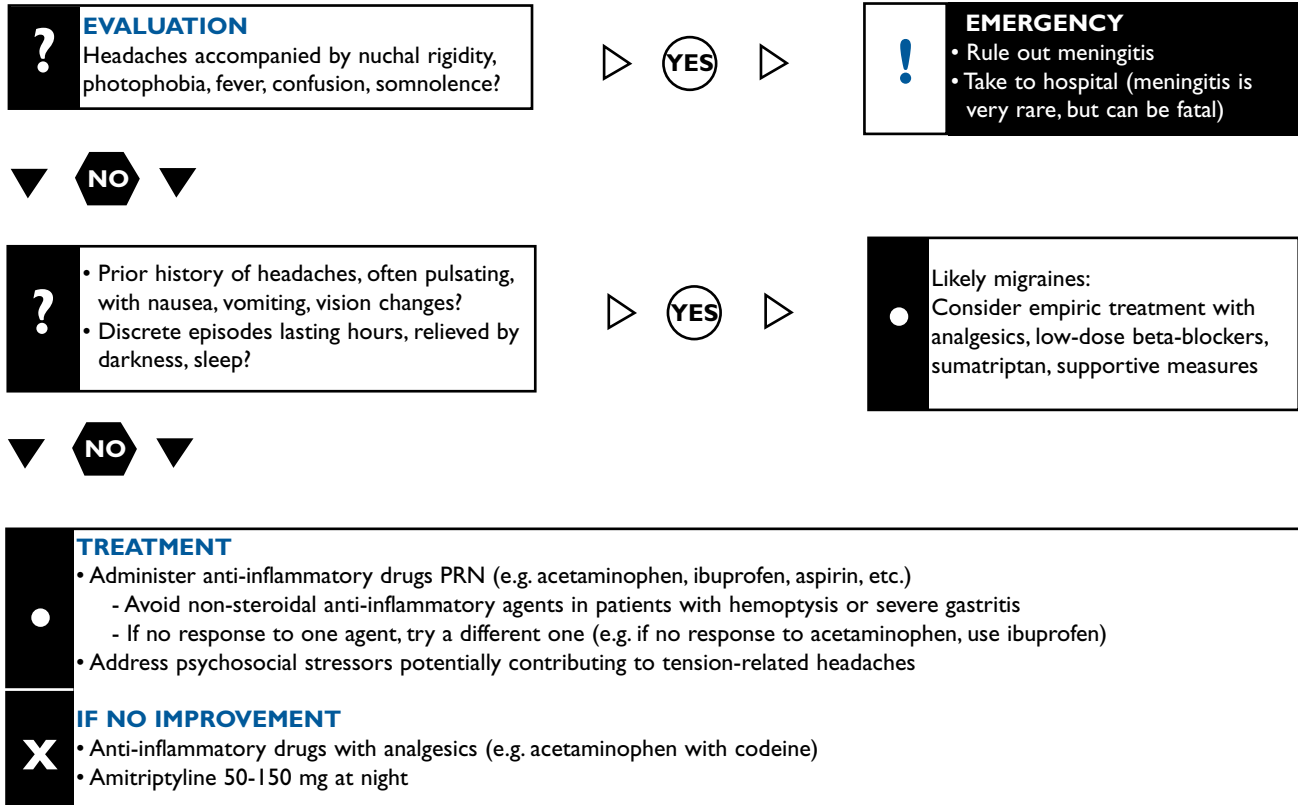
Gastritis refers to the inflammation of the stomach. Multiple causes (including infection, alcohol, diet, and medications, including non-steroidal anti-inflammatory drugs and antituberculous medications) should be considered. If left untreated, gastritis can progress to ulcers and gastrointestinal bleed.



●	<p>TREATMENT</p> <ul style="list-style-type: none"> • Administer antituberculous medications with food or after eating • If taking PAS, administer with acidic drink • Avoid spicy foods, caffeine (coffee, tea, soda), cigarettes • If symptoms in the morning, eat before going to bed and sleep with head elevated
X	<p>IF NO IMPROVEMENT</p> <ul style="list-style-type: none"> • Administer antacids before taking antituberculous medications • Antacids include: <ul style="list-style-type: none"> - Calcium carbonate for patients who need a calcium supplement (elderly, pregnant women, etc.) - Aluminum hydroxide helpful in cases with diarrhea - Magnesium hydroxide may improve constipation • Take fluoroquinolones at least 30-60 minutes after antacids to minimize interaction of reduced fluoroquinolone absorption
X	<p>IF NO IMPROVEMENT</p> <ul style="list-style-type: none"> • Administer gastric-acid suppressants such as: <ul style="list-style-type: none"> - H2-blockers (e.g. cimetidine, ranitidine) - Proton-pump inhibitors (e.g. omeprazole)
X	<p>IF NO IMPROVEMENT</p> <ul style="list-style-type: none"> • If receiving THA, reduce to 750 mg • If receiving CFZ, reduce to 200 mg • If receiving PAS, take with yogurt rather than orange juice
X	<p>IF REFRACTORY AND SEVERE SYMPTOMS</p> <ul style="list-style-type: none"> • Consider treatment for <i>Helicobacter pylori</i> • Consider GI consult

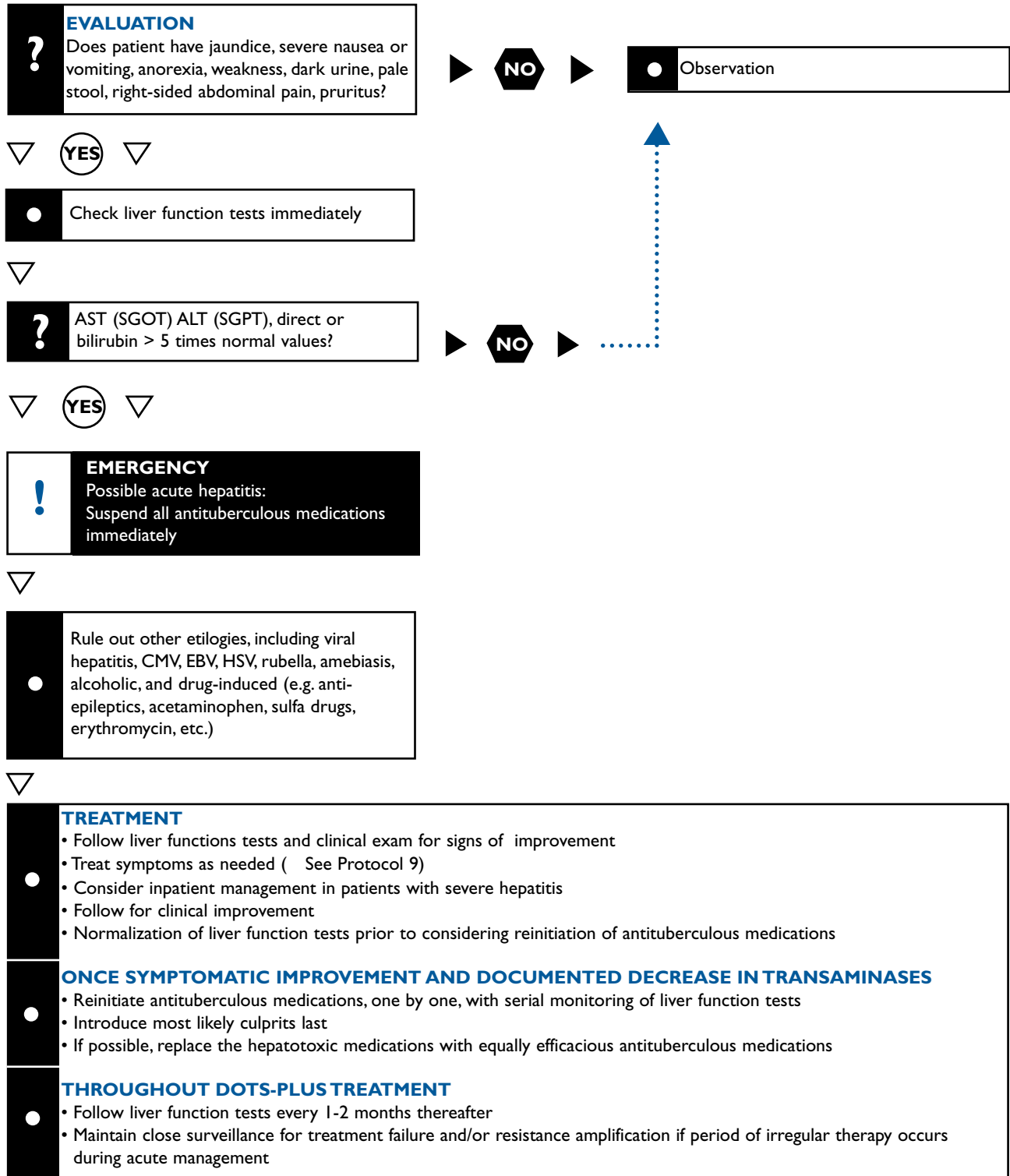
**Protocol 6:
Management of Headaches**

Although headaches are often a side effect of antituberculous treatment, it is important to rule out other types of headaches, including migraines and cluster headaches.



