The goal of this program is to improve diagnosis and treatment of neuroinfectious diseases. After hearing and assimilating this program, the clinician will be better able to:

1. Diagnose early and late forms of neurosyphilis.
2. Recognize common manifestations of neurocysticercosis.
3. Manage a patient with neuroschistosomiasis.
4. Provide appropriate treatment regimens for tuberculosis of the CNS.
5. List the five criteria that justify limiting autonomy and allowing a governmental body to impose a quarantine.

Educational Objectives

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, the following was disclosed: Dr. Marra receives royalties from Wolters Kluwer Health and UpToDate, Inc, and receives research support from the National Institutes of Health. Dr. Thakur serves as a consultant for the World Health Organization. Dr. Webb has received personal compensation for speaking engagements from C. R. Bard, Inc, and provided expert legal testimony and case review for Sturgill, Turner, Barker & Moloney, PLLC. Unlabeled Use of Products/Investigational Use Disclosure: Dr. Marra discusses the unlabeled/investigational use of antibiotics, including ceftriaxone and doxycycline, for the treatment of neurosyphilis. Drs. Thakur and Webb report nothing to disclose. To view disclosures of planning committee members with relevant financial relationships, visit: audidigest.org/continuumaudio/committee. All other members of the planning committee report nothing to disclose.

Expiration: This CME activity qualifies for AMA PRA Category 1 Credit™ for 3 years from its date of publication.

Term of approval for use of Continuum Audio as a Self-Assessment Activity for the ABPN MOC program expires March 14, 2017.

Estimated time to complete this educational activity:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review Educational Objectives and Faculty Disclosure</td>
<td>5 min</td>
</tr>
<tr>
<td>Take pretest</td>
<td>10 min</td>
</tr>
<tr>
<td>Listen to audio</td>
<td>1 hr</td>
</tr>
<tr>
<td>Review complete written summary</td>
<td>35 min</td>
</tr>
<tr>
<td>Take posttest</td>
<td>10 min</td>
</tr>
</tbody>
</table>

Continuum Audio pretests and posttests can be completed online at: www.audidigest.org/onlinetesting. Note: Use of this issue of Continuum Audio for MOC Self-Assessment credit requires that you utilize online testing for both the pretest and posttest.
Neurosyphilis

Christina M. Marra, MD, FAAN, Seattle, WA

Epidemiology: Syphilis-reportable disease in United States and other countries; incidence of syphilis has increased since 2000, especially among men who have sex with men; neurosyphilis may be more common in patients with HIV.

Pathophysiology: *Treponema pallidum* highly neuroinvasive and may be found in CSF in early syphilis; however, some patients clear spirochete or experience transient meningitis followed by clearance; patients who cannot clear organism remain at risk for symptomatic forms of neurosyphilis; mechanism of clearance from CSF may be similar to that in periphery (ie, opsonization and ingestion by macrophages).

Clinical manifestations: Neuroinvasion that does not clear may lead to asymptomatic meningitis or asymptomatic neurosyphilis (abnormalities in CSF in absence of clinical findings); clinically evident neurosyphilis develops in ~30% of such patients, if untreated; early forms more common and affect meninges, spinal fluid, and vasculature; late forms affect brain and parenchyma of spinal cord.

Early forms: Most commonly seen; characterized by typical symptoms of aseptic meningitis, including loss of vision or hearing, or vascular disease with stroke affecting brain, spinal cord, or vascular system (meningovascular syphilis); early forms seen weeks to years after onset of infection; most cases of meningovascular syphilis occur in patients with secondary syphilis.

Late forms: Uncommon; appear years to decades after primary infection; include general paresis, rapidly progressive dementia, and tabes dorsalis; *tabes dorsalis* — form of neurosyphilis that takes longest time to develop after primary infection (typically, 20 years or more); causes injury to posterior column; CSF may be normal, which suggests parainfectious process; dysfunction of posterior column accompanied by sensory ataxia, loss of vibration sense, loss of vision, lightning pains, sensory loss in pseudoradicular distribution (eg, over elbows or knees), urinary and bowel dysfunction, optic atrophy, and Argyll Robertson pupil.

