COMPLICATIONS OF HIV DISEASE

9

HIV-infected patients are at risk of complications that might or might not be related to the degree of immune compromise. Patients' immune status (CD4+ cell count) will be important in considering the potential etiology of presenting symptoms and signs. Some complications can be investigated and managed by primary care physicians depending on comfort level, expertise, acuity of patients' illness, and access to investigations and therapy. In advanced disease, patients sometimes have more than one opportunistic infection or malignancy. Referral to internal medicine subspecialists is recommended for investigation, management, or hospitalization, particularly for patients with more advanced immunosuppression (CD4+ count < 200 cells /μL).

9.1 RESPIRATORY INFECTIONS

Sinusitis, chronic bronchitis, and bacterial pneumonia are common. *Streptococcus pneumoniae*, *Hemophilus influenzae,* and *Staphylococcus aureus* are the most common bacterial pathogens. *Pseudomonas aeruginosa* should be considered in patients with late-stage disease who have previously been hospitalized and have had neutropenia and corticosteroid therapy. Aspergillus pneumonia occurs in patients with advanced immunocompromise (CD4+ count < 50 cells/μL) with additional risk factors of neutropenia, corticosteroid use, marijuana use, structural disease of the lung, and exposure to broad-spectrum antibiotics. Treatment should be directed toward the specific organism with empiric therapy based on likelihood of a particular pathogen and individual patient's risk factors. Bronchoscopy might be indicated to make a specific diagnosis, particularly for fungal or more unusual organisms.

9.1.1 *PNEUMOCYSTIS CARINII* PNEUMONIA

Pneumocystis carinii pneumonia should be suspected in untreated patients with CD4+ counts < 200 cells/μL and symptoms of fever, non-productive cough, and dyspnea. Chest x-ray results might be

normal but typically reveal diffuse interstitial infiltrates and might demonstrate pneumatoceles. Patients have hypoxemia and elevated lactate dehydrogenase. Diagnosis can be confirmed by demonstration of *Pneumocystis carinii* cysts on cytology of respiratory secretions obtained by induced sputum production or bronchoalveolar lavage (the former is less sensitive). Treatment of choice is trimethoprim-sulphamethoxazole, two double-strength doses three or four times a day (TID or QID) for 21 days. Alternative therapy includes dapsone, 100 mg daily, with trimethoprim 15 to 20 mg/kg divided every 6 hours (Q6H), clindamycin, 450 mg QID, with primaquine, 30 mg base daily, pentamdine intravenously, 4 mg/kg daily, or atovaquone, 750 mg TID. Adjunctive corticosteroids should be considered if the partial pressure of oxygen (pO_2) is <70 mm Hg; use prednisone, 40 mg twice daily (BID) for 5 days, 40 mg once daily, or 20 mg BID for 5 days, then 20 mg daily for 11 days. Pneumothorax might be a complication. Following successful completion of therapy, patients should receive secondary prophylaxis.

9.2 NEUROLOGIC MANIFESTATIONS

Neurologic complications of HIV infection could be due to opportunistic infections, opportunistic neoplasms, or HIV itself.

Aseptic meningitis—with primary HIV infection, patients might present with symptoms of fever, headache, stiff neck, and lymphocytic pleocytosis. Symptoms can recur during the course of infection.

Myelopathy—HIV-related spinal-cord involvement is uncommon but presents as a spastic paraparesis with bowel and bladder dysfunction, gait ataxia, and variable sensory loss, usually in the context of advanced immunodeficiency.

Distal symmetric polyneuropathy—this can occur as a consequence of HIV infection but more commonly is associated with use of antiretroviral (ARV) drugs, specifically zalcitabine (ddC), didanosine (ddI), and stavudine (d4T). Symptoms are typically distal paresthesias, with burning sensations and numbness of fingertips and toes that progresses proximally. The possibility of vitamin B_{12} deficiency should be excluded. Management consists of dose reduction, or if necessary, discontinuation of any potentially offending agents. Symptomatic treatment with tricyclic antidepressants, anticonvulsants (eg, carbamazepine, gabapentin) and narcotic analgesics has had variable success.

Myopathy—polymyositis can result from HIV infection itself, but myopathy is most often associated with zidovudine therapy and due to mitochondrial toxicity. It is characterized by myalgia, proximal

muscle wasting, and elevated creatine kinase levels (elevated levels can be found in HIV disease without myopathy). Symptoms might respond to discontinuation of zidovudine, and some patients might improve with corticosteroid therapy.

Cerebral toxoplasmosis—patients with evidence of prior toxoplasmosis (ie, positive toxoplasma IgG antibodies) are at risk of reactivation when CD4+ count falls to <75 to 100 cells/μL. Clinical manifestations include headache, seizures, and focal neurologic findings. Computed tomography scan usually reveals multiple ring-enhancing lesions with a predilection for basal ganglia involvement. Diagnosis can be confirmed by demonstration of the organisms on histopathology of brain tissue obtained by sterotaxic biopsy or craniotomy. Treatment can be empiric in the presence of typical lesions in susceptible patients (CD4+ cell count <100 cells/μL and positive serology). Radiologic improvement should be expected within 10 to 14 days. Pyrimethamine can be used at a 100- to 200-mg loading dose, then 50 to 75 mg daily and folinic acid, 15 mg daily, with either sulfadiazine, 1 gm Q6H, or clindamycin, 600 mg QID for 6 weeks, followed by suppressive maintenance therapy using the same agents.

Cryptococcal meningitis—cryptococcal meningitis presents insidiously with fever, headache, and malaise in patients with CD4+ count <100 cells/μL. Diagnosis can be made by detection of serum cryptococcal antigen and demonstration of the causative agent in cerebrospinal fluid (CSF) (India ink preparation) and confirmed with culture. Treatment should be initiated with amphotericin B, 0.7 mg/kg IV for 10 to 14 days with or without flucytosine, 100 mg/kg/day divided Q6H by mouth, followed by fluconazole, 400 mg daily for 8 to 10 weeks. Chronic suppressive therapy with fluconazole, 200 mg daily, is recommended to prevent recurrence. Increased intracranial pressure is a potential complication.

Progressive multifocal leukoencephalopathy—progressive multifocal leukoencephalopathy is caused by a human papovavirus, JC virus, usually in patients with CD4+ cell count <100 /μL. Onset is subacute, and patients present with limb weakness, impairment of cognitive function, gait disturbance, uncoordination, speech and visual disturbances, headache, and seizures. Computed tomography and magnetic resonance imaging scans reveal white-matter lesions. Brain biopsy is indicated for definitive diagnosis, but CSF polymerase chain reaction (PCR) for JC virus is diagnostic if positive. A negative result cannot exclude the diagnosis. Prognosis is poor, but remissions have been reported in response to highly active antiretroviral therapy (HAART).

AIDS dementia complex (HIV-associated cognitive-motor complex)—AIDS dementia complex is a subcortical dementia affecting

cognition, motor performance, and behaviour. Patients experience progressive symptoms of mental slowing, forgetfulness, poor concentration, apathy, social withdrawal, loss of spontaneity, and reduced libido. They lose interest in social and work-related activities and undergo personality changes, including reduced emotional expression or increased irritability, mania, and disinhibition. Loss of fine motor control, slowing of gait, unsteadiness, urinary incontinence, and tremor might be seen. Seizures occur in about 10% of patients, and transient neurologic deficits have been reported in advanced disease. Just before death, patients lapse into coma. Highly active ARV therapy might be effective and should include at least two drugs likely to penetrate the blood-brain barrier.

