Neurological Emergencies for Non-Neurologists

Mark Gaertner, MD

Clinical Assistant Professor, UCLA Department of Neurology

Neurology Residency Site Director and Director of Inpatient Neurological Services at UCLA - Olive View Medical Center

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Mark L. Gaertner, M.D.

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Learning Objectives

Title: Neurological Emergencies for Non-Neurologists
Speaker: Mark L. Gaertner, M.D.

Learning Objectives:
1. Achieve appropriate diagnosis and treatment of seizures in the ICU
2. Identify neurological disorders such as Myasthenic Crisis and Guillain-Barré Syndrome
3. Recognize intercranial hemorrhage and treatment
4. Describe treatment of status epilepticus

Vignette and Question

- 48-y/o woman presents with history of chronic migraine, with nausea, photophobia.
- Now has continuous migraine for 15 days.
- Vital signs are normal, focused exam is normal.
- *I don’t see many red flags, should I get a CT scan?*
- *If negative, how to abort the headache?*

Secondary (Pathological Headaches)

Acute headaches = 4.5% of all ED visits.

Secondary headaches account for about 12-13% of headache patients

7-8% are due to medication overuse.

- PLoS One. 2012;7(12):e50898.

Secondary headaches due to true life threatening causes are rare in the ED, occurring in only 5% in one study.

- *Pari et al Neurol Sci **36,** 1153–1160 (2015)*

Red flags are helpful, but when applied in large population (30,000) in an outpatient setting, only 2.1% have abnormality on CT/MRI.

- *The Akershus study of chronic headache. Cephalalgia. 2008 Jul;28(7):705-13.*
- *Neurology 2019*

RED FLAGS from SNOOP 15

- ❑ Fever or Systemic Features
- ❑ History of Neoplasm
- ❑ Neuro Deficit or Abnormal Neurological Exam
- ❑ Sudden Onset Headache
- ❑ Age > 50
- ❑ New, Worsening or Pattern Change in Headache
- ❑ Positional Headache
- ❑ PPT by Valsalva
- ❑ PAPILLEDEMA
- ❑ Pregnancy or Post partum
- ❑ Painful eye
- ❑ Post Traumatic Headache
- ❑ Headache with Syncope
- ❑ Immunocompromised (e.g. HIV, immunosuppression)
- ❑ Excessive NSAID or medication Overuse

Migraine Cocktail and Magnesium In Acute Headache

Cocktails are highly effective

Common Cocktail

- 1-Liter IV 0.9 NS
- 25 mg of IV diphenhydramine (Benadryl)
- 30 mg of IV ketorolac (Toradol)
- 5-10 mg of IV/IM Prochlorperazine (Compazine) or Odansetron (Zofran) 8 mg po/IV

IV Magnesium

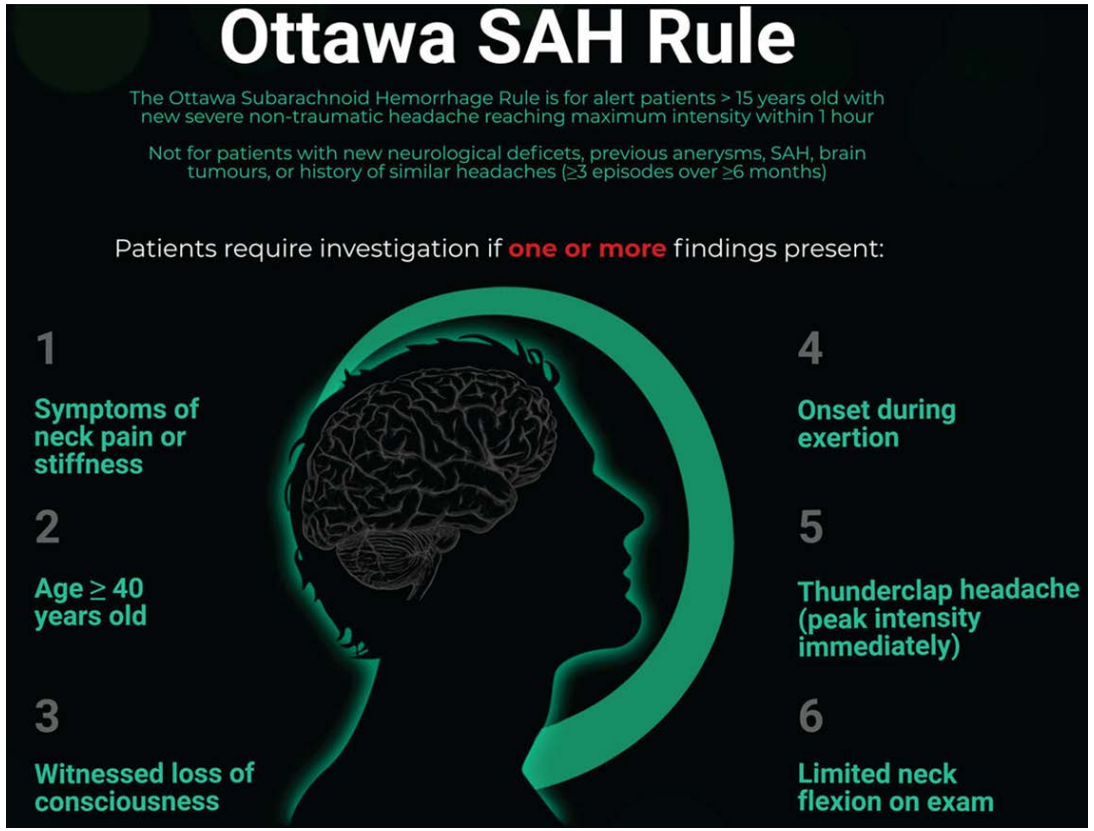
- **1 gram Magnesium sulfate given over 15 minutes resulted in resolution of headache in 86.6% in a small clinical trial**
  - *Efficacy of Intravenous Magnesium Sulfate in the Treatment of Acute Migraine Attacks. Headache: 41: 171-177.*
- **Metanalysis**
  - IV magnesium appears beneficial
  - Of 6 RCTs of migraine, pain improved significantly at 1 and 2 hours
    - *Headache 2019;59: 1674-1686.*

Vignette and Question

- 55 y/o female with history of migraine
- Presents to the ER with sudden onset of new onset headache in the last 6 hours
- Thunderclap in nature, onset over 30-60 seconds
- Headache was not pulsatile, no nausea or vomiting BP = 220/120.
- Felt lightheaded, blurring of vision, passed out.

