Acute Flaccid Myelitis 100 90 80 70 60 50 40 30 20 10 Aug-14 Dec-14 Dec-14 Jun-15 Jun-15 Apr-15 Dec-15 Aug-16 Dec-17 Apr-17 Apr-17 Apr-17 Apr-17 Apr-17 Apr-18 Apr-18 Apr-18 Apr-18 Apr-18 Apr-18 Apr-19 Dec-18 Apr-19 Jun-19 Apr-19 Apr-10 Ap





Kevin Messacar, MD

Assistant Professor of Pediatric Infectious Diseases University of Colorado/ Children's Hospital Colorado

(kevin.messacar@childrenscolorado.org, @kmess44)



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• I will discuss off-label use of medications



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- Siegel Rare Neuroimmune Association, John Hopkins University, Kennedy Krieger Institute, and Acute Flaccid Myelitis Working Group
- Advances in this field have been driven by the dedication and hard-work of many basic scientists, clinicians, researchers, and public health experts working collaboratively
- Thank you to the patients and families affected by AFM for teaching us and your contributions to research efforts



Overview

• The Past: How far we have come...



• The Present: ...our current understanding of AFM...

• The Future: ... how far we still need to go.

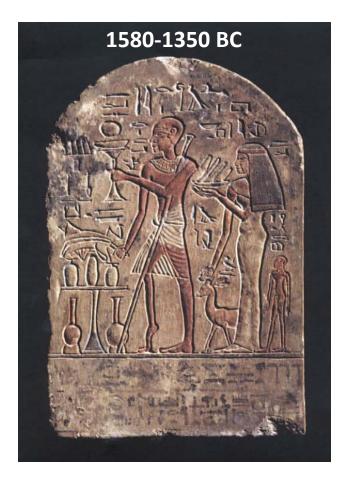






Historical Context

Infantile paralysis

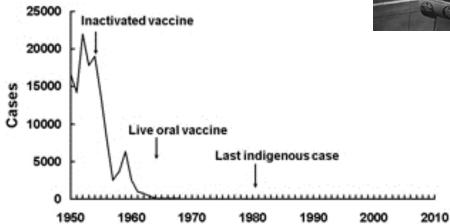




Historical Context

- Infantile paralysis
- Poliomyelitis





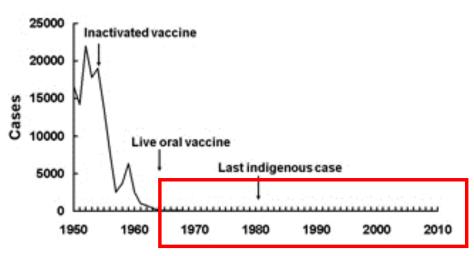




Centers for Disease Control and Prevention (2015). Poliomyelitis. Epidemiology and Prevention of Vaccine-Preventable Diseases 13th Edition. J. Hamborsky, A. Kroger and S. Wolfe. Washington D. C., Public Health Foundation.

Historical Context

- Infantile paralysis
- Poliomyelitis
 - Poliovirus vaccine:



- Sporadic non-polio acute flaccid paralysis
 - Flaviviruses (West Nile virus, Japanese encephalitis virus)
 - Non-polio EVs (EV-A71, EV-D70)

Kincaid O, Lipton HL. Viral myelitis: an update. Current neurology and neuroscience reports. 2006;6(6):469-474. Bitnun A, Yeh EA. Acute Flaccid Paralysis and Enteroviral Infections. Curr Infect Dis Rep. 2018;20(9):34.