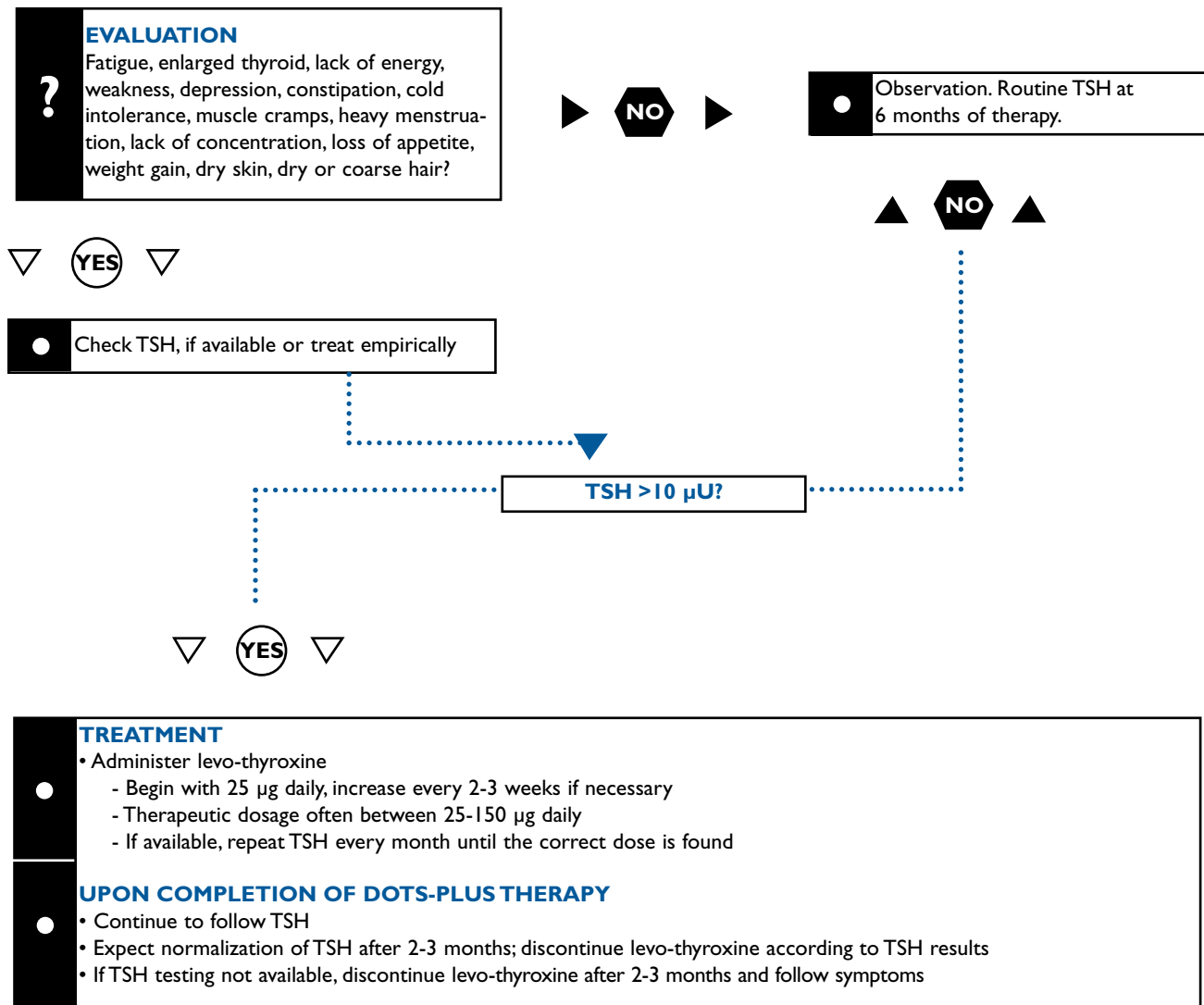
Protocol 7: Evaluation and Management of Hepatitis

Hepatitis refers to inflammation of the liver. Diverse causes include infections (e.g. viral, amebic, etc.), alcoholism, and medications, including antituberculous drugs. Any signs or symptoms of hepatitis (including nausea, severe vomiting, scleral icterus, jaundice, dark urine, pale stool) merit immediate evaluation of liver function tests.



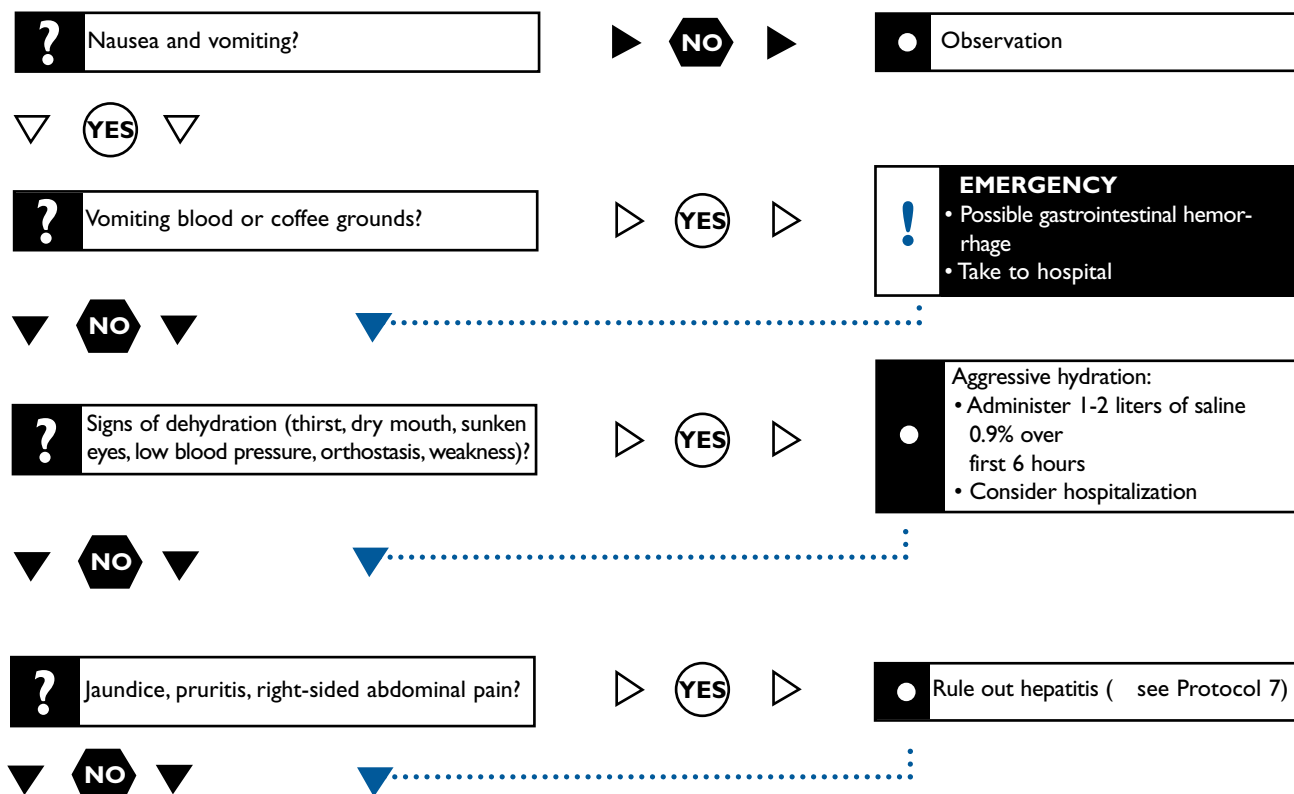
**Protocol 8:
Management of Hypothyroidism**

Hypothyroidism, caused by suppression of the thyroid gland can be diagnosed by serum thyroid stimulating hormone (TSH) above 10 µU. Chief among causes of hypothyroidism in patients with MDR TB are medications, particularly ethionamide and PAS when used in combination. Hypothyroidism need not lead to the discontinuation of antituberculous medications as the disease can be managed with levo-thyroxine replacement and abates once the patient has completed treatment.