- Could this be still be a migraine?
- Are there any red flags?
- Should we get a stat CT?
- Do I need to get an LP?

Ottawa SAH rule and 6-hour CT rule



Perry et al. Clinical decision rules to rule out subarachnoid hemorrhage for acute headache. JAMA. 2013;310(12).

- **Ottawa CT rule designed to identify patients with SAH early with only CT**.
- SAH can be due to aneurysm, AVM, or venous angioma
  - Study excluded obvious pts who require imaging: Neurological deficit, prior SAH or aneurysms, brain tumors, or prior similar headaches.

  Get CT If any one of these are +,
  - Neck pain or Neck Stiffness, age > 40
  - Loss of consciousness
  - Onset during exertion, Thunderclap Onset
  - Reduced neck flexibility on exam
    - **CT is 100% sensitivity if within 6 hours,**
  - **Cortnum et al Neurosurgery 2010;66:900-3**
    - In a retrospective study of 499 patients, 296 found to have SAH by CT or LP. From Day 1 to 5, CT was sensitive in 100% of cases. LP detected only one case of SAH on day 6 missed by CT.
    - **CT 100% sensitive in first 5 days**

Vignette and Question

65 y/o female with atrial fibrillation, now has a large ischemic stroke > 1.5 cm in cerebellum.

It is now 48 hours, can I start Apixaban or Xarelto?

How can I weigh the risk of hemorrhage versus recurrent stroke?

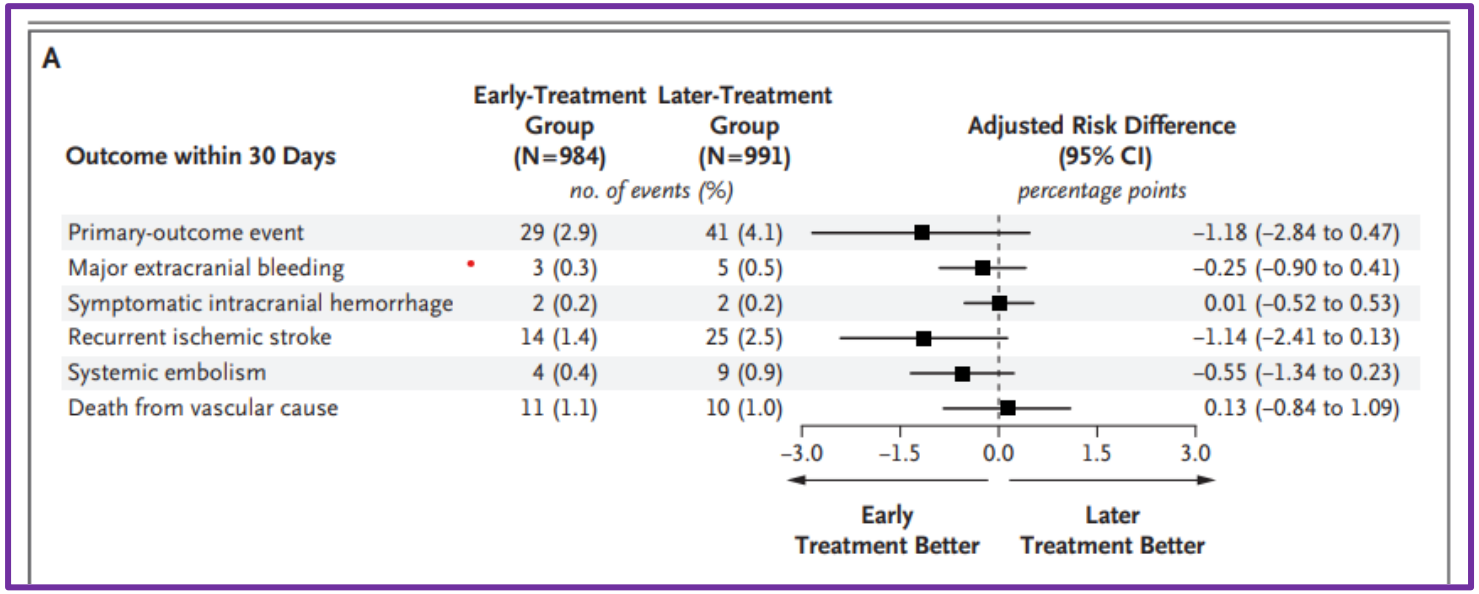
Early versus Late Anticoagulation for Stroke with Atrial Fibrillation NEJM 2023