2012: Polio-like Illness Reports in CA

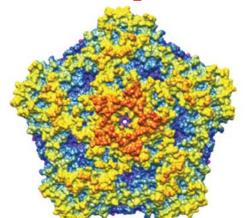
- 2012-13: Cluster of 5 pediatric cases of a polio-like syndrome reported to California Department of Public Health
 - All poliovirus vaccinated, all poliovirus testing negative
 - 3 with preceding respiratory illness
 - 2 tested positive for enterovirus D68

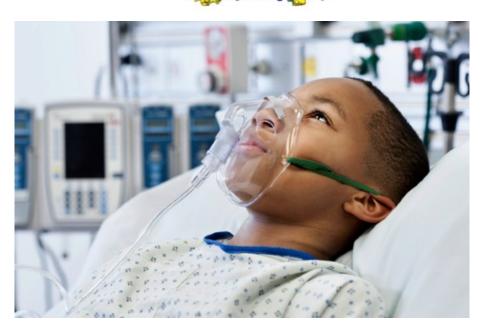
August 2012: Passive statewide surveillance established in CA



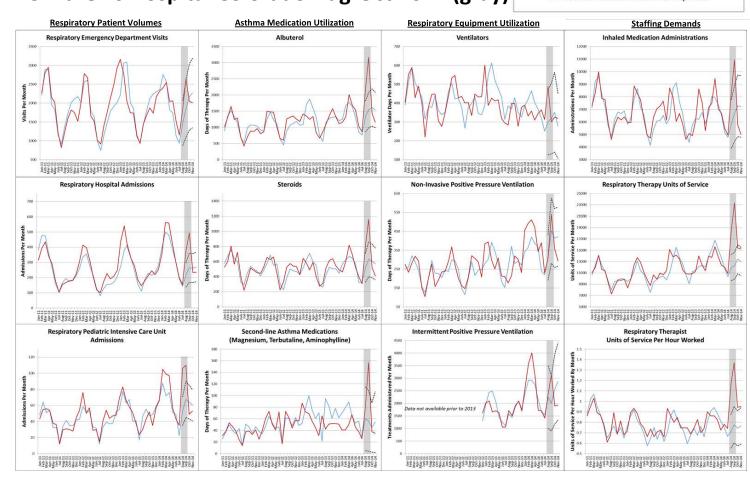
Roux A, Waubant E, Glaser C, Van Haren K. (2014) A Polio-Like Syndrome in California: Clinical, Radiologic, and Serologic Evaluation of Five Children Identified by a Statewide Laboratory over a Twelve-Months Period. AAN Abstract Van Haren K, Ayscue P, Waubant E, et al. Acute Flaccid Myelitis of Unknown Etiology in California, 2012-2015. JAMA. 2015;314(24):2663-2671.

Fall 2014 Enterovirus D68 Outbreak: An Unexpected Strain





Observed vs. Expected Resource Utilization at Children's Hospital Colorado Aug-Oct 2014 (gray)



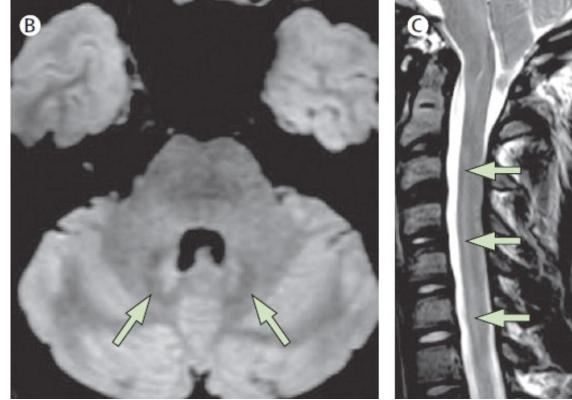
Expected Value (SARIMA modeling)

---95% Confidence Interval of Expected

Messacar K, Hawkins SM, Baker J, et al. Resource Burden During the 2014 Enterovirus D68 Respiratory Disease Outbreak at Children's Hospital Colorado: An Unexpected Strain. JAMA pediatrics. 2016;170(3):294-297.

In the midst of the outbreak...

