PSYCHIATRIC ASPECTS of

INFECTIOUS DISEASE SYNDROMES

Robert K. Schneider and James L. Levenson

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INTRODUCTION: Psychiatric symptoms are part of the clinical presentation of many infectious processes. Recently, several factors have combined to increase the prevalence of infectious diseases and their significance. Rapid cultural and economic changes affecting regional and international mobility, sexuality, and other behaviors have led to worldwide spread of new epidemics (e.g., HIV) and more limited spread of previously geographically isolated diseases (e.g., Ebola virus). Evidence has accumulated implicating a possible role of infectious diseases in the pathogenesis of psychiatric disorders (e.g., viral antibodies in schizophrenia). Causal links between specific infections and a subset of psychiatric conditions provide intriguing models of etiology (e.g., streptococcal infection and early onset childhood OCD with tics).

As a result of these developments, consulting psychiatrists should carefully consider relevant aspects of patients’ histories, including immune status, regions of origin and
residence, travel, high risk behaviors, occupation and recreational activities. Physicians must consider which infectious diseases are endemic in the practice area, and in the areas where the patient has traveled or resided. Similar psychiatric symptoms might represent Lyme disease in a hiker in the northeastern United States and neurocysticercosis in an immigrant from Central America.

Prior brain injury or degeneration of all types renders patients more vulnerable to the effects of metabolic or toxic effects even from minor insults, and this is true of infectious diseases as well. For example, a simple upper respiratory infection or urinary tract infection may cause only discomfort in a normal individual, but agitation, personality change, and frank delirium in a demented individual.

The chapter is broadly divided into bacterial, viral, fungal, and parasitic infections, followed by a section on the psychiatric side effects of anti-microbial drugs, and drug interactions with psychotropic medications.

**BACTERIAL INFECTIONS**

**BACTEREMIA AND SEPSIS:** Bacteremia, literally meaning entry of bacteria into the bloodstream, may be part of the progression of an infection with some organisms, but not all bacteremia is sepsis. Sepsis refers to the systemic response to bacteremia. Systemic symptoms of sepsis, including CNS symptoms may result via many different mechanisms including bacterial toxins, release of cytokines, hyperthermia, shock (poor perfusion),
acute renal insufficiency, pulmonary failure ("shock lung"), coagulopathy, disruption of
the blood-brain barrier, and/or spread of the organism into the CNS. An acute change in
mental status may be the first sign of impending sepsis, and may sometime precede the
development of fever. Any patient who has an abrupt change in mental status
simultaneously with a shaking chill should be presumed to have a high risk for
impending sepsis. Diagnosis focuses on identifying the organism by blood culture or by
obtaining organisms from the presumed original nidus of infection. Standard treatment is
broad spectrum antibiotics at first, then tailored to the identified organism and its
sensitivities.

**OCCULT INFECTIONS:** Occult infections, irrespective of location, by definition are
concealed or mysterious, often requiring diligent detective work. Such infections may
occur essentially anywhere in the body (see table). Psychiatric symptoms may result
from even a small focus of chronic infection. The psychiatric symptoms most likely to be
present are subtle cognitive dysfunction or personality changes consistent with a mild
encephalopathy, but depression, psychosis, and delirium may also occur. Elderly patients
(especially with pre-existing dementia) are at higher risk, and may develop dramatic
encephalopathic symptoms with an otherwise uncomplicated bacterial urinary tract
infection.

The diagnosis is made by looking for secondary signs of infection, specifically
temperature dysregulation, increased white blood cell count or increased granulocyte
count. A careful history and physical examination may identify overlooked clues to
guide the physician’s search (e.g. chronic toothache or lymphadenopathy). If repeat history and physical examination are not fruitful, studies may be needed such as chest x-rays, CT-scans, and ultrasounds. Gallium scans may be useful in a “shotgun” search for a site of infection, but they have a high frequency of false-positive and false-negative results.

Note: Table of common occult infections that will include pneumonia, UTI, perirectal abscess, wound infection, sinus infections, otic infections, pharyngitis, cholecystitis, diverticulitis, and intraabdominal abscess, osteomyelitis, dental abscess, pelvic inflammatory disease.

**TOXIC SHOCK SYNDROME:** Toxic Shock Syndrome (TSS) typically occur in otherwise healthy people with intact immune systems. TSS is caused by either *Staphylococcus aureus* or *Streptococcus pyogenes*. TSS generally presents with rapid onset of fever, rash, and hypotension (shock) and is a multisystem disease with at least three organ systems involved, including the central nervous system. Most cases of TSS are associated with a wound and/or foreign body. The vast majority of staph TSS occur in young menstruating white women.

Staphylococcal TSS is most likely caused by the production of a toxin (TSS toxin 1) that acts as a superantigen, a substance that rapidly initiates a multisystem inflammatory response.
There may be a prodromal period of 2 to 3 days of malaise, myalgia and chills followed by confusion and lethargy. Early CNS symptoms may be confusion, weakness, or headache. These early features rapidly progress to hypotension and shock. Following recovery, CNS sequelae may persist for years including deficits in memory, computation, and concentration. It is unclear to what extent sequelae are a result of the toxin or the shock.

Early diagnosis of Staphylococcal TSS must rely on clinical suspicion. There are no available tests for the antigen, and cultures of blood, CSF and throat are usually negative. In contrast, blood cultures are positive in 60% of cases of Streptococcal TSS. The differential diagnosis for shock and hypotension in an otherwise healthy young adult is fortunately limited. Treatment includes aggressive supportive care, removal of foreign body, drainage of abscess, and antimicrobial agents. Experimental antitoxin agents are being explored.

There is a great peril in missing this diagnosis since TSS usually occurs in healthy, young women, the onset of the disease is fast, and there is high early morbidity and mortality. TSS should be suspected in any patient with a recent wound who acutely develops unexplained pain, lethargy and confusion and may occur even when a surgical wound appears non-inflamed.