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 29, 2023 VOL. 388 NO. 26

Early versus Later Anticoagulation for Stroke with Atrial Fibrillation

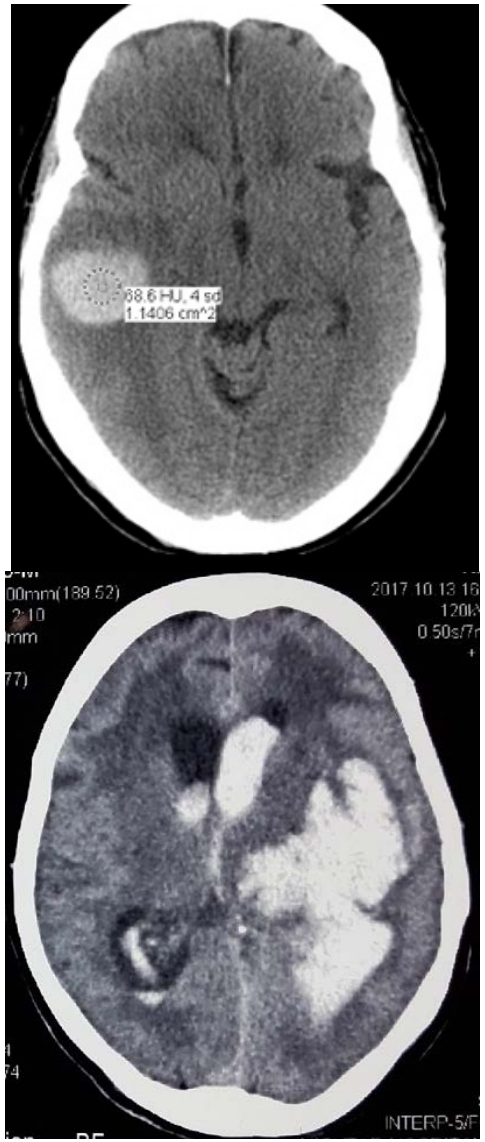
Definitions
- Minor Stroke: < 1.5 cm
- Moderate Stroke < 1.5 cm in cortex
- Major > 1.5 cm

- Early anticoagulation with DOAC
  - < 2 days minor or moderate
  - 6-7 days major
- Late anticoagulation with DOAC
  - 3-4 days minor
  - 6-7 days moderate
  - 12-14 days major
- Intervention: Any approved DOAC
- Primary Outcome: Stroke, bleeding, intracranial hemorrhage, vascular death at 30 days
- Early treatment with NOAC is superior, and non inferior for symptomatic intracranial hemorrhage, which was a rare event



- **<u>Early DOAC is associated with reduced risk of major bleeding, recurrent stroke and systemic embolism</u>**
- Symptomatic intracranial hemorrhage was rare in both groups (0.2% in either group at 30 days, no difference also at 90 days)

Intracerebral Hemorrhage Score



Intracerebral Hemorrhage (ICH) Score ☆

Based on age and CT findings; estimates mortality.

When to Use ⌄ | Pearls/Pitfalls ⌄ | Why Use ⌄

Glasgow Coma Score	3-4 +2	5-12 +1	**13-15 0**
Age ≥80	**No 0**	Yes +1	
ICH volume ≥30mL	**No 0**	Yes +1	
Intraventricular hemorrhage	**No 0**	Yes +1	
Infratentorial origin of hemorrhage	**No 0**	Yes +1	

0 points

0% mortality.

Hemphill et al Stroke. 2001;32:891–897

Table 3. The Intracerebral Hemorrhage Score[a]

Factors	Points
GCS score	
3-4	2
5-12	1
13-15	0
Age, y	
≥ 80	1
< 80	0
Infratentorial hemorrhage	
Yes	1
No	0
Volume, mL	
≥30	1
< 30	0
Intraventricular hemorrhage	
Yes	1
No	0
Total score	**Risk of mortality, %**
0	0
1	13
2	26
3	72
4	97
5	100

Abbreviation: GCS, Glasgow Coma Scale.

[a] Adapted from data from Hemphill et al.[35]

JAMA 2019

Intraparenchymal Hemorrhage

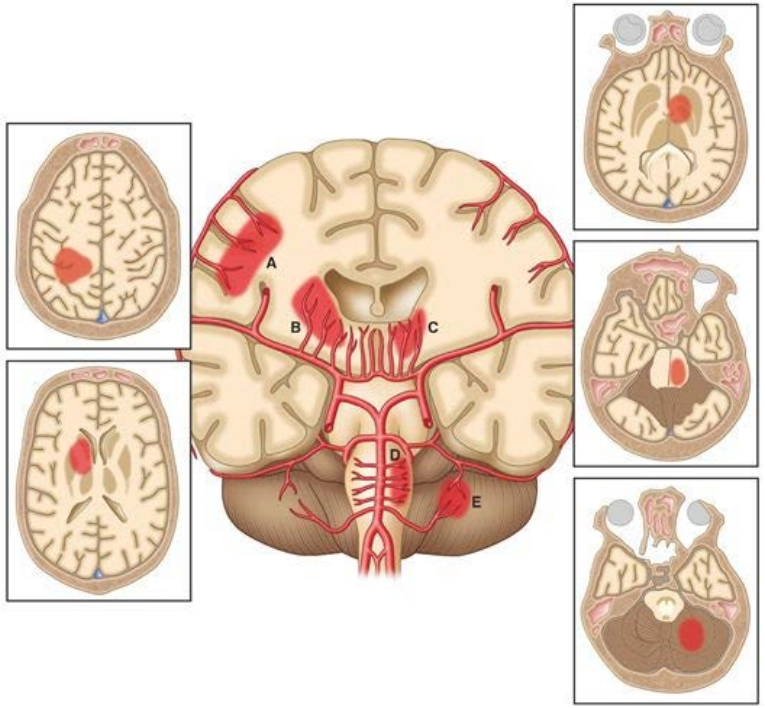


FIGURE 7-3 Hemorrhagic location based on etiology. Hemorrhages are often classified by location. In this figure, hemorrhages in locations B to E are often due to hypertension, whereas A is most often caused by CAA. Hemorrhage due to tumor, AVM, and other etiologies can occur anywhere. *(From Hemphill, J. C., Bonovich, D. C., Besmertis, L., Manley, G. T., & Johnston, S. C. [2001]. The ICH score: A simple, reliable grading scale for intracerebral hemorrhage.* Stroke, *32[4], 891–897.)*

- Detected by CT > 98% within 6 hours
- MRI yield, detected after 12-24 hours
  - Poorly controlled HTN
    - In order: Basal Ganglia, Thalamus, Cortex, Cerebellum, Brainstem
  - Hemorrhagic conversion from ischemic stroke
  - Anticoagulant use
  - Amyloid angiopathy
  - Drug use
- Evidence Based Treatment, from JAMA. 2019;321(13):1295-1303

Table 2. Summarized Clinical Practice Recommendations for the Management of Intraparenchymal Hemorrhage (IPH)[a]