- 18 yo M with fever, nasal congestion, cough, sore throat
- 7 days later develops headache, stiff neck, and cannot move his L arm
- CSF pleocytosis, MRI with longitudinal gray matter and brainstem lesions
- Within 24 hours intubated for airway protection due to bulbar paralysis
- No response to IVIG
- Tracheostomy, gastrostomy

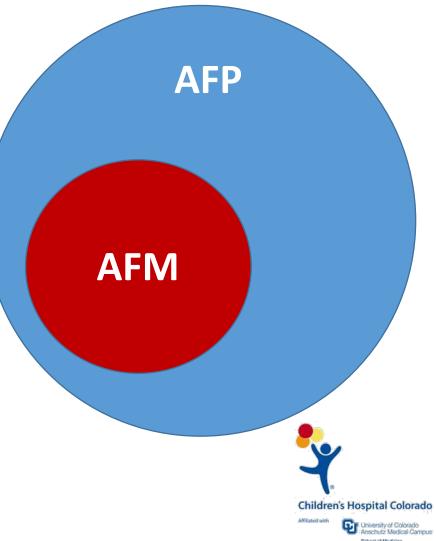




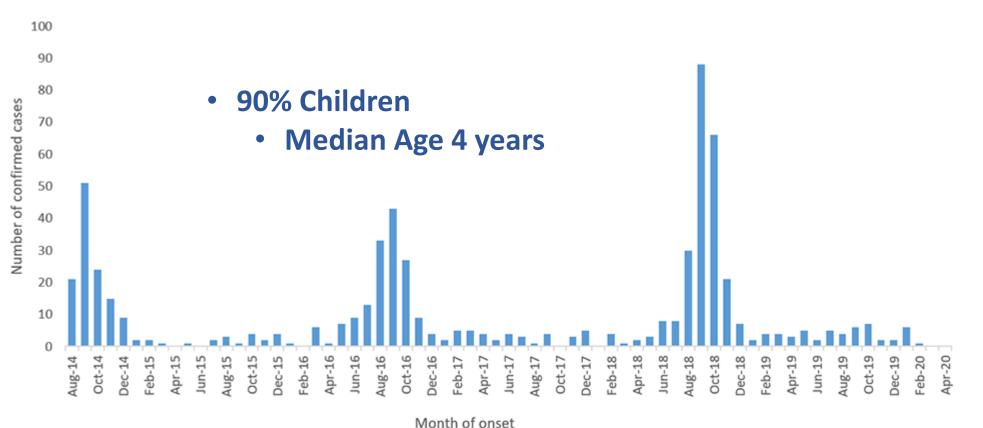


Acute Flaccid Myelitis: Surveillance Case Definition

- Clinical criteria: Acute onset flaccid limb weakness (AFP)
- + Imaging criteria: MRI with spinal cord lesion with predominant gray matter involvement spanning one or more vertebral segments