**PANDAS:** Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) represents a newly identified subgroup of patients
with Obsessive Compulsive Disorder (OCD) and tic disorders including Tourette’s disorder. The syndrome is defined by childhood onset of symptoms; an episodic course characterized by abrupt onset of symptoms or by dramatic exacerbations; association with neurological abnormalities especially tics; and temporal association with group A B-hemolytic streptococcal infections (most commonly pharyngitis). Though treatment recommendations are not different for this syndrome, it constitutes a fascinating etiological model of psychiatric illness.

**BACTERIAL ENDOCARDITIS:** The study of bacterial endocarditis and its psychiatric symptoms presents an opportunity to view the disease process focally, systemically, and traversing into the central nervous system. It may produce psychiatric symptoms in all of its stages. Osler first described the triad of fever, heart murmur and cerebral infarction in 1885. Endocardial infections are focal infections that usually occur on one of the valves of the heart. Rheumatic heart disease was originally the typical cause of the predisposing cardiac abnormality. The incidence of rheumatic heart disease has decreased, but the incidence of senescent valvular disease, prosthetic valve placement and intravenous drug use have increased, thus changing the risk factors in the United States. Malaise and fatigue may represent early symptoms before progression of the infection is evident. CNS symptoms are related to (1) occlusion of cerebral arteries by septic emboli (2) expansion, leakage or rupture of mycotic aneurysms (3) direct infection of meninges or by abscess. Neurological or psychiatric deficits resulting from septic emboli will reflect which cerebral vessels have been affected. The most common psychiatric symptoms are encephalopathic changes which may occur at any stage of
infection. Their onset may be acute to insidious, paralleling the course of the endocarditis (acute, subacute, chronic).

Diagnosis is based on a good clinical history and physical examination. This should focus on detecting new or changing heart murmurs, signs of microembolism (splinter hemorrhages, retinal hemorrhages, microscopic hematuria), and positive blood cultures in a patient with fever. Echocardiographic studies are important for evaluation of valvular abnormalities. MRI-scans are more sensitive than CT-scans in detecting cerebral infarction. Treatment is based on blood culture results. The choice of antibiotics and length of parenteral treatment required varies with the specific organism, its antibiotic susceptibilities, first versus recurrent episode, presence of a prosthetic heart valve, and other factors.

ROCKY MOUNTAIN SPOTTED FEVER: The etiological agent for Rocky Mountain Spotted Fever (RMSF) is *Rickettsia rickettsii*. This is a tick-borne disease that has a seasonal distribution paralleling human contact with ticks, peaking May through September. After the tick bite, *R. rickettsii* enters the vascular endothelial cells, proliferates and disseminates, causing a diffuse vasculitis in many organ systems. As the name suggests, RMSF typically (though not invariably) includes fever and a rash characterized by erythematous macules that later progress to maculopapular lesions with central petechiae. Central nervous system involvement occurs in 25% of all cases, including lethargy, confusion, and occasionally fulminant delirium. Subtle changes like irritability, personality changes, or apathy may occur before the rash, particularly in children. Initially appearing as a nonspecific severe febrile illness, the diagnosis is seldom suspected until the rash forms.
While *R. rickettsii* may be demonstrated by direct immunofluorescence of skin biopsies, serology is the usual diagnostic method, though confirmation requires convalescent titers. Since mortality is high in untreated patients, a provisional clinical diagnosis (e.g., fever, rash in the appropriate season, and geographic setting) is sufficient to initiate treatment definitive antimicrobial therapy. Only half of patients report exposure to ticks. Response to the treatment is quick and usually heralded by defervescence and mental clearing.

**TYPHUS FEVERS:** Typhus fevers are caused by two species of rickettsiae. *R. prowazekii* is the cause of mouse-borne and squirrel-borne typhus. *R. typhi* is the cause of flea-borne typhus. Mouse-borne typhus usually occurs in epidemics related to war or famine where communal hygiene deteriorates. Flea-borne typhus is associated with fleas found on rodents. The annual disease frequency in the United States was 2,000 to 5,000 cases in the 1940's. It is now 60 to 80 cases with most in Texas. This dramatic change is due to the initiation of rat control programs. Clinical manifestations, diagnosis, and treatment are similar to Rocky Mountain Spotted Fever.(ref) The psychiatric manifestations are confusion, lethargy, and particularly headache in a febrile illness with rash.

**TETANUS:** Tetanus is uncommon in the United States, but remains significant internationally. *Clostridium tetani* produces a potent neurotoxin called tetanospasmin which is the cause of tetanus. The greatest risk factor remains lack of immunization. In the U.S. 60% of cases occur in people older than 60, older women are especially at risk. The first mass vaccinations were offered during World War II and many women never received vaccination then. Infections generally occur because an open wound comes in
contact with soil contaminated with spores from \textit{C. tetani}. After initial inoculation, tetanospasmin is disseminated via blood, lymph, and nerve and produces symptoms by binding to receptors at the neuromuscular junction. The classic symptom is muscle stiffness particularly in the muscles of mastication, thus the descriptive term "lockjaw". If the muscle stiffness extends across the entire face, “risus sardonicus” occurs, an expression of continuous grimace. Also stiffness may progress to the entire body if left untreated. Tetanospasmin may enter the central nervous system causing encephalopathic symptoms. Diagnosis is made by clinical manifestations and an epidemiological history. On initial presentation, patients with tetanus have been misdiagnosed as having an anxiety disorder or a conversion disorder. If the patient had previously been receiving neuroleptics, a physician could easily mistake the symptoms as drug-induced acute dystonia. Treatment centers on reducing exposure to the neurotoxin, including tetanus immunoglobulin, debridement of the wound, and high dose penicillin G. Infection does not always result in immunity, so active immunization is needed following treatment for the infection.