	Classification[b]	Level of Evidence[c]
Initial diagnosis and assessment		
Baseline severity score should be performed	I	B
Rapid CT or MR imaging	I	A
More advanced imaging for underlying lesion (CT angiogram, CT venogram, MR, DSA)	IIa	B
Hemostasis and coagulopathy		
Repletion for coagulation factor deficiency or thrombocytopenia	I	C
If taking a VKA and INR is elevated, vitamin K should be administered	I	C
If taking a VKA and INR is elevated, PCC is recommended over FFP	IIb	B
Protamine sulfate to reverse heparin	IIb	C
rFVIIa is not recommended	III	A
Early medical management		
Initial management in ICU or dedicated stroke unit with nurses with nursing neuroscience acute care expertise	I	B
SBP <140 mm Hg, if presenting with SBP 150-220 mm Hg, is safe	I	A
Aggressive reduction of BP via continuous infusion if SBP >220 mm Hg	IIb	C
Monitor glucose; hyperglycemia and hypoglycemia should be avoided	I	C
Seizures should be managed with AED	I	A
Prophylactic AED is not recommended	III	B
Early, formal dysphagia screening before oral intake	I	B
Electrocardiogram and Tn for screening	IIa	C
Steroids are not recommended	III	B
Intermittent pneumatic compression for DVT prophylaxis on admission	I	A
SC heparin or LMWH 1-4 d after IPH ceases for DVT prophylaxis	IIb	B

Vignette and Question

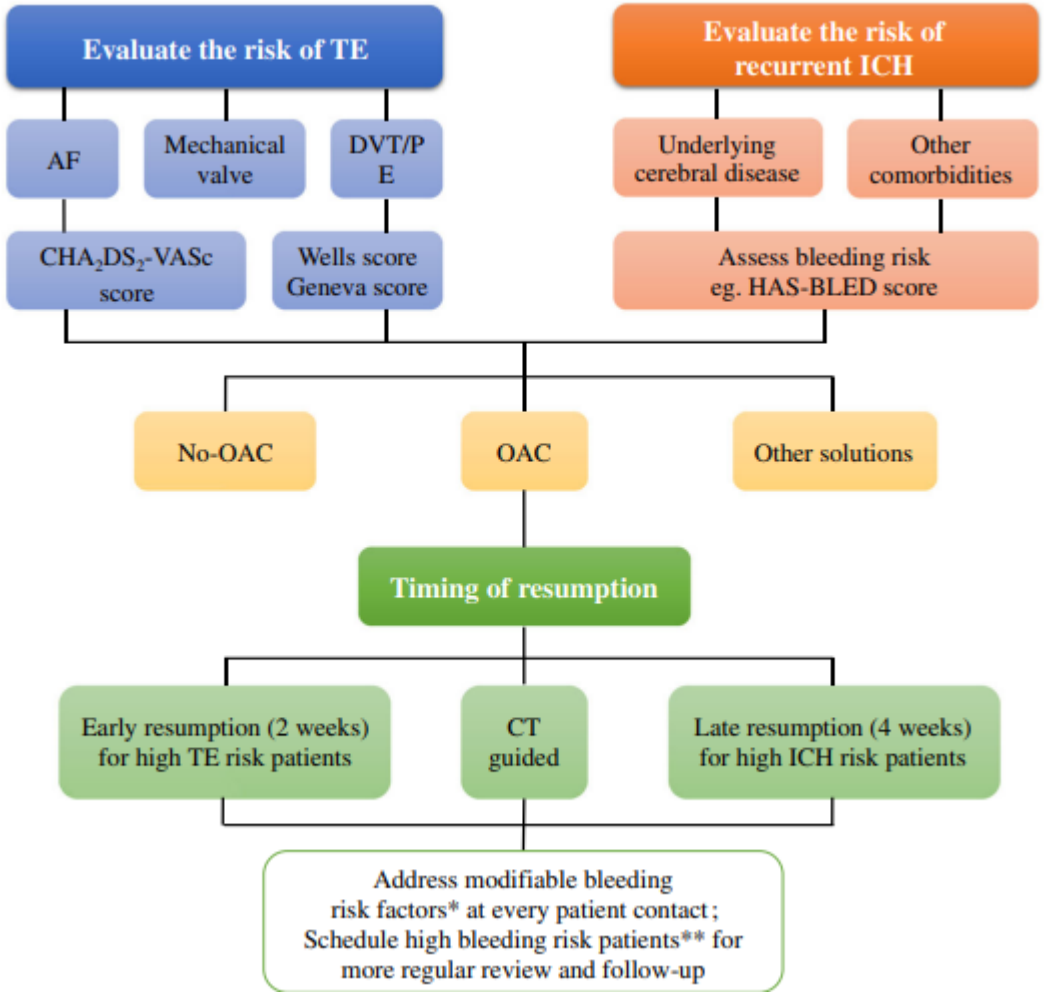
56 y/o male with hypertension, atrial fibrillation sustained a large cerebral hemorrhage.

CHADS VASC Score =

When is it safe to start or restart anticoagulation after cerebral hemorrhage?

Anticoagulation after Intracerebral Hemorrhage

- In non-anticoagulated patients with ICH, the risk of recurrence ranges from 0-8.6% (Li et al 2018)
- In previously anticoagulated patients with ICH, risk of recurrence ranges from 2.5-8%
- DOAC's associated with a lower risk of ICH than warfarin.
  - Comparing risk of ICH between resuming warfarin versus DOACs, rate of ICH was 2.5 per 100 patient years for warfarin, versus 1.3 per 100 patient years for DOACs
- ODDs ratio for warfarin versus DOAC = O 1.9;95% CI 0.7–6.7
  - Poli et al Eur J Int Medicine 2020 80;73



Li et al Curr Atheroscler Rep 2018: 20: 32

Vignette and Question

18-year-old male presents with two discrete tonic clonic seizures, eyes open, head turns to the side, tongue biting, each lasts 3 minutes, no recovery in between.

Has a fever T = 101.1,

Elevated CK to 1000, Pulse oximetry = 91%, BP is 88/60

Mom says never had a seizure before, has had some confusion and visual hallucinations for the last 3 months

What are the immediate concerns?