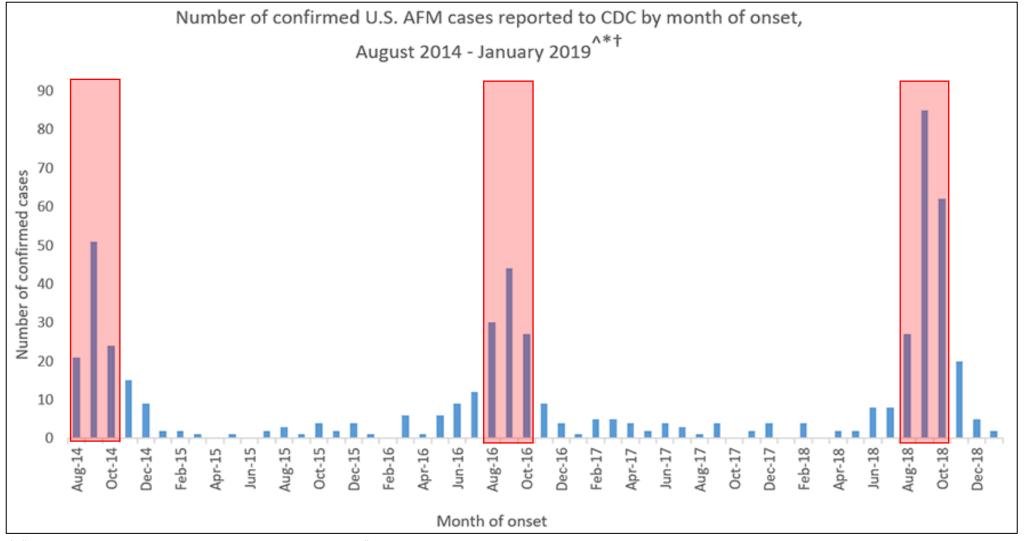




- 2014: 120 cases
 - 34 states
- 2015: 22 cases
 - 17 states
- 2016: 153 cases
 - 39 states
- 2017: 38 cases
 - 17 states
- 2018: 238 cases
 - 42 states
- 2019: 46 cases
 - 18 states



Temporal Association Between AFM Cases and EV-D68 Circulation in US



Messacar K, et al. (2019). "Acute Flaccid Myelitis Surveillance: A Signal Through the Noise" Pediatrics.

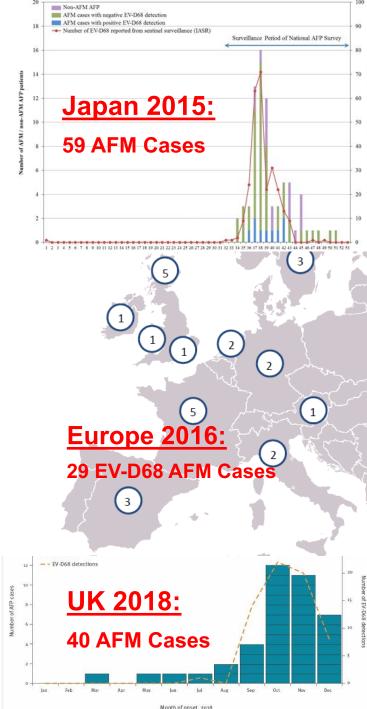
Global Epidemiology: EV-D68 Acute Flaccid Myelitis

>150 cases in 20 countries on 6 continents

Messacar, K., et al. (2018). "Enterovirus D68 and acute flaccid myelitis-evaluating the evidence for causality." *Lancet Infect Dis.* Updated with new reported cases. Chong, P. F., et al. (2017). "Clinical Features of Acute Flaccid Myelitis Temporally Associated with an Enterovirus D68 Outbreak: Results of a Nationwide Survey of Acute Flaccid Paralysis in Japan, August-December 2015." Clin Infect Dis.

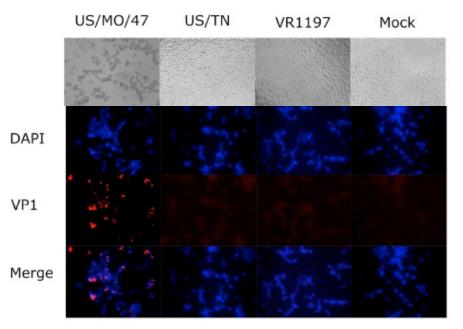
Knoester M, Helfferich J, Poelman R, et al. (2018) Twenty-Nine Cases of Enterovirus-D68 Associated Acute Flaccid Myelitis in Europe 2016; A Case Series and Epidemiologic Overview. The Pediatric infectious disease journal.

The United Kingdom Acute Flaccid Paralysis Afp Task, F. (2019). "An increase in reports of acute flaccid paralysis (AFP) in the United Kingdom, 1 January 2018-21 January 2019: early findings." Euro Surveill 24(6).