Serologic tests: *Treponemal tests* — include fluorescent treponemal antibody absorption (FTA-ABS), *T pallidum* particle agglutination assay (TPPA), and several specific enzyme immunoassays that measure antibodies to *T pallidum*; *nontreponemal tests* — include Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR); these tests measure antibody to cardiolipin-lecithin-cholesterol antigen; nontreponemal tests reflect nonspecific tissue injury and disease activity; interpretation — patient with positive nontreponemal test needs confirmation with treponemal test; false-positive findings on VDRL or RPR associated with drug abuse, aging, pregnancy, and collagen vascular disease; rash or chancraceous eruption may lead to false-positive diagnosis of syphilis, but neurologist more likely to encounter other presentations (eg, meningitis, stroke, dementia); unlike nontreponemal tests, treponemal tests remain reactive for life; US Centers for Disease Control and Prevention (CDC) recommends reverse testing algorithm beginning with treponemal test; if treponemal test positive, nontreponemal test may be performed using inexpensive automated enzyme immunoassay; nontreponemal immunoassays good screening tests with high negative predictive value; positive test must be confirmed with immunoassay using different antigen, TPPA, or FTA-ABS; when symptomatic neurosyphilis suspected, treponemal test should be performed first; negative treponemal test rules out neurosyphilis.

Diagnosis: If neurosyphilis suspected and treponemal test positive, lumbar puncture should be obtained to assess white and red cells, glucose, and protein, and to perform VDRL; VDRL of CSF specific but not sensitive; VDRL of CSF negative in 30% to 70% of patients with neurosyphilis; however, normal CSF not expected in patients with neurosyphilis; to make diagnosis of neurosyphilis, patient should have reactive VDRL in CSF, white blood cell pleocytosis, or elevated protein; however, presence of hearing or vision loss in patient with reactive serum treponemal test suggests neurosyphilis, even if CSF negative.

Imaging: May be negative; patients with meningo(vascular) disease have cortical or subcortical stroke; *two patterns suggesting neurosyphilis* — (1) increased signal on fluid-attenuated inversion recovery or diffusion-weighted images in one or both medial temporal lobes; findings mimic herpes encephalitis; (2) CNS gumma (focal accumulation of meningeal inflammation that may resemble meningioma); lesion may enhance, dip into sulci, and have dural tail or nodular component.

Management: CDC recommends either high-dose IV penicillin (4 million U IV every 4 hours) for 10 to 14 days or 24 million U daily given as continuous infusion; outpatient regimen includes 2.4 million U IM procaine penicillin daily for 10 to 14 days, given with oral probenecid 500 mg 4 times daily; outpatient regimen not appropriate for patients with allergies to sulphonamides; ceftriaxone not recommended by CDC, but 2 g IV daily effective and included in European guidelines; high-dose doxycycline (200 mg twice daily for 28 days) removed from European guidelines; doxycycline regimen not recommended but may be used if patient refuses parenteral therapy; *patients with allergy to penicillin* — CDC recommends desensitization; ceftriaxone may be used for patients without serious allergy.
Prognosis of neurosyphilis: With early treatment, good outcomes seen in patients with neurosyphilis; patients with meningitis or hearing or visual loss may recover completely if treated early; however, patients with strokes usually have sequelae; dementia or tabes dorsalis may stabilize or improve, but most patients remain disabled.

Monitoring: CDC recommends lumbar puncture and follow-up every 6 months until abnormalities of CSF resolve; as most patients normal by 3 to 4 months after treatment, first lumbar puncture at 3 months reasonable, followed by additional procedures at 6-month intervals until white cells normalize and VDRL of CSF nonreactive; protein need not be followed (nonspecific because elevation may persist for long period).

Immigrants: Neurologist may encounter patients from Africa or Southeast Asia with positive serum treponemal test, negative non treponemal test, and cognitive impairment; serum treponemal tests may be positive in patients who have had other treponemal diseases, such as yaws (common disease in parts of Africa and Asia; causes skin disease in childhood; most adults do not recall their infection); in such patients, determining whether patient had syphilis or yaws not possible; if dementia of short duration and no other explanation exists, lumbar puncture to look for evidence of neurosyphilis reasonable.

Evaluation of dementia: Guidelines from American Academy of Neurology no longer recommend routine screening for syphilis in patients with dementia; however, in patients at risk, such as those with HIV, screening should be performed; speaker recommends low threshold for screening; dementia of syphilis often rapidly progressive.

