Clinical Decision Making in Autoimmune Neuromuscular Disease:

Diagnosis, Treatment, and Management

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Topics of Today's Discussion

- Clinical and laboratory diagnostic features used to distinguish among a series of treatable autoimmune neuromuscular diseases, including GBS, CIDP, MMN, and MG
- The role of expert opinion, consensus statements, and evidence-based medicine in clinical decision making in autoimmune neuromuscular disease
- Current issues and clinical trial data relating to the long-term prognosis and management of autoimmune neuromuscular diseases

Objectives

On completion of this activity, participants should be able to:

- Recognize the clinical presentations of chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), Guillain-Barré syndrome (GBS), and myasthenia gravis (MG)
- Evaluate the diagnostic evidence of CIDP, MMN, GBS, and MG
- Outline appropriate therapy based on disease course, therapeutic mechanisms, and safety and efficacy data
- Determine the appropriate timing, dosage, and duration of specific therapies used in the treatment of autoimmune muscular disease based on available evidence and expert opinion

Case 1—25-year-old Man With Flaccid Paralysis

- 25-year-old Caucasian man with a history of diarrheal illness 4–5 weeks ago who initially noted mild paresthesia in his feet
- Clinical course over the next 7 days was marked by:
  - History: Subacute onset of lower-extremity weakness > upper extremities
  - Physical exam:
    - Mild bilateral facial weakness, swallowing intact; symmetrical 1/5 strength in the IP and 0/5 in AT muscles; deltoid 3/5 and grip 1/5
    - Loss of deep tendon reflexes (DTRs)
    - Sensory exam within normal limits (WNL)
  - Cerebral spinal fluid (CSF): protein 40 mg/dL, <6 monocytes

IP=Ileopsoas; AT=anterior tibial; CSF=cerebrospinal fluid

Case 1–Nerve Conduction Study Results

Nerve	Amplitude	Distal Latency	Duration	Conduction Velocity	F-wave Latency
Sural	15 µV	3.9 ms		55 m/s	
Peroneal Motor	NR				
Median Sensory	20 µV	3.0 ms		52 m/s	
Median Motor	5.0 mV 2.2	2.7 ms	8.5 ms 8.7	50 m/s	32 ms
Ulnar Motor	5.5 mV 4.2 3.2	4.2 ms	9.0 ms 10.0 10.2	48 m/s 45	28 ms

GBS–Immunotherapy: A Systematic Review

Therapy	Number of Trials	Number of Patients	Results
PE	5	585	Patients improved at 4 weeks vs placebo
IVIG	5	582	Results similar to PE
PE followed by IVIG	1	148	No additional benefit
IVIG in children	3 (open-label)	91	IVIG hastens improvement
Corticosteroids	6	587	Less improvement compared to no treatment

Adapted from: Hughes RA et al. *Brain*. 2007;130:2245-2257.

