

## **Acute Flaccid Myelitis: Interim Considerations for Clinical Management**

*Please note: these considerations are intended to apply to “acute flaccid myelitis” as defined in the document, and are not intended to be generalized to all forms or etiologies of childhood acute flaccid paralysis, such as Guillain-Barré syndrome, transverse myelitis, or other immune-mediated etiologies. If an alternative diagnosis for the acute paralysis is under consideration, all efforts should be made to explore the alternative diagnosis, and if found, appropriate intervention should be rendered.*

### **I. Background**

Beginning in August 2014, an unusual cluster of neurologic illness presenting as acute limb weakness was noted in hospitals in the Denver area of Colorado, USA.<sup>1</sup> Among the cases in this cluster, the clinical and radiologic features seemed most consistent with a poliomyelitis – like presentation, with limb and cranial nerve weakness occurring in the setting of a febrile illness, and spinal magnetic resonance imaging (MRI) with signal abnormalities largely restricted to the gray matter, producing an illness akin to that caused by polio virus. Of note, prior to the cluster in Colorado, clinicians in California, USA had noted that they seemed to be seeing cases of acute flaccid paralysis (AFP) in children in excess of what they would normally expect;<sup>2</sup> in light of this, clinicians and public health officials in California began doing both retrospective and prospective assessment for such cases – some of these cases had a similar clinical and radiologic picture as those seen in Colorado. Given the unusual clustering of neurologic illness, the Colorado Department of Health Services (CDHS) notified the U.S. Centers for Disease Control and Prevention (CDC) on 16 September, 2014, of the cluster. In response, on 21 September, a joint investigation of the cluster between CDPH, CDC, and the physicians caring for these patients was initiated. This investigation confirmed the initial clinical and radiologic impressions. Given concern that the illness observed in Colorado may be occurring elsewhere in the U.S., on 26 September, 2014, CDC sent out a health advisory (HAN) to public health officials and clinicians nation-wide, and began active surveillance for such cases.

Of note, the unusual clustering of acute limb weakness occurred against a background of a nationwide outbreak of severe respiratory illness among children due to enterovirus-D68 (EV-D68). Several of the patients in California and nearly half of the 11 cases identified in Colorado had tested positive for EV-D68 from nasopharyngeal (NP) swabs at the time of admission for their neurologic illness. This raised a possible association between these neurologic illnesses and the ongoing outbreak of respiratory disease due to EV-D68. While such an association remains to be substantiated, there are ongoing and planned investigations to explore this possible association. To date, however, a clear etiology for the neurologic illness has not been identified.

Following release of the HAN, CDC began receiving information about persons with similar illness from other U.S. states. As of 29 October, CDC had received information about a total of 64 cases meeting the CDC national case definition (acute onset of limb weakness occurring in a person ≤21 years of age with onset on or after 01 August, 2014, and with spinal MRI lesions largely restricted to spinal grey matter) from 28 U.S. states. CDC is also aware of similar cases occurring in various provinces in Canada.

Since initiation of the national request for cases, CDC has received numerous requests from clinicians and public health officials for guidance on how to manage and treat these children with the illness. Anecdotally, CDC has been hearing of clinicians using various therapeutics for clinical management including corticosteroids, intravenous immune globulin (IVIG), and other interventions. Faced with the challenge of providing information on management of an illness of unknown etiology, in October 2014, CDC sought input from a pan-disciplinary group of subject matter experts to assist CDC in drafting suggestions for management of children with this neurologic illness. These experts were from the fields of infectious diseases, neurology, pediatrics, critical care medicine, public health epidemiology, and virology. The input and advice from these consultations formed the basis of the interim considerations for clinical management of 'acute flaccid myelitis' as outlined in this document.

Prior accounts and publications had referred to this syndrome by various terms, including acute limb weakness syndrome, polio-like illness, anterior myelitis, acute anterior horn cell illness, and others. Weighing the options for the most clinically and anatomically accurate nomenclature, the experts decided to refer to the illness as “**acute flaccid myelitis**” (AFM) throughout this document.

