

## Progressive Multifocal Leukoencephalopathy (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- The main approach to treatment of Progressive Multifocal Leukoencephalopathy (PML) is treatment with an effective antiretroviral regimen that suppresses HIV viremia and preserves or restores CD4 T-lymphocyte (CD4) cell-defined immune function (**AII**).
- Intrathecal cytosine arabinoside and cidofovir are not routinely recommended for treatment of PML (**BIII**).
- Immunomodulatory approaches, such as interferon alfa, are not routinely recommended for treatment of PML (**BIII**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## Epidemiology

First described in association with disorders of B-cell function, such as chronic lymphocytic leukemia and Hodgkin disease, progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system (CNS) that occurs in immunocompromised patients.<sup>1</sup> In HIV-infected adults, CD4 T lymphocyte (CD4 cell) counts less than 100 cells/mm<sup>3</sup> are associated with development of PML, and persistence of CD4 counts less than 50 to 100 cells/mm<sup>3</sup> are associated with fatal PML. Not all patients with PML have severe immune dysfunction, however, and PML has been reported in HIV-infected patients with high CD4 counts who are receiving successful combination antiretroviral therapy (cART).

PML is caused by JC virus (JCV), a ubiquitous polyomavirus, named using the initials of the patient, John Cunningham, from whom it was first isolated. Most humans are infected with JCV early in life; in a seroepidemiology study, 50% of Swedish children were seropositive for JCV by ages 9 to 11 years, and 72% of adult women aged ≥25 years in the Finnish Maternity Cohort were JCV seropositive.<sup>2</sup> The exact mode of transmission of JCV between individuals is unknown. Because the virus is commonly detected in urine, JCV has been detected in sewage effluent. It is also detectable in peripheral blood mononuclear cells of both healthy and immunocompromised individuals. Vertical transmission from mother to newborn also has been documented.<sup>3,4</sup> Lymphocytes, renal tubular epithelium, bone marrow, and possibly spleen and lymphoid tissue likely represent sites of viral latency, and lymphocytes also may be a vehicle for spread of the virus to other organ systems, including the CNS.<sup>5,6</sup>

The evolution of asymptomatic infection with JCV to symptomatic PML probably involves a series of events that are both virologic and immunologic. The original infecting strain of JCV—the strain that is commonly detected in urine and blood—mutates and alters a regulatory gene through rearrangement of a non-coding region (at-NCCR to rr-NCCR) to become a neurotropic strain of JCV capable of replicating in neuronal glial cells.<sup>7</sup> Failed immune surveillance allows replicating virus to persist in peripheral blood cells and serum. If the neurotropic form of JCV gains entry into the brain, it can then establish a productive infection in oligodendrocyte cells, which leads to PML in the absence of proper CNS immune surveillance.<sup>8</sup> Serotonin receptor 5-HT(2a) appears important for JCV infection of brain glial cells.<sup>9</sup> Recently, in HIV-uninfected adults, an increased incidence of PML has been associated with use of therapeutic monoclonal antibodies,

including natalizumab (an alpha 4 beta 1 and alpha 4 beta 7 antagonist that targets activated lymphocytes), efalizumab (an anti CD-11a antibody that targets T-lymphocytes), rituximab (an anti CD-20 antibody that targets B-lymphocytes), and alemtuzumab (an anti-CD52 antibody that depletes both T and B cells).<sup>8,10-12</sup>

PML is an AIDS-defining illness in HIV-infected individuals. It has rarely been seen in reports from large series of HIV-infected children,<sup>13-15</sup> but cases have been reported in children with a wide range of ages and a broad geographical distribution.<sup>16-22</sup> The incidence of PML has decreased from 3.3 cases per 1000 person-years at risk during the era before cART, to 1.3 cases per 1000 person-years after the introduction of cART.<sup>23</sup> During the pre-cART era, survival was extremely poor in adults and children with PML.<sup>15</sup> Survival among adults has improved during the cART era<sup>24-26</sup> from 10% to 50%, and mean survival time from time of diagnosis of PML has increased from 0.4 years to 1.8 years.<sup>27</sup> No comparable data exist for children.

## Clinical Manifestations

No symptoms are known to be associated with acute or latent JCV infection. Asymptomatic urinary shedding is common. PML is the primary disease caused by JCV and clinical manifestations in children are similar to those in adults. The disease has an insidious onset and produces a neurologic syndrome that steadily progresses over weeks or months, characterized by confusion, disorientation, lack of energy, loss of balance, cognitive dysfunction, dementia, seizures, ataxia, aphasia, cranial nerve deficits, visual abnormalities (blurred or double vision or loss of vision), hemiparesis or quadriparesis, and eventually coma.