9.3 MYCOBACTERIAL INFECTION

M. tuberculosis—Tuberculosis (TB) in HIV-infected patients occurs as a consequence of reactivation of latent infection, new infection with rapid progression to active disease (progressive primary TB), or second episodes from exogenous reinfection. Pulmonary disease is found in 70% to 90%, but extrapulmonary disease is common with lymphadenitis, central nervous system (CNS) involvement, cutaneous lesions, and bacteremia. Chest x-ray findings are dependent on degree of immunosuppression. When the CD4+ cell count is > 200/µL, upper-lobe infiltrates and cavitation are seen, but mediastinal adenopathy, miliary infiltrates, and pleural effusions are associated with CD4+ cell count < 200/µL. Minimum duration of therapy is 6 months, but if clinical or bacteriologic response is slow, treatment should be given for a total of 9 months or for 4 months after cultures become negative. With no drug resistance, treatment consists of isoniazid, 300 mg daily, rifampin, 600 mg daily (or rifabutin, 300 mg daily), pyrazinamide 25 mg/kg daily, and ethambutol 15 mg/kg daily for 2 months followed by isoniazid and rifampin (rifabutin) for 4 to 7 months. If isoniazid resistance is identified, a combination of rifampin, pyrazinamide, and ethambutol is recommended. In the case of rifampin resistance, a combination of isoniazid, pyrazinamide, and ethambutol should be given for 18 to 24 months. Rifabutin can be substituted for rifampin for patients on protease inhibitors with appropriate dose adjustment to 150 mg daily; indinavir and nelfinavir are preferable because pharmacokinetic data are most reliable for these agents. Suppressive or maintenance therapy is not indicated after successful completion of therapy. Paradoxical reactions (fever, worsening chest infiltrates, new pleural effusions and ascites, and peripheral and mediastinal lymphadenopathy) could develop in patients receiving antituberculous therapy and ARV therapy concomitantly. Reac-

tions are usually self-limiting and last 10 to 40 days. In some cases, corticosteroids are required.

Disseminated *M. avium complex* infection—fever, night sweats, weight loss, diarrhea, and anemia are common clinical manifestations of disseminated *M. avium complex* infection in patients with CD4+ counts of <50 cells/µL. *M. avium complex* can be isolated from blood cultures and bone marrow aspirates. Isolation from respiratory secretions or stool predicts disseminated disease. Combination clarithromycin, 500 mg BID, ethambutol 15 mg/kg daily, and rifabutin, 150 mg BID, is effective therapy and is continued as suppressive maintenance treament. Reducing the dose of rifabutin might be required if it is used in combination with protease inhibitors.

9.4 OTHER OPPORTUNISTIC INFECTIONS

Cytomegalovirus infection—cytomegalovirus (CMV) can cause retinitis, esophagitis, colitis and polyradiculopathy, and encephalitis in patients with CD4+ counts <50 cells/µL. Patients experience blurred vision, floaters, and flashing lights in the visual field. Typical retinal findings are perivascular hemorrhage and exudates. Demonstration of cytopathologic changes or isolation of virus from appropriate biopsy specimens is necessary to confirm diagnosis at other sites. Ganciclovir, 5 mg/kg Q12H IV for 14 to 21 days, followed by chronic suppressive therapy at 5 mg/kg IV daily or oral ganciclovir (except for lesions near the optic nerve or fovea), 1000 mg TID, is recommended. Alternative agents include foscarnet and cidofovir.

Candidiasis—the most common manifestation is oral candidiasis, which can progress to esophageal candidiasis associated with dysphagia. Oral thrush can be managed with topical therapy, such as mycostatin, 500 000 U swish and swallow five times daily, or clotrimazole troches, 10 mg five times daily. Esophageal involvement can be suspected based on history but endoscopic diagnosis might be required. Fluconazole, 200 mg daily for 2 to 3 weeks, might be necessary with chronic suppression thereafter. Prolonged azole therapy can lead to resistance. Itraconazole, 200 to 400 mg daily, can be used as an alternative agent for treatment and suppression.

Herpes zoster—herpes zoster is not uncommon in HIV infection and has been associated with progression of disease. Lesions might be confined to a single dermatome, but multidermatomal involvement with cutaneous dissemination can be seen. Treatment should be started as soon as possible after diagnosis is made, preferably within 72 hours, and continued until lesions have dried and crusted. Treatment

options include acyclovir, 800 mg every 4 hours while awake (five times daily), valacylcovir 1 gm TID, or famciclovir, 500 mg TID, for 7 to 14 days. Intravenous acyclovir might be required for patients with disseminated disease or visceral organ involvement or patients who cannot tolerate oral medications at a dose of 10 mg/kg Q8H for 7 to 14 days.

9.5 GASTROINTESTINAL MANIFESTATIONS

Esophagitis—retrosternal pain on swallowing can be associated with CMV or herpetic esoghageal ulceration, candidiasis, or idiopathic esophageal ulceration. Endoscopy with biopsy is often necessary to confirm diagnosis. Pathogen-directed therapy should then be initiated; idiopathic esophageal ulceration responds to corticosteroid therapy or thalidomide in recalcitrant cases.

Diarrhea—investigation of diarrhea should begin with stool cultures, examination for parasites, and tests for presence of *Clostridium difficile* toxin. The latter is not uncommon in HIV-infected patients because they are often taking antimicrobial agents. Upper gastrointestinal endoscopy with small-bowel biopsy and colonoscopy might be necessary to make a diagnosis, the latter particularly in the case of CMV colitis. Salmonella and campylobacter bacteremia are sometimes found in febrile patients without overt gastrointestinal symptoms. Diarrhea might be an adverse effect of ARV agents, specifically didanosine, nelfinavir, ritonavir, and saquinavir.

Cryptosporidiosis and microsporidiosis—profuse watery diarrhea with profound electrolyte abnormalities is the typical manifestation of cryptosporidial infection in patients with CD4+ cell counts <100/µL. Treatment is supportive with fluid and electrolyte replacement. Paramomycin, 1 gm BID, with azithromycin, 500 mg daily, for 4 weeks followed by paramomycin alone has shown benefit. Microsporidiosis presents in a similar manner. Albendazole, 400 mg BID, for 4 weeks or longer might be of some benefit. Hepatobiliary duct dilation can be seen on ultrasound or CT scan. Diagnosis is made on demonstration of the organisms during stool examination for parasites or small bowel biopsy.

Pancreatitis—elevations in pancreatic enzymes might be noted with didanosine in patients with no symptoms. Clinical pancreatitis can be a serious adverse event. Pancreatitis has also been associated with stavudine, zalcitabine, and lamivudine. Concomitant use of pentamidine increases risk, although pancreatitis is a recognized adverse effect of pentamidine itself.