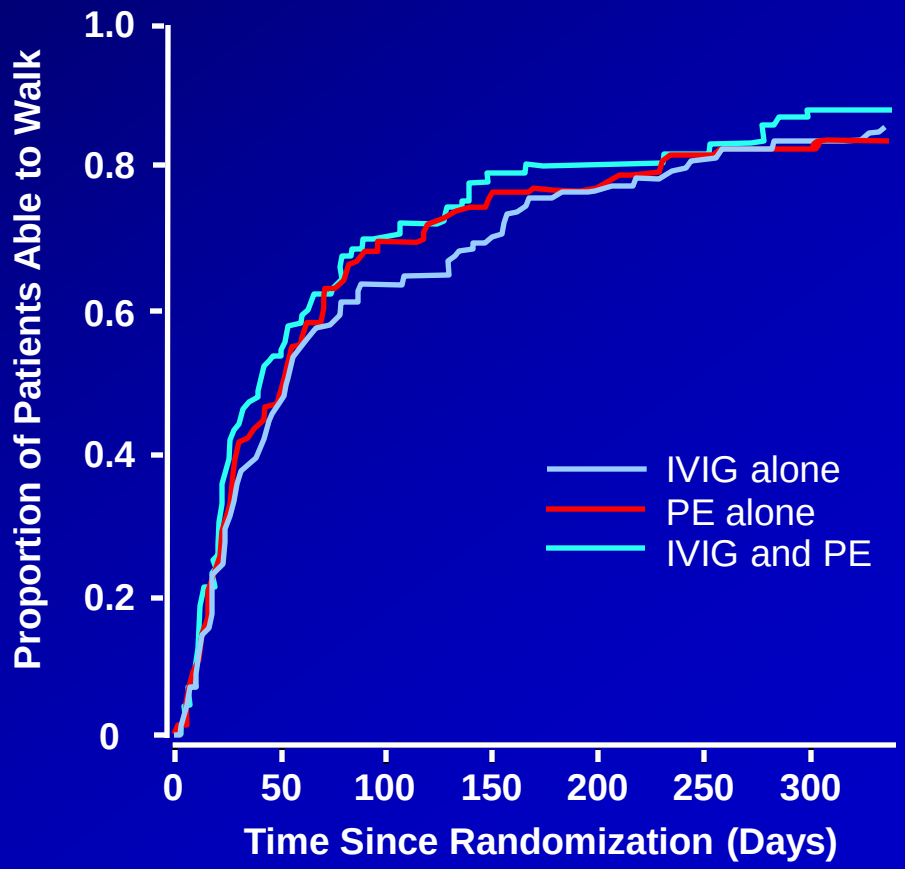
GBS—Why do some patients experience incomplete recovery after the standard dose of IVIG?

- IVIG clearance may play a role, or the dose may be suboptimal for certain patients
- Patients with small increase in serum IgG at 2 weeks had worse outcome; a second IVIG may be beneficial
- A controlled study (IVIG-SD) is in progress

Kuitwaard K et al. *Ann Neurol*. 2009;66:597-603.

GBS–IVIG vs Plasma Exchange vs Combination

- 383 patients
- 3-arm study
  - IVIG group (5 infusions of 0.4 g/kg)
  - Plasma exchange group (5 exchanges of 50 mL/kg)
  - Plasma exchange followed by IVIG group
- Benefit of IVIG=plasma exchange at 4 weeks
- Combination therapy no better than either treatment



Adapted from: Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. *Lancet*. 1997;349:225-230.

GBS–Long-Term Prognosis

- 6- to 7-year long-term follow-up studies
- 20%–40% will continue to have some motor weakness
- An even greater percentage may still have sensory impairment

Vedeler CA et al. *Acta Neurol Scand* .1997;95:298-302. Dornonville de la Cour CD, Jakobsen J. *Neurology.* 2005;64:246-253. Koeppen S et al. *Neurocrit Care.* 2006;5:235-242.

GBS–Long-term Functional Status

- n=42 vs age and sex-matched control population from southwestern Norway
- Mean follow-up 6.4 yrs
- Scores worse for GBS group
  - Pain VAS ($p<0.05$)
  - Disability rating index ($p<0.001$)
  - SF-36: physical function and general health domains ($p\leq0.02$)
  - Fatigue severity scale (NS)
- No difference for shorter (<6 yrs) vs longer follow-up since onset
- Correlations
  - Higher age at GBS onset and disability rating
  - Higher Hughes disability at onset and fatigue severity
- Over time, the social and emotional distress seen in short-term studies recedes
  - Adaptation to deficits
  - Recalibration of expectations

Rudolph T et al. *Eur J Neurol* 2008;15:1332-1337.

Case 2—25-year-old Man With Tingling in His Feet

- Patient from Case 1
- Clinical course over the next 4 wks was marked by:
  - Progressive lower-extremity weakness and facial numbness
- Physical and laboratory findings included:
  - Bilateral facial weakness; symmetrical lower extremity weakness, loss of DTRs; decreased large fiber sensory loss
  - NCV: prolonged DL, F waves; temporal dispersion CMAP
  - CSF: 85mg % protein <10 monocytes
- Treated for AIDP; initial improvement in strength and less numbness, but weaker 1 month later
- Time course: chronic, progressive
- Diagnostic considerations: chronic neuropathy

Classic CIDP–Diagnostic Criteria

- No universally accepted diagnostic criteria[1–5]
- No biomarker[1]

1 Clinical
- – Motor/sensory impairment
- – Disease duration/progression (≥8 weeks)
- – Hyporeflexia/areflexia

2 Electrophysiology
- – Evidence for demyelination

3 CSF analysis

4 Nerve biopsy

5 Additional potentially supportive evidence
- – MRI
- – Response to immunomodulatory treatment

Mandatory

Not mandatory

CSF=cerebrospinal fluid; MRI=magnetic resonance imaging.