Demyelination is at first patchy, involving subcortical regions, and then spreads to deep white matter in a confluent pattern; thus, PML initially may present with focal neurologic deficits that involve different brain regions.

## Diagnosis

The established criteria for clinical diagnosis are focal signs and symptoms on neurologic examination, focal white matter lesions on magnetic resonance imaging (MRI) or computerized tomography (CT) without mass effect, and exclusion of other causes of the clinical and neuroradiologic findings.<sup>28</sup> A confirmed diagnosis of PML requires a compatible clinical syndrome and radiographic findings, coupled with brain biopsy demonstrating a characteristic triad of pathologic foci of demyelination, enlarged hyperchromatic oligodendrocytes with enlarged nuclei and basophilic-staining intranuclear material, and enlarged astrocytes with bizarre hyperchromatic nuclei. When only two of these features are present, JCV can be demonstrated by *in situ* hybridization or by electron microscopy for definitive diagnosis.

Brain biopsy remains the gold standard confirmatory test for diagnosis of PML, but brain imaging with MRI or CT can reveal characteristic lesions. The radiologic features of PML are typically non-inflammatory (unless associated with immune reconstitution inflammatory syndrome [IRIS] related to initiation of cART). Typical CT abnormalities include single or multiple hypodense, non-enhancing cerebral white matter lesions; cerebellum and brain stem occasionally are involved. MRI may be more sensitive for detecting changes in the brain associated with PML, and may be positive before JCV DNA is detected in the cerebrospinal fluid (CSF). MRI depicts white matter lesions of low T1 signal intensity and high proton density on T2-weighted images with absence of edema or mass effect. Post-contrast enhancement is unusual, and when present, usually is sparse, with a thin or reticulated appearance adjacent to the edge of the lesions.

PML diagnosis is now facilitated by use of a polymerase chain reaction (PCR) assay to detect JCV DNA in CSF, which may obviate the need for brain biopsy in patients with a compatible clinical syndrome and radiographic findings. Nested JCV DNA PCR on CSF is highly sensitive (90%–100%) and specific (92%–100%) for PML in adults, and in the absence of comparative data for children, similar performance characteristics are anticipated but not proven in that population.<sup>29</sup> False-negative tests occur, however, and PML may be present and diagnosed by brain biopsy in patients with a negative JCV DNA PCR test in the CSF. Measurement of JCV DNA levels in CSF samples can be a useful virologic marker for managing PML

in patients receiving cART.<sup>30</sup> With the advent of multiple modalities to support PML diagnosis, diagnostic criteria can be stratified according to the following terminology and levels of certainty of diagnosis:

- **Biopsy-confirmed PML:** JCV antigens detected by immunohistochemistry, JCV DNA detected by *in situ* nucleic acid hybridization, or JC virions detected by electron microscopy in brain tissue obtained by cerebral biopsy, associated with typical histology, in patients with typical clinical and radiological findings
- **Laboratory-confirmed PML:** JCV DNA detected by PCR of CSF in patients with typical, clinical, and radiological findings (detection of intrathecal antibody production may also support the diagnosis)
- **Possible PML:** Patients with typical clinical and radiological findings, without virologic or histologic confirmation in brain tissue or CSF.<sup>31,32</sup>

Presence of antibodies to JCV in the serum or presence of JCV DNA in the blood or urine of patients does not establish the diagnosis of PML because these studies can be positive in individuals without PML. Conversely, while most patients with JCV-associated PML have moderate to high anti-JCV antibodies and JCV DNA in their peripheral blood, serum, and CSF, some patients with PML diagnosed by brain biopsy will not have detectable anti-JCV antibody or JCV DNA in their blood or CSF. Most patients with JCV-associated PML, however, have moderate to high anti-JCV antibodies and JCV DNA in their peripheral blood, serum, and CSF.

## Prevention Recommendations

### *Preventing Exposure*

There is no known way to prevent exposure to JCV.

### *Preventing First Episode of Disease*

Use of cART can prevent or reverse the severe immunosuppression that increases the risk of PML. Incidence of PML has decreased in the cART era. There are no means of preventing PML in severely immunosuppressed individuals.

### *Discontinuing Primary Prophylaxis*

No means of primary prophylaxis of JCV infection or development of PML have been demonstrated.

## Treatment Recommendations

### *Treating Disease*

No effective specific therapy has been established for JCV infection or PML. Survival in HIV-infected adults with PML has substantially improved during the post-cART era, with an increase in median survival from 14 to 64 weeks.<sup>27,33</sup> A CD4 count >100 cells/mm<sup>3</sup> at PML diagnosis is associated with improved survival, and use of cART after diagnosis of PML is strongly associated with improved survival.<sup>33</sup> Thus, the main approach to treatment involves optimizing cART to reverse the immunosuppression that interferes with normal host response to this virus (**AII**).