9.6 MALIGNANCIES

9.6.1 KAPOSI'S SARCOMA

This is the most common malignancy found in patients with HIV infection although incidence has declined over the past 5 years with the introduction of HAART. Human herpes virus 8 (HHV8) has been associated with this malignancy. Lesions are papular and violaceous. Biopsy should be considered to confirm diagnosis. Cutaneous involvment is most common, but lesions can be found on the mucous membranes and involve the lungs, gastrointestinal tract, and lymph nodes. Therapeutic options have included α-interferon, chemotherapeutic agents (liposomal anthrayclines, paclitaxel), and radiation therapy. Dramatic responses with regression of lesions have been noted with HAART.

9.6.2 NON-HODGKIN'S LYMPHOMA

Incidence of this malignancy is higher among patients with HIV infection. It occurs at any CD4+ cell count. Most lymphomas are histologically classified as high-grade. Extranodal disease is common, involving the gastrointestinal tract, bone marrow, liver, and CNS. Primary CNS lymphoma occurs in patients with more advanced immunosuppression, and appears on CT scan as contrast-enhancing lesions that might appear similar to toxoplasmosis. Brain biopsy is essential to confirm diagnosis. Cranial radiation has been recommended for treatment of primary CNS lymphoma. Multiagent reduced-dose chemotherapy or standard dose supplemented with granulocyte colony-stimulating factor (G-CSF), often with intrathecal chemotherapy has been associated with fair response rates.

9.6.3 OTHER MALIGNANCIES

Incidence of Hodgkin's disease appears to be higher among people with HIV infection. Anal neoplasia is linked to human papillomavirus infection, as is cervical neoplasia in HIV+ women.

9.7 DERMATOLOGIC COMPLICATIONS

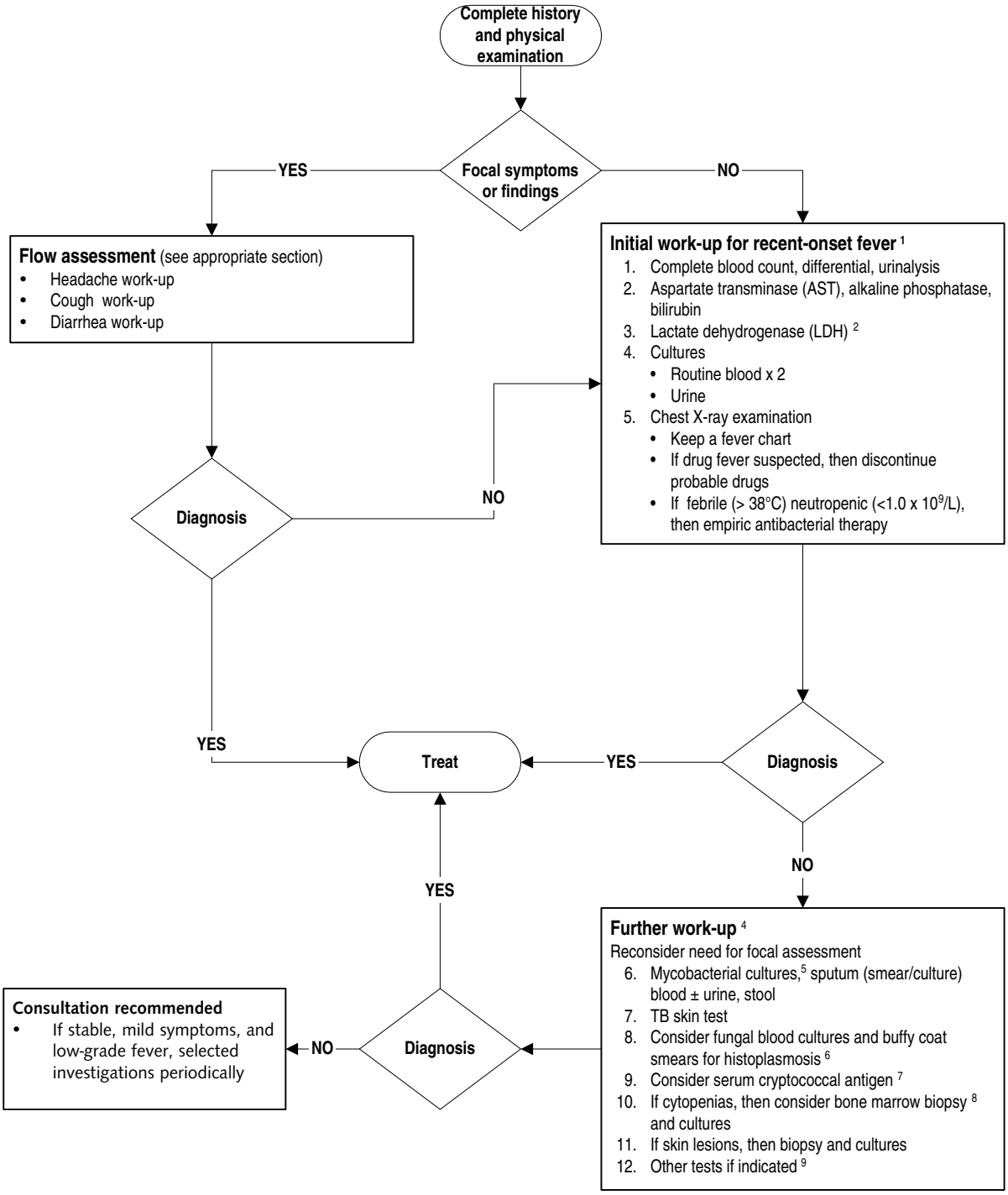
Skin manifestations are often an early indication of underlying HIV infection. Common dermatologic conditions include seborrheic dermatitis, psoriasis, and eosinophilic folliculitis. Molluscum contagiosum usually presents when a CD4+ cell count is < 100/μL.

9.8 SYMPTOM-SPECIFIC APPROACH IN IMMUNOCOMPROMISED HIV-INFECTED PATIENTS (ALGORITHMS)

The following four algorithms were adapted and updated from "A Comprehensive Guide for the Care of Persons with HIV Disease — Module 1: Adults" published by the College of Family Physicians of Canada in 1996.

9.8.1 FEVER AND/OR NIGHT SWEATS

Symptom-specific approach: fever and/or night sweats in immunocompromised HIV-infected patients



Notes

1. Recent onset fevers (eg, < 1 week) might not require anything more than the initial work-up. Patients with more prolonged fevers and no obvious cause should proceed with investigations 1 to 12 from the outset.

2. Elevation of serum lactate dehydrogenase (LDH) is nonspecific, but should prompt consideration of PCP (*Pneumocystis carinii* pneumonia), lymphoma, liver or muscle disease, toxoplasmosis, histoplasmosis, hemolytic anemia, etc.

3. Broad-spectrum antibacterial therapy, eg, imipenem, or ceftazidime or combination therapy (antipseudomonal beta-lactam + aminoglycoside) (*Clin Infect Dis* 1997;25:551)

4. The time interval between "initial" (1-5) and "further" (7-12) work-up depends upon the severity of the illness. In a moderate to severely ill hospitalized patient, "initial" and "further" work-up should be carried out simultaneously in consultation with a qualified specialist (eg, AIDS or infectious diseases).