**TYPHOID FEVER:** Typhoid fever is the classic example of enteric fever caused by salmonellae. The incidence of typhoid fever has steadily declined in the U.S. over the last century. This decline is due primarily to improved sanitation. Typhoid fever is still endemic in many places in the world. Sixty percent of the cases in the U.S. are acquired outside the country most often in Mexico and India.
Classic symptoms involve gastrointestinal symptoms and fever. However, where typhoid fever is endemic or not treated promptly, psychiatric symptoms are seen. *Salmonella typhi* enters a bacteremic phase, and the typhoid bacilli can localize in the central nervous system. The high fever and electrolyte imbalances may also cause encephalopathic changes as well. Published cases cite a range of psychiatric symptoms that include irritability, personality change, and hallucinations that can persist after definitive treatment. It appears that most symptoms in survivors completely resolve following treatment. Diagnosis is made after isolation of the typhoid bacilli. The treatment of course of choice has been chloramphenicol, but there has been an increased incidence of multi-drug resistance.

**SYPHILIS:** Syphilis is a chronic systemic disease caused by the spirochetal bacterium Treponema pallidum. Though *T. pallidum* was not identified until 1905, syphilis was described in the medical literature before the 16\(^{th}\) century. A hundred years ago, syphilis was the leading diagnosis in psychiatric inpatients, the incidence declining as the antibiotic era began. The rates of syphilis have increased in the 1990s exceeding the previous 40 years, probably linked with the global pandemic of HIV infection. With the current trend, psychiatrists must relearn this disease.

The clinical manifestations are varied and can be confused with other diseases. Syphilis was the original “great imitator.” In the adult, syphilis passes through several stages. Primary syphilis develops as first a small papule at the site of inoculation that progresses to an ulcer called a chancre. About 6 to 24 weeks after the initial infection, the chancre
has disappeared, secondary syphilis occurs, and constitutional symptoms may appear. It is during this stage that multiple organ systems, including the CNS, may become involved. Most symptoms are constitutional (malaise, fatigue, anorexia, and weight loss). Skin, GI tract, lymphatics, bones, kidneys and eyes all may be affected. Most syphilitic meningitis occurs within the first year of infection. Symptoms of headache, stiff neck, nausea and vomiting prevail and focal neurological findings may be present. Often signs and symptoms of secondary syphilis disappear and the infection becomes latent. It should be noted that HIV-infected patients are at increased risk for syphilis’ neurologic complications.

Tertiary syphilis refers to infection years to decades after initial infection. It has been divided into three forms: late benign (gummatous), cardiovascular syphilis, and neurosyphilis. Cardiovascular and gummatous forms were very prevalent prior to antibiotics; now neurosyphilis is the prominent form of tertiary syphilis. Neurosyphilis is divided into asymptomatic, meningial, meningo-vascular, and parenchymatous. The later three are of particular significance to the psychiatrist. Meningeal syphilis may occur early in the course as mentioned above or later. Meningo-vascular syphilis occurs typically 4 to 7 years after infection. Presenting symptoms include memory change, personality change, dizziness, and encephalopathic changes that can mimic atherosclerotic disease. Parenchymatous neurosyphilis syndromes are tabes dorsalis and general paresis. Tabes dorsalis occurs 20 to 25 years after infection and results from demyelination of the posterior columns and dorsal roots. Symptoms of paresthesias, Argyll Robertson pupils, impotence, incontinence and truncal ataxia may develop. General paresis is an insidious
dementia that can include seizures and personality change. This form of syphilis presents 15 to 20 years after infection and if untreated maybe fatal. From clinical experience there are patients in whom the infection has “burned out”; they are demented, have positive CSF and serum serology and yet show no clinical response to penicillin G.

Diagnosis relies on serological testing because T. pallidum cannot be cultivated on artificial media. A table of the most frequently used tests shows their sensitivities. (see table) Treatment involves penicillin at varying dosages depending on the stage. If a definitive diagnosis cannot be made, it is prudent to treat presumptively.

**LYME DISEASE:** Lyme disease (LD) is a multisystem illness that can cause neurological and psychiatric symptoms. Lyme disease or Lyme Borreliosis is caused by the tick-borne spirochete Borrelia burgdorferi. LD is the most common tick-borne infection in the United States. B. burgdorferi is very similar to syphilis and has become the new "great imitator." Lyme disease is increasing in incidence and is geographically spreading.

B. burgdorferi is rapidly transmitted to the body and is known to invade the central nervous system (CNS) within the first few weeks after initial infection. B. burgdorferi has a long replication time and may remain latent in the CNS only to cause symptoms months to years later. It seems to produce neurological and psychiatric symptoms by at least two mechanisms. B. burgdorferi causes early symptoms by directly attacking the central or peripheral nervous systems. B. burgdorferi seems to produce late symptoms by
either initiating an immune response directly specifically against neuronal tissue, or through a non-specific inflammatory response.

Clinical presentation is variable from patient to patient and from area to area because of *B. burgdorfi’s* strain variation and ability to undergo genetic alteration once infection occurs. For diagnosis the CDC requires: 1) history of exposure to an endemic area; 2) physician-diagnosed erythema migrans rash of 5 cm in diameter; 3) evidence of at least one system’s involvement (e.g. musculoskeletal, neurological, cardiac); and 4) laboratory confirmation of *B. burgdorferi*. These criteria are helpful for epidemiological studies, but at least one-third of patients do not recall erythema migrans. Serological testing has been unreliable and the clinical spectrum of Lyme disease is expanding. Recent reviews suggest that psychiatric manifestations of Lyme disease are broad, ranging from depressive states to dementia. Depressive states may occur in late Lyme disease at a rate ranging from 26 to 66%. Cognitive dysfunction can occur in late Lyme disease, with abnormal short-term memory, verbal fluency, and executive functioning, suggesting frontal lobe involvement.

*Note:* Table that includes paranoia, thought disorder, anorexia nervosa, obsessions or compulsions, major depression, mania, irritability, panic attacks, disorientation, confusion, and personality change.