States of States

• EV-D68 infects motor neurons

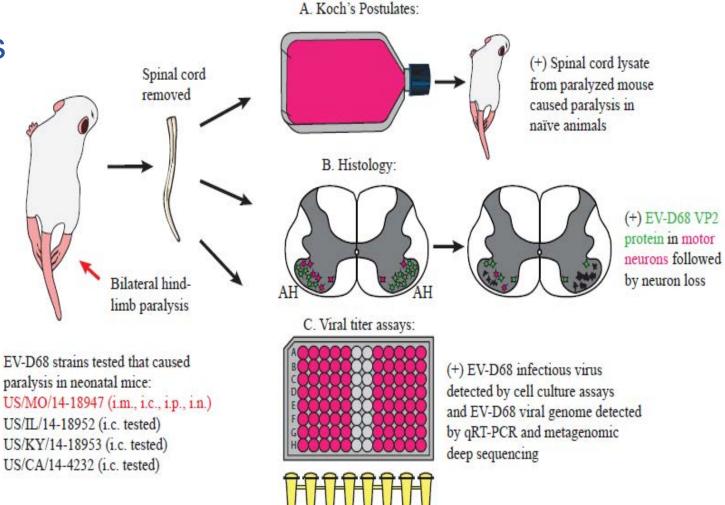


Neuroblastoma-derived SH-SY5Y neuronal cell line



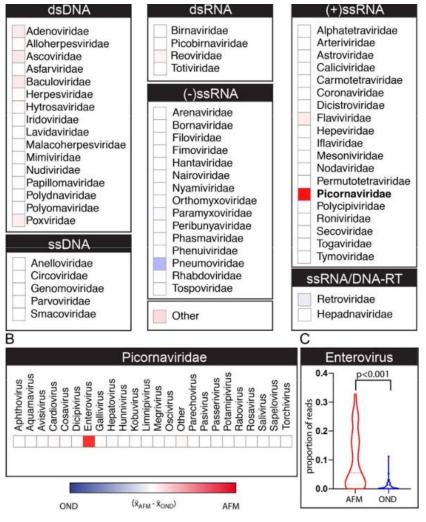
Brown DM, Hixon AM, Oldfield LM, et al. Contemporary Circulating Enterovirus D68 Strains Have Acquired the Capacity for Viral Entry and Replication in Human Neuronal Cells. MBio. 2018;9(5). Rosenfeld AB, Warren AL, Racaniello VR. Neurotropism of enterovirus D68 isolates is independent of sialic acid and is not a recently acquired phenotype. bioRxiv. 2017.

- EV-D68 infects motor neurons
- EV-D68 causes AFM in mice



Hixon, A. M., et al. (2017). "A mouse model of paralytic myelitis caused by enterovirus D68." <u>PLoS Pathog</u> **13**(2): e1006199.

- EV-D68 infects motor neurons
- EV-D68 causes AFM in mice
- No viruses present in CSF
 - EV antibodies identified



Children's Hospital Colorado

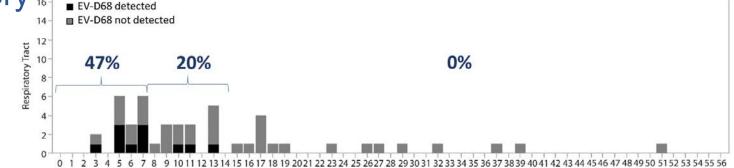
G University of Colorado Anschutz Medical Campus

School of Medicine

Athliated with

Schubert, R et al. (2019) Serological and metagenomic interrogation of cerebrospinal fluid implicates enteroviruses in pediatric acute flaccid myelitis. <u>Nature Medicine</u>. Mishra, N et al. (2019) Antibodies to Enteroviruses in Cerebrospinal Fluid of Patients with Acute Flaccid Myelitis. <u>MBio</u>

- EV-D68 infects motor neurons
- EV-D68 causes AFM in mice
- No viruses present in CSF
 - EV antibodies identified
- EVs most commonly identified viruses in AFM cases
 - EV-D68: NP respiratory specimens
 - EV-A71: stool>OP>NP respiratory 16