How would you approach initial stabilization and treatment?

What are the likely causes?

Status Epilepticus

Definition: Continuous seizures > 5 minutes, or ≥ 2 seizures without recovery of LOC

Leading Causes: Sub-therapeutic AED levels, severe epilepsy, drug/ETOH withdrawal, encephalitis, meningitis, sepsis, stroke, neoplasm, trauma, autoimmune encephalitis

Epidemiology: 120-180,000 episodes per year

- Mortality = 3-5%, higher for refractory cases > 24 hours and for the elderly
- Initial treatment:
  - Benzodiazepines: rapid onset, crosses BBB, long half life
    - Lorazepam 0.1 mg/kg, range 4-6 mg in adults at 1-2 mg/minute
      - Minimum effective dose usually defined as 4 mg IV in adults Lancet 2020;395:1217

Question: What is the best 2nd medication for Status if benzodiazepines fail?

- Efficacy of Levetiracetam, Fosphenytoin, and Valproate for established status epilepticus by age group. Lancet 2020;395:1217
- 462 children and adults with confirmed status epilepticus treated with a benzodiazepine
  - 225 children, 186 adults, 51 older adults with initial SE duration of > 5 minutes
  - Continued to have GTC seizures for at 5-30 minutes after last dose of benzodiazepine
    - Adequate dose of benzodiazepine defined as lorazepam 4 mg, diazepam 10 mg, or midazolam 10 mg for those > 32 kg (mg/kg dosing if < 32 kg)
  - Randomized to
    - Fosphenytoin 20 mg/kg max = 1500 mg
    - Valproate 40 mg/kg max = 3000 mg
    - Levetiracetam 60 mg/kg max = 4500 mg

Safety and Efficacy

- Safety and Efficacy of all three drugs is equivalent.
- Levetiracetam 50 mg/kg, valproate 40 mg/kg, or Fosphenytoin 20 mg/kg are equally safe and **effective, and resolve status epilepticus in** 46-49% of patients with refractory status epilepticus

Safety Outcomes

	Children (aged <18 years)			Adults (aged 18–65 years)			Older adults (aged >65 years)		
	Levetiracetam	Fosphenytoin	Valproate	Levetiracetam	Fosphenytoin	Valproate	Levetiracetam	Fosphenytoin	Valproate
ITT population	85	71	69	71	54	61	19	17	15
Admission to ICU	53 (62%)	45 (63%)	43 (62%)	38 (54%)	26 (48%)	34 (56%)	15 (79%)	13 (76%)	8 (53%)
Length of ICU stay, days	1 (0–2)	1 (0–2)	1 (0–2)	1 (0–3)	0 (0–3)	1 (0–3)	3 (1–6)	2 (1–7)	2 (0–6)
Length of hospital stay, days	2 (1–3)	2 (1–3)	2 (1–4)	3 (1–6)	3 (1–7)	2 (1–6)	7 (5–12)	5 (3–16)	5 (3–16)
Safety population	86	73	70	74	58	64	20	18	15
Life-threatening hypotension within 60 min of start of study drug infusion	0	2 (3%)	3 (4%)	0	2 (3%)	0	1 (5%)	1 (6%)	0
Life-threatening cardiac arrhythmia within 60 min of start of study drug infusion	0	0	0	1 (1%)	0	0	0	0	0
Acute respiratory depression	5 (6%)	13 (18%)	7 (10%)	10 (14%)	6 (10%)	5 (8%)	0	2 (11%)	0
Endotracheal intubation within 60 min of start of study drug infusion	7 (8%)	24 (33%)	8 (11%)	19 (26%)	13 (22%)	14 (22%)	7 (35%)	5 (28%)	2 (13%)
Acute seizure recurrence 60 min–12 h after start of study drug infusion	8 (9%)	11 (15%)	6 (9%)	5 (7%)	3 (5%)	5 (8%)	4 (20%)	4 (22%)	3 (20%)
Death	1 (1%)	0	1 (1%)	2 (3%)	2 (3%)	1 (2%)	4 (20%)	1 (6%)	0

Data are n, n (%), or median (IQR). No patients had anaphylaxis or purple glove syndrome. ITT=intention-to-treat. ICU=intensive care unit.

Table 3: **Secondary efficacy outcomes and safety analysis by age group**

Status Epilepticus Treatment Protocol

Time is of the essence to reduce risk of brain injury and refractory status

Stage 1 ACUTE SEIZURES 0-5 minutes

- Pulse oximetry, check airway, vitals,
- POC blood glucose, start large bore IV, IV fluids at 90-100 cc/hour
- Draw Labs (CBC, CMP, tox screen, antiseizure medication levels)
- Large bore IV (1 or 2)
- Start Lorazepam (rapid onset, long T1/2)
  - 2 mg IV at 1-2 mg/min. Increase up to 6 mg
  - Or Midazolam 5 mg IV, up to 10 mg if > 30 kg
  - If hypoglycemia suspected
    - IV bolus of Dextrose 50% with 100 mg Thiamine IVPB
    - If seizures stop obtain CT, LP if appropriate, check lab results

Stage 2 STATUS EPILEPTICUS > 5min

- Levetiracetam **60** mg/kg over 10 minutes, or
- Fosphenytoin 15-20 mg/kg IVPB (monitor for hypotension at 50 mg/min, or
- Depacon (IV Valproate) at 40 mg/kg over 10min
- If seizures stop obtain CT, LP if appropriate, check lab results, ICU care