## **II. Objectives of this document**

- a. To summarize the evidence for clinicians and public health personnel on methods of management and care of children with acute flaccid myelitis.
- b. In the absence of science-based evidence, to provide consensus expert opinion on management of children with acute flaccid myelitis, in areas in which evidence is sparse or nonexistent.

## **III. A priori presumptions and rationale**

- a. The cases described in Colorado, and several of the cases in California, as well as those identified by CDC, have had in common, clinical features similar to poliomyelitis. The illness predominantly affected children, mainly under the age of 18 years (median, 8 years). As a result, CDC solicited information for cases aged  $\leq 21$  years. As of October 29<sup>th</sup>, 2014, CDC had received information about 64 cases in 28 states that met the case definition. Among these, 80% of cases had described a preceding respiratory illness, and 75% described a fever in the days prior to the limb weakness onset. Onset of limb weakness is generally abrupt, with rapid progression to weakness nadir within hours to a few days; limb weakness is often asymmetric, and in many cases may result in monoplegia. Cranial nerve abnormalities, resulting in facial weakness, ophthalmoplegia, and bulbar signs such as dysarthria and dysphagia, may be variably present. The majority of cases have had a cerebrospinal fluid (CSF) with mild to moderate lymphocytic pleocytosis, normal or mildly elevated protein, and normal glucose. Testing for viral pathogens has not identified enterovirus-D68 (EV-D68) or other viral pathogens in blood or CSF in any patient. Spinal MRI findings are strikingly similar, with predominant involvement of the central grey matter of the cord with relative sparing of adjacent white matter, and often with surrounding edema. These grey matter lesions are generally present in both anterior and posterior segments of the cord, and can extend through multiple levels of the cord. There is also notable signal abnormality and enhancement of ventral nerve roots in some patients, as well as variable lesions noted in the brainstem, particularly the dorsal pons in some. Seizures, altered mental status, nuchal

rigidity, and other features of meningitis or encephalitis have largely been absent. Though data on long-term outcomes including recovery among patients is at present sparse, it appears that in the short term (weeks), patients experience minimal or no recovery in limb strength.

- b. Collectively, the clinical, laboratory, and radiologic picture of these children led the experts to suspect that acute flaccid myelitis (AFM) is likely to be due to a neuroinvasive infectious process, likely of viral etiology. An exact etiology or pathogen –viral, bacterial, parasitic, or otherwise-has yet to be determined, however.
- c. The experts thought it less likely that this illness was of post-infectious immune-mediated etiology. First, CSF has been characterized by pleocytosis and mildly elevated protein, and not cytoalbuminologic dissociation (elevated CSF protein in the absence of pleocytosis) as seen in Guillain-Barré syndrome. Second, the radiologic picture of predominantly grey matter involvement with sparing of white matter tracts is inconsistent with post-infectious neurologic phenomena.
- d. Acute infectious flaccid myelitis may be due to a myriad of viral pathogens, including poliovirus, non-polio enteroviruses (e.g., enterovirus-71), flaviviruses (e.g., West Nile virus, Japanese encephalitis virus), herpesviruses (cytomegalovirus and Epstein-Barr virus), certain strains of adenoviruses, and others. These viruses share a particular tropism for the grey matter of the brainstem and spinal cord, and as a result, the clinical phenotype is largely the same. Thus, it is expected that these management suggestions should be applicable to all forms of AFM, even in the absence of an identified pathogen. If a pathogen with a known definitive treatment is identified (e.g., herpesviruses), specific treatment, if available, for the identified infection should be given.
- e. In general, it should be noted that for nearly all of the therapeutic interventions listed in this document, there is a paucity, or absence, of any data based upon clinical trials. As such, most of the considerations provided here are based upon expert opinion. As controlled data become available for some of these therapeutics, it is probable that some of the considerations will be amended.