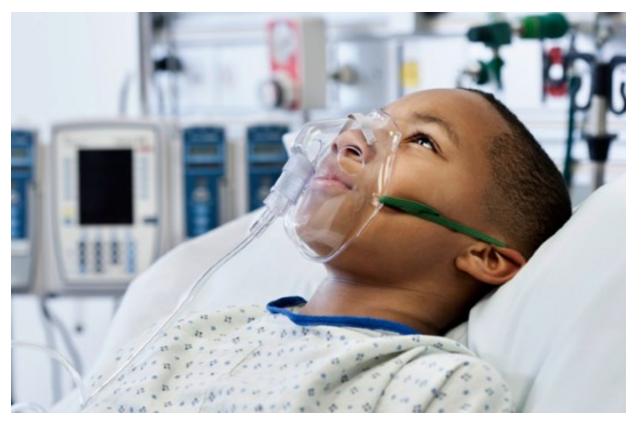


Sejvar, J. J., et al. (2016). "Acute Flaccid Myelitis in the United States-August -December 2014: Results of Nation-Wide Surveillance." <u>Clin Infect Dis.</u>



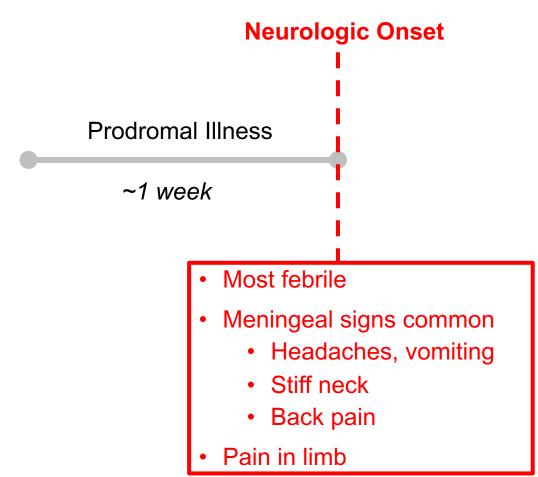
Prodromal Illness

~1 week





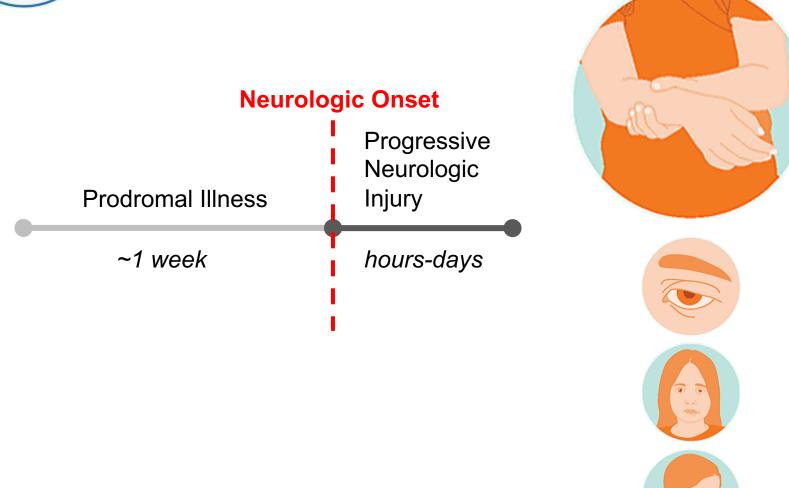




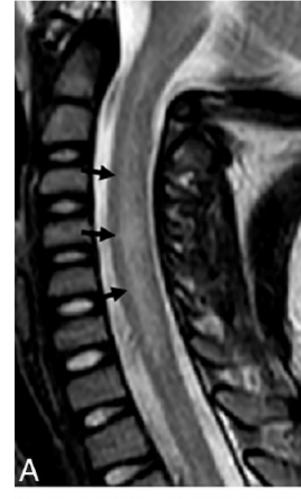
Messacar, K., et al. (2016). "Acute flaccid myelitis: A clinical review of US cases 2012-2015." Ann Neurol 80(3): 326-338.

