Weak in the Knees: Evidence Based Case Studies of Acute Flaccid Paralysis: Differential Diagnosis and Management

Session # 314
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Speaker Introduction

- Jamie Tumulty has been practicing as a PNP in the PICU at University of Maryland Medical Center since 2002. She is author of several book chapters on various topics. She has presented at local and national conferences including NTI and NAPNAP. She has participated in several research studies including two national multicenter studies, and was the recipient of AACN funded research grant.

Disclosures

Nothing to disclose

Learning Objectives

- Distinguish between upper and lower motor neuron disease based on history, physical exam, and diagnostic studies.
- Describe pharmacologic and other supportive therapies for the patient with neuromuscular weakness based on the current literature.
- Describe strategies to minimize or prevent ICU related myopathy and polyneuropathy.

Anatomy of Motor Control

- Primary Motor cortex: generates nerve impulses to execute movement
- Posterior Motor cortex: transforms visual input into motor commands
- Premotor cortex: involved in sensory guidance of movement
- Supplementary motor cortex: coordinates complex movements (two hands)
- Cerebral nerves

https://brainconnection.brain HQ.com/2013/03/05/the-anatomy-of-movement/

Nerve Conduction & Muscle Contraction

https://brainconnection.brain HQ.com/2013/03/05/the-anatomy-of-movement/
Case 1

General Impression

- Previous healthy 4yr male
- Several days emesis and watery diarrhea (no fever)
- Leg pain and weakness refusal to walk → admitted to community hospital
- What additional history would you obtain?
- No URI, sex, travel or bites
- Family history of lupus and migraine

Inspection: atrophy, hypertrophy, resting posture/tone, movement (gait, balance), asymmetry

Palpation: tenderness, PROM/tone

DTRs: absent, hyper‐reflexia

Muscle strength

T 38.9, bp 110/70, RR 48, HR 110, pulse ox 97% on 2 L NC

HEENT: drooling, clear secretions. extraocular muscles intact, neck supple. no meningeal signs.

Respiratory: Tachypneic to the 40s, coarse breath sounds bilaterally.

Cardiovascular: warm well perfused

GI: Soft, nontender, nondistended. No HSM

Neurologic: Alert and appropriate. Answers questions.

Musculoskeletal: Cachectic appearance and unsteady gait, difficulty balancing upright. Decreased muscle bulk and tone. Decreased swallow, 3/5 upper and lower extremity strength. Unable to elicit patellar ankle reflexes.

Upper vs Lower Motor Neuron Disease

Upper motor neuron signs
- Spasticity
- Hypertonia
- Positive Babinski
- Increased DTRs
- Clonus
- Pronator drift

Lower motor neuron signs
- Flaccidity
- Hypotonia
- Absent Babinski
- Decreased DTRs/Hyporeflexia
- Fasciculations
- Muscle atrophy

http://i.ytimg.com/vi/MuJEmuqks6s/0.jpg

http://slideplayer.com/slide/6373570/22/images/33/The%20Babinski%20Reflexes.jpg

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Does this patient have upper or lower motor neuron disease?
Upper Motor Neuron Disease

- Cerebral palsy
- Multiple Sclerosis
- Traumatic brain injury
- Intracranial hemorrhage
- Stroke
- Tumor
- Todd’s paralysis
- Hemisyndromic migraine

- CNS Demyelinating diseases
- Immune mediated
- MS
- ADEM
- NMO
- Transverse myelitis
- Metabolic (Vitamin B12 deficiency)
- Genetic (Lou Gehrig’s/ALD)
- Infectious

Lower Motor Neuron

- Usually flaccid

- Anterior horn
- SMA
- Polio
- Arthrogryposis
- Peripheral nerve
- Guillain-Barre syndrome
- Heavy metal poisoning
- Paraphymia

- Neuromuscular
- Botulism
- Myasthenia gravis
- Organophosphate poisoning
- Tick paralysis
- Snake bite

Case 1 differential diagnosis

- Myositis
- Meningitis
- Infectious encephalitis
- Demyelinating process (ADEM or rhombencephalitis)
- GBS
- CNS vasculitis
- Toxic/metabolic etiologies