However, the ascription of psychiatric symptoms to Lyme disease by physicians and patients has sometimes been uncritical, driven by the wish to find a “real disease” behind
depression, anxiety, or somatoform disorders. Erroneous attribution of psychiatric symptoms has increased with widespread serological testing, giving rise to new problems of overdiagnosing and overtreating. The American College of Physicians has recently published helpful guidelines. In a community with a low incidence of LD and in the absence of objective findings, a positive serological result is more likely to be a false positive than a true positive. Therefore exposure to a high incidence area, a tick bite or objective findings should be present before ordering ELISA Lyme serology. The guidelines also note that with rare exception the serum ELISA is positive when the CSF ELISA is positive arguing against the use of CSF Lyme serology. (Jim: I add this because people are performing LPs on serum negative folks to “check” CSF serology)

In most patients with LD symptoms resolve with one course of treatment. However in as many as one third of cases objective findings resolve but fatigue, arthragias, and myalgias may persist of several months.

**BACTERIAL MENINGITIS:** Bacterial meningitis is an acute, serious illness associated with significant morbidity and mortality. Psychiatric symptoms play an important role in its presentation. General considerations of all pyogenic meningitides will be considered first. Several organisms with specific clinical syndromes will be considered later. Irrespective of the organism, most cases of bacterial meningitis result from hematogenous spread of bacteria from a primary site to the subarachnoid space. Once the organism crosses the blood brain barrier at the choroid plexus and enter the subarachnoid space, host defenses become activated. Psychiatric symptoms are produced by several mechanisms including cytopathic effects of the organism, mediators of
inflammation and secondary events, edema and cerebral hypoxia. Symptom severity generally correlates with the magnitude of the host’s immune response.

The classic sign of meningeal inflammation is nuchal rigidity. Headache, nausea, vomiting, confusion, lethargy, and apathy also may occur. The most common psychiatric symptoms are associated with encephalopathy. As in other infections, encephalopathy may present subtle changes in personality, motivation, or mentation. When the inflammatory response is blunted, the classic symptoms may not occur. In elderly or immunocompromised patients the only clinical signs may be irritability or minor changes in mentation or personality.

Once clinically suspected, the diagnosis is usually confirmed by examination of the cerebral spinal fluid (CSF), typically revealing pleocytosis, low glucose, high protein, and evidence of the offending organism on appropriate staining. Though neuroimaging is routinely performed to rule out other central nervous system processes, it rarely makes the diagnosis of bacterial meningitis. The morbidity and mortality of bacterial meningitis are associated with the time to treatment.

Initially, antibiotics are chosen to cover a broad range of organisms common to the population in which the patient falls (e.g. age and immune status). Two recent developments affect medication choice. The Haemophilus influenza type B vaccine has greatly reduced cases of meningitis caused by this agent, and penicillin resistance has emerged in streptococcus pneumonia infections.
**BRAIN ABSCESS:** Brain abscesses deserve special mention because the classic triad of headache, fever, and focal neurological deficits occur in less than half of patients with this condition. Psychiatric symptoms may occur during the initial presentation of brain abscess. Personality change and encephalopathy with seizures may represent initial presentation. Though mortality rates have markedly improved over the last decade due to improved neuroimaging and antimicrobials, morbidity remains high. Early detection and aggressive treatment are necessary to further reduce morbidity and mortality. After successful treatment of the infection, psychiatric symptoms may continue to complicate the picture.

The etiology and mechanism of infection of brain abscesses are similar to bacterial meningitis. In fact, brain abscesses frequently occur as a secondary complication of bacterial meningitis. But unlike in bacterial meningitis, neuroimaging can be very helpful in making the diagnosis of brain abscess. CT-scans and MRI-scans can demonstrate these focal infections in the CNS with very good sensitivity. Prompt treatment includes empiric antibiotics with primary excision or aspiration of the abscess.

Following successful treatment, a broad spectrum of psychiatric symptoms may occur depending on the size and location of the abscess(es), as in other types of brain injury. Affective illness, cognitive dysfunction, psychosis, and aggression are the most common psychiatric complications.
**TUBERCULOUS MENINGITIS:** Tuberculosis remains a major world health problem. It is endemic in many developing countries. Where AIDS is prevalent, the epidemiology of tuberculosis has markedly changed. Tuberculosis now represents the most common serious HIV-related complication worldwide. Where tuberculosis is not endemic, the diagnosis of tuberculous meningitis is difficult as the clinical manifestations are often nonspecific. Early treatment for tuberculous meningitis is essential because delayed treatment is associated with morbidity and death.

Tuberculous meningitis is caused by tubercular bacilli that are believed to be discharged from small tuberculous lesions adjacent to the meninges. These small tuberculous lesions arise early following a primary infection or as a consequence of reactivation.

Clinical presentation begins with low-grade fever, generalized malaise, and mild headache. Over the course of a week, symptoms progress to high-grade fever, severe nuchal rigidity, and encephalopathy. Fatigue, personality change, and confusion are the most common early psychiatric symptoms. Those patients infected with the HIV virus, the elderly, substance abusers, and others with impaired immunity are more likely to present without nuchal rigidity and headache. It is this special population patient that is more likely to present with the psychiatric symptoms including fatigue, apathy, cognitive and personality changes.

Diagnosis can be difficult. The organisms are difficult to find in the CSF so diligent search is needed to identify them when present. Early in the course when symptoms are
mild, CSF glucose may be unchanged and protein only marginally elevated. As the disease progresses, glucose falls drastically and protein becomes markedly elevated, with white cell counts typically between 50 and 200. Later findings include vasculitis and cranial nerve involvement. Diffuse meningeal involvement by TB may be demonstrated on magnetic resonance imaging.