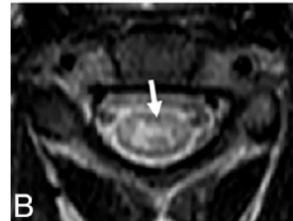




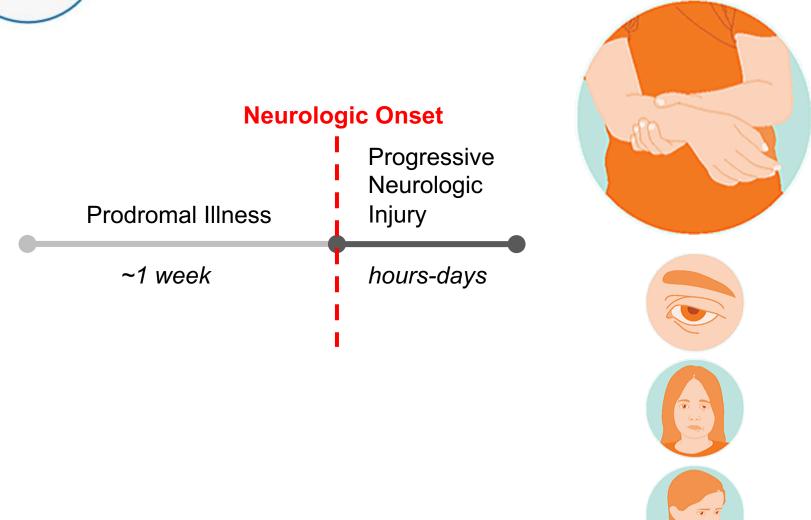


Maloney JA, Mirsky DM, Messacar K, et al. (2015) MRI findings in children with acute flaccid paralysis and cranial nerve dysfunction occurring during the 2014 enterovirus D68 outbreak. AJNR





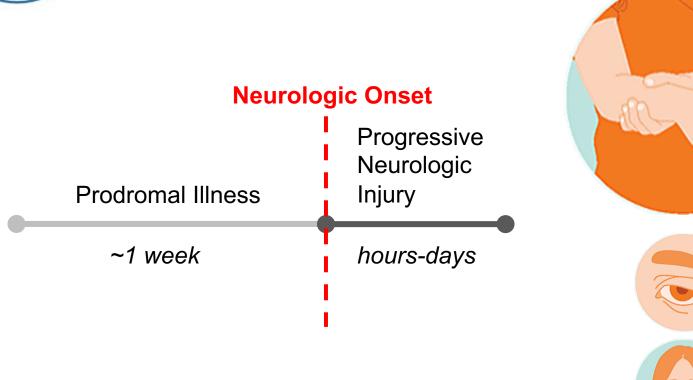


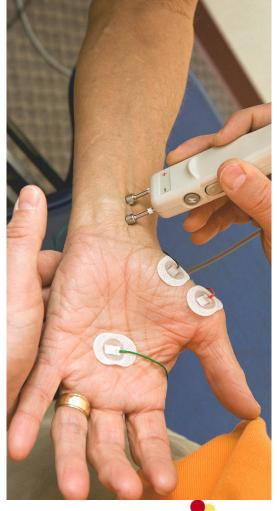


Maloney JA, Mirsky DM, Messacar K, et al. (2015) MRI findings in children with acute flaccid paralysis and cranial nerve dysfunction occurring during the 2014 enterovirus D68 outbreak. AJNR





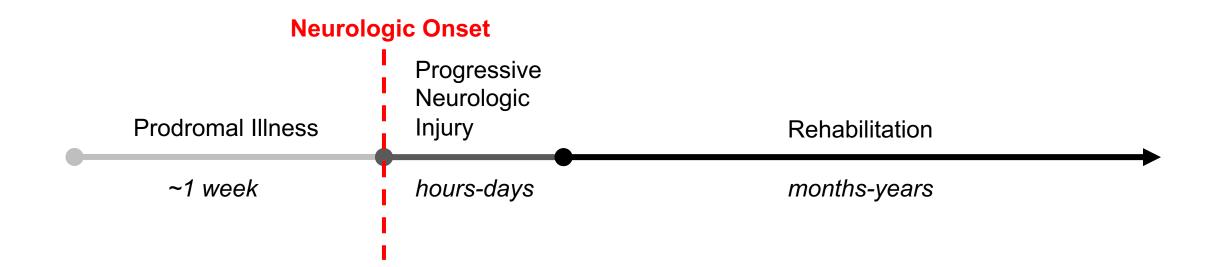






Martin, J. A., et al. (2017). "Outcomes of Colorado children with acute flaccid myelitis at 1 year." <u>Neurology</u> 89(2): 129-137.