Case 1 Diagnostic Studies

- $6.6/9.6$ $266 (79 s, 11 b, 6 L, 4 m)$ $\text{Bld Cx negative}$
- $27.5$
- $136/97/7/144$ $34/90$ $6.9$ $\text{CRP 2.8}$
- $3.7/26/0.21$ $19/0.3/3.4$ $\text{Tox screen neg}$
- $\text{Lactate 0.8}$
- $\text{Resp panel paraflu+, bld cx negative}$
- $\text{ANA neg}$
- $pANCA neg$
- $\text{CSF glu 79, protein 11, wbc 6, rbc 0}$
- $\text{cANCA neg}$
- $\text{CSF Cx negative bacteria, HSV, Lyme, enterovirus}$

Case 1 Imaging

- Head CT (community hospital) - neg
- CKR - pneumonia
- Brain MRI - enhanced signal concerned for ADEM, rhombencephalitis or toxic metabolic disease
- Spine MRI – negative
- EMG - slowing without demyelination (consider axonal GBS)

Acute Disseminated Encephalomyelitis (ADEM)

- Neuroinflammatory demyelinating disease of CNS
- Multiple sclerosis borderline disorder (sx similar to MS) but can be more severe
- Acute onset, single flare up, 1-3 weeks after viral infection
- Seasonal (winter and spring)
- Symptoms worsen over time and peak at ~4 days, including rapid development of high fever
- Autoimmune mechanism
- Incidence: 1 in every 125,000 - 250,000 individuals/yr
- Children>adults (80% pediatric cases <10 yr)
- Boys and girls affected nearly evenly (boys>girls 1.3 : 1)
Infections Associated with ADEM

**VIRAL**
- Influenza virus
- Parainfluenza
- Dengue
- Enterovirus
- Mumps
- Rubella
- Varicella zoster
- Epstein Barr virus
- HIV
- HHV6
- Cytomegalovirus
- Herpes simplex virus
- Hepatitis A
- Coxsackievirus
- Mycoplasma pneumoniae
- Beta-hemolytic Streptococci
- Borrelia burgdorferi
- Leptospira
- Rickettsia
- Chlamydia
- Legionella

**BACTERIAL**
- Mycoplasma pneumoniae
- Beta-hemolytic Streptococci
- Campylobacter
- CMV, EBV, Mycoplasma, influenza like illnesses
- Campylobacter, CMV, EBV, Mycoplasma, influenza like illnesses
- Lyme disease
- Tuberculosis
- Chlamydia
- Legionella

ADEM

- General symptoms
  - Fever
  - Headache
  - Nausea and vomiting
  - Confusion
  - Agitation
  - Vision impairment
  - Drowsiness
  - Seizures
  - Coma
- Motor symptoms
  - Ataxia
  - Hemiparesis
  - Paraparesis
  - Cranial nerve palsies

ADEM Diagnostic Criteria

- First episode of inflammatory/demyelinating disease in the CNS
- Acute onset
- Multiple areas of CNS affected/polysymptomatic
- Must include encephalopathy:
  - Acute behavioral change (confusion/intubility) and/or
  - Alteration in consciousness (somnolence/coma)
- Attack should be followed by clinical or radiographic improvement
- Sequelae may include residual deficits
- No other etiologies can explain the event

Guillain–Barré Syndrome

(Acute Inflammatory Demyelinating Polyneuropathy)

- Autoimmune destruction of myelin sheath of peripheral neurons (Schwann cells), or axon (AMAN)
- Often with antecedent URI or gastroenteritis 3-6 weeks prior
- Most common cause of acute flaccid paralysis in children
- Incidence 1-2/100,000 children < 18 annually

Symptoms:
- Symmetric tingling, pain followed by ascending pattern of weakness
- May progress to respiratory failure
- Hyporeflexia/areflexia
- Autonomic dysfunction (variable)
- Absence of fever

GBS Diagnosis

- History & clinical exam with ascending pattern of weakness
- CSF: elevated protein (>55) without elevated WBC (<10)
- MRI: rule out other causes such as spinal cord compression
  - may show enhancement of cauda equine nerve roots
- Electrodiagnostic studies
  - Nerve conduction studies show slowing
  - EMG show acute denervation
- Antiganglioside antibodies present in some forms

Spectrum of Disorders in the Guillain–Barré Syndrome and Associated Antiganglioside Antibodies