Protocol 9: Management of Nausea and Vomiting

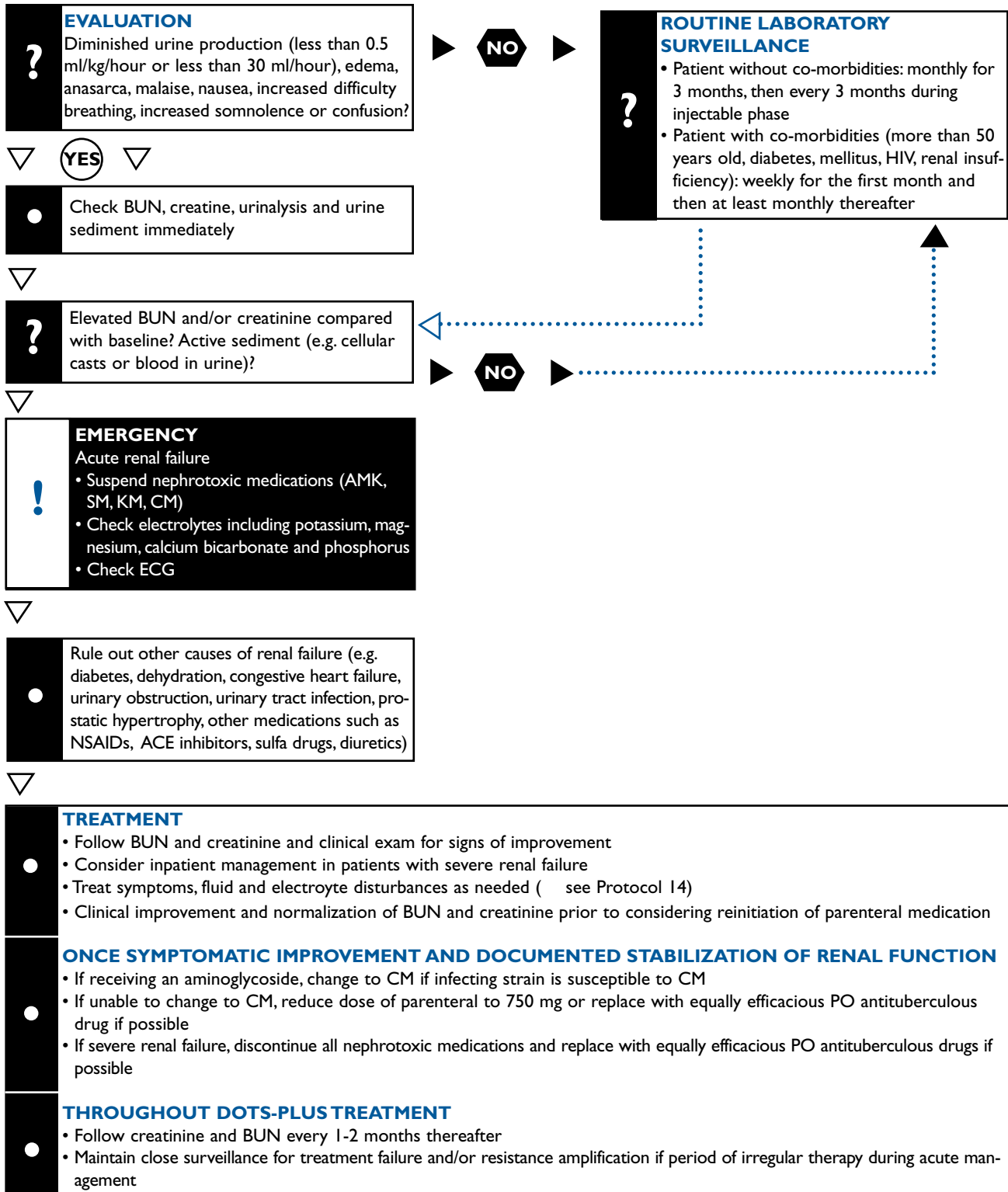
While the majority of patients experiences nausea and/or vomiting as an adverse effect during MDR TB therapy, these symptoms rarely prevent delivery of adequate therapy. Symptoms should be controlled, and any medications lost due to emesis recuperated. Volume and electrolyte management is also essential if emesis is significant. Refractory nausea and vomiting may suggest the need for further investigation, including addressing the possibility of hepatitis.



●	<p>TREATMENT</p> <ul style="list-style-type: none"> • Check electrolytes and replete as necessary (see Protocol 14) • Adjust administration of medications <ul style="list-style-type: none"> - Administer THA or CFZ in three separate doses - Administer medication associated with nausea at night with short-acting benzodiazepine - Administer PAS one hour after taking other antituberculous medications
X	<p>IF NO IMPROVEMENT</p> <ul style="list-style-type: none"> • Administer oral anti-emetics 30 minutes prior to taking antituberculous medications (e.g. prochlorperazine, diphenhydramine, lorazepam, dimenhydranate, metoclopramide, phenergan, etc.) • Watch closely for neurologic disturbances as centrally acting anti-emetics (e.g. metoclopramide, prochlorperazine) may interact with antituberculous, anti-psychotic, and/or antidepressant drugs • Use benzodiazepines if anxiety (avoid benzodiazepines in patients with tenuous respiratory status at risk of CO₂ retention)
X	<p>IF NO IMPROVEMENT</p> <ul style="list-style-type: none"> • Administer anti-emetics IV or IM as needed
X	<p>IF NO IMPROVEMENT</p> <ul style="list-style-type: none"> • If taking THA, reduce to 500-750 mg QD • If taking CFZ, reduce to 200 mg QD

**Protocol 10:
Management of Nephrotoxicity, Part I**

While many recommend a six-month maximum of parenteral administration and maximum cumulative aminoglycoside doses of ≤ 150 grams, our cohort of relatively young patients with few co-morbidities has demonstrated remarkable tolerance to far larger cumulative doses of injectable agents. Blood urea nitrogen (BUN) and creatinine should be documented at the beginning of therapy, and renal function should be followed regularly throughout DOTS-Plus treatment.



**Protocol 10:
Management of Nephrotoxicity, Part II**

Drug	Method of modification	Glomerular filtration rate, ml/min		
		>50	10-50	<10
Streptomycin	D, I	7.5 mg/kg /24 hr	7.5 mg/kg /24-72 hr	7.5 mg/kg /72-96 hr
Kanamycin	D, I	7.5-15 mg/kg /24 hr	4-7.5 mg/kg /24 hr	3 mg/kg /48 hr
Ethambutol	I	/24 hr	/24-36 hr	/48 hr
Pyrazinamide	D	30 mg/kg /24 hr	30 mg/kg /24 hr	15-30 mg/kg /24 hr
Ciprofloxacin	D	100%	50-75%	50%
Levofloxacin	D	100%	50%	25-50%
Ehionamide	D	100%	100%	50%
Cycloserine	D	100%	50-100%	50%
PAS	D	100%	50-75%	50%
Clofazimine		100%	100%	100%
AMX/CLV	I	1.5 g /24 hr	1g / 24 hr	1g / 24 hr

D = Dose adjustment I = Interval adjustment

Creatine Clearance	24 h	48 h	72 h
	Dose (mg/kg)		
0	1.29	2.58	3.87
10	2.43	4.87	7.30
20	3.58	7.16	10.7
30	4.72	9.45	14.2
40	5.87	11.7	
50	7.01	14.0	
60	8.16		
80	10.4		
100	12.7		
110	13.9		