5. Mycobacterial blood cultures mainly indicated for patients with CD4+ < 100/μL. One blood culture might be inadequate. Positive results can require up to 4 to 6 weeks' incubation. Repeat mycobacterial blood cultures could be needed periodically (eg, after a few weeks) if unexplained fevers continue. In Canada, HIV-related mycobacteremia is commonly due to *M. avium,* but rarely caused by *M. tuberculosis.* Radiographically clear lung fields do not exclude pulmonary TB in HIV-infected patients (*Can Med Assoc J* 1999;161:47*).* If respiratory tract specimen or lymph node is smear-positive for AFB, then treat for *M.tuberculosis* pending culture results.

6. Disseminated histoplasmosis should be considered in patients with history of travel/residence in endemic areas (mainly southern Ontario and Quebec, and the Midwestern USA, particularly the Mississippi River Valley area, certain Caribbean countries and South America)

7. Cryptococcosis is less likely if patient has been receiving long-term daily systemic azoles (ketoconazole, itraconazole, or fluconazole) for conditions such as mucosal candidiasis. However, histoplasmosis could be less successfully prevented by fluconazole 100 mg/day (*AIDS* 1992;6:191). Serum cryptococcal antigen is quite sensitive for extrapulmonary cryptococcosis; sensitivity > 95% for cryptococcal meningitis (*N Engl J Med* 1989;321:794).

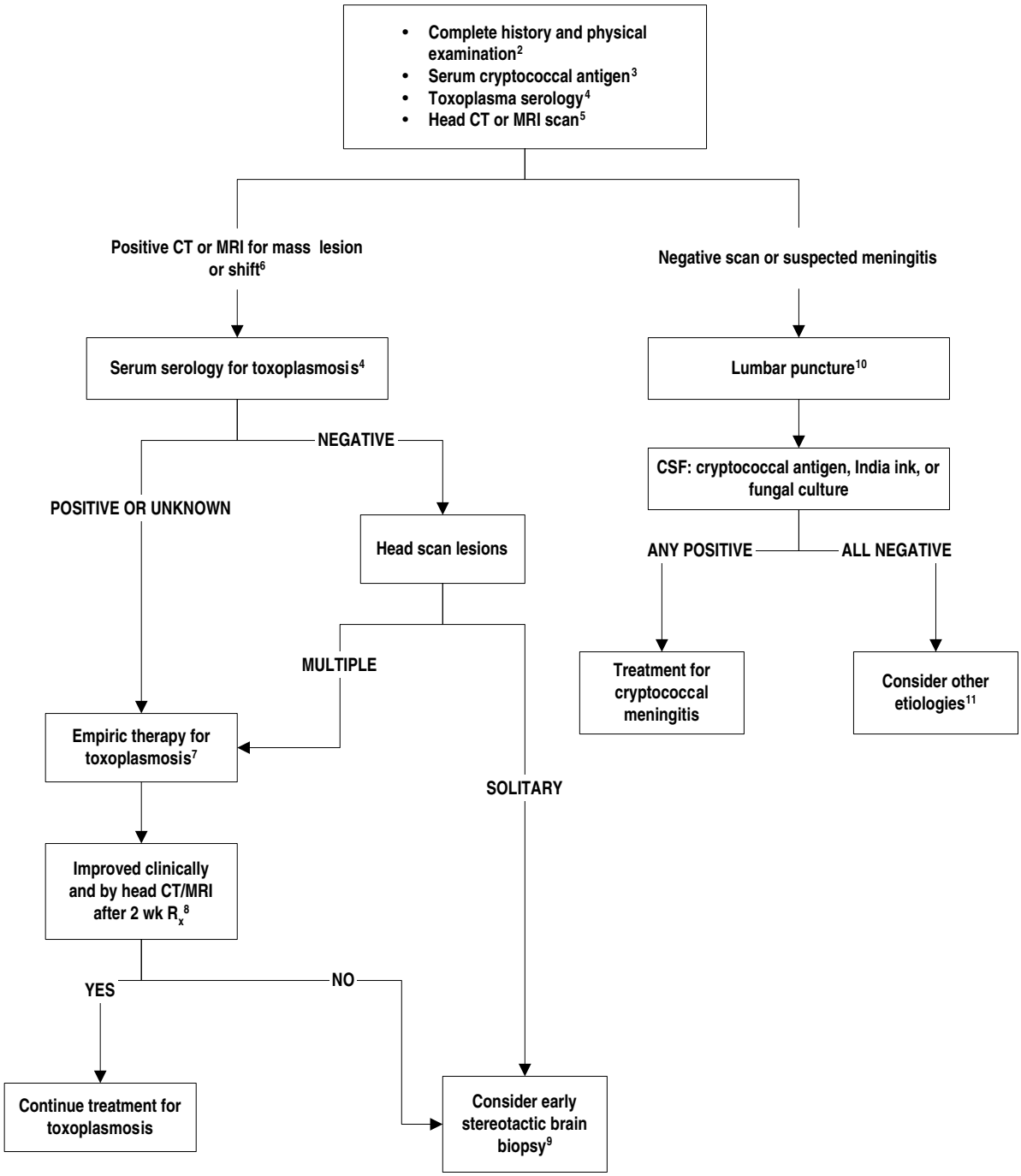
8. Bone marrow (BM) biopsy might detect mycobacterial infection, histoplasmosis, cryptococcosis (easier by serum antigen test), toxoplasmosis, or lymphoma. For HIV+ patients, a diagnosis of opportunistic infection has been made on BM biopsy in 23% and 27% of cases, when the indications for biopsy were fever of unknown origin or cytopenias (neutropenia or anemia), respectively (*Arch Pathol Lab Med* 1991; 115:1125*).*

9. Other tests that might be appropriate include:

   - Gallium scan, technecium bone scan, indium WBC scan
   - Abdominal ultrasound or CT scan, serum amylase/lipase
   - Gastroenterology evaluation with upper GI endoscopy, sigmoidoscopy, and biopsies
   - Needle or open biopsy for histology and cultures of any lesions identified by imaging
   - Positive toxoplasmosis serology (IgG, ±IgM) identifies patient at risk for reactivation disease. Occasionally toxoplasmosis presents as disseminated infection with a sepsis-like syndrome (*Chest* 1993;104:1054)
   - CMV antigenemia and PCR tests sometimes predict development of CMV disease but diagnosis relies on demonstration of characteristic histopathology, virus isolation from appropriate specimens, or typical retinal lesions (*AIDS* 1997; 11:F21)
   - Sinus x-ray examination
   - Liver biopsy: occasionally helpful for patients with unexplained fever, but in general results are seldom useful for HIV-infected patients (*Hepatology* 1987;7:925)

9.8.2 HEADACHES OR CNS DYSFUNCTION

Symptom-specific approach: headaches or CNS dysfunction in immunocompromised HIV-infected patients[1]



Notes

1. Opportunistic infections (eg, cryptococcosis, toxoplasmosis) or neoplasms (primary lymphoma) involving the CNS usually occur only in advanced HIV disease associated with severe CD4+ lymphopenia (ie, < 200/μL).
   - **Differential diagnosis of CNS or mass lesions** include toxoplasmosis, lymphoma, progressive multifocal leukoencephalopathy (PML), and occasionally vascular disorders, syphilis, aspergillosis, cryptococcoma, tuberculoma, or viral encephalitis (CMV, HSV, VZV [*Varicella zoster*]).
   - **Differential diagnosis of diffuse brain disease (without meningitis)** is dependent upon whether alertness is preserved (eg, AIDS dementia complex) or depressed (eg, metabolic/toxic encephalopathies, encephalitic toxoplasmosis, and CMV or *Herpes* encephalitis).