- Miller Fisher variant
- Starts with ophthalmic involvement
- Blurry vision
- Diplopia
- Progresses downward
- Facial weakness
- Slurred speech
- Decreased gag
- Trunk and limbs
- Ataxia
- Hyporeflexia
GBS Treatment

- Steroids not recommended (AAN, Cochrane review)
- IVIG
- Plasma exchange
- No evidence that combining therapies improves outcome
- Insufficient evidence for CSF filtration and immunoabsorption

Case 1 continued

- Intubated x 2 weeks
- IVIG x3 days → improvement in strength
- GQ1b Ab sent to rule out GBS negative (but after IVIG)
- 5 days high dose steroids (for rhombencephalitis and new vertical nystagmus) → further improvement in strength
- Gabapentin, topiramate and amitriptyline for HA and leg pain
- GT placement (aspiration on saliva gram)
- Aggressive PT and OT with improvement in strength
- Discharged home after 6 wk with rolling walker and home PT

Case 1 continued

- Readmitted 1 mo later with 1 day h/o leg pain, HA, fever, weakness, difficulty walking
- General: agitated alert, awake, and irritable.
- HEENT: PERRL, EOMI, neck has limited range of motion with flexion, unable to perform full extension.
- Respiratory: Breath sounds are clear, no increased work of breathing
- Cardiovascular: Regular rate and rhythm, no murmurs, 2+ pulses, no edema.
- Lymphatic: No cervical lymphadenopathy.
- Musculoskeletal: No gross joint deformities, symmetric strength, arms 4/5, legs 4/5, pain on movements, refusal to walk, gait not assessed.
- Neurologic: Cranial nerves II through XII grossly intact. Normal bulk and tone. Sensation intact. Unable to elicit reflexes.
- Psychiatric: Irritable, but oriented to mother and surroundings in time of day.

Case 1 readmission

Concern for infection → antibiotics initiated pending laboratory evaluation

| CRP | < 5 |
| CRP | < 5 |
| Blood culture - pending |
| Blood culture - pending |
| AST 132 | ALT 132 |
| Ca 9.6 | Alk ph 190 |
| Mg 2.2 | T protein 8.7 |
| ALT 322 | bilirubin 0.5 |
| albumin 4.7 |
| Phos 5.6 |

CSF – clear. Glucose 34, protein 308 WBCs 1370 (S 86 s, L 12 L, M 2 m) RBCs 288 CSF culture – pending

CT - no intracranial process

NMO – Neuromyelitis Optica

- Demyelinating disease primarily affects optic nerves and spinal cord

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Diagnostic criteria for neuromyelitis optica (NMO).

1 – Acute myelitis

2 – Optic neuritis

3 – At least two of three supportive criteria:

* Contiguous spinal cord magnetic resonance imaging (MRI) lesion over ≥3 vertebral segments

* Brain MRI not meeting diagnostic criteria for multiple sclerosis

* Anti-aquaporin 4 (anti-AQP4) seropositive status

Pereira (2015)
NMO Management
• No cure, goal is symptom management
• Acute
  • High dose IV steroids
  • Plasma exchange, 5 sessions recommended
  • Immunosuppressive therapy
    • First line: azathioprine, mycophenolate mofetil, and rituximab
    • Second line: mitoxantrone, methotrexate, cyclosporin
  • IVIG for children and if immunosuppression is contraindicated
• Suppressive
  • Low dose steroids
  • Immunosuppressive therapy
• Under investigation: aquaporinum (non-pathogenic antibody blocker of AQP4-IgG binding), sivelestat (neutrophil elastase inhibitor), and eculizumab (complement inhibitor)
• Recovery possible, but many experience visual/limb impairment, which can be severe

Diagnostic Algorithm
CIS=clinically isolated syndrome

Treatment Algorithm

Case 2
• 7 mo presents with pallor, poor po intake and lethargy
  • Difficulty opening his mouth
  • Difficulty lifting his head
• Interval history/ROS
  • Hand foot and mouth 1 month ago
  • Several episodes of vomiting (NBNB x 4-5 times) a week ago, no diarrhea or constipation, decreased urine output
  • Cough and congestion 2 days ago
  • Dx bronchiolitis, treated with steam, saline drops and suctioning
  • Age appropriate development