Creatine Clearance: normals

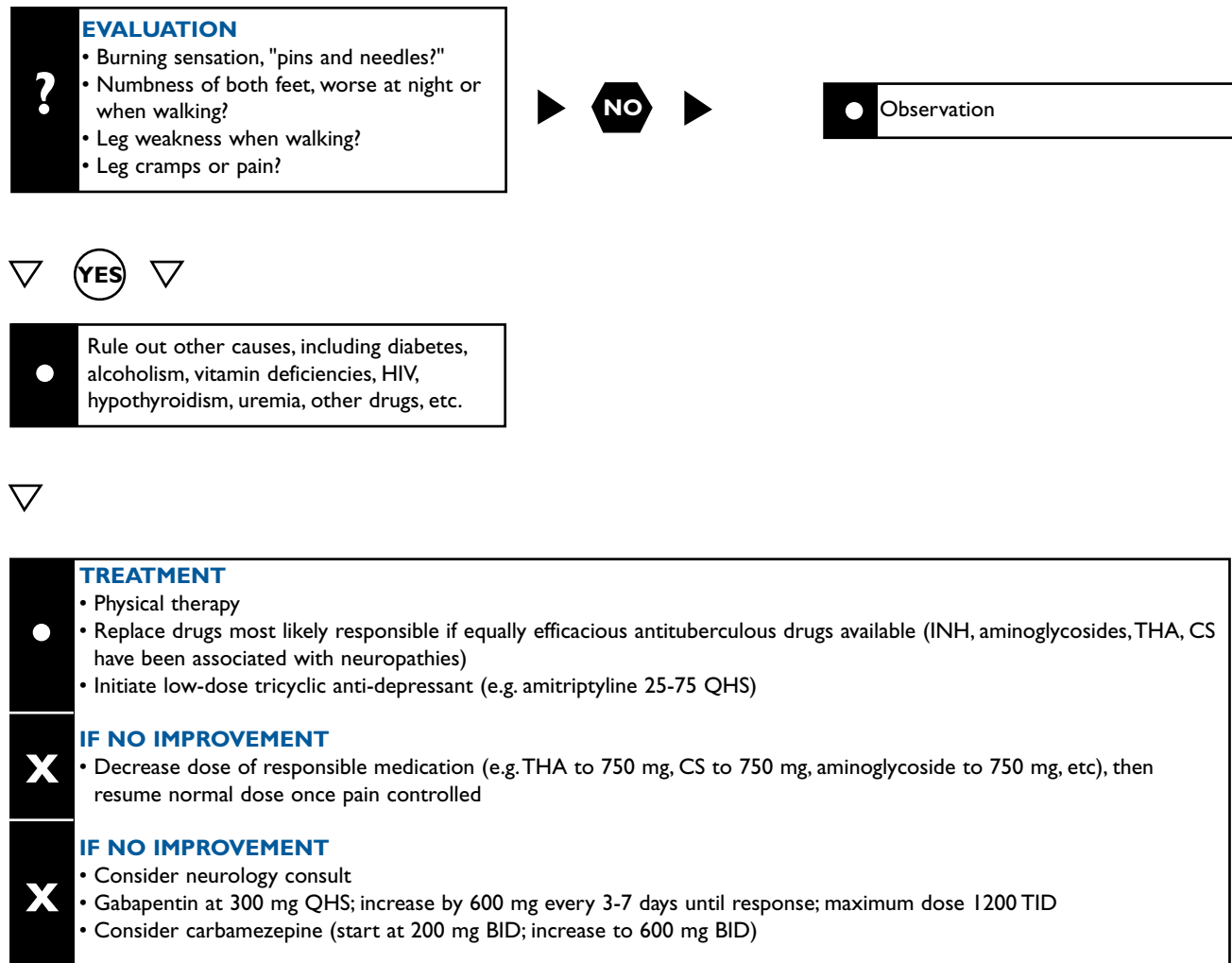
Men: 97 to 137 ml/min

Women: 88 to 128 ml/min

Estimated Glomerular Filtration Rate (GFR) =
Weight (kg) x (140 -age) (x0.85 for women) / 72 x Serum Creatine

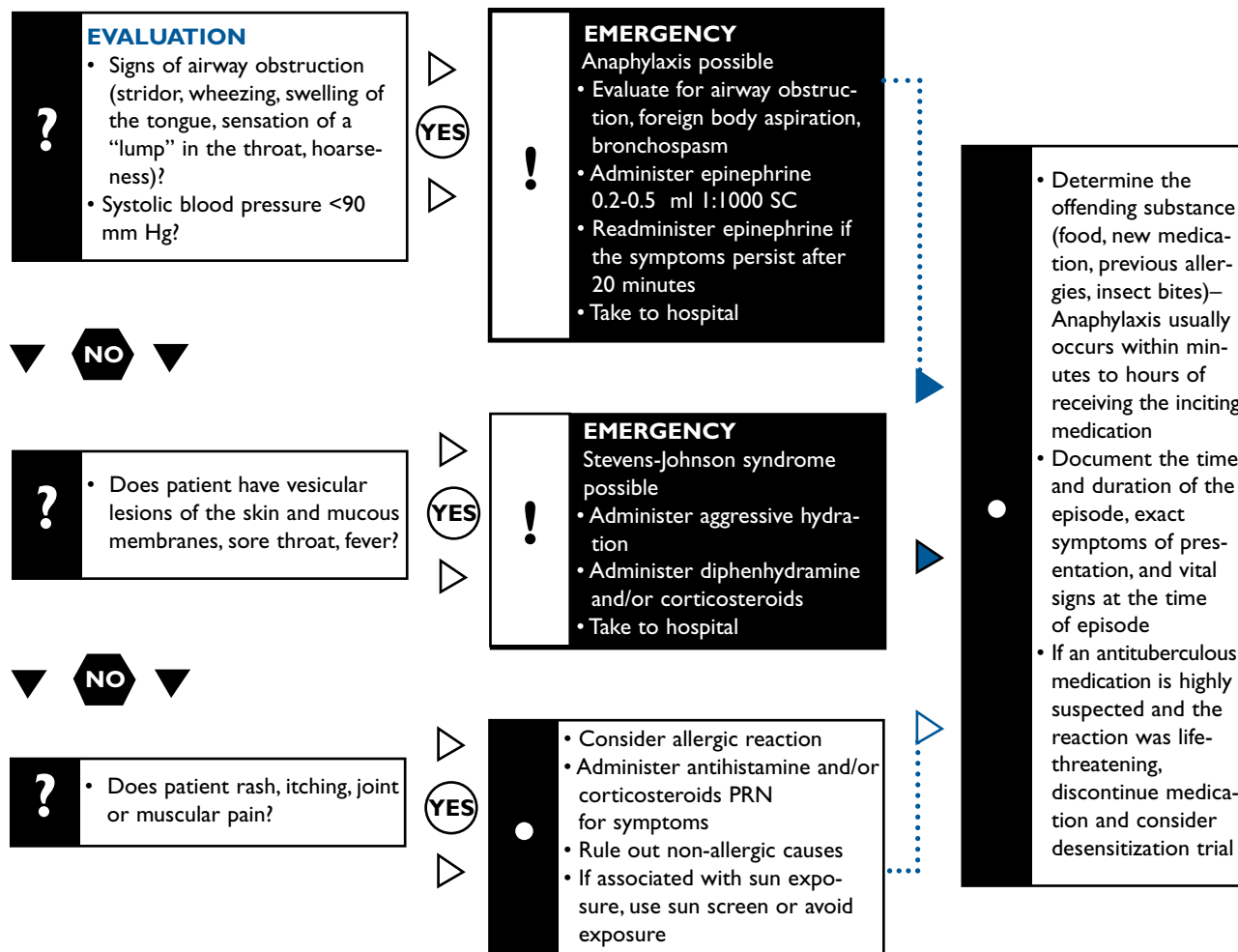
Protocol II: Management of Peripheral Neuropathy

The term neuropathy refers to a degenerative, infectious or inflammatory process that causes damage to the nerves. Peripheral neuropathy refers to those neuropathies located outside of the central nervous system. In a patient presenting with symptoms of peripheral neuropathy, it is important to consider causes other than antituberculous drugs (e.g. alcoholism, diabetes, other medications, etc.).