2. Neuropsychologic evaluation might also be indicated regarding AIDS dementia complex (*Arch Neurol* 1991;48:704).

3. The serum cryptococcal antigen assay (CRAG) is a rapid, accurate, and noninvasive method for identifying cases of cryptococcal and meningitis (*N Engl J Med* 1989;321:794) among HIV-infected patients presenting with headache or other neurologic symptoms and signs.
   - Note that most patients with cryptococcal meningitis do not have meningismus.
   - Results of CRAG might be available well before CT/MRI and lumbar puncture. Moderate to severely ill patients with positive CRAG results can be started on empiric systemic antifungal therapy if long delays are anticipated in completing other investigations (CT/MRI and lumbar puncture) because CSF cultures and antigen titres remain positive during the first few days or weeks of treatment.
   - Occasionally cryptococcal antigen titres are falsely positive and usually low titre (eg, < 1:8).

4. **Toxoplasma serology.** AIDS-related *Toxoplasma* encephalitis (TE) is usually reactivation disease, and serum serology for toxoplasmosis (IgG) is useful for identifying those with previous infection (approximately 20% of the general population in North-America [*Medicine* 1992;71:224]) and therefore at risk for reactivation. TE develops in 38% of AIDS patients who are seropositive for *Toxoplasma* antibodies (IgG) (*J AIDS* 1993;6:414). In acute AIDS-related TE, a fourfold rise in IgG or positive IgM titre are usually absent. However, the IgG titre is positive in approximately 84% *(N Engl J Med* 1992; 327:1643) to 97% (*Medicine* 1992; 71:224) of cases, and in association with typical neuroradiographic findings can have a predictive value for diagnosis of acute TE as high as 80% (*Am J Med* 1989; 86:521). Seronegative patients with solitary lesions on head scan should be considered for early brain biopsy, but treated empirically for toxoplasmosis while waiting for a definitive diagnosis.

5. Enhanced CT or MRI should be done urgently, particularly for patients with obtundation, focal neurologic findings, papilledema, or seizures.
   - Other patients presenting with acute onset of fevers and headache associated with neck stiffness (compatible with acute bacterial meningitis) should have a lumbar puncture performed as the initial investigation, provided there are no contraindications (eg, papilledema, focal neurologic deficit, or coagulopathy). In such patients, delays involved in obtaining CT or MRI before lumbar puncture and delay in initiation of empiric antimicrobial therapy could adversely affect outcome.
   - Patients presenting with headache alone or in association with lethargy and confusion should have CT or MRI as the initial investigation. If unacceptable delays (as judged by the urgency of the clinical situation) are involved in obtaining CT or MRI, however, lumbar puncture should be considered, provided there are no contraindications.
   - Sinusitis is common in HIV-infected people, and could be asymptomatic. Radiologic findings of sinusitis might be incidental in HIV-infected patients with headache, and concomitant (unrelated) intracranial pathology might still need to be excluded.

6. **Multiple lesions** demonstrated by CT most likely indicate toxoplasmosis (63%) rather than lymphoma (23%) or progressive multifocal leukoencephalopathy (PML) (14%). A **solitary lesion** on CT usually indicates lymphoma (40%), toxoplasmosis (34%), or PML (8%) (*J Neurosurg* 1991;74:1029). These results do not take into account other radiologic features.

7. **Empiric therapy** should be started if clinical presentation and enhanced CT or MRI are compatible with a diagnosis of CNS toxoplasmosis (*N Engl J Med* 1993;329:995). Steroids should be reserved for patients with life-threatening cerebral edema related to mass lesions. Steroid treatment might be associated with improvement in primary CNS lymphoma, and, therefore, confuse the results of empiric therapy for toxoplasmosis.

8. Consider diagnoses other than toxoplasmosis if further clinical deterioration is noted after 1 week, or if there is no response after 10 days of empiric therapy.

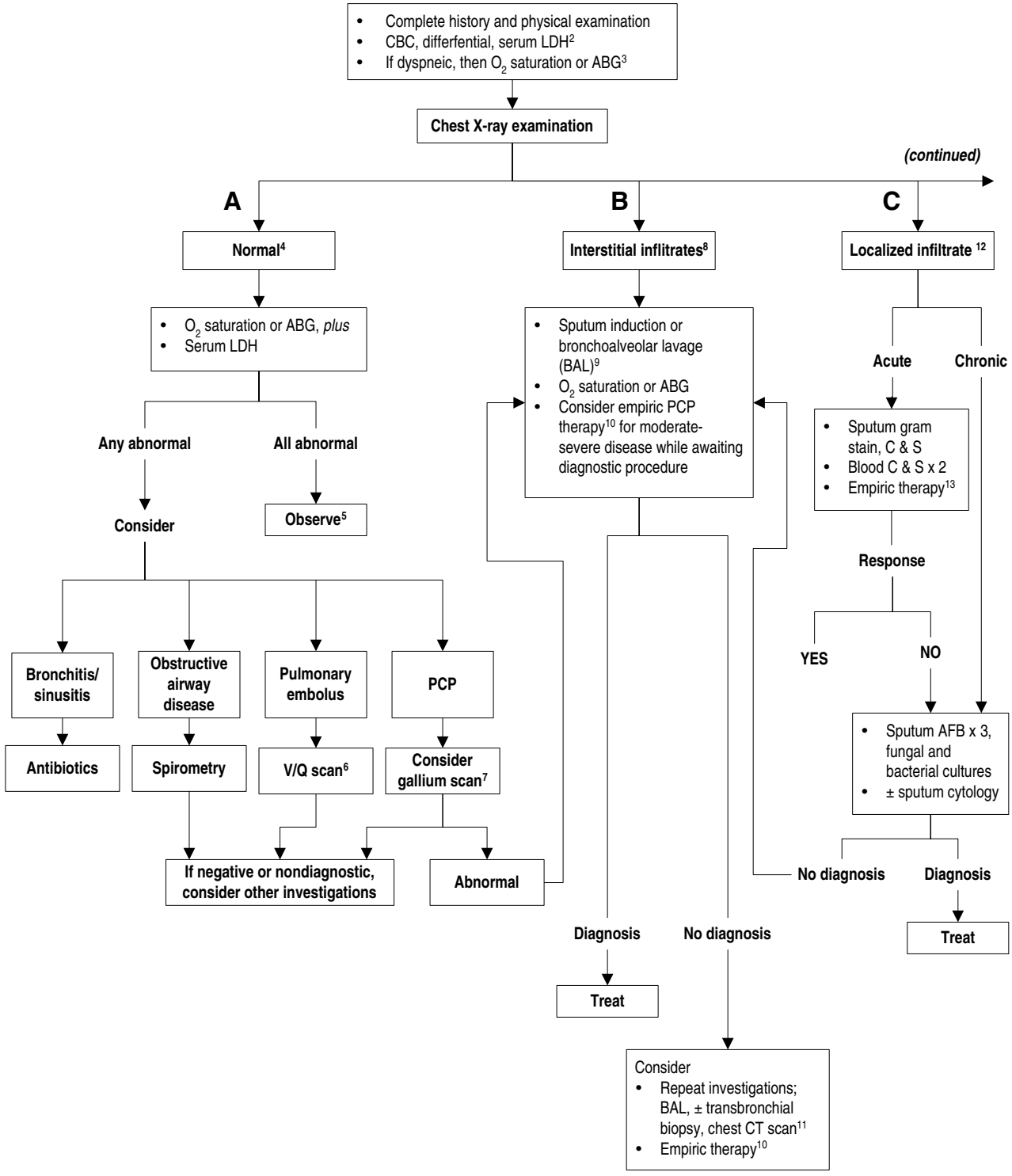
9. **Stereotactic brain biopsy** *(Neurosurgery* 1992; 30:186) is usually not appropriate for patients whose general medical condition and short-term prognosis are poor. Brain biopsy specimens should be examined for cultures and histology. If routine histology is negative, immunoperoxidase or electron microscopy might demonstrate *Toxoplasma* antigens or organisms, respectively. Diagnosis of lymphoma should be confirmed by tissue biopsy. Radiation therapy of primary CNS lymphoma is associated with improvement or stabilization of disease in 85% of patients (*J Neurosurg* 1990;73:206), but cannot be recommended empirically for patients not responding to empiric therapy for toxoplasmosis (*West J Med* 1993;158:249).