#### **IV. Management of Acute Flaccid Myelitis: General**<sup>3</sup>

- a. Evaluate for other etiologies of acute limb weakness (e.g., herpes simplex virus neurologic infection, bacterial infections of the central nervous system, Guillain-Barre syndrome) that have not been adequately excluded as a cause of limb weakness.
- b. Manage chronic medical conditions that may be exacerbated by acute febrile or neurologic illness (e.g., asthma, diabetes mellitus)
- c. Disposition
  - i. Consider ICU Admission in case(s) of:
    - 1. Respiratory muscle weakness as determined by:
      - a. Clinical exam
      - b. Hypoxia
      - c. Hypercarbia
      - d. Vital capacity < 15 mL/kg
      - e. Negative inspiratory force (NIF) < 30 cmH<sub>2</sub>O

2. Impaired airway protection due to bulbar weakness
3. Altered mental status
4. Autonomic instability
5. Cervical lesion(s) on MRI
6. Rapidly progressive course

ii. If obtaining MRI, patient should be closely monitored (telemetry, pulse oximetry, blood pressure)

d. Respiratory

- i. Carefully monitor patients for any evidence of respiratory muscle or bulbar involvement
- ii. If evidence of respiratory muscle weakness, with intact cough and gag reflexes, consider non-invasive positive pressure ventilation (NIPPV)
- iii. If evidence of bulbar weakness, consider invasive positive pressure ventilation (IPPV)
- iv. If evidence of atelectasis or impaired airway clearance, consider chest physiotherapy and airway clearance devices

e. Cardiovascular

- i. Carefully monitor patients for autonomic instability or arrhythmias

f. Neurologic

- i. Pain relief may be required for neuropathic pain
- ii. Intubated patients may require sedation in addition to pain control
- iii. Monitor for signs of rhombencephalitis or meningoencephalitis
- iv. Maintain head of bed elevation at 30°

g. Nutrition

- i. In patients without respiratory compromise, bulbar weakness, altered mental status, or cervical lesions on MRI, consider early initiation of oral feeds
- ii. In patients with respiratory insufficiency, bulbar weakness, altered mental status, or cervical lesions on MRI, consider placement of post-pyloric feeding tube for early initiation of enteral feeds

h. Hematology

- i. Consider deep vein thrombosis (DVT) prophylaxis (compression stockings, anticoagulation) for patients with immobility due to lower extremity weakness, need for mechanical ventilation, or altered mental status

i. Immunology

- i. For immunocompromised patients, if possible, consider reducing immunosuppressive medications for a limited period of time; ideally, as short a time as possible.

j. Dermatologic

- i. In patients with limited mobility, consider measures to prevent skin breakdown

k. Genitourinary / Gastrointestinal

- i. Monitor for urinary retention and place foley catheter as needed
- ii. Monitor for constipation. Avoid opioids if possible.

## **V. Management of Acute Flaccid Myelitis: Physical Therapy and Rehabilitation**

- a. No randomized controlled data on the utility of physical therapy are available. Suggestion is based upon expert opinion, and the thought that potential risk is low.
- b. Initiate early physical and rehabilitative therapy for patients with acute flaccid myelitis. Initiation of active physical therapy as soon as patient is clinically stable may be beneficial in preventing muscular atrophy, joint contractures, and other sequelae of severe and persistent limb weakness, and may improve functional outcomes.

## **VI. Management of Acute Flaccid Myelitis: Specific Interventions / Therapies**

### **a. Corticosteroids**

- i. The experts found no evidence of benefit of corticosteroids beyond anecdotal accounts of improvement in cases of infection with various enteroviruses, West Nile virus, and Japanese encephalitis virus, and several other viruses.
- ii. Conversely, the use of corticosteroids seemed to be associated with poorer outcome in the setting of a large outbreak of neuroinvasive disease due to enterovirus – 71 (EV-71) in Cambodia. This led to the conclusion among a WHO-convened joint commission that corticosteroids were contraindicated in the management of EV-71 associated neuroinvasive disease (*World Health Organization. Global alert and response (GAR): Severe complications of hand, foot and mouth disease (HFMD) caused by EV-71 in Cambodia — Conclusion of the joint investigation. Jul 13, 2012.*)
- iii. The majority of experts expressed considerable concern about the possible ramifications of administration of corticosteroids in the setting of an apparent infectious process, which may compromise the innate immune response to the infection, thus propagating the infectious process and leading to further neuronal damage and leading to worse clinical outcome.