Tropical Neuroinfectious Diseases

Kiran Thakur, MD, New York, NY

Overview: Tropical and subtropical diseases spreading internationally as people travel and emigrate and climate patterns change.

Neurocysticercosis: Case — middle-aged Laotian immigrant presented with first-time seizure; neurologic examination normal, but CT showed several calcified cysts in brain; epidemiology — common in Central and South America, sub-Saharan Africa, and Asia; 50 million persons infected worldwide; among these, 2.1 to 7.7 million have epilepsy that may be associated (globally, most common preventable cause of epilepsy); in United States, large proportion of reported cases in southwestern regions, in which many immigrants from Central and South America reside; pathophysiology — manifests as parenchymal or extraparenchymal disease; case patient has parenchymal disease with multiple calcified cysts; patients with extraparenchymal disease may have intraventricular, subarachnoid, intraocular, or spinal cord disease; tissue cysticerci appear 3 to 8 weeks after ingestion of eggs of *Taenia solium* and may remain dormant for years; parasite evades destruction by inhibiting immune system of host; clinical manifestations — immune response accompanied by inflammation around cysts and symptoms; seizures most common presentation in patients with parenchymal disease; in patients with intraventricular disease, intracranial pressure often increased because of obstructive hydrocephalus; patients with subarachnoid disease may have diffuse encephalopathy; disease of spinal cord less common and may present with myelopathy.

Diagnosis of neurocysticercosis: History — detailed history should assess living situation, exposure, and symptoms (eg, visual changes, headaches, nausea, vomiting, systemic illness); immunocompetence should be assessed; imaging — infection occurs in several phases; scolex of cyst most pathognomonic feature; seizures associated with scarring of calcified lesions in parenchyma of brain; laboratory tests — enzyme-linked immunoelectrotransfer blot assay has high sensitivity and specificity; other tests — because cysticercosis often invades tissue, muscular involvement may be visible on imaging.

Management of neurocysticercosis: Patient described in case received anticonvulsant medication and referral to infectious disease clinic; calcified cysts inert and do not require antiparasitic treatment; however, patients who develop seizures related to these areas may require long-term antiepileptic medications; viable cysts treated with albendazole or praziquantel (combination may be superior to monotherapy); in patients with numerous viable cysts, steroids should be given concurrently with antiparasitic treatment; *intraocular cysts* — may lead to visual loss and retinal detachment, so all patients should undergo ophthalmologic examination; surgery required before initiation of antiparasitic treatment.

Schistosomiasis: Has two presentations, depending on species of organism; cerebral presentation most common with *Schistosoma japonicum*; with *Schistosoma mansoni*, most common presentation subacute to acute myelopathy; history of exposure important in establishing diagnosis; schistosomiasis transmitted through larvae released from the intermediate snail host in fresh water in endemic regions of Southeast Asia, Africa, Caribbean, and South America; cerebral form has several presentations, including focal neurologic deficits, weakness, sensory symptoms, or seizures; diagnosis of cerebral form made with ancillary testing of stool and urine, neuroimaging, and blood tests.

Management of schistosomiasis: Usually treated with praziquantel; oxamniquine and artemisinin may be used for *S mansoni*; recommendations for duration of treatment range from 1 day to 2 weeks; duration of treatment should be longer for travelers without previous exposure to schistosomiasis; praziquantel effective for persons exposed to fresh water 4 to 7 weeks earlier; earlier treatment
less effective because worm has not had time to travel beyond liver.

Prognosis of neuroschistosomiasis: Patients diagnosed early have good prognosis; however, disease disseminated throughout CNS may occur as parasite travels through spinal cord via venous system, leading to poor prognosis; patients from endemic regions with multiple exposures or chronic infection may have poor prognosis, cognitive impairment, and devastating myelopathy; goal to diagnose and treat before organism enters CNS; in patients with liver dysfunction, urine and stool should be tested for *Schistosoma hematobium*.

Cerebral malaria: Two populations affected by cerebral malaria, and these present differently; children — in sub-Saharan Africa, disease most often presents in children under 5 years of age, who develop fever followed by rapidly progressive coma, status epilepticus, anemia, renal dysfunction, and/or highly elevated lactate; mortality rate 15% in these children; survivors recover rapidly, but one-third have sequelae such as epilepsy, motor signs and symptoms, or movement disorder; malarial retinopathy with orange pigmentation of retinal vessels highly sensitive and specific for infection in children; adults — often present with multiorgan failure and cerebral dysfunction related to systemic involvement; diagnosis of cerebral malaria may be challenging in patients from endemic areas, who may have incidental findings of malarial parasitemia (retinal findings useful in such patients).