10. Lumbar puncture should include opening pressure measurement, cell counts, glucose, protein, gram stain, India ink smear, AFB stain, VDRL, cryptococcal antigen titre, cultures (bacterial, fungal, mycobacterial, ±viral), and cytology, PCR for CMV, JC virus (PML), EBV (lymphoma) (*AIDS* 1997;11:1).

11. Differential diagnosis includes tuberculous meningitis, bacterial meningitis (including *Listeria monocytogenes)*, aseptic meningitis (HIV), neurosyphilis, HIV dementia, *Herpes simplex* or CMV encephalitis, metabolic encephalopathy, Wernicke's encephalopathy, and thrombotic thrombocytopenic purpura.

9.8.3 COUGH AND/OR DYSPNEA

Symptom-specific approach: cough and/or dyspnea in immunocompromised HIV-infected patients[1]



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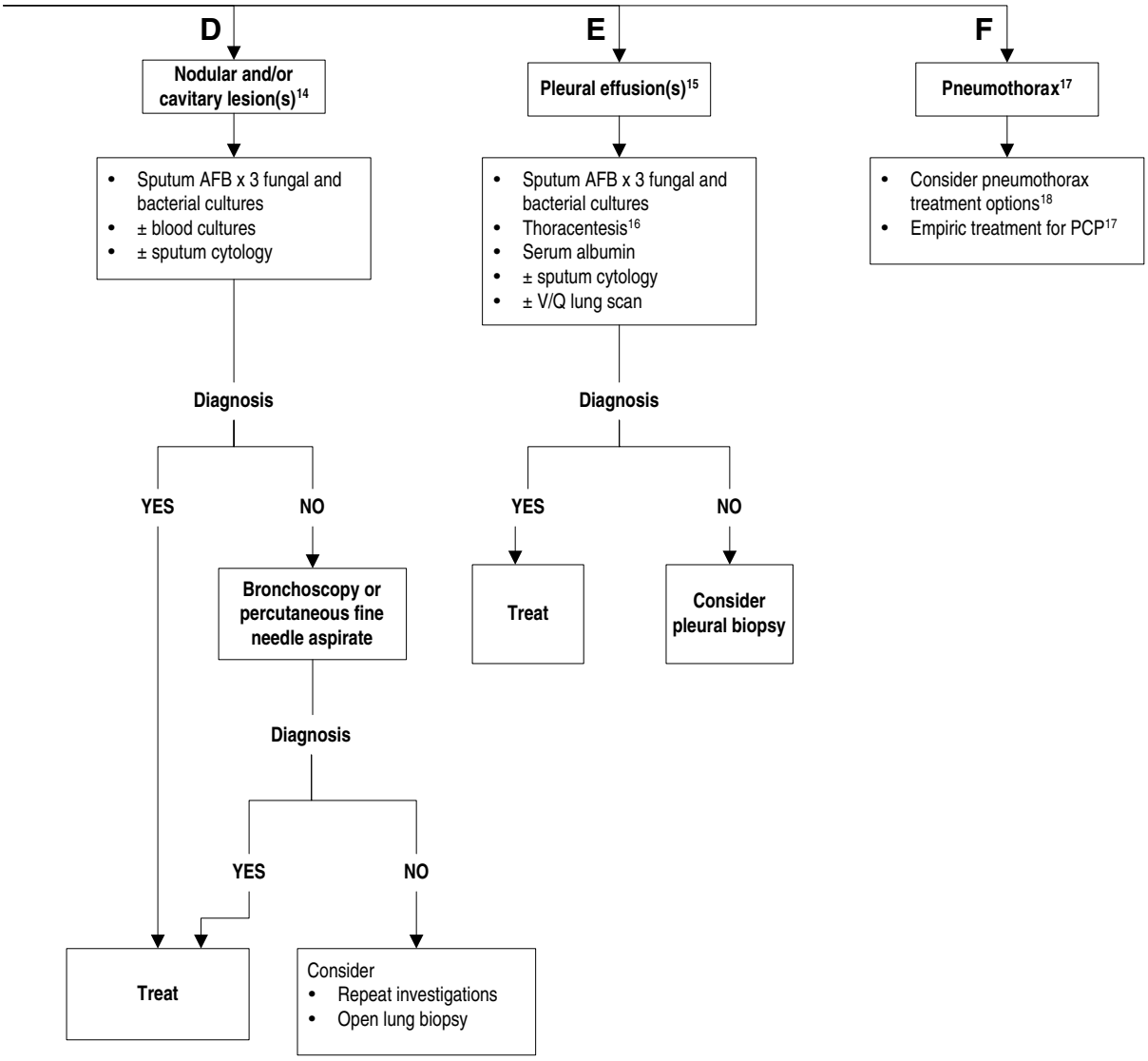

D
Nodular and/or cavitary lesion(s)[14]
• Sputum AFB x 3 fungal and bacterial cultures
• ± blood cultures
• ± sputum cytology
Diagnosis
YES
NO
Bronchoscopy or percutaneous fine needle aspirate
Diagnosis
YES
NO
Treat
Consider
• Repeat investigations
• Open lung biopsy
E
Pleural effusion(s)[15]
• Sputum AFB x 3 fungal and bacterial cultures
• Thoracentesis[16]
• Serum albumin
• ± sputum cytology
• ± V/Q lung scan
Diagnosis
YES
NO
Treat
Consider pleural biopsy
F
Pneumothorax[17]
• Consider pneumothorax treatment options[18]
• Empiric treatment for PCP[17]

Notes

1. A recent (within 3-6 months) absolute CD4+ lymphocyte count is needed to determine the degree of immunodeficiency in patients without prior AIDS-defining diseases. Most episodes of PCP occur in patients with absolute CD4+ counts of < 200/μL (0.2×10^9/L), and rarely when the CD4+ count > 300/μL. (*N Engl J Med* 1990;322:161)

2. **Serum lactate dehydrogenase (LDH)** supports the diagnosis of PCP and is elevated in 95% of patients (*Chest* 1989;95:136). This is nonspecific, however, because it might also be associated with other conditions, including pulmonary embolism, hemolysis, lymphoma, ZDV therapy, cardiac or hepatic injury, disseminated toxoplasmosis, or histoplasmosis.

