opening pressure for the CSF may be elevated, with pressures ≥25 cm CSF in 60% to 80% of patients.[7,8]

Cryptococcal disease can be diagnosed by culture, CSF microscopy, cryptococcal antigen (CrAg) detection, or CSF polymerase chain reaction (PCR). In HIV-related cryptococcal meningitis, most blood cultures and CSF cultures will be positive (47% to 70% and 90% to 94%, respectively).[5] Visible *Cryptococcus* colonies on a fungal Sabouraud dextrose agar plate, or even a standard aerobic bacterial culture, generally can be detected within 7 days. *Cryptococcus* may be identified occasionally on a routine Gram stain preparation of CSF as poorly staining Gram-positive yeasts. India ink staining of CSF demonstrates encapsulated yeasts in 60% to 80% of cases, but many laboratories in the United States no longer perform this test. India ink is relatively insensitive early in disease when <1,000 *Cryptococcus* colony-forming units (CFU)/mL are present.[9] In tissue or fluids, yeasts will stain with Grocott methenamine silver stain, and the capsule will stain with mucicarmine or alcian blue stains. Positive cultures are required to prove yeast viability because strains can be stain positive with nonviable yeasts.

Cryptococcus can infect any part of the body, but brain and lungs are frequently target organs. Cultures and/or histopathology are essential for precise diagnosis. However, in many patients with advanced HIV, the presentation is more commonly a meningeal syndrome rather than a pulmonary syndrome.

CSF CrAg is usually positive in people with cryptococcal meningoencephalitis; however, early meningitis can present with negative CSF studies and a positive CrAg in blood only.[10] Thus, serum CrAg testing always should be performed in an immunocompromised individual with an unknown CNS disorder.[10] Serum CrAg is positive in both meningeal and non-meningeal cryptococcal infections and may be present weeks to months before symptom onset.[11] All positive CrAg tests in patients with HIV require consideration for therapy.

Three methods exist for antigen detection: latex agglutination, enzyme immunoassay (EIA), and lateral flow assay (LFA). The IMMY CrAg LFA (IMMY, Norman, Oklahoma) is the only LFA test for CrAg approved by the U.S. Food and Drug Administration (FDA). It is a useful initial screening tool for diagnosing cryptococcosis in people with HIV when applied to serum or plasma,[9,12] and it also can be used with whole blood or CSF. CrAg testing of serum or plasma may be particularly useful when a lumbar puncture is delayed or refused. In a person with HIV, when serum CrAg LFA titers are ≥1:160, disseminated disease becomes increasingly more likely, and when CrAg LFA titers are ≥1:640, or when there is high clinical suspicion, disseminated and/or CNS involvement should be assumed, regardless of CSF antigen titer results.[13,14] Antigen titers by the LFA are approximately fourfold higher than those with latex agglutination or EIA testing; thus, a titer of 1:640 by LFA is approximately equal to a titer of 1:160 by EIA or latex agglutination. A prozone effect needs to be checked when CrAg with latex agglutination and LFA testing is negative despite observing yeasts in tissues or fluids.

In 2016, the BioFire FilmArray Meningitis/Encephalitis Panel PCR assay (BioFire Diagnostics, Salt Lake City, Utah) was approved by the FDA. This multiplex PCR tests for 14 targets, including *C. neoformans* and *C. gattii,* and performs well in infections with a moderate-to-high fungal burden.[15-17] False negative results have been noted to occur when there is a low burden of yeasts; in one study, when there were <100 CFU/mL, the sensitivity of the PCR test fell to 50%.[15] In one well-described case, a woman who had two negative results with this PCR assay later had a positive result on a CrAg test done by IMMY LFA.[18] Thus, a negative CSF PCR does not completely exclude