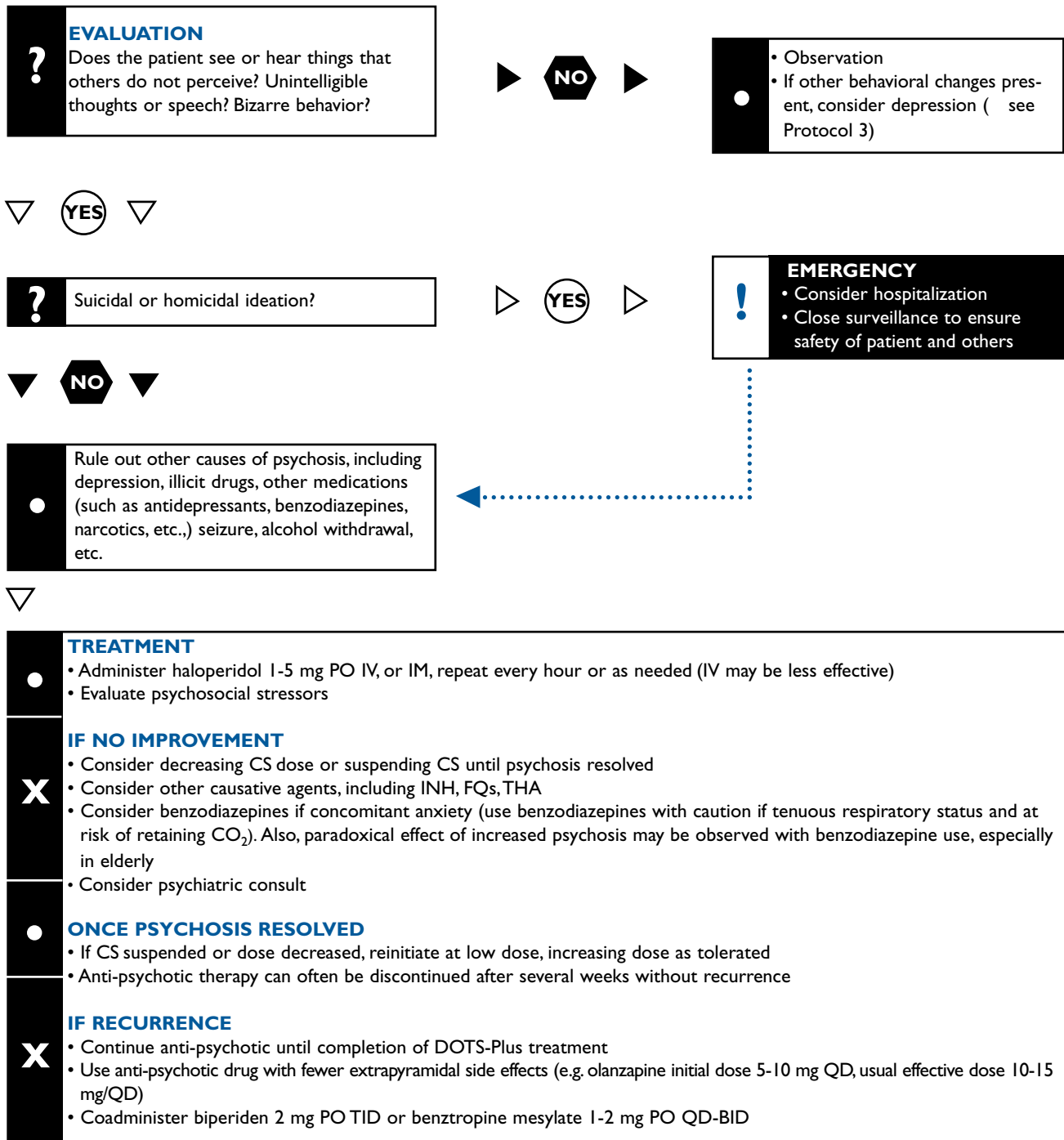
Protocol 12: Management of Anaphylaxis and Allergic Reaction

There are many types of adverse reactions, but it is important to be able to promptly identify anaphylaxis. The anaphylactic response can be fatal and appears within minutes of the administration of the offending medication. Symptoms include: difficulty breathing (often with wheezing), shock, pruritis, urticaria (with or without angiodema), nausea, vomiting, cramps, and diarrhea. At times, the patient can also present with fever, arthralgia (joint pain) and myalgias (muscle pain).



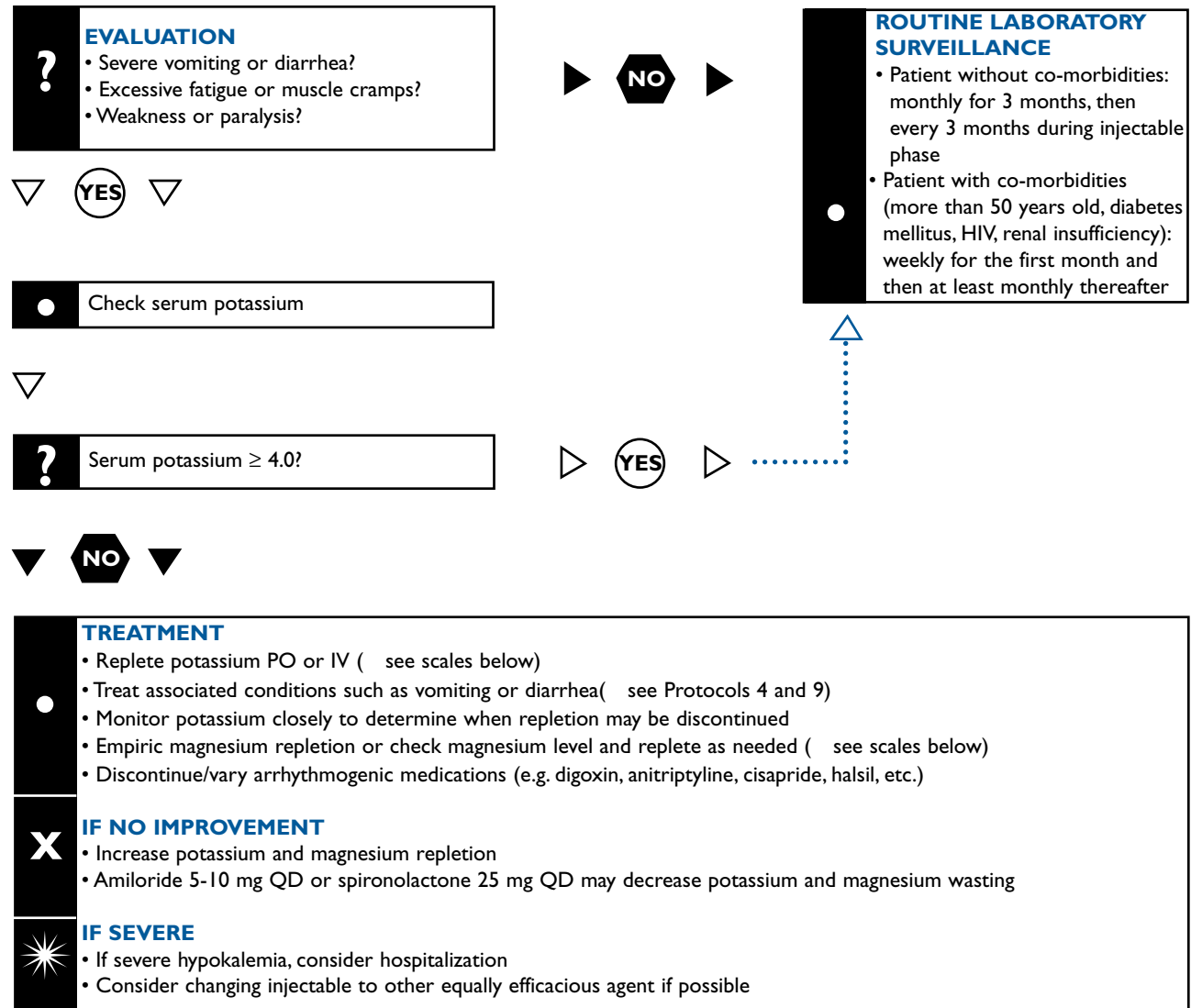
Protocol 13: Management of Psychosis

Psychotic symptoms refer to a constellation of symptoms that indicate a disintegration of personality or a loss of contact with reality. Patients tend to present with hallucinations or delusions. The causes of psychotic symptoms in patients with MDR TB may be related to underlying psychiatric disorders, antituberculous medications (especially CS), and other medications. Decompensation may occur in the context of stressors such as socioeconomic problems, additional medications, substance abuse, etc.