3. **Oxygen saturation or arterial blood gases** (ABG) should be investigated in dyspneic patients. ABGs might demonstrate hypoxemia, increased A-aO_2 gradient, or acid-base disturbance. Oxygen saturation on room air is considered abnormal if < 97% or if the oxygen desaturation with exercise is > 5%. Single-breath diffusing capacity for carbon monoxide (DLco) is another measure of pulmonary function that is usually abnormal (< 80% of predicted) in PCP, but is often not readily available.

4. **Differential diagnosis** includes PCP, pulmonary embolus, obstructive airway disease, bronchitis, bronchiectasis, metabolic acidosis, and respiratory alkalosis.

5. When oxygen saturation and serum LDH are normal but a patient is dyspneic, ABGs shuld be measured to exclude acid-base disturbance. In severely immunosuppressed patients, consider atypical presentation of TB.

6. Use a ventilation-perfusion (V/Q) lung scan to investigate pulmonary embolic disease, which is more common in HIV-infected patients.

7. **Gallium scan** characteristically shows increased bilateral diffuse uptake in PCP, but it is nonspecific. Isolated perihilar or mediastinal uptake suggest other diagnoses (eg, mycobacterial disease or lymphoma).

8. **Differential diagnosis** includes PCP, viral pneumonia (eg, influenza, occasionally CMV); *Mycoplasma* (and other agents of atypical pneumonitis); lymphoid interstitial pneumonia; nonspecific interstitial pneumonitis; pulmonary edema; adult respiratory distress syndrome; and occasionally cryptococcosis, histoplasmosis, or toxoplasmosis.

9. **Sputum induction** is specific but less sensitive than bronchoalveolar lavage (BAL) for diagnosis of PCP (*N Engl J Med* 1988;318:589). BAL specimens should be examined for bacteria (gram stain), PCP (toluidine blue or methenamine silver, etc), AFB (Ziehl-Neelsen stain or auramine-rhodamine), and fungi (lactophenol cotton blue) and cytology. Bacterial, mycobacterial, and possibly viral and fungal cultures are indicated. Diagnosis of PCP is more difficult in patients receiving aerosol pentamidine because of more frequent atypical radiologic and gallium scan findings and reduced yield of approximately 60%, compared with > 90% with BAL (*Ann Intern Med* 1990;112:750).

10. Empiric therapy in patients with bilateral diffuse interstitial (±airspace) infiltrates should be directed against PCP (if LDH is elevated and CD4+ count < 300) and/or other agents of atypical pneumonitis (eg, *Mycoplasma*, etc). One such regimen could be trimethroprim-sulfamethoxazole (TMP-SMX) with or without clarithromycin or azithromycin.

11. Chest CT-scan might be of some help in differentiating HIV-related pulmonary disorders, but requires an experienced observer.

12. **Differential diagnosis** includes bacterial, (including Legionella), mycobacterial, nocardia or fungal pneumonia; PCP; pulmonary infarction; and malignancy (Kaposi's sarcoma, lymphoma). Concomitant PCP occurs in 10% of HIV+ patients with bacterial pneumonia.

13. Culture and sensitivities of sputum and blood should be obtained if presentation is compatible with acute bacterial pneumonia. Empiric therapy should be directed against the predominant organism (if seen) on sputum gram stain. If sputum gram stain is unhelpful or unavailable, apply empiric treatment against community-acquired pathogens (eg, *Pneumococcus, Hemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* and agents of atypical pneumonitis such as *Mycoplasma,* and *Legionella,* with levofloxacin alone or TMP-SMX or cefuroxime ±clarithromycin or azithromycin. TMP-SMX is an ideal choice when PCP remains a consideration. (Note that high-dose TMP-SMX is required for PCP.) If a patient has hospital-acquired pneumonia, apply empiric treatment against nosocomial

pathogens (eg, *Enterobacteriaceae*, *Pseudomonas, S. aureus,* etc).

14. **Differential diagnosis** includes mycobacterial disease, fungal infections (eg, aspergillosis, cryptococcosis, occasionally endemic mycoses); necrotizing bacterial pneumonia; right-sided endocarditis; nocardiosis; and malignancy. PCP may be associated with cystic lesions, pneumatoceles, and thin-walled cavities (rarely thick-walled).

15. **Differential diagnosis** includes parapneumonic effusion or empyema; mycobacterial or fungal infection (eg, cryptococcosis, aspergillosis); hypoalbuminemia; congestive heart failure; malignancy (eg, Kaposi's sarcoma); and occasionally pulmonary embolism (*Ann Intern Med* 1993;118:856).

16. Thoracentesis specimens should be sent for cell count and gram stain, cultures (aerobic/anaerobic, mycobacterial, fungal, ±viral), and cytology. Serum LDH, total protein, and glucose should also be measured.

17. Pneumothorax develops in approximately 2% of AIDS patients, more frequently among those with a history of PCP and particularly among patients receiving aerosol pentamidine prophylaxis when PCP develops (*Ann Intern Med* 1991;114:455). Patients receiving aerosol pentamidine who develop pneumothorax should receive empiric treatment for PCP.

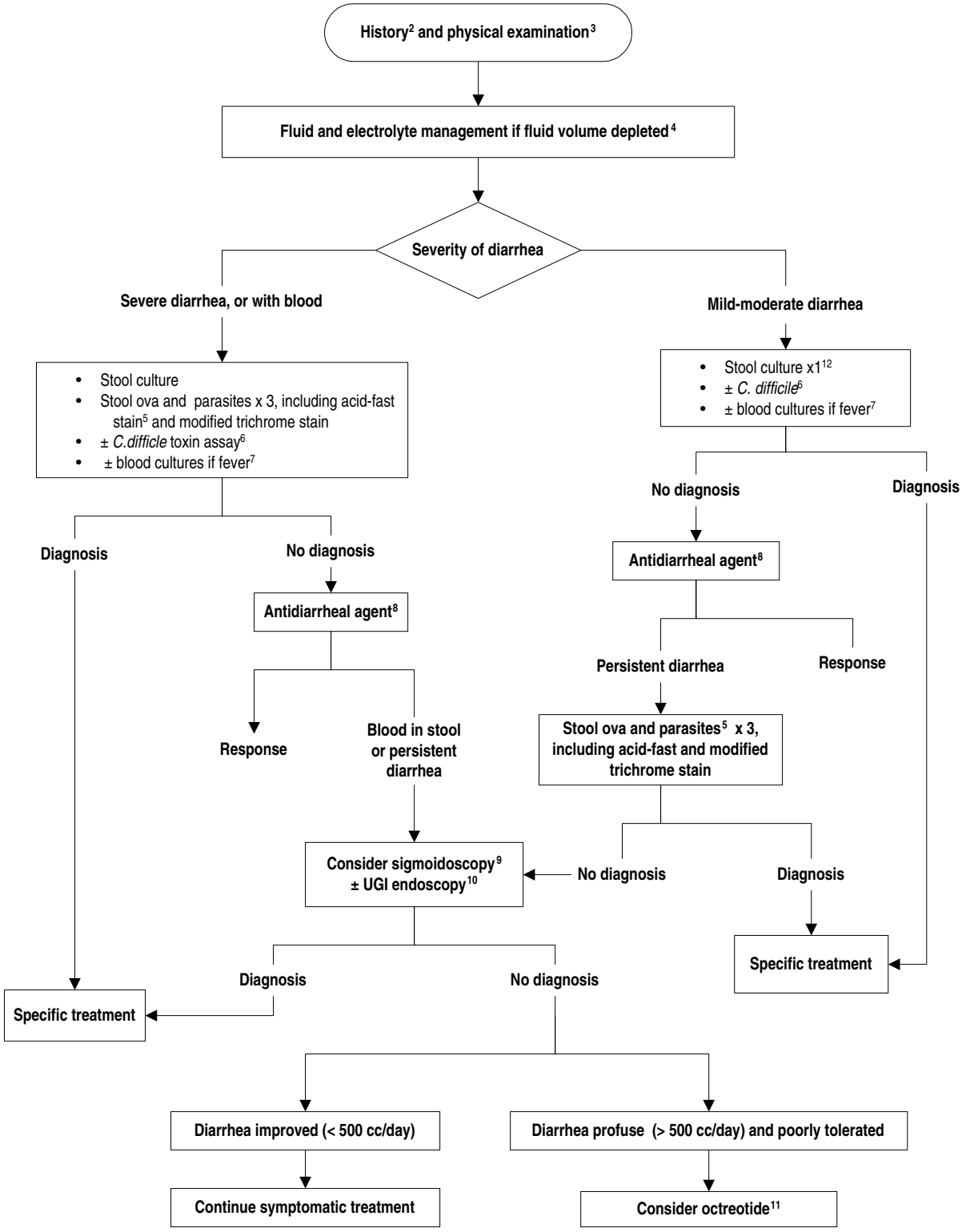
18. Treatment options for pneumothorax include:

    - observation,
    - chest tube, and
    - pleurodesis following lung re-expansion (eg, pleural space installation of tetracycline, bleomycin, or talc).

    If there is a bronchopleural fistula with persistent pneumothorax, consider bronchoscopy-directed plugging of the involved bronchus; pleuroscopic repair; or thoracotomy with resection of involved lung, or pleural stripping (*Arch Surg* 1991;126:1272).

9.8.4 DIARRHEA

Symptom-specific approach: diarrhea in immunocompromised HIV-infected patients[1]



Notes

1. Opportunistic infections involving the gastrointestinal tract, such as *Mycobacterium avium* or cytomegalovirus (CMV), usually occur in patients with absolute CD4+ counts < 100/μL. Cryptosporidiosis is infrequently self-limited if CD4 count is < 200/μL *(Ann Intern Med* 1992;116:840).

2. Inquire regarding:
   - Use of diarrhea-inducing drugs and caffeinated beverages
   - Recent antibiotic use (*C.difficile)*
   - Sexual activity (people who have receptive anal sex are at risk for proctitis due to *Herpes simplex*, gonococcus, *Chlamydia*, and syphilis)
   - Ingestion of inadequately cooked seafood (eg, Vibrio, Norwalk-like viruses)
   - Travel to tropical areas (eg, enterotoxigenic *E. coli, Giardia, Entamoeba histolytica, Strongyloides,* Norwalk-like viruses or rotavirus, and invasive bacterial infections)
   - Bloody diarrhea (eg, *E. coli* 0157, amebiasis, *campylobacter*, CMV, *shigella*)

3. Physical examination should include assessment of intravascular volume, including supine/standing blood pressure and pulse, and jugular venous pressure.

4. Initial management for fluid volume-depleted patient should be oral or intravenous fluids and electrolytes. A simple oral rehydration solution consists of 1 level teaspoon of table salt, plus 4 heaping teaspoons of sugar, added to 1 litre of water (*J Trop Med Hyg* 1981;84:73). Give volume equivalent to 5% to 7% of body weight for mild-moderate dehydration.

5. Stool acid-fast staining is needed for identification of *Cryptosporidium* and *Isospora belli.* Stool smear for acid-fast bacilli, however, is not routinely recommended because of variable results of sensitivity and specificity for true mycobacterial infection versus colonization. Positive stool smear might be more likely than mycobacterial stool culture to reflect invasive infection rather than colonization.

   Modified trichrome stain is the optimal method for light microscopy identification of microsporidia in stool and duodenal aspirate sample *(N Engl J Med* 1992;326:161).

   E. histoytica is a nonpathogenic commensal in most infected homosexual men (*N Engl J Med* 1986; 315:353) and rarely causes invasive colitis in AIDS patients.

6. If recent antibiotic use, then also include *C. difficile* toxin assay.

7. Routine blood cultures should be obtained for patients with fever and diarrhea to exclude bacteremia due to *salmonella, shigella*, and *campylobacter*. Salmonellosis is 20 times more common in AIDS patients and five times more likely to be associated with bacteremia than in the general population (*J Infect Dis* 1987;156:998). Mycobacterial blood cultures are indicated if persistent or recurrent fever develops in association with CD4+ lymphopenia.

8. The antidiarrheal agent of choice is loperamide (Imodium), which is not associated with narcotic dependency, as is diphenoxylate (Lomotil) (*Gastroenterology* 1980;79:1272). Diarrhea and abdominal cramps respond earlier with loperamide than bismuth subsalicylate (*JAMA* 1986;255:757). Antimotility agents should usually be avoided in patients with fever or bloody stools, because they may worsen dysentery due to *shigella (JAMA* 1973; 226:1525) or *C. difficile* (*JAMA* 1976;235:1454). Loperamide dosing: 4 mg initially, then 2 mg after each unformed stool (maximum 16 mg/day). When a daily dose is established, then it is given as 1 to 4 divided doses/day. (*Clin Infect Dis* 2000;30:908-14)

9. Sigmoidoscopy specimens should include wet mount (*E. histolytica).* Biopsies are obtained for pathology, viral (CMV, adenovirus, *Herpes simplex)* and mycobacterial culture. Barium enema and colonoscopy are seldom useful for investigation of chronic diarrhea in HIV-infected patients (*AIDS* 1990;4:687).

10. Upper gastrointestinal endoscopy for duodenal fluid specimens should be sent promptly for parasitology (wet mount, acid-fast, and modified trichrome stains), and biopsies for hematoxylin and eosin (H & E), acid fast, ±Giemsa stains looking primarily for protozoa (microsporidia, *Isospora, Giardia)*, mycobacteria, and CMV.

11. Octreotide (sandostatin) is a synthetic analog of somatostatin, and in dosages of 50 to 500 μg subcutaneously three times daily might provide benefit in severe refractory AIDS-associated watery diarrhea, particularly when no pathogens have been identified (*Ann Intern Med* 1991;115:705).

12. Initial investigation of mild-moderate AIDS-related diarrhea should be limited to a stool culture (*Ann Intern Med* 1990;112:942). More extensive investigations, which are expensive and might be associated with patient discomfort, should be reserved for those with a negative stool culture and persistent diarrhea despite symptomatic antidiarrheal treatment. Certain ARV agents however, particularly didanosine, nelfinavir and ritonavir, are associated with diarrhea. (*Clin Infect Dis* 1999;28:701-7)