Management of cerebral malaria in children: Treatment of choice IV artemesunate, based on randomized controlled trials comparing agent with quinine; management may require antiepileptic agents, correction of hypoglycemia, and monitoring for hemodynamic instability.

Tuberculosis of CNS: Populations at risk include immunosuppressed patients (those with, eg, HIV infection, transplantation, cancer); children under 5 years of age more susceptible to disseminated tuberculosis, including tuberculosis of CNS; history of exposure (eg, dwelling in crowded areas, travel to endemic regions) important; patients classically present with subacute to chronic basal meningitis with multiple cranial neuropathies and may develop strokes of basal ganglia, midbrain, or upper brainstem; tuberculosis should be suspected in patient with preexisting cough, meningismus, and fever; tuberculosis common cause of meningitis in children in southern Africa; tuberculosis in CNS has variety of presentations (eg, in spinal cord, causing myelopathy; or focally, causing cranial neuropathies).

Diagnosis of tuberculous meningitis: White cells, glucose, and protein in CSF should be assessed; white blood cell count often elevated (100 cells/μL); lymphocytosis common, but increased polymorphonuclear leukocytes may be seen in early infection; elevated protein and low glucose nonspecific signs of infection; PCR-based examination (CSF GeneXpert) — endorsed by World Health Organization for diagnosis of pulmonary tuberculosis in serum; use in CSF currently under investigation; detects resistance to rifampicin (rising rates of resistance to rifampicin in endemic areas concerning because, among drugs in four-drug regimen, rifampicin best penetrates CSF).

Management of tuberculosis in CNS: Treated with rifampicin, isoniazid, pyrazinamide, and ethambutol; therapy includes intensive and continuation phases; 9 to 12 months of treatment recommended for CNS tuberculosis; doses same for pulmonary and extrapulmonary disease; recent studies have assessed use of higher doses of rifampicin, IV rifampicin, and substitution of moxifloxacin for ethambutol in intensive phase (because ethambutol poorly penetrates CSF); these regimens associated with 60% decrease in mortality and currently being investigated in patients infected with HIV and in children.

Dengue: May be difficult to diagnose; may present with shock, hemorrhagic fever, encephalopathy, isolated CNS infection, Guillain-Barré syndrome, neuropathy, and radiculopathy; may present similarly to viral encephalitis; supportive therapy only available treatment.

Summary: Resources available from CDC, local and state governments, and physicians in endemic regions familiar with tropical infections.

Quarantine, Isolation, and Health Care Workers

Adam Webb, MD, Atlanta, GA

Case: In response to public concern over spread of Ebola virus, several states instituted mandatory 21-day quarantines for health care workers returning from West Africa who had contact with patients with Ebola virus; nurse who had treated patients with Ebola virus in Sierra Leone registered low-grade fever on forehead scanner at US customs for health care workers returning from West Africa with tropical infections.

Social distancing: Refers to public health strategies to reduce frequency of person-to-person contact, with intention of limiting transmission of disease; two major strategies quarantine and isolation; quarantine — restricting movement of healthy individuals exposed to communicable diseases; usually imposed for defined period of time; isolation — separation of persons with infection or probable infection; other strategies — include limiting travel, closing schools, canceling public gatherings, and encouraging nonessential workers to stay at home.

History of quarantine: Dates from period of Black Death in 14th century, when arriving ships had to remain at anchor for 40-day period before unloading personnel or goods; in United States, quarantines have been used to prevent spread of epidemics (eg, yellow fever, cholera).
Authority for quarantines: Mandated quarantines legal; in its review of *Jacobson v Massachusetts* in 1905, Supreme Court upheld statutes of states intended to preserve public health and safety; Public Health Service Act of 1944 established authority of federal government to institute quarantine for preventing spread of communicable diseases from foreign countries; responsibility for quarantines shared by states and federal government; per Tenth Amendment, states may control public health emergencies within their borders, but federal government regulates foreign and interstate commerce; recent acts of bioterrorism led to Model State Emergency Health Powers Act, which attempted to reduce variability among states in responses to public health emergencies.