Protocol 14: Management of Hypokalemia

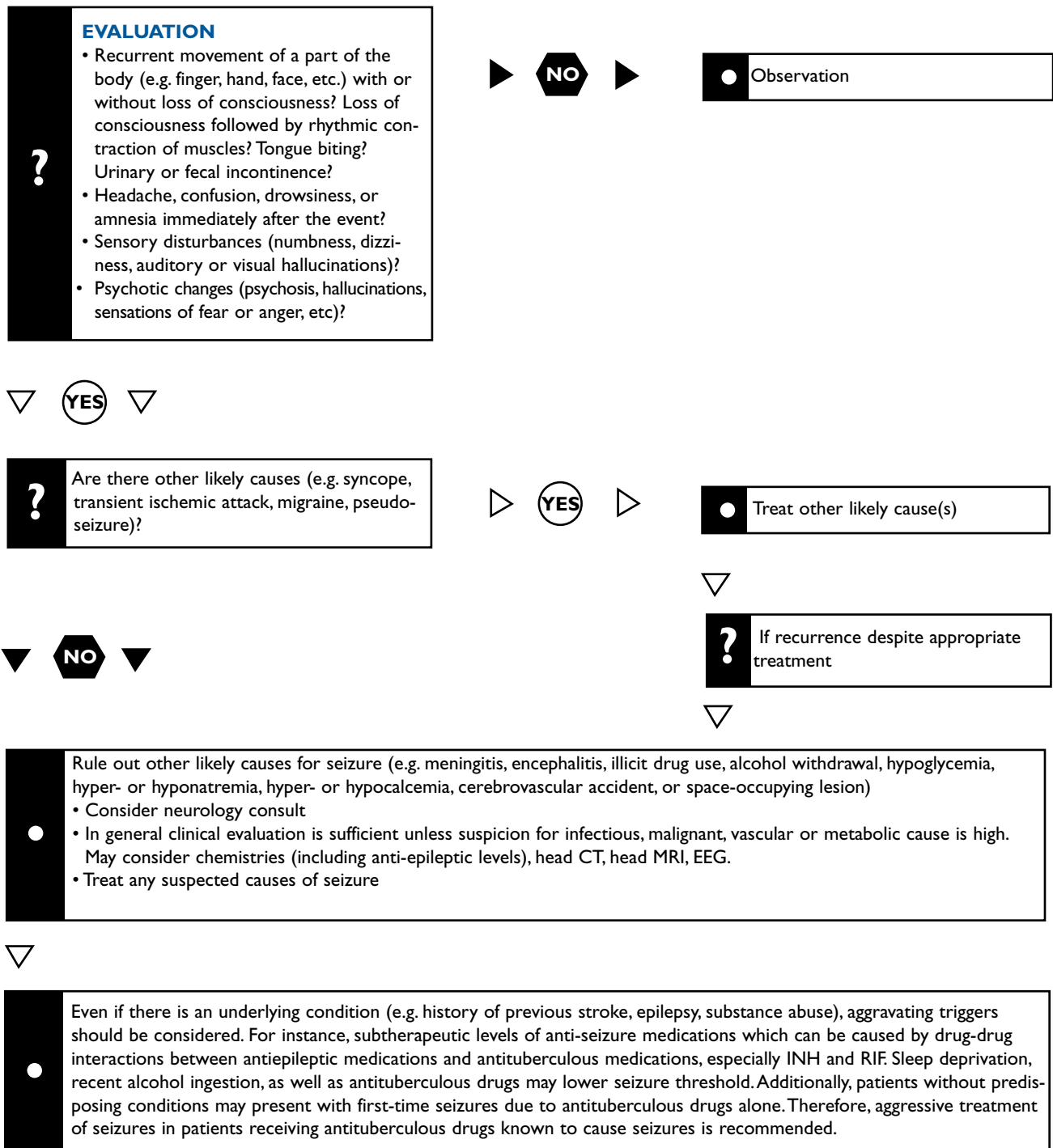
Hypokalemia signifies a low level of potassium in the blood (<4.0). It can also be associated with other electrolyte abnormalities, such as hypomagnesemia. Persistent vomiting and diarrhea is a common cause of hypokalemia. Some of the antituberculous medications – in particular the aminoglycosides and capreomycin– cause renal wasting of potassium and magnesium. In most patients with MDR TB and hypokalemia, the cause of the electrolyte abnormality is likely multifactorial. Because hypokalemia can occur without clinical signs or symptoms and because it can be life-threatening, we recommend checking potassium levels frequently while receiving injectable therapy. Potassium levels are difficult to correct, when magnesium levels are low; thus aggressive magnesium repletion is as important as potassium supplementation.



POTASSIUM LEVEL	PO POTASSIUM	IV POTASSIUM	MAGNESIUM LEVEL	PO MAGNESIUM	MAGNESIUM LEVEL	IV MAGNESIUM
≥4.0	none	none	>2.0	none	>2.0	none
3.7-3.9	20 mEq	10 mEq	1.5-1.9	1000 mg	1.8-1.9	2000 mg
3.4-3.6	40 mEq	20 mEq	1.0-1.4	2000 mg	1.6-1.7	3000 mg
3.0-3.3	60 mEq	30 mEq	<1.0	3000 mg	1.4-1.5	4000 mg
2.7-2.9	80 mEq	40 mEq			< 1.4	5000 mg
2.4-2.6	120 mEq	60 mEq				
2.0-2.3	160 mEq	80 mEq				
<2.0	250 mEq	100 mEq				

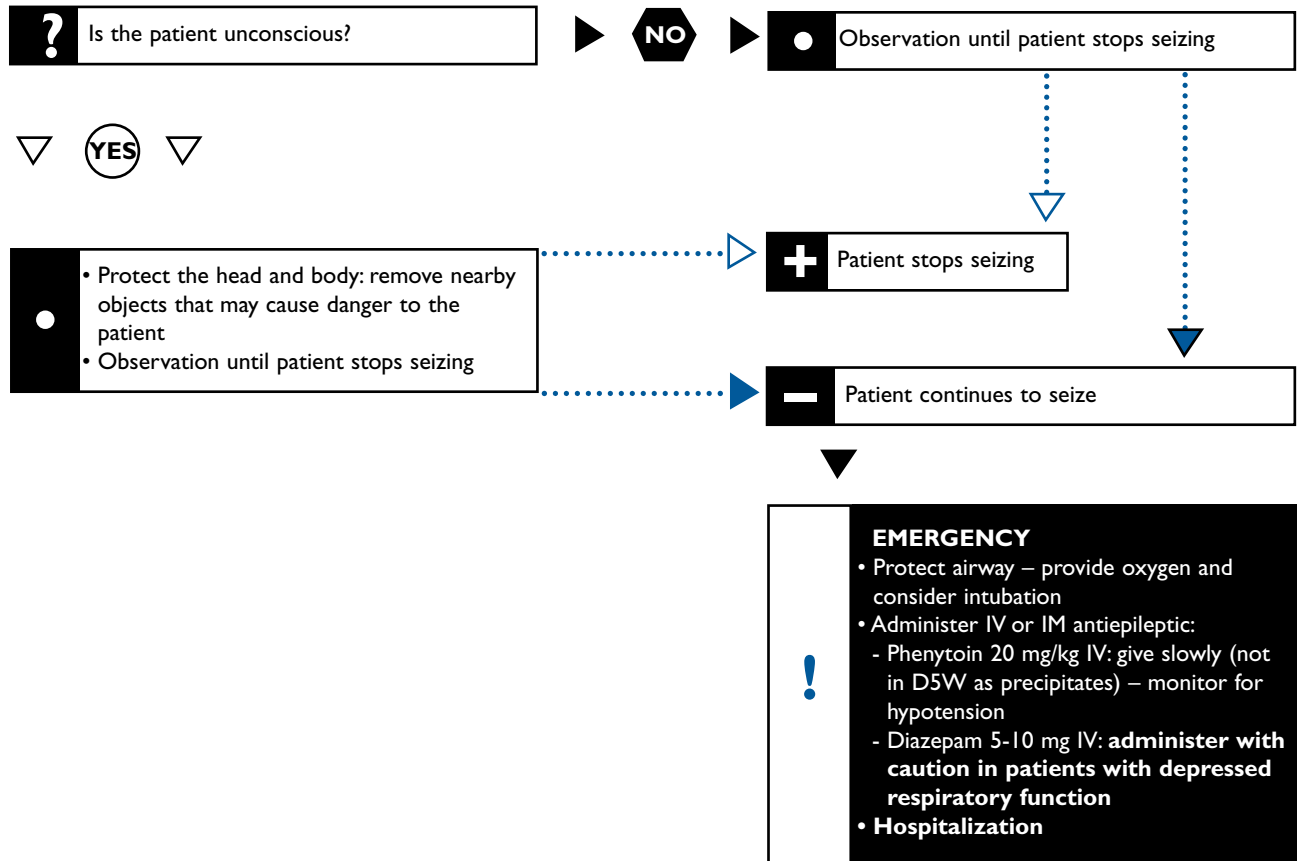
Protocol 15: Management of Seizure, Part I

The term seizure applies to a paroxysmal neurological dysfunction caused by abnormal electrical activity of the brain. While epilepsy describes the syndrome of recurrent episodes, a seizure may also occur as an isolated episode. Prompt identification of a seizure is essential for timely management; however, the spectrum of presentations is diverse and, at times, subtle. While convulsive seizures present with motor activity disturbances, other seizures may manifest as mere sensory or cognitive changes. Along with many other etiologies, certain antituberculous drugs have been associated with seizures, as has TB of the central nervous system.