Early antibiotic treatment is paramount. It is preferable to over-treat suspected cases than delay and risk additional complications. Regimens of multiple antitubercular drugs should be used until sensitivities are determined after cultures. In many parts of the world today, multiresistant tuberculosis is present, requiring different drug combinations.

**VIRAL INFECTIONS**

The overwhelming majority of viral infections are asymptomatic or do not receive medical attention. Many viruses are hard to detect, most are hard to treat and none are cured by treatment. Viruses can produce psychiatric symptoms by acute chronic, or relapsing direct CNS involvement, effects on the other organ systems, or CNS form or by autoimmune activation. Despite viral syndromes ubiquity and non-specificity, there are specific viral syndromes that are particularly important to the psychiatrist.

**Epstein-Barr Virus (EBV):** EBV, one of the herpesviruses, causes an acute lymphoproliferative disease called infectious mononucleosis, common in children and young adults. The prodromal stage of infectious mononucleosis is characterized by headaches, fatigue, and malaise, with progression to fever, sore throat, and
lymphadenopathy. Diagnosis is made by a combination of typical clinical symptoms and a positive heterophil antibody test (Monospot). Therapy is supportive and most cases completely resolve, though some may take several months.

When fatigue and malaise do not resolve, the diagnostic possibility of depression often arises. Since EBV may persist life-long in a latent state following acute infection, periodic reactivation may occur. Such patients typically report overwhelming fatigue, malaise, depression, low-grade fever, lymphadenopathy, and other nonspecific symptoms. Often, there are no other findings. This picture is essentially that of the chronic fatigue syndrome, though only a small fraction of the latter may be attributable to the EBV infection. In the more severe rarer form, anemia, leukopenia, eosinophilia, thrombocytopenia, pneumonitis, hepatosplenomegaly, uvetis, and abnormal concentration of serum globulins may occur. The role of the psychiatrist is to help the infectious disease clinician or the primary care provider distinguish which patients have primary psychiatric diagnoses (affective, anxiety, or somatoform disorders). Chronic EBV infection should not be diagnosed based solely on a positive Monospot. The absence of any objective findings (eg. significant lymphadenopathy, atypical lymphocytes, lymphocytosis, elevated sedimentation rate, fever, heptosplenomegaly) increases the likelihood of a primary psychiatric diagnosis but the latter should be based on positive criteria, never made by just exclusion of an identifiable medical diagnosis like EBV.

**Cytomegalovirus (CMV):** Like EBV, CMV is a common herpesvirus and most often infection is subclinical. CMV is differs demographically, in that it occurs in a broader age
group than EBV. Incidence in adults over age 35 ranges from 38% in Rochester, New York to 99% in Tanzania. In adults, CMV can produce a syndrome identical to the EBV mononucleosis, except that heterophil antibody testing is negative in CMV. CMV may also cause hepatitis, retinitis, colonitis, and pneumonitis. CNS involvement is particularly important in the immunocompromised host as CMV has been implicated as causing depression or dementia, CMV should always be considered in the differential diagnosis of acute depression of cognitive dysfunction on the first few months following organ transplantation. Diagnosis is most accurately made when CMV is recovered in body fluids. In addition, there are antiviral agents that are associated with excellent responses but significant side effects.

**Viral Meningioencephalitis:** Viral meningitis refers to infection of the meninges, and viral encephalitis to infection of the brain parenchyma. Most viruses that cause encephalitis cause meningitis as well. Enteroviruses, mumps, and lymphocytic choriomeningitis primarily affect the meninges. Eighty percent of identifiable viral meningitis is caused by the enteroviruses. The clinical syndrome viral meningitis (often referred to as “aseptic meningitis”) includes headache, fever, nuchal rigidity, malaise, drowsiness, nausea, and photophobia. Typically, the CSF shows pleocytosis, elevated protein and no evidence of an organism. Treatment is generally supportive.

Arboviruses are the most common cause of viral encephalitis worldwide. Japanese encephalitis is the most common worldwide and in the U.S. there are four major types: St. Louis Encephalitis, Eastern Equine Encephalitis, Western Equine Encephalitis, and
California Encephalitis, all mosquito-borne. The typical clinical presentation is typically a rapid progressive encephalitis that appears in the summer or fall and is often fatal. Clinical presentation includes an abrupt onset of fever, headache, nausea, photophobia and vomiting. Psychiatric symptoms include confusion, cognitive changes, and psychosis. HSV encephalitis differs by causing more unilateral and focal findings given the predominance of temporoparietal involvement of the brain. HSV encephalitis is more likely to cause focal seizures, olfactory hallucinations and personality changes. Although there is no specific treatment available for viral encephalitis caused by arboviruses, rapid diagnosis is important for the institution of public health measures. For those who survive permanent damage usually lingers.

**Herpes Simplex Virus:** Herpes encephalitis is caused by invasion of the brain by herpes simplex Type 1 virus in 90% of herpes encephalitis cases. Symptoms may include personality changes, dysphasia, seizures, autonomic dysfunction, ataxia, delirium, psychosis and focal neurological symptoms. Level of consciousness and age are the major prognostic indicators. CSF typically shows pleocytosis, red blood cells because of the hemorrhagic nature of encephalitis, and elevated protein. Glucose is usually normal. EEG is a sensitive neurodiagnostic test showing periodic temporal spikes and slow waves as opposed to more diffuse changes in other forms of viral. MRI scan may show diffuse inflammation, particularly in the temporoparietal areas. Serologic evaluation is helpful only retrospectively. Brain biopsy is reliable, has high yield and low complication rate. Clinical diagnosis is correct only 50% of the time. Therapeutic decisions must be made rapidly because only early treatment improves outcome. Acyclovir is the drug of choice.
One possible sequela of HSV encephalitis is the Kluver-Bucy syndrome, which includes oral touching compulsions, hypersexuality, amnesia, placidity, agnosia and bulimia.