### **Summary**

1. There is presently no indication for use of corticosteroids in the treatment of AFM, and there is a potential risk of worsening outcome due to the immunosuppressive aspects of corticosteroids. The use of corticosteroids is discouraged in the treatment of AFM.
2. Judicious use of corticosteroids should be used to manage severe cord edema in the setting of spinal cord edema that may result in additional cord injury. Monitoring of such progression is largely based upon clinical progression, supported by sequential MRI findings when deemed clinically appropriate. Possible benefits of the use of corticosteroids to manage spinal cord edema in AFM should be balanced with the potential for harm due to immunosuppression in the setting of possible viral infection.

### **b. Intravenous Immune Globulin (IVIG)**

- i. IVIG has been utilized for neurologic complications in infectious diseases associated with neurologic involvement. Enteroviruses cause chronic, severe CNS infections in agammaglobulinemic children, suggesting humoral immunity plays an important role in attenuating enteroviral infection.<sup>4</sup> Similarly, infants who fail to acquire neutralizing antibody from their mothers have been described as having more severe disease when infected with enteroviruses.<sup>5</sup>

- ii. IVIG has been shown to modulate cytokine production (IFN- $\gamma$ , IL-6, IL-8, IL-10, IL-13) in the CNS and systemic inflammatory response. In addition, there is a theoretical risk of IVIG interfering with naturally acquired innate immunity, due to the immunomodulatory effects of the F(ab') region of the immunoglobulin molecule, which may impact cell-mediated immunity.
- iii. For IVIG to modify disease in an active viral infectious process, early administration is likely required, and possibly prior to exposure. Pre-poliovirus vaccine era trials in the 1950s demonstrated potential efficacy of gamma globulin for prevention of poliomyelitis with mass gamma globulin administration to susceptible populations in an outbreak situation.<sup>6</sup> However, a randomized, non-blinded trial of intramuscular (IM) gamma globulin treatment in 49 children (48 controls) with pre-paralytic poliomyelitis (CSF WBC > 10 cells/mm<sup>3</sup> without development of weakness) did not impact development or severity of paralysis during a poliovirus outbreak in New York City in 1944.<sup>7</sup>
- iv. There has been recent experience with the use of both polyclonal and monoclonal IVIG in the treatment of WNV neuroinvasive disease; both have been shown to have some efficacy in prevention of progression to neuroinvasive disease in rodent models. However, clear efficacy of IVIG has not been demonstrated in humans with WN associated paralysis with most data limited to case reports or small case series.
- v. IVIG is generally safe and well tolerated, though expensive. Common intra-infusion adverse effects of IVIG include fever, headache, myalgia, chills, nausea, and vomiting which are typically infusion rate-dependent.<sup>8</sup> Less commonly, hypersensitivity and anaphylactoid symptoms of flushing, tachycardia, hypotension can be seen. Post-infusion adverse events include headaches and aseptic meningitis, fatigue, and arthralgias.<sup>9</sup> IVIG is occasionally associated with severe adverse events such as acute renal failure, thromboembolic events, hemolytic anemia and neutropenia.

### **Summary**

There is no clear indication for efficacy of IVIG in the treatment of AFM; in the absence of such data, the use of IVIG in the setting of AFM is not endorsed.

### **c. Interferon**

- i. Anecdotal accounts of improvement with interferon  $\alpha$ -2b in the treatment of West Nile poliomyelitis-like illness were reviewed. In addition, a case series assessing the efficacy of IFN- $\alpha$  in the treatment of Saint Louis encephalitis, including AFP presentations, suggested some improvement in a non-randomized pilot trial; however, subsequent non-controlled assessments failed to replicate this improvement in cases of SLE and WNV.
- ii. A randomized trial performed in Vietnam from 1996–1999 evaluated 117 children with Japanese encephalitis randomized to receive interferon (10 million units/m<sup>2</sup> daily for 7 days) or placebo. Outcome at discharge and 3 months did not differ between the two

treatment groups; 20 (33%) of 61 children in the interferon group had a poor outcome (death or severe sequelae), compared with 18 (32%) of 56 in the placebo group ( $p=0.85$ , difference 0.1%, 95% CI  $-17.5$  to 17.6%).<sup>10</sup>

- iii. Although there are limited in vitro, animal, and anecdotal human data suggesting activity of some interferons against viral infections, sufficient data are lacking in the setting of AFM.