Stage 3 REFRACTORY STATUS EPILEPTICUS

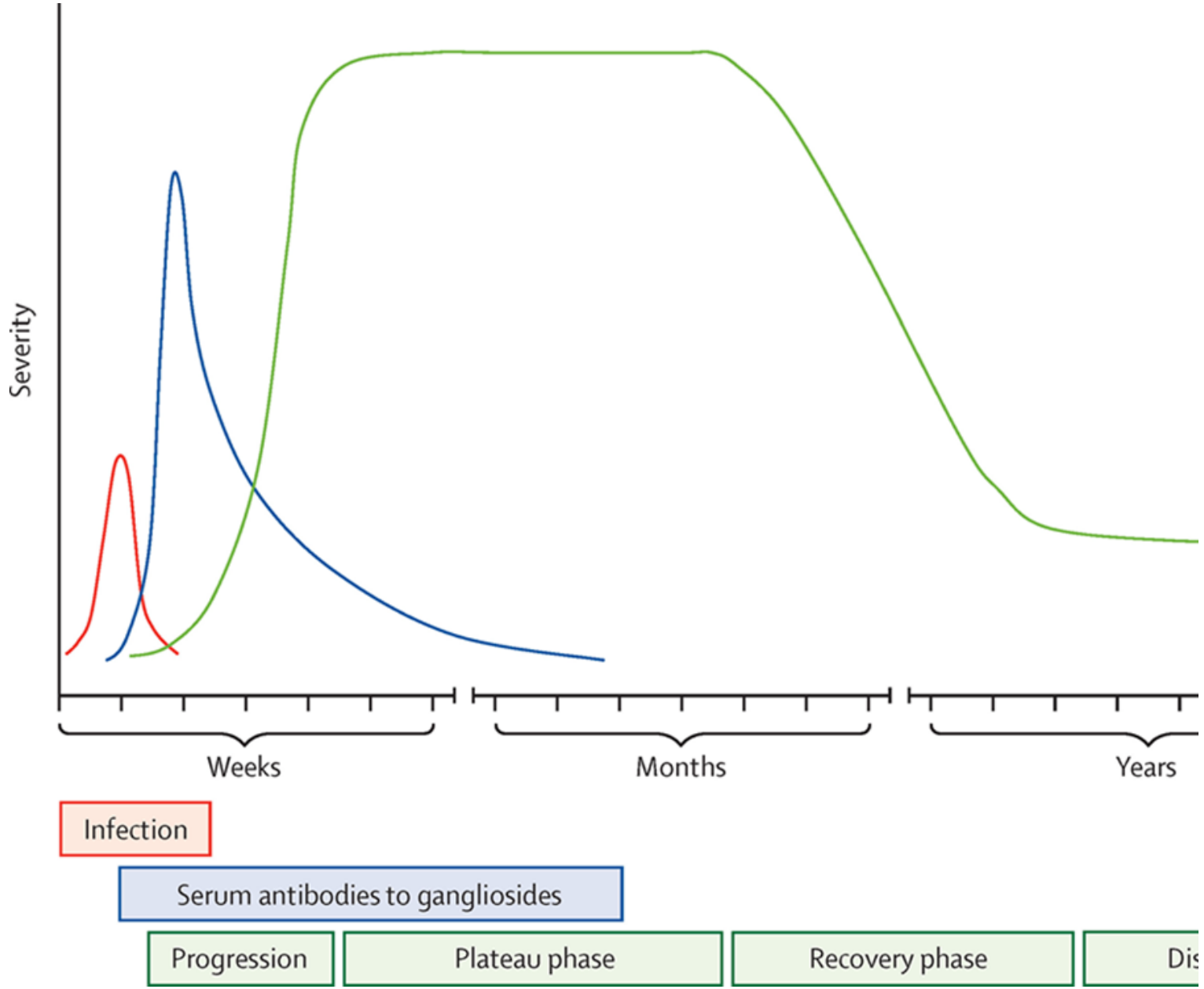
- Call Anesthesia to Intubate and ventilate
- Start Midazolam 0.2 mg/kg bolus, then .0.2 mg/hour, titrate up to 0.6 mg/kg/hour, or
- Propofol 1-2 mg/kg followed by infusion of 2-10 mg/kg/hour, watch for hypotension in medically ill or elderly

27 y/o female, presents with symmetric weakness and mild numbness in feet, no urinary incontinence

Guillain Barre Syndrome Willison et al, Lancet 2016: 388:717-127

- Classic post-infectious disorder
- Incidence: lifetime risk is 1:1000
- Mortality: 3-10 %
- Presentation: Peaks in 2-4 weeks, usually starts 1-2 weeks after infection with Campylobacter jejune (up to 50% of all cases), influenza, CMV, EBV, mycoplasma, rarely zika
- Three primary variants:
  - Demyelinating
  - Axonal
  - Miller Fisher variant
- Disability: 80% regain ability to walk at 6 months

Natural History of Guillain-Barre



Diagnostic Criteria: Guillain Barre

- Progressive bilateral weakness of legs and arms, usually starting in legs
- Absent Deep Tendon Reflexes