Discriminatory use of quarantine and isolation: Examples of ethnic and gender discrimination occurred during quarantines imposed for bubonic plague in early 1900s and during World War I; at beginning of AIDS epidemic, some parties called for isolation of infected individuals, and some infected children isolated from school.

Ethical principles: Include autonomy and justice; to justify limiting autonomy for greater good, five criteria must be met; *evidence of harm* — must be clear and measurable harm to others if autonomy not restricted; *least-restrictive means* — least-restrictive means of limiting autonomy should be used; limitation of autonomy should be voluntary when possible; mandatory restrictions should be imposed only in case of noncompliance; *reciprocity* — when individual asked to curtail liberties for common good, society should provide assistance in meeting basic needs including food, shelter, psychological and medical support; affected individuals should be discharged from other obligations; ie, individual should not receive penalty for limiting their autonomy; *transparency* — public officials must clearly communicate justification for limitation of autonomy and allow for process of appeal; protocols should be established before public health crisis occurs; *equity* — restrictions to autonomy should be applied equally.

Ebola quarantines: Recent quarantines in United States ethically troubling; rationale for quarantine not based in science; only symptomatic individuals with Ebola virus contagious; Ebola spread only by contact with bodily fluids; mandatory quarantine implemented without first attempting less restrictive voluntary quarantine; quarantine of health care workers treating patients with Ebola virus abroad inequitable if health care workers treating patients with Ebola in United States not subject to same restrictions.

Responsibilities of health care workers: American Medical Association condones participation of health care workers in implementing quarantine and isolation measures during epidemics but cautions that interest of individual patients takes precedence over concerns about public health; physicians with communicable illnesses should stay home from work; physicians should obtain recommended vaccinations for influenza and other diseases.

Suggested Reading

**Neurosyphilis**

**Tropical Infectious Diseases**

**Quarantine, Isolation, and Health Care Workers**
1. The late form of neuroinvasive syphilis typically affects which of the following?
   (A) CSF
   (B) meninges
   (C) parenchyma of spinal cord
   (D) vasculature

2. Which of the following is recommended by the US Centers for Disease Control and Prevention for patients with syphilis who are allergic to penicillin?
   (A) ceftriaxone
   (B) desensitization
   (C) doxycycline
   (D) probenecid

3. Which of the following manifestations of neurosyphilis is most likely to result in permanent disability among patients who received early treatment?
   (A) hearing loss
   (B) meningitis
   (C) tabes dorsalis
   (D) vision loss

4. Which of the following is the most common preventable cause of epilepsy worldwide?
   (A) cerebral malaria
   (B) dengue fever
   (C) neurocysticercosis
   (D) neuroschistosomiasis

5. Patients infected with Schistosoma mansoni are most likely to present with which of the following?
   (A) acute myelopathy
   (B) focal neurologic deficits
   (C) seizures
   (D) stroke affecting basal ganglia

6. Which of the following is the usual treatment for schistosomiasis?
   (A) albendazole
   (B) artemisinin
   (C) oxamniquine
   (D) praziquantel

7. Orange pigmentation of retinal vessels is highly sensitive and specific for which of the following infections?
   (A) cerebral malaria
   (B) neuroschistosomiasis
   (C) tuberculosis of the CNS
   (D) yaws

8. Which of the following drugs best penetrates the CSF for treatment of tuberculosis in the CNS?
   (A) ethambutol
   (B) isoniazid
   (C) pyrizinamide
   (D) rifampicin

9. The responsibility for imposing a quarantine to prevent the spread of communicable diseases rests with which of the following entities?
   (A) county governments
   (B) state governments
   (C) federal government
   (D) state and federal governments jointly

10. A quarantine was recently imposed on a health care worker upon her return to the United States after caring for patients with Ebola virus overseas. The failure to first arrange a voluntary quarantine may have violated which of the following criteria for limiting autonomy?
    (A) evidence of harm
    (B) least-restrictive means
    (C) reciprocity
    (D) transparency

Answers to the previous issue of Continuum Audio (Volume 04, Issue 23): 1-D, 2-D, 3-A, 4-A, 5-C, 6-B, 7-D, 8-D, 9-D, 10-B