A number of agents have been proposed or reported anecdotally as more specific treatments for PML, but none has proven effective after greater scrutiny or more extensive study. In a randomized, open-label trial of intravenous (IV) and intrathecal cytosine arabinoside<sup>34</sup> and a non-randomized, open-label trial of IV cidofovir,<sup>35</sup> neither drug was effective in producing clinical improvement of PML in HIV-infected adults, and neither agent is routinely recommended (**BIII**). Immunomodulatory approaches such as interferon-alfa (IFN- $\alpha$ ) also have been described in case reports in HIV-infected adults; however, none have been studied in a controlled clinical trial and, in one analysis, these approaches did not provide any benefit beyond that with cART.<sup>36</sup> Thus, they are also not routinely recommended (**BIII**). Anecdotal reports have been published about

use of mirtazapine (a 5-HT(2a) receptor antagonist) plus either cidofovir or cytosine-arabioside, with tapering of immunosuppressive therapy, to treat PML in HIV-uninfected adults who developed the disease while on immunosuppressive therapy. While the results with this adjunctive treatment are encouraging, there is insufficient evidence to recommend it at this time.<sup>31,37,38</sup> In addition, recent *in vitro* studies have shown that CMX001, an investigational oral ester form of cidofovir, suppresses JCV replication in human brain cell cultures, and the compound may be evaluated in clinical trials in the near future.<sup>39,40</sup> No therapeutic trials have been conducted in children.

### ***Monitoring and Adverse Events, Including IRIS***

Patients may develop PML before starting cART or may manifest PML as an unmasking IRIS event after immune reconstitution with antiretroviral therapy (ART). Neurologic stability or improvement and prolonged survival are associated with reduced levels of JCV DNA in CSF, appearance of JCV-specific antibody in CSF, and presence of JCV-specific cytotoxic T-cell responses in patients receiving cART.<sup>41</sup>

After cART is initiated and CD4 counts rise, some patients will experience neurologic improvement; however, reports have documented worsening neurologic manifestations after initiation of ART.<sup>26</sup> Clinical worsening may represent the natural history of PML in these patients. However, this apparent worsening may also be a paradoxical reaction from inflammatory responses to JCV potentiated by cART-induced immune reconstitution, called IRIS,<sup>26,42-44</sup> examples of which have occurred in children.<sup>45</sup> The underlying mechanism of cART-associated PML IRIS is controversial. One hypothesis is that a reduction in inhibitory cytokines (e.g., IFN- $\alpha$  and interleukin-12) after cART promotes JCV re-activation within the brain or increases trafficking of JCV-infected peripheral lymphocytes into the brain.<sup>46</sup> Another possibility is that JCV infection occurring coincidental to cART initiation results in a beneficial inflammatory response, with lack of disease progression.<sup>46</sup> This may be particularly likely in cases of perinatal HIV infection, because JCV acquisition is most common early in life. The overall prevalence of PML-associated IRIS in children is unknown. Inflammatory PML should be suspected in cART-treated children with advanced HIV who show acute neurologic deterioration and contrast-enhancing demyelinating lesions on MRI, even if immunological and virological measures show improvement in HIV status.<sup>22</sup> Retrospective data suggest that early and prolonged treatment with steroids may be beneficial for some patients in whom immune reconstitution with ART activates an inflammatory response to JCV. No clinical trial data exist, however, to substantiate the anecdotal evidence.<sup>47</sup>

### ***Managing Treatment Failure***

PML remission with cART may take several weeks, and no criteria exist that define progression of disease. A working definition of treatment failure used for HIV-infected adults is continued clinical worsening and continued detection of CSF JCV DNA at 3 months (see [Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults](#)).<sup>48</sup> In addition, lack of JCV antibody response or JCV-specific cytotoxic T-cell immune responses are associated with poor prognosis. In some patients, PML worsens despite cART, either because of IRIS or because of the natural history of PML. Whichever is the case, cART should be continued. If cART fails to suppress HIV RNA or to increase the CD4 count, then attention should focus on modifying and optimizing the cART (**AII**). In HIV-infected children responding well to cART but with continued worsening of PML, an expert in pediatric HIV infection should be consulted for consideration of investigational therapies.

### ***Preventing Recurrence***

On the basis of its role in reversing the disease, the main measure for preventing PML recurrence is an effective cART regimen that suppresses HIV viremia and preserves or restores CD4-defined immune function (**AII**).

### ***Discontinuing Secondary Prophylaxis***

No methods for secondary prophylaxis of JCV infection or PML have been proven effective.

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