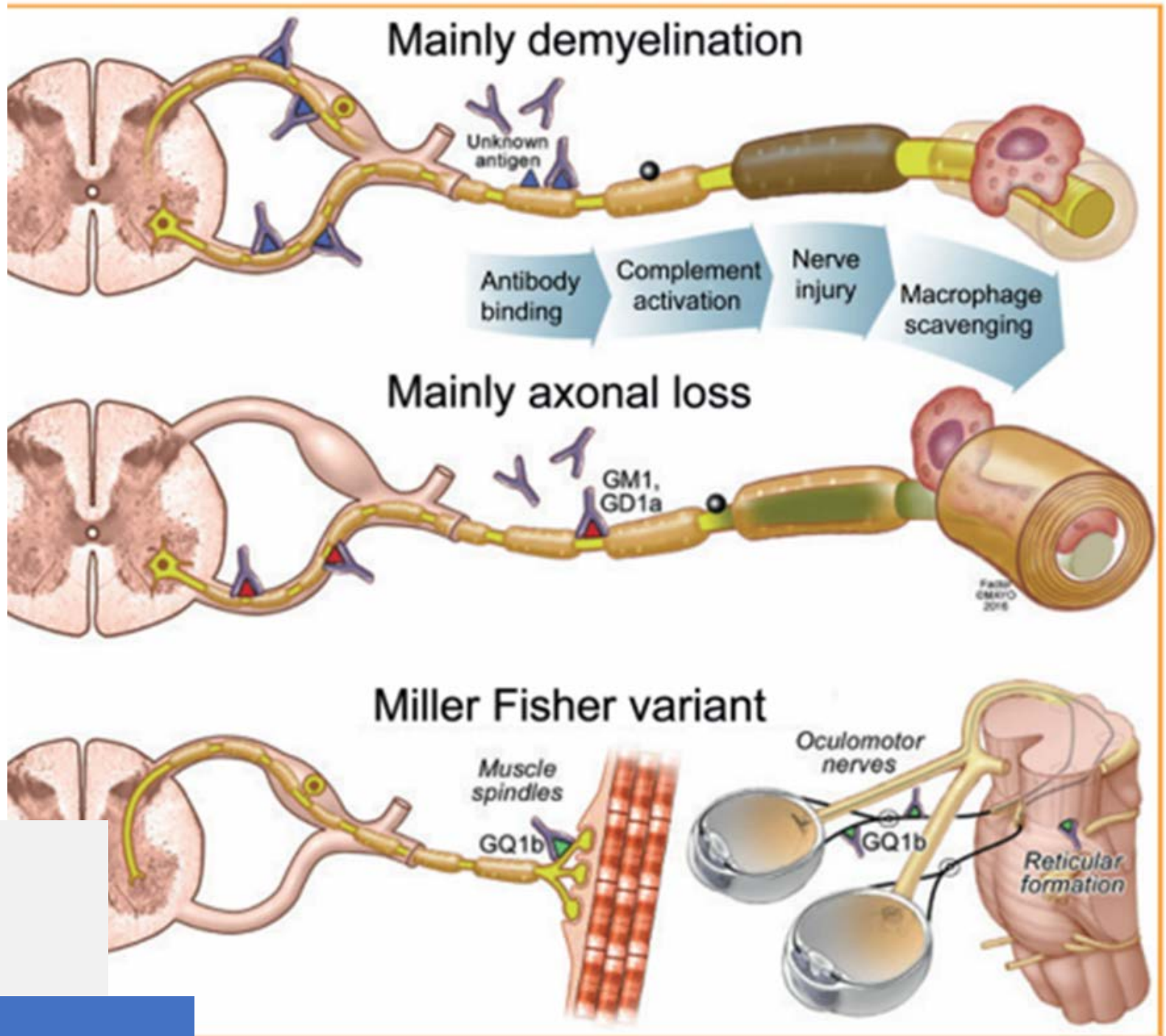
Supportive Features

- Onset over days to weeks (usually < 2 weeks)
- Relative Symmetry
- Mild sensory features
- Bilateral facial weakness or cranial nerve involvement
- Increased protein level in CSF (normal in 10-30% @ 2 weeks, High albumin, low cell count)

RED Flags!!!!

- Sensory Level-suggest spinal cord injury
- Marked Asymmetry
- Bowel or Bladder dysfunction at onset
- Hyperreflexia/Babinski
- High cell count (> 10 should cause clinician to look for alternate disorders, but > 50 is not consistent with GBS)
- Continued progression after 4-weeks
- Abdominal pain at onset

Three variants of Guillain Barre Demyelinating Axonal Miller-Fisher



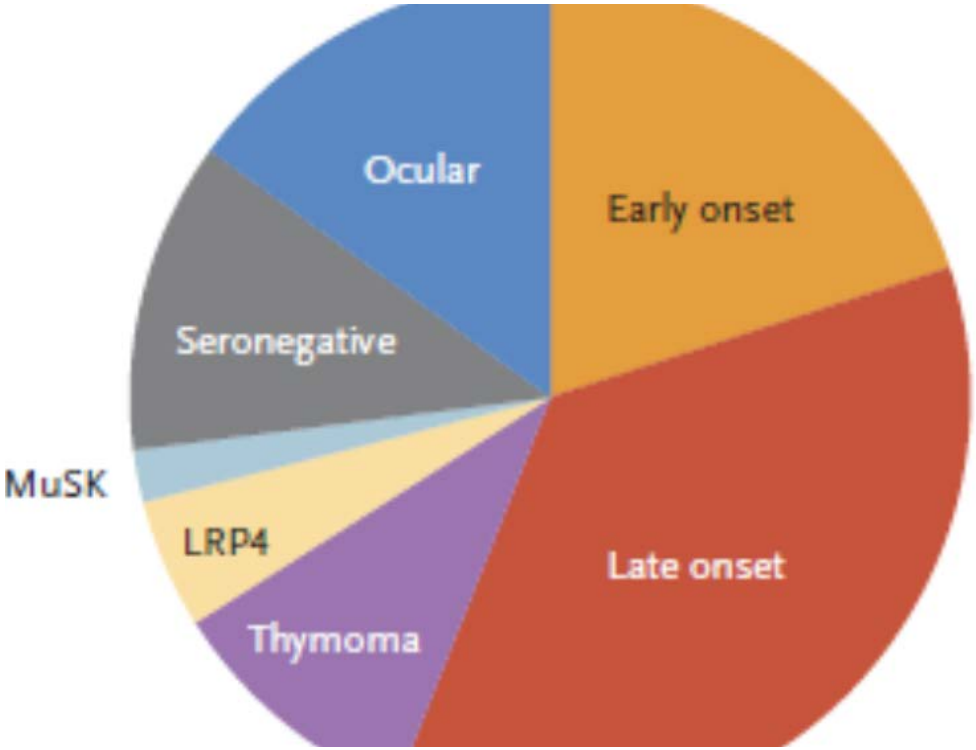
Guillain Barre Treatment

	PE (n=121)	IVIg (n=130)	PE+IVIg (n=128)
Mean (SD) change in disability grade after 4 weeks	0·9 (1·3)	0·8 (1·3)	1·1 (1·4)
Number ventilated after randomisation	28 (23·1%)	29 (22·3%)	21 (16·4%)
Median (IQR) days to stop artificial ventilation (for all ventilated patients)	29 (14–57)	26 (15–45)	18 (10–56)
Median (IQR) days to unaided walking	49 (19–148)	51 (20–164)	40 (19–137)
Median (IQR) days to hospital discharge	63 (28–124)	53 (21–135)	51 (24–117)
Median (IQR) days to return to work	290 (122–>400)	371 (129–>400)	281 (96–>400)
Number unable to walk unaided after 48 weeks*	19 (16·7%)	21 (16·5%)	17 (13·7%)
Deaths	5 (4·1%)	6 (4·6%)	8 (6·3%)