**Summary**

1. There is no indication for the use of interferon to treat AFM. There is a potential for harm given the experience of use of interferon to treat Japanese encephalitis.
2. Concern was also expressed about the potential for harm from the use of interferon given the immunomodulatory effects in the setting of possible ongoing viral replication. The use of interferon is not endorsed in the management of AFM.

d. Plasmapheresis

- i. It is presumed that there are beneficial effects from the innate humoral immune response to an acute viral infection, in which the body produces neutralizing antibodies to the infectious pathogen.<sup>11</sup> Removal of these antibodies induced in response to acute infection could cause potential harm. Additionally, plasmapheresis requires placement of invasive intravenous access and procedure-associated risks.

**Summary**

The use of plasmapheresis is discouraged in the treatment of AFM.

e. Antiviral medications

i. Current knowledge:

1. It is important to point out that, while the experts viewed that this illness is of viral etiology, rather than another infectious pathogen or autoimmune phenomena, a specific pathogen associated with AFM has yet to be identified.
2. Any guidance regarding antiviral medications should be interpreted with great caution, given the unknowns about the pathogenesis of this illness at present. Health departments, CDC, and other academic entities are working to try to identify a causative agent for this AFM, which will help provide further guidance regarding the use of anti-microbial therapies for this illness.

**Summary**

1. There is no clinical indication for use of antiviral medications in the treatment of AFM, unless there is suspicion of herpesvirus infection (e.g., concomitant supratentorial disease or other clinical or radiologic features of herpesvirus infection), appropriate antiviral medications (acyclovir, ganciclovir) should be empirically administered until herpesvirus infection has been excluded.
2. An effective antiviral would be an attractive treatment option, but none are available at this time. Testing has been conducted at CDC for antiviral

3. activity of compounds pleconaril, pocapavir, and vapendavir, and none have significant activity against currently circulating strains of EV-D68 at clinically relevant concentrations (<http://www.cdc.gov/non-polioenterovirus/hcp/EV-D68-hcp.html>). The use of antivirals is not endorsed in the management of AFM.

f. Other immunosuppressive medications / biological modifiers

- i. In the setting of suspected viral infection, biologic modifiers may have an adverse impact on patients, presuming infectious etiology. The combination of immunosuppressive agents directly impairing T-cell function (and B-cell function indirectly), or therapy directed against primary humoral immunity (e.g., rituximab) may further worsen the ability to clear infection.

**Summary**

There is no known indication for the use of other immunosuppressive agents in the management of AFM, and there is a possibility of causing harm. The use of such biologic modifiers is discouraged in the management of AFM.

**VII. Summary of Interim Considerations**

- a. General routine clinical management of children with AFM should adhere to basic standards of care for children with severe neurologic disease.
- b. Physical and occupational therapy should be implemented as soon as the child is physically stable in order to optimize functional outcomes.
- c. There are currently NO targeted therapies / interventions that are felt to have definitive efficacy in the treatment or management of AFM. Reviewing numerous possible targeted interventions, the experts found no concrete evidence for indication of corticosteroids, IVIG, plasmapheresis, interferon, antivirals, or other immunomodulatory agents in the treatment of AFM.
- d. Plasmapheresis and immunosuppressive biologic modifiers, including corticosteroids, should be discouraged in the management of AFM.
- e. The considerations for management described in this document will be revised as needed if more information becomes available.

**For further information / questions regarding AFM, please visit**

<http://www.cdc.gov/ncird/investigation/viral/sep2014.html>, or send inquiry to [limbweakness@cdc.gov](mailto:limbweakness@cdc.gov).

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