Case 2: Exam/Initial Management
• VS: afibrile, HR 160, RR 45, pos 93%
• Exam: poor tone, weak cry, weak gag, difficult to elicit reflexes, dehydrated, copious secretions
  • Received 60 ml/kg fluid, seemed more alert/eye contact with parents, but still unable to move extremities
• Attempt to intubate for airway protection, unsuccessful, LMA placed for transport
• Initial work up
  • CXR-no focal infiltrate
  • CBC-no left shift
  • RSV and flu negative
  • BMP-glucose 86

Some institutions may favor plasma exchange first so as not to remove IVIG

Benson, Olsen & Gorman, 2017
Case 2: Laboratory Evaluation

- Expanded respiratory viral panel + rhinovirus
- Blood culture: negative
- Urine culture: negative
- Sputum culture: consistent with normal upper respiratory flora
- LP: glucose 133 (serum glucose 140), Protein 60 (normal 12-60)
- LP: RBC 0, WBC 0 (90L, 10m), IgG 1.7 (normal 0-6)
- CSF culture: negative

Differential Diagnosis

- Infection: CBC reassuring, CRP negative, Cx negative
- Meningitis
- Stroke: MRI normal
- Opioid overdose
- Acute flaccid myelitis
- Botulism
- Myasthenia gravis
- Polio
- SMA
- Guillain Barre syndrome
- Distinguish between ascending and descending motor weakness (clinical history)

Case 2: Initial MRI

- Normal appearance of the brain
- No evidence of cavernous sinus thrombosis
- No evidence of arterial or venous occlusion
- No evidence of aneurysm
- Normal appearance of the spinal cord

Initial workup was largely unrevealing

Patient failed extubation attempt due to respiratory insufficiency, hypoxia, hypercarbia and poor secretion clearance prompting further investigation

Case 2 Continued: Consults

- Surgical consult given emesis and diffuse gaseous distention of bowel
  - Non concerning given soft nontender abdomen
  - Likely ileus related to viral infection
- Genetics consult given weakness
  - IEM possible but unlikely
  - Considering genetic testing for SMA mild types, or other testing if more symptoms develop
- Neurologic consult given weakness
  - Stool sample
  - EMG

EMG

Motor nerve conduction amplitude is decreased
Motor nerve conduction velocity is prolonged
Fasciculations persist
Sensory nerve conduction amplitude and velocity are normal

Neurology

- EMG/NCS
  - Fasciculations - consistent with a presynaptic motor neuron disease (such as botulism)
  - If botulism, this presentation is atypical
    - preserved pupillary reflex, gag, and DTRs
    - lack of significant constipation or obvious exposures
  - Treatment is appropriate due to possibility and seriousness of disease
  - If improvement is not seen, would consider workup for SMA (SMN mutation) or other viruses that can mimic botulism
  - F/u botulism studies and enterovirus genotyping
**Botulism (Neuromuscular Junction Disorder)**

- Ingested spores of clostridium botulinum germinate and colonize the colon producing botulism toxin
- Toxin irreversibly blocks acetylcholine release in peripheral cholinergic synapses
- Cranial nerves affected first and most severely
- Incidence (CDC 2016): 205 cases, 149 infant (74%)
- Diagnosis: History, Exam, Botulism toxin present in stool

**Botulism Treatment**

- Botulism Immune Globulin Intravenous (BIG-IV)
  - Introduced in 2003
  - Dose: 50mg/kg over slow infusion
  - Treatment should **NOT** be delayed if botulism suspected
  - Report to health department
  - Shown to decrease ICU LOS, length of mechanical ventilation, and overall hospital stay
- Supportive care
- Respiratory support
- Tube feeding
- Bowel regimen

**Case 3**

- 11 yr old with hx of asthma, allergies, scoliosis, 2 day h/o URI, admitted with hypoxic respiratory failure
- Required VV ECMO x 6 days, ventilation x 12 days + 7 days
- Following ECMO decannulation and weaning of sedation
- Lower extremity paraplegia
- Patellar reflexes diminished
- Ankle reflexes absent
- Inability to elicit ankle or Babinski
- Decreased strength of the upper extremities
- Sensation was intact