**Postencephalitis Syndromes:** Following recovery from acute viral encephalitis, psychiatric sequela are common and constitute a major cause of disability, especially affective disorders. Depression, hypomania, irritability, and disinhibition of anger, violence, or sexuality have been frequently noted months after recovery and rarely psychosis. Depressive symptoms often respond to treatment with antidepressants or stimulants. Hypomania, irritability, and disinhibition have responded to mood stabilizers and behavior modification may be helpful for aggressive and sexual behaviors. The epidemic encephalitis in 1917-1926 known as encephalitis lethargia (von Economp’s disease) frequently included psychosis and catatonia. It also resulted in severe Postencephalitis syndrome including Parkinsonism and depression in adults, conduct disorder and emotional liability in children with relatively little cognitive impairment. Mania and obsessive-compulsive disorder also occurred. Sporadic cases of encephalitis lethargia continues to occur.

**Hepatitis:** Hepatitis is inflammation of the liver caused by various agents. Viruses including, Hepatitis-A, B, C, EBV, and CMV cause hepatitis presenting with fatigue, malaise and anorexia, and may cause “secondary depressions” especially in the chronic forms of hepatitis caused by hepatitis-B and C. Treatment with interferon commonly causes depression itself, further complicating the diagnostic picture. Depression
associated with hepatitis of interferon is amenable to treatment with antidepressants, but dosing should be cautious if the patient has impaired liver function.

**Rabies:** Rabies is a viral infection of mammals transmitted by bite. Transmission to humans is rare but has been misdiagnosed as an anxiety disorder. Initial symptoms are nonspecific and include generalized anxiety, fever, melancholia, hyperesthesia, and abnormal sensations at the site of inoculation (e.g., pain, burning, cold, and puritus). The initial phase is usually followed by an excitatory phase, when the classic symptom of hydrophobia may occur. Hydrophobia is an aversion to swallowing liquids (not a phobia of water) secondary to the spasmodic contractions of the muscles of swallowing and respiration, resulting on pain and aspiration. The final phase is the paralytic phase, where a progressive, general, flaccid paralysis develops and progresses to death. There is no effective treatment for Rabies once symptoms are evident. If a person has been bitten by an infected animal, then the Rabies vaccine should be given as soon as possible because outcome is correlated to the proximity in time to the bite.

**Prion Diseases:** Prions are proteinaceous agents that cause spongiform changes in the brain. Prion diseases are rare and universally fatal. The incubation period can be months to years hence the term, “slow viruses.” Symptoms include severe ataxia, myoclonic or choreiform movements and dementia rapidly progressing to death. Kuru occurs only in Papua New Guinea. It is spread by the cannibalistic consumption of dead relatives during mourning rituals. Creutzfeld-Jakob (CJD) disease occurs sporadically. It may be
inherited or transmitted by intracerebral electrodes, grafts of dura mater, corneal transplants and human derived growth hormone and gonadotropin.

Scrapie is a spongiform encephalitis found in sheep. Though present in Great Britain for almost three centuries, it has never been shown to cause a case of spongiform encephalitis in a human. However, bovine spongiform encephalitis (BSE or “mad cow disease”) appears to have been transmitted to cattle by the practice of feeding cattle recycled sheep carcasses in the form of nutritional supplements. In Great Britain, within a three year period, there has been 21 cases of a “new variant” CJD (nvCJD) with unusual clinical and pathological features. As a group nvCJD patients compared with CJD patients are younger (average age 27 vs 60), an onset with psychiatric symptoms and/or sensory symptoms, the absence of typical EEG findings and an average duration of 14 months vs 4 months. Though BSE and nvCJD are temporally associated, there has been no causative link established. Precautionary steps have been taken to minimize risk for the potential transmission of BSE to humans.

FUNGAL INFECTIONS

The frequency of fungal infection has steadily increased over the last three decades. This increase has been coincident with the growing number of immunosuppressed patients who survive longer periods of time than in the past. An aging population, an increased number of malignancies, the spread of AIDS, the use of immunosuppressive and cytotoxic drugs, intravenous catheters, hyperalimentation, illicit drug use, extensive surgery, and the development of burn units have also contributed to the increased
frequency of fungal infection. CNS symptom development depends on the size and shape of the fungi. The smallest fungi have access to the cerebral microcirculation and infect the subarachnoid space. Large hyphae obstruct large and intermediate arteries giving rise to extensive infarcts (e.g., Aspergillosis). Fungi with pseudohyphae occlude small blood vessels producing small infarctions and microabscesses (e.g., Candida). Most fungi are opportunistic such as Aspergillosis, Mucormycosis, and Candidiasis. Others (e.g., Coccidioidomycosis and Cryptococcosis) are pathogenic irrespective of the hosts’ defenses.

**Aspergillosis:** This opportunistic infection takes place only in debilitated patients. *Aspergillus* genus is commonly found in soil. CNS involvement usually follows infection of the lungs or GI tract. Symptoms of confusion, headache and lethargy often accompany focal neurological signs.

**Cryptococcosis:** Cryptococcosis is an infection caused by *Cryptococcus* species, a pathogen distributed worldwide, found in bird excreta, the soil and other animals. *Cryptococcus* may act as a solo pathogen, but in up to 85% of cases, it is associated with another illness. The portal of entry is usually the respiratory tract from which hematogenous spread occurs, though at the time of presentation pulmonary infection may not be evident. This pathogen has a predilection for the subarachnoid space. *Cryptococcus* is the most common form of fungal meningitis. It is typically insidious in onset and slowly progressive. Headache is present in up to 75% of the cases, varying from mild and episodic, to progressively incapacitating and constant. Other findings include cerebellar signs, cranial nerve deficits, and motor deficits. Psychiatric presentations are broad in scope too; from irritability to psychosis and lethargy to coma. Periods of remission and relapse are common in undiagnosed and untreated patients. Isolation of the fungi provides definitive diagnosis. Serological testing of patients with
Cryptococcal meningoencephalitis reveals Cryptococcal antigen in serum, CSF or both 90% of the time. Treatment is typically a prolonged course of an antifungal agent.