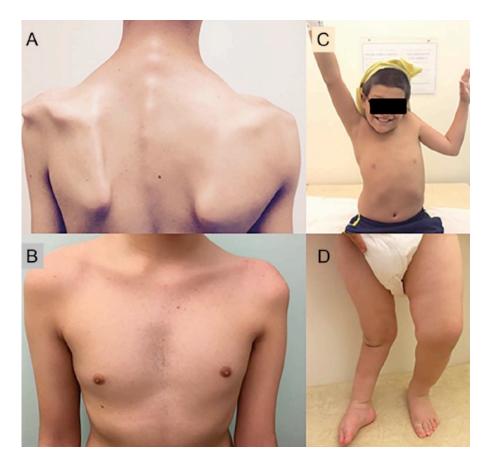






AFM Outcomes

- Functional improvements with rehabilitation therapies
 - Most recovery occurs early
 - Improvement still noted after 12 months
 - Distal, less-affected muscles > proximal, more-affected muscles > completely denervated muscles
- Motor deficits persist in ~75% at 1 year
- Nerve and tendon transplants→ functional gains in certain patients



Polio-like muscle atrophy in affected limbs



Martin, J. A., et al. (2017). "Outcomes of Colorado children with acute flaccid myelitis at 1 year." Neurology 89(2): 129-137.

Yea, C., et al. (2017). "Longitudinal Outcomes in the 2014 Acute Flaccid Paralysis Cluster in Canada." J Child Neurol 32(3): 301-307.

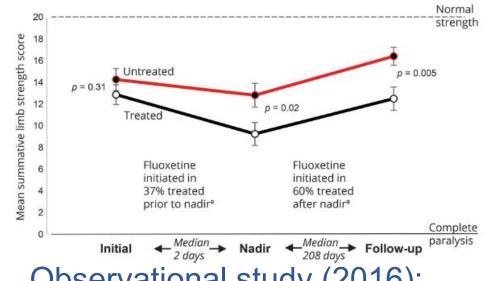
Gordon-Lipkin, E., et al. (2018). "Comparative quantitative clinical, neuroimaging, and functional profiles in children with acute flaccid myelitis at acute and convalescent stages of disease." Dev Med Child Neurol

Saltzman EB, Rancy SK, Sneag DB, et al. (2018) Nerve Transfers for Enterovirus D68-Associated Acute Flaccid Myelitis: A Case Series. Pediatric neurology. 88:25-30.



Addressing AFM Future Challenges

- Why are certain children affected?
 - Host genetics studies
- Role of infection vs. immune response?
 - Basic science, NIH Natural History Study
- Which treatments are most effective?
 - No controlled human studies
 - EV-D68 monoclonal antibodies created
 - Screening antivirals in vitro, animal models
- How can we prevent AFM?
 - EV vaccine candidate identification underway



Observational study (2016): Fluoxetine administered off-label due to *in vitro* EV-D68 activity

 No signal of efficacy in retrospective analysis

Early Recognition: Key to AFM Advances

• THINK AFM in any patient with new onset weakness, particularly:

- Children with asymmetric, flaccid weakness in arms > legs
- Following a febrile illness
- Summer-fall season during enterovirus outbreaks
- **DIAGNOSE AFM** by neurologic exam, neuroimaging, lumbar puncture
 - Look for cause by collecting early biologic specimens (CSF, blood, stool, NP/OP)
- MANAGE AFM with respiratory & neurological supportive care, rehabilitation
 - Get help from neurology and infectious disease consultants, physician support portal

• **REPORT AFM** to your state health department as soon as you suspect it

• Submit requested data and biological specimens using CDC Job Aid



A Parent Perspective



Rachel Scott AFM Parent and Co-Founder Acute Flaccid Myelitis Association