**ICU Acquired Weakness**

- Many names (ICU-AW, CINMA, CIM, CIP) no universal definition or consensus
- Many proposed mechanisms
  - Direct inflammation of muscle or nerve
  - Cytokine mediated
  - Metabolic/energy related
  - Pre-admission factors/comorbidities
  - ICU factors
    - Steroids, NMB, hyperglycemia, bedrest

**Case 3: Differential Diagnosis**

- ICU polyneuropathy/myopathy
- Post viral/post-infectious autoimmune myelitis
- Inflammatory and/or demyelinating myelopathy
- Guillain-Barre syndrome
- Hopkins syndrome (acute myelitis after asthma attacks)
- Acute disseminated encephalomyelitis

**ICU Acquired Weakness**

- Associated with sepsis, SIRS, ARDS, MOF

Wilcox (2017)
ICU Factors
- Steroids – direct nerve and muscle toxin, but decrease inflammation and severity of illness
  - Review by Jolley (2017) conflicting data:
    - Unadjusted analyses suggest increased frequency of weakness in patients receiving steroids,
    - Multivariate analysis including RTC failed to show association
- NMB – vecuronium, rocuronium, atracurium, & cisatricurium
  - Small unadjusted studies suggest increased weakness with NMB, RTC in ARDS failed to show association (Papazian, 2010)
  - Increasing trend of lower doses and daily breaks (ABCDE of ICU liberation)

ICU Factors
- Bedrest/Immobilization – results in atrophy
  - Early mobilization shown to have better outcomes
    - Decreased LOS and ICU days (Morris, 2008) prospective study n=330
    - Increased ambulation and ADLs (Schweickert, 2009) RTC n=204
    - Electrical stimulation x 60 min at 50 Hz
      - Improved increased walking distance and strength (Kho, 2015) RTC n=36
    - Ergonomics x 20min on bicycle (Burtin, 2009) RTC n=90
      - Increased physical functioning score and increased quadriceps strength

Diagnosing ICU Weakness
- Rule out other pathology
- Biopsy
- EMG/NCS
- Ultrasound
- MRC strength testing
- Hand grip strength

Case 3: Diagnostic Evaluation
- MRI spine and brain
  - No mass effect, hemorrhage or infarct
  - Cervical spinal cord signal abnormality in anterior horn seen at the C4-C5
  - Signal abnormality scattered in the thoracic spinal cord
  - Signal abnormality on T2 within the conus medullaris and associated enhancement of the conus and the nerves of the cauda equina
  - Lumbar puncture for CSF studies
    - LP glucose 101, Protein 596
    - RBC 30,000, WBC 160 (86P, 7L, 6m)

Neuro Consult for Paraplegia
Para-infectious process
  - Polyradiculitis
  - Transverse myelitis
Recommendations
  - Await viral serologies
    - Enterovirus D68
    - NMOSD (AQP4, antiMOG)
  - Pharmacotherapy
    - Methylprednisone
    - Plasma exchange
    - IVIG
    - Consider Rituximab

https://birthfit.com/blog/2018/05/08/dr-poop/
Transverse Myelitis

- Inflammation of entire width spinal cord
- Weakness and numbness (sensory and motor)
- Limbs, urethral and anal sphincter, autonomic sx
- Depending on level can produce upper and lower motor neuron sx
- C3-5 phrenic nerve, all 4 limbs + diaphragm
- C5-T1 Lower limbs: upper motor sx
  Upper limbs: upper and lower sx
- T1-12 (most common) Lower limbs: upper motor sx
- L1-S5 Lower limbs: upper and lower sx

Jacob & Weinshenker (2008)

TM Diagnosis

- Inclusion criteria
  - Motor, sensory or autonomic dysfunction attributable to spinal cord
  - Sx bilaterally (not necessarily symmetrical)
  - Clearly defined sensory level
  - Sx of inflammation (pleocytosis of the CSF, or ↑IgG, or seen on MRI with gadolinium)

- Exclusion criteria
  - Irradiation of the spine, thrombosis of the anterior spinal artery, extra-axial compression on neuroimaging, arteriovenous malformation, connective tissue disease, optic neuritis (diagnostic of NMO), infection, multiple sclerosis

Jacob & Weinshenker (2008)

TM Treatment

- High dose steroids
- Plasmapheresis
- Physical therapy
- Supportive Care
  - Respiratory support
  - Bowel and bladder regimen
- Recovery is variable