**Coccidioidomycosis:** Coccidioidomycosis is restricted to warm, dry areas such as the Southwestern United States, Mexico, and parts of South America (particularly Argentina and Paraguay). Its spores are inhaled in infected dust. Initial infection produces a mild febrile illness, often followed by a pulmonary infection. Dissemination beyond the lung is relatively rare and the CNS is not the most common extrapulmonary site. When the CNS is involved it usually becomes apparent one to three months after initial infection. Typically insidious in onset, a severe headache is associated with confusion, restlessness, hallucinations, lethargy and transient neurological signs. Diagnosis is made by neuroimaging and serological testing of the CSF. Amphotericin is the best treatment agent.

**Histoplasmosis:** Histoplasmosis is a common respiratory infection found throughout the world and is especially common in the central U.S. *Histoplasma capsulatum* is inhaled with dust contaminated with chicken, bird or bat excreta. Most infections are asymptomatic and involve the lungs or the reticuloendothelial system. CNS involvement is rare. Two peaks of increased incidence occur in infancy and the fifth or sixth decades. The onset of CNS symptoms is insidious. After a few weeks of irregular pyrexia and a persistent cough, extreme nervousness and irritability progress to marked lethargy and if untreated, coma.

**Blastomycosis:** *Blastomyces dermatitidis* is an uncommon mycotic infection that rarely causes CNS infections. Blastomycosis is co-endemic with histoplasmosis in the central U.S. CNS manifestations are most often stiff neck and headache, eventually progressing to confusion and lethargy.
Mucormycosis: Mucormycosis refers to any infection caused by a member of the family Mucoraceae, an opportunistic fungi is found in common bread and fruit molds. This infection represents the most acute and fulminant fungal infection known. Mucormycosis prefers conditions such as diabetes. The classic triad of Mucormycosis is diabetes, orbital infection and meningoencephalitis. Mucoraceae directly invades tissue and disseminates by attacking contiguous structures. Therefore, a diabetic patient with a purulent, febrile infection of the face or nose should be aggressively evaluated for mucormycosis, since it may erode into cerebrum in a matter of hours. Early mild signs of encephalopathy may rapidly progress to severe delirium. Treatment involves aggressive debridement and antifungal treatment.

Candidiasis: Candida causes limited local infections (cutaneous, vaginal, oral) in immune-competent hosts, especially after broad spectrum antibiotics. Disseminated candidiasis occurs only in the immune compromised host. Psychiatric symptoms occur from the “toxic” effects of fungemia or from direct invasion of the CNS. Cerebral lesions generally occur late in the course of disseminated candidiasis. Candida may cause meningitis, microabscesses, macroabscesses or vasculitis. Symptoms are nonspecific: confusion, drowsiness, lethargy and headache. Most diagnoses of CNS candidiasis are made at autopsy. In life, diagnosis is made by isolation of the organism. However, neuroradiographic changes and isolation of Candida in a non-CNS site in an immunocompromised patient should prompt treatment with appropriate antifungal agents.

There is an alternative medicine belief that occult systemic Candida infection is the cause of a wide array of somatic and psychological symptoms. There is no scientific support for this theory or its associated treatments.
PARASITES

NEUROCYSTICERCOSIS: The larvae (cysticerci) of the tapeworm Tanemia solium cause an infection known as Cysticercosis. When the cysticerci reach the central nervous system (CNS) it is called Neurocysticercosis (NCC). NCC is the most frequent and widely disseminated human neuroparasitosis. It is particularly common in Latin America, Africa, and Asia, but endemic areas exist throughout the world. In the U.S., NCC is reported in immigrants and travelers from endemic areas. The southwest of the U.S. has seen a dramatic increase in reported cases since the mid-1970's. The life cycle of T. solium involves humans as definitive host and swine as intermediate host. Humans acquire intestinal taeniasis (the tapeworm) by eating uncooked or undercooked pork infected with cysticerci (larvae) and cysticercosis by ingesting the eggs of T. solium. Eating raw or undercooked swine is essential to the propagation of cysticercosis. Once ingested, the eggs hatch in the duodenum. The released embryos penetrate the intestinal mucosa and enter the circulatory system. They are then distributed to extraenteric sites undeveloped as larval cysts (cysticerci). In humans, the cysticerci locate primarily in skeletal muscles, but the recognition of disease usually emanates from central nervous system involvement.

The variable, nonspecific clinical spectrum is determined in part by the number of cysticerci, the location in the CNS, and the intensity of the host immune inflammatory response. The initial immune response to the cysticerci is minimal, which explains the potentially long asymptomatic latency period after infection. The inflammatory response is intensified when the cysticercus dies and releases a large number of antigens. The most frequent manifestation of NCC is seizures. Dementia, other cognitive dysfunction, and a broad spectrum of other psychiatric manifestations have been reported, but the
literature is largely retrospective reports by nonpsychiatric physicians. The clinical picture of a patient with new psychopathology and unexplained seizures from an endemic area should raise the possible diagnosis of NCC. Diagnosis is difficult because of the varied and nonspecific clinical presentation. The diagnosis is often only considered after a failed treatment. Diagnosis hinges on a high index of suspicion in a patient with a history of exposure to an endemic area or an individual from an endemic area, neuroimaging and positive immunological CSF tests. MRI is superior to CT given its ability to demonstrate cysticerci and the inflammatory response. The CSF may show an inflammatory response with elevated protein and pleocytosis. Immunodiagnostic tests include complement fixation, indirect immunofluorescence, passive hemagglutination, and ELISA depending on the laboratory's availability.

Treatment depends on symptoms, location of the cysticerci, stage of development, involution of the cysticerci, and inflammatory response. Surgery, anticonvulsants, glucocorticosteroids, and anthelminthic therapy are used with varying degrees of overlap. Concomitant intestinal taeniasis always needs to be excluded and treated at present.