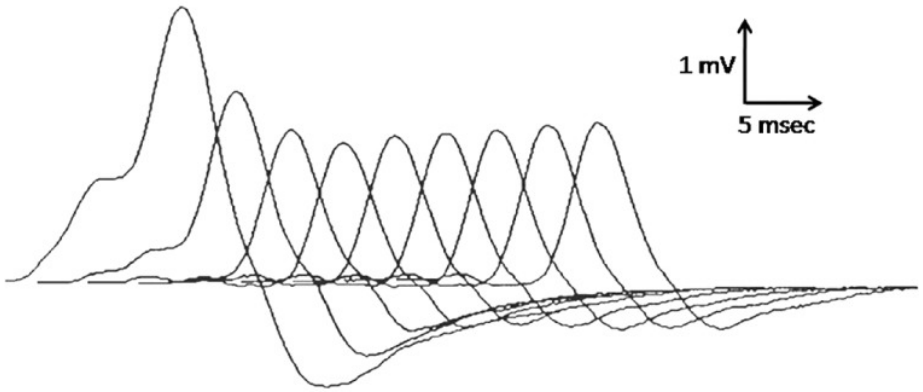
*Missing for 7 patients in PE group, 1 in IVIg group, and 6 in PE+IVIg group.

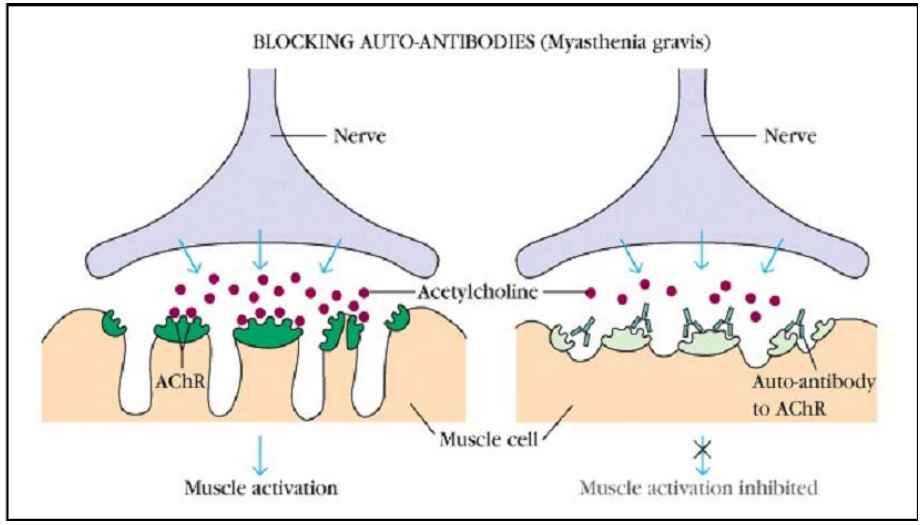
Randomized trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome
Lancet 1997;349:225-30

Myasthenia Gravis



- Neuromuscular Junction Disorder characterized by fluctuating weakness and muscle fatigue with repetitive use
- Prevalence: 150-250 cases per million
- Bimodal Distribution: Early (female>male) and Late onset (male>female)
- 50% present with ptosis or diplopia (ocular myasthenia).
- Of these, 50% will progress to generalized myasthenia within 2 years
- 10-15% have a thymoma





Myasthenia Gravis

- Diagnosis is confirmed by presence of antibodies directed against neuromuscular junction (anti-Ach binding, blocking, anti-MUSK (muscle kinase ab, and lipoprotein receptor related protein LRP4).
- ICE pack test is sensitive and reverses ptosis
- Repetitive Nerve Stimulation showing progressive reduction of compoi8nd motor action potential supports the diagnosis

Myasthenic Crisis Recommendations from *Neurology 2016 Consensus Guidelines*
and
Roper et al Myasthenia Gravis and Crisis: Evaluation and Management in the Emergency Department J Emergency Medicine 2017;53:843-853

- Mysasthenic Crisis: Defined as respiratory failure or failure to protect airway in patient with MG
- Occurs in 15-20% with MG
- Precipitants:
  - Upper Respiratory Infection, pneumonia, aspiration cause
  - Medications (aminoglycosides, quinolones, pregnancy, thyroid dysfunction)
- **Treatment**
- ICU admission
- Intubation and Mechanical ventilation if
  - Negative Inspiratory force (NIF) < -20 to -30cm H20
  - Forced vital Capacity (FVC) < 10-20 ml/kg
  - Single-breath test normal = 40-50 words with single breath
  - Consider ventilatory support if <15-20 words

Myasthenic Crisis

- PLEX and IVIG **are similar in efficacy** and are used short term
- Because corticosteroids may cause transient worsening, may be appropriate to wait several days after PLEX or IVIG
- PLEX cannot be used in sepsis, and has greater risk of hemodynamic and venous access complications
- PLEX complications may be minimized by using peripheral rather than central venous access.
- IVIG is contraindicated in hypercoagulable states, renal failure, or hypersensitivity to immunoglobulin

RCT of IVIG versus Plasmapheresis (PLEX)
Barth et al Neurology 2011;76:2017–2023

RCT of IVIG 1 gm/kg/day x 2 days versus Plasmapheresis 1 plasma volume every other days x five sessions of PLEX

84 patients with moderate to severe weakness, worsening requiring intervention. Mean age = 55; 57% female, 43% male

Primary Outcome was measured at 14 days, change in quantified MG score

69% improved with IVIG versus 65% with PLEX

No patients in either group required intubation

Conclusion: PLEX and IVIG are equivalent treatments