Case 3 also received IVIG

Jacob & Weinshenker (2008)

Case 3: Nerve Conduction

Severe motor neuropathy, polyradiculopathy, or neuronopathy, clinical picture c/w acute flaccid myelitis

Acute Flaccid Paralysis vs. Acute Flaccid Myelitis

- AFP
  - Rapid onset weakness often associated with bulbar palsy
  - May affect
    - Spinal cord
    - Peripheral nerve
    - NMJ
    - Muscle

- AFM
  - Subtype of AFP
  - Affects spinal cord gray matter

https://en.wikipedia.org/wiki/Anterior_grey_column

Nelson (2016)
Infectious Causes of Acute Flaccid Paralysis

- **Enteroviruses**
  - Coxsackievirus
  - Echovirus
  - Enterovirus D68 – chemically similar to rhinoviruses, grow in Cx at 33°C (nasal temp.)
- **Flaviviruses**
  - Japanese encephalitis virus
  - Zika
  - Lyme (Borrelia Burgdorferi)

Case 3's CSF + Enterovirus D68

Enterovirus D 68

- Member of picornaviridae family (includes polio, echo, coxsackie)
- SS RNA virus
- Proliferates at 33C (infests nose)
- Most common sx's cough, wheezing, fever, dyspnea
- May present with pneumonia or respiratory failure
- Can develop acute flaccid myelitis

Enterovirus D 68

Laboratory evaluation:
- LP shows pleocytosis
- PCR may not demonstrate virus (may be related to timing of collection)
- Nasal swab + D68

Management: No cure, preventive/supportive;
- PT, respiratory and nutrition support
- No evidence of improvement with steroids, IVIG or plasmapheresis (persistent motor deficits)
- Fluoxetine may inhibit replication
- Antivirals under investigation pleconaril, pocapavir, vapendavir

Case 3: Progression

- Extubated HD 20 to HFNC and Bipap at night
- Discharged to aggressive rehab facility after 6 weeks as in patient
- Respiratory: nocturnal BiPap, budesonide BID with cough assist, albuterol PRN
- PT/OT for persistent lower extremity weakness
- Prolonged steroid taper
- Pain control: Gabapentin TID, Acetaminophen and/or Ibuprofen prn
- Modified barium swallow safe for solids and nectar thickened liquids
- Bowel regimen polyethylene glycol prn constipation
- Spontaneous voiding, intermittent bladder fullness requiring catheterization
- Psych consult for coping mechanism, Melatonin daily
- Enoxaparin bid (DVT prophylaxis)
Summary: Diagnostic Approach

- History (acute, chronic, relapsing, regressing, static)
- Exam (include CN, strength and DTRs, note symmetry)
- Upper (primarily spastic, may involve sensory or CN deficits), tone more decreased
- Lower (primarily flaccid, may be neuronal, muscular, or neurotransmission related), strength more decreased

Laboratory
- Electrolytes
- Muscle markers (CK)
- Immune markers (IgGs)
- Infection markers (Cx, viral panel, PCR)
- Metabolic labs (consider) (serum amino acids, urine organic acids, ammonia, and carnitine, review new born screen in infants)
- Imaging (CT, MRI) - obtain STAT if concern for trauma, stroke, bleed

Muscle & nerve testing (EMG, EPG/NCS)

Summary: Management

- Stabilize life threatening complications
- Respiratory support/ventilation
- Autonomic stabilization (circulatory support)
- Specific medical interventions and pharmacotherapy based on diagnosis
- Many include immunomodulatory therapies such as plasma exchange, IVIG and other immunomodulating medications
- Surgical interventions
  - Feeding tube
  - Trach
  - Orthosurgery (tendon release, scoliosis repair)
- Multidisciplinary supportive care & prevention of complications
  - PT (prevent contractures, maintain ROM)
  - SLP/feeding (provide nutrition, prevent aspiration)
  - Respiratory (airway clearance and ventilation)
  - DVT prophylaxis
  - Psychosocial support

References

- Underwood, K et al. (2007). Infant Botulism: A 30‐Year Experience Spanning the Introduction of Botulism Immune Globulin Intravenous in the Intensive Care Unit at Children's Hospital Los Angeles. Pediatrics; 120; e1380