**TOXOPLASMOsis:** Toxoplasmosis refers to the disease caused by Toxoplasma gondii, a parasite ubiquitously affecting all kinds of mammals, some birds, and probably some reptiles. It is significant to the psychiatrist because of its central nervous system manifestations in the immunocompromised patient especially the AIDS patient. The reader is referred to that section for further information. (*Alan: I still am not sure what is covered in the HIV chapter*).
TRYPANOSOMIASIS: The family of protozoa Trypanosomatidae causes two clinically different syndromes, African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas' disease). African trypanosomiasis occurs in a number of sub-Saharan African countries. The disease is caused by a subspecies of Trypanosoma brucei and is transmitted to humans and animals by the bite of the blood-sucking Tsetse fly. Early stages of the disease include headache, fever, malaise, weight loss, arthralgia, and myalgia. These nonspecific signs are often confused with malaria. If left untreated, it will progress to other organ systems, including the central nervous system. CNS infection is heralded by new disturbances such as depression and mania. Excessive sleeping and other neurological findings are later manifestations. Diagnosis relies on identification of the protozoa. Treatment is complicated and the medications to treat late stage disease may themselves be lethal, so early detection and subsequent treatment is important.

American trypanosomiasis or Chagas' disease is caused by Trypanosoma cruzi. T. Cruzi is carried by Triatomine bugs commonly called kissing bugs or assassin bugs, who live in the cracks in walls or roofs particularly in houses in rural areas located in Central and South America. The bugs emerge at night painlessly obtaining their blood meal. Transmission occurs through defecation of infected feces in the wound. Transmission is so inefficient that years of exposure are required to acquire the infection.

Reactivated disease is of particular importance to the psychiatrist. Asymptomatic people with quiescent disease may emigrate to a non-endemic area. Many immigrants of Latino-American countries are now living in the United States and Europe. If such a person were to experience significant immunocompromise, the Trypanosomia can become active again. Reactivated disease with central nervous system involvement occurs in leukemia, lymphoma, Hodgkin's disease, transplantation, and AIDS. CNS symptoms cover a broad
spectrum dependent on the location of the lesions. On CT-scan of the brain, the lesions are indistinguishable from toxoplasmosis and the blood is often negative for the organism. Therefore, in presumed cases of toxoplasmosis that is not responsive to chemotherapy, reactivated Chagas' disease should be considered.

**MALARIA:** Malaria is one of the most prevalent diseases in the world. It is the leading cause of morbidity in young children and pregnant women internationally. In the United States, cases occur in immigrants, travellers and visitors to malarial areas. Plasmodium species is transmitted to humans by the bite of mosquitoes. Plasmodium enters the bloodstream where it rapidly travels to hepatocytes. The complete reproduction and maturation cycle of the parasite is described elsewhere. However, several important features should be highlighted. (1). Erthyrocytes infected with late maturing Plasmodium disappear from the peripheral blood and localize in the deep vascular beds of vital organs. This process is called sequestration. This process is significant in the formation of symptoms in Cerebral Malaria. (2). In the life cycle, merozoites (stage of plasmodium development) are released from erythrocytes causing paroxysms of chills and fever typical of malaria. Definitive diagnosis is made by the identification of Plasmodium in the blood.

Malaria is important for the psychiatrist to consider for several reasons. During the febrile stage, the patient may become encephalopathic. The fever in excess of 41 C (105 F) is common. The relapsing nature is the key to the malarial diagnosis. Cerebral malaria, the most catastrophic complication of malaria occurs with P. falciparum. Clinically, this picture may present with disorientation, mild stupor or even psychosis. However, it rapidly progresses to seizures and coma with decerebrate posturing. The severity of the symptoms is correlated with the amount of sequestered parasitised red blood cells in the central nervous system.
Plasmodium is particularly adept at developing resistance to chemotherapy. This means that even prophylaxed or treated, the person may still have an active infection. Antimalarials commonly cause psychiatric side effects (see Table XX).

**SCHISTOSOMIASIS:** Schistosomiasis is an infection caused by blood flukes (trematodes) of the genus schistosoma. Humans can be infected when the skin comes in contact with the infected larval stage. This contact usually occurs while swimming in infected waters. The infection affects about 200 million people in 74 countries. Most infections are asymptomatic. Central nervous system involvement is rare. Psychiatric symptoms may occur in two settings. One is acute toxemic schistosomiasis in previously unexposed people such as travelers. The symptoms of headache, malaise, and muscle aches usually occur several weeks after exposure. These symptoms dramatically progress several weeks later when the egg laying of the trematodes begin. The clinical picture is one of toxemia and associated encephalopathy. The other psychiatric presentation may occur in the chronically infected individual. Migration of the eggs to the central nervous system can induce granulomatous reaction, leading to symptoms of increased intracranial pressure (e.g., headache, visual changes, nausea, and papilledema). Focal neurological findings may occur as well. Treatment is effective peroral schistosomicidal drugs.

**TRICHINOSIS:** Trichinosis is a world-wide disease caused by the ingestion of larvae encysted in the muscles of infected animals. They are most commonly found in pork in the United States and Europe, 150 species of mammals from all latitudes may acquire the infection. Outbreaks of Trichinosis are associated with ethnic group or immigrants that prefer raw or undercooked pork or wild animals, such as polar bear or walrus. Typical symptoms of infection include a febrile illness with myalgias and diarrhea. Symptomatic
cases have CNS involvement in 10 to 24%, including headache, delirium, insomnia, meningeal signs and seizures. CT-scan shows multiple small hypodense lesions with ring-like enhancement with contract. A muscle biopsy is usually diagnostic. Treatment in severe cases involve glucocorticosteroids for the inflammation and Medendavol to kill the trichinella.

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VI Anti-infectious agents and neuropsychiatric effects