Protocol 15: Management of Seizure, Part II

The goals of seizure management are the stabilization of the patient during an acute episode and the prevention of seizure recurrence.



TREATMENT

Initiate antiepileptic treatment for the remainder of MDR TB therapy:

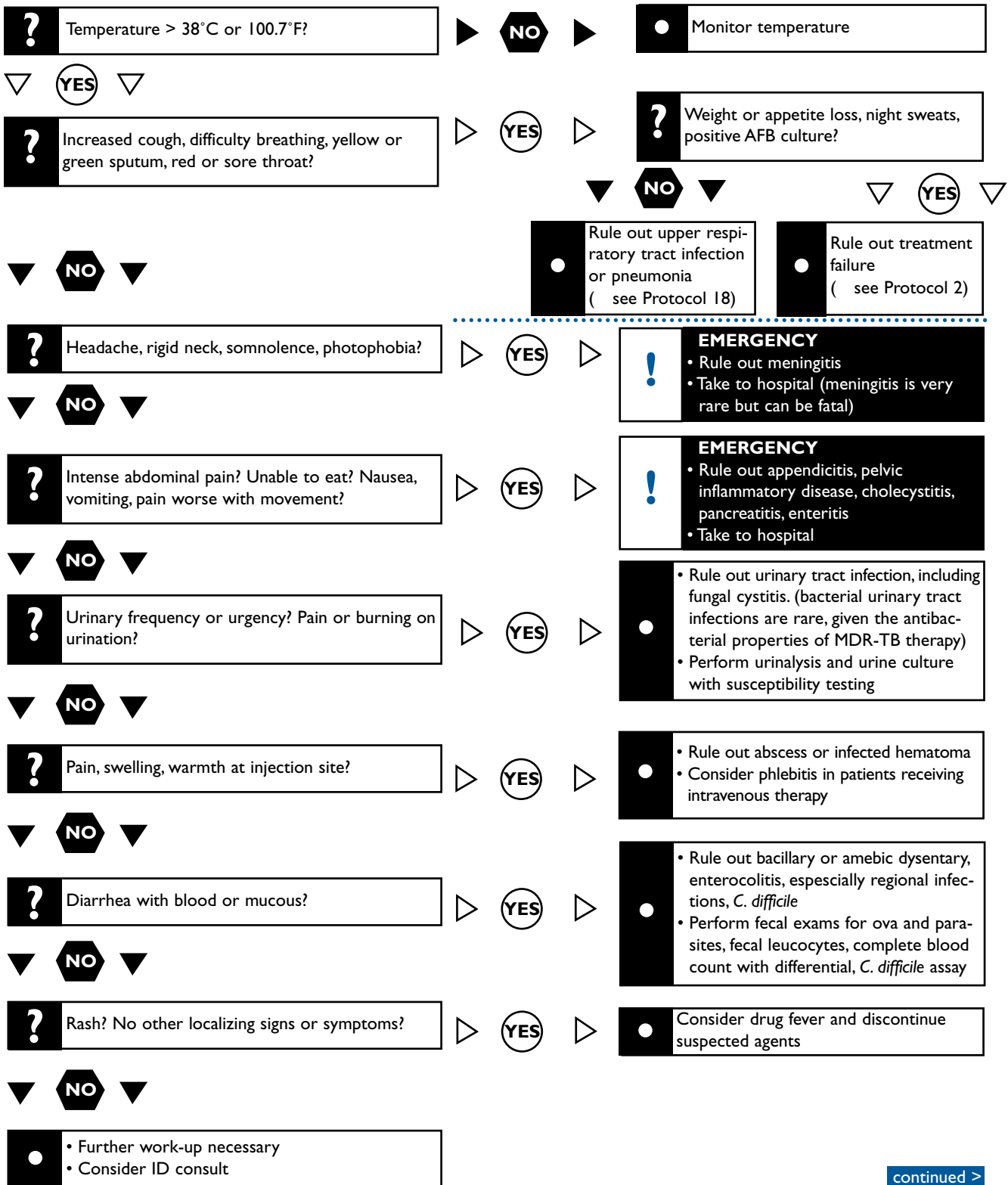
- Phenytoin (3-5mg/kg/d)
 - Potential adverse effects: ataxia, incoordination, confusion, skin rash, cerebellar dysfunction, hepatotoxicity, gingival hyperplasia, lymphadenopathy, hirsutism. Levels increased by INH, RIF, FQS.
- Carbamazepine (600-1200 mg/d)
 - Potential adverse effects: ataxia, dizziness, diplopia, vertigo, GI upset, hepatotoxicity, skin rash
- Phenobarbital (60-120 mg/d)
 - Potential adverse effects: sedation, ataxia, confusion, dizziness, decreased libido, depression, skin rash. Enhances metabolism of other drugs, including INH.
- Valproic acid (750-1250 mg/d)
 - Potential adverse effects: ataxia, sedation, tremor, hepatotoxicity, bone marrow suppression, GI upset, weight gain

IF NO IMPROVEMENT

- Decrease CS to 750 mg or 500 mg/d or hold CS until therapeutic antiepileptic levels achieved
- If available, check CS level and adjust if supratherapeutic
- Decrease fluoroquinolone dose

Protocol 16: Management of Fever, Part I

Fever is defined as an elevation in body temperature in excess of normal range, although temperatures within 1 or 2 degrees of normal (98.6°F or 37°C) are not generally considered significant. When a patient receiving MDR TB treatment has a fever, various sources must be ruled out.



continued >

**Protocol 16:
Management of Fever, Part II**

POSSIBLE CAUSE	PRESENTATION	TREATMENT
URINARY TRACT INFECTION		
Bacterial	<ul style="list-style-type: none"> • Urine leukocytes • Positive Gram stain • Positive urine culture 	<ul style="list-style-type: none"> • Treat according to susceptibility testing
Fungal	<ul style="list-style-type: none"> • Urine leukocytes • Positive Gram stain • Negative urine culture 	<ul style="list-style-type: none"> • Treat with fluconazole 200 mg QD first dose, then 100 mg QD for 4 days
ABSCESS, HEMATOMA		
	<ul style="list-style-type: none"> • Injection site • Pain • Warmth • Swelling • Fluctuance 	<ul style="list-style-type: none"> • Aspirate with 18 gauge needle or incise and drain • If abscess, treat with dicloxacillin 500 mg four times a day (or other antistaphylococcal therapy)
GASTROENTERITIS, ENTEROCOLITIS		
Viral	<ul style="list-style-type: none"> • Diarrhea, usually without mucous or blood • Negative fecal studies 	<ul style="list-style-type: none"> • Give rehydration salts
Bacterial/Parasitic	<ul style="list-style-type: none"> • Diarrhea, can be with mucous or blood • Positive fecal leukocytes • Possible <i>C. difficile</i> if positive fecal leukocytes, elevated white blood count fever 	<ul style="list-style-type: none"> • Give rehydration salts • Treat according to fecal study results • If <i>C. difficile</i> suspected or confirmed, treat with metronidazole 500 mg TID for 10-14 days

**Protocol 17:
Management of Hemoptysis, Part I**

Hemoptysis is the expectoration of blood originating from the larynx, trachea, bronchi or lungs. Because hemoptysis may present as anything from blood-streaked sputum to a large quantity of blood, it is essential to specify the quantity of blood loss and the period of time over which the loss occurred. During an episode of hemoptysis, the blood pressure, heart rate and respiratory rate should be quickly obtained and documented. All patients who have a history of hemoptysis should have their blood type identified on initiation of DOTS-Plus therapy, as blood transfusion may be required.

<p>? Does the blood exit from the nose and not the mouth?</p>	<p>▶ YES ▶</p>	<p>● Observation: likely epistaxis</p>
<p>▼ NO ▼</p>		
<p>? Is the patient vomiting blood?</p>	<p>▶ YES ▶</p>	<p>! EMERGENCY Rule out gastrointestinal bleed</p>
<p>▼ NO ▼</p>		
<p>? • Quantity of blood > 1/2 cup • Total quantity in 48 hours > 600 ml?</p>	<p>▶ NO ▶</p>	<p>● Minor or moderate hemoptysis</p>
<p>▽ YES ▼</p>		
<p>● Massive hemoptysis</p>		
<p>▽</p> <p>! EMERGENCY</p> <ul style="list-style-type: none"> • Hospitalization • Obtain IV access and administer IV fluids • Monitor for signs of shock (systolic blood pressure <90, heart rate >120, respiratory rate > 30, somnolence, nausea, weakness, pallor, cold or blue skin) • Perform analysis STAT 		

continued >

Protocol 17: Management of Hemoptysis, Part II

ANALYSIS

- Chest radiograph
- Hematocrit (Hct)
- Type and crossmatch
- If fever and productive sputum: AFB and culture, sputum Gram stain and culture

TREATMENT

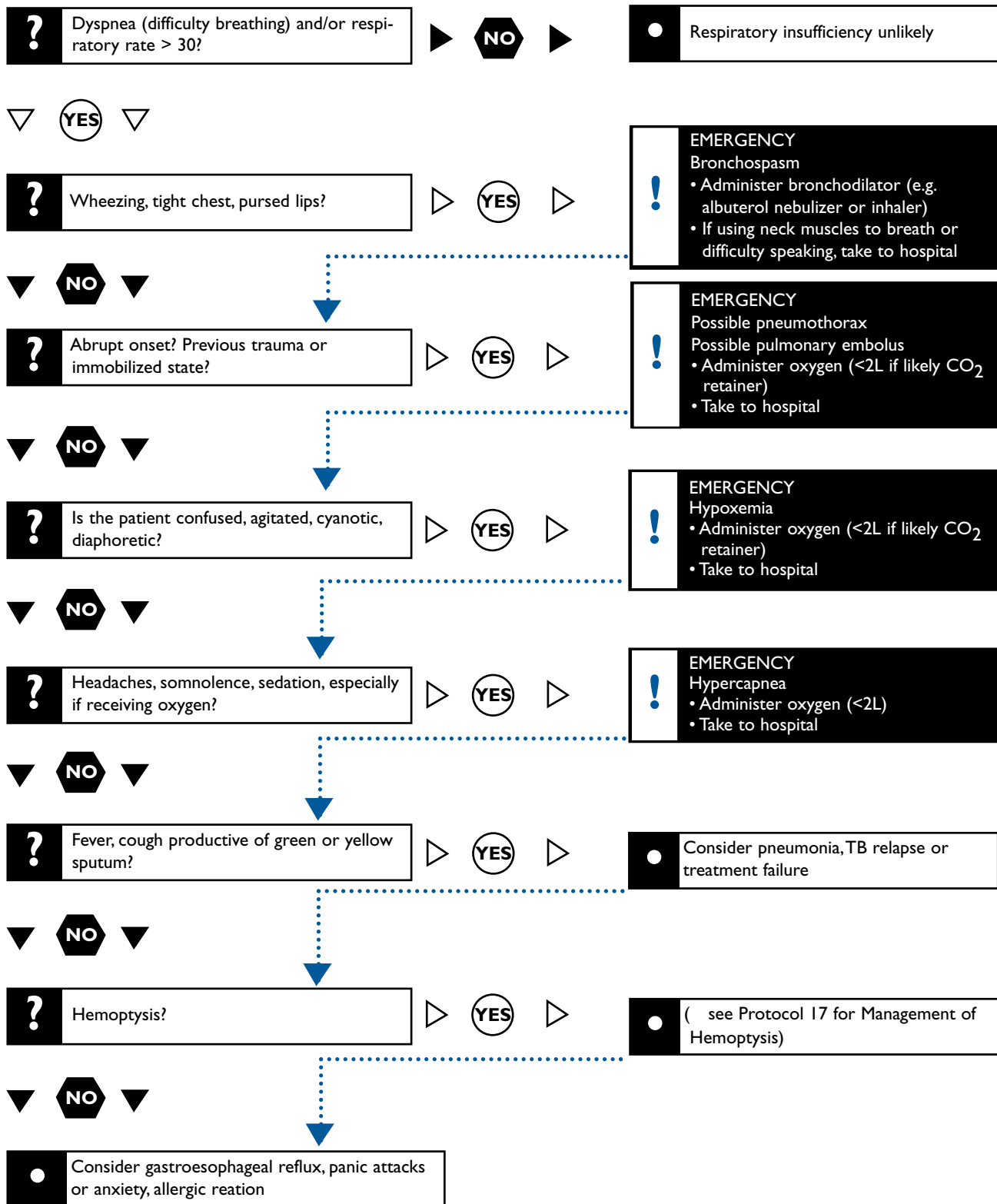
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| Phase I | <ul style="list-style-type: none">• Prescribe bed rest• Monitor patient closely• Avoid NSAIDs and aspirin• If evidence of respiratory superinfection, initiate appropriate antibiotic treatment |
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| Phase II
For massive hemoptysis | <ul style="list-style-type: none">• Place large bore IV and resuscitate with 1-2 liters of normal saline within the first hour• Thereafter, maintain fluid (normal saline 0.9%)• Lie patient with likely source of hemorrhage in dependent position• Provide oxygen, if needed• Check vital signs frequently• Administer vitamin K 5 SC if malnutrition or coagulopathy present |
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| Phase III
If Hct < 30% | <ul style="list-style-type: none">• Transfuse with matched blood• Follow Hct closely |
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| Phase IV
If recurrent episodes
without improvement | <ul style="list-style-type: none">• Consider bronchoscopy• Consider surgical evaluation: bronchiectasis, cavities, or coin-shaped lesions may be hemorrhagic sources (e.g. tuberculous destruction, erosion of blood vessels, aspergilloma) |
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**Protocol 18:
Management of Respiratory Insufficiency, Part I**



continued >

Protocol 18: Management of Respiratory Insufficiency, Part II

ANALYSIS

- Chest radiograph
- Complete blood count with differential
- Sputum AFB and culture, Gram stain and culture
- Pulse oximetry, if available
- If severe symptoms, arterial blood gas, if available

POSSIBLE CAUSE	PRESENTATION	TREATMENT
Bronchospasm	<ul style="list-style-type: none"> • Wheezing, prolonged expiration • May be associated with respiratory superinfection 	<p>Phase I • Inhaled broncodilators</p> <ul style="list-style-type: none"> • Treat for infection, if suspected <p>Phase II • Administer oral or intravenous steroids</p> <p>Phase III • Consider long-term use of inhaled bronchodilators and/or inhaled steroids</p> <p>Phase IV • Nebulized bronchodilators</p>
Pneumothorax	<ul style="list-style-type: none"> • Sharp pain, sudden onset, previous trauma • Positive chest x-ray • May have decreased O₂ sat and PO₂ 	<ul style="list-style-type: none"> • Administer O₂ • Take to hospital • Thoracic surgery consult
Pulmonary Embolus	<ul style="list-style-type: none"> • May have fever, chest pain, tachycardia positive ECG, positive chest x-ray and/or diminished O₂ sat/PO₂ • History of previous immobilization or surgery 	<ul style="list-style-type: none"> • Administer O₂ • Take to hospital • Perform ventilation and perfusion scan, if available • Anticoagulation, if no contraindication
Respiratory Infection	<ul style="list-style-type: none"> • Fever, productive cough • May have bronchospasm • Infiltrate on chest x-ray • Leukocytosis, positive sputum • Gram stain/culture 	<ul style="list-style-type: none"> • Treat with antibiotics according to sputum/Gram stain/culture results • Treat concomitant bronchospasm as needed • Administer O₂ as needed
Tuberculosis Relapse/ Treatment Failure	<ul style="list-style-type: none"> • Productive cough, fever, night sweats, weight loss, diminished appetite • Chest radiograph may reveal new infiltrate • Positive AFB and/or culture 	<ul style="list-style-type: none"> • Confirm positive AFB and/or culture • See Protocol 2 for positive AFB and/or culture