1. Koski CL et al. *J Neurol Sci.* 2009;277:1-8. 2. Hughes RAC et al. *Eur J Neurol.* 2006;13:326-332. 3. Saperstein DS et al. *Muscle Nerve* 2001;24:311-324. 4. Saperstein DS, Barohn RJ. *Curr Neurol Neurosci Rep.* 2003;3:57-63. 5. Berger AR et al. *J Peripher Nerv Syst.* 2003;8:282-284.

CIDP–Electrodiagnostic Criteria

- Goal: criteria to distinguish primary demyelination in chronic neuropathies
- Many criteria: 60%–70% sensitive to primary demyelination

Bromberg MB. *Muscle Nerve*. 1991;14:968-976.

CIDP—Electrodiagnostic Criteria (cont)

- Practical concepts
  - Slower than expected for level of axonal loss: >25% (<75% of LLN; >125% of ULN)
  - Evidence of primary demyelination

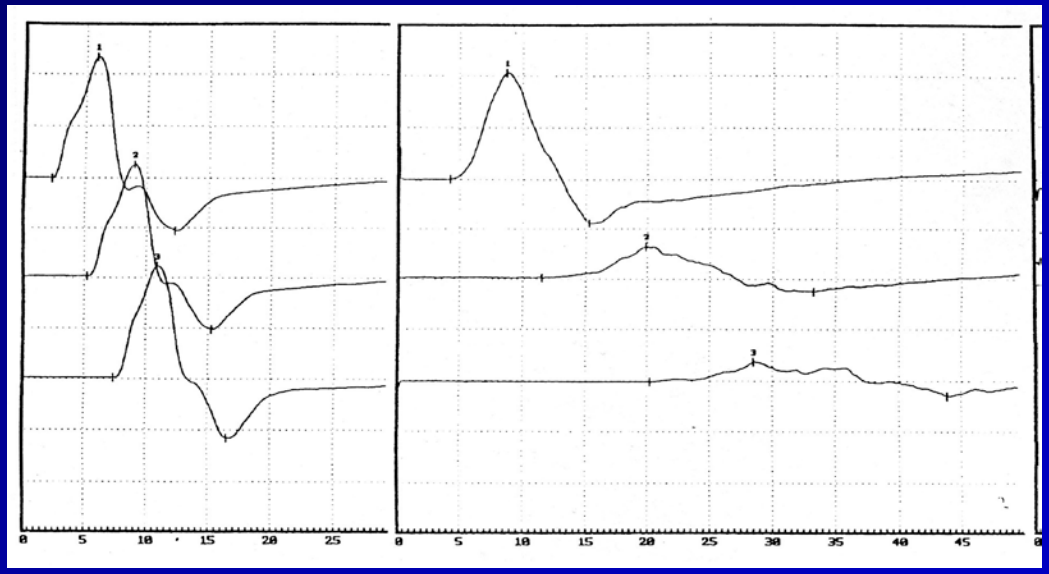


Image courtesy of Mark B. Bromberg, MD, PhD.

CIDP Diagnosis— Proposed 2009 Criteria

- Patients with a chronic polyneuropathy, progressive for at least 8 weeks, would be classified as having CIDP if:
  - No serum paraprotein ***and***
  - No documented genetic abnormality

AND EITHER

- At least 75% of motor nerves had recordable responses AND one of the following conditions is satisfied according to AAN criteria:
  - Abnormal distal latency in >50% of nerves ***or***
  - Abnormal motor conduction velocity in >50% of nerves ***or***
  - Abnormal F-wave latency in >50% of nerves

OR

  - Symmetrical onset of motor symptoms
  - Symmetrical weakness of 4 limbs ***and***
  - Proximal weakness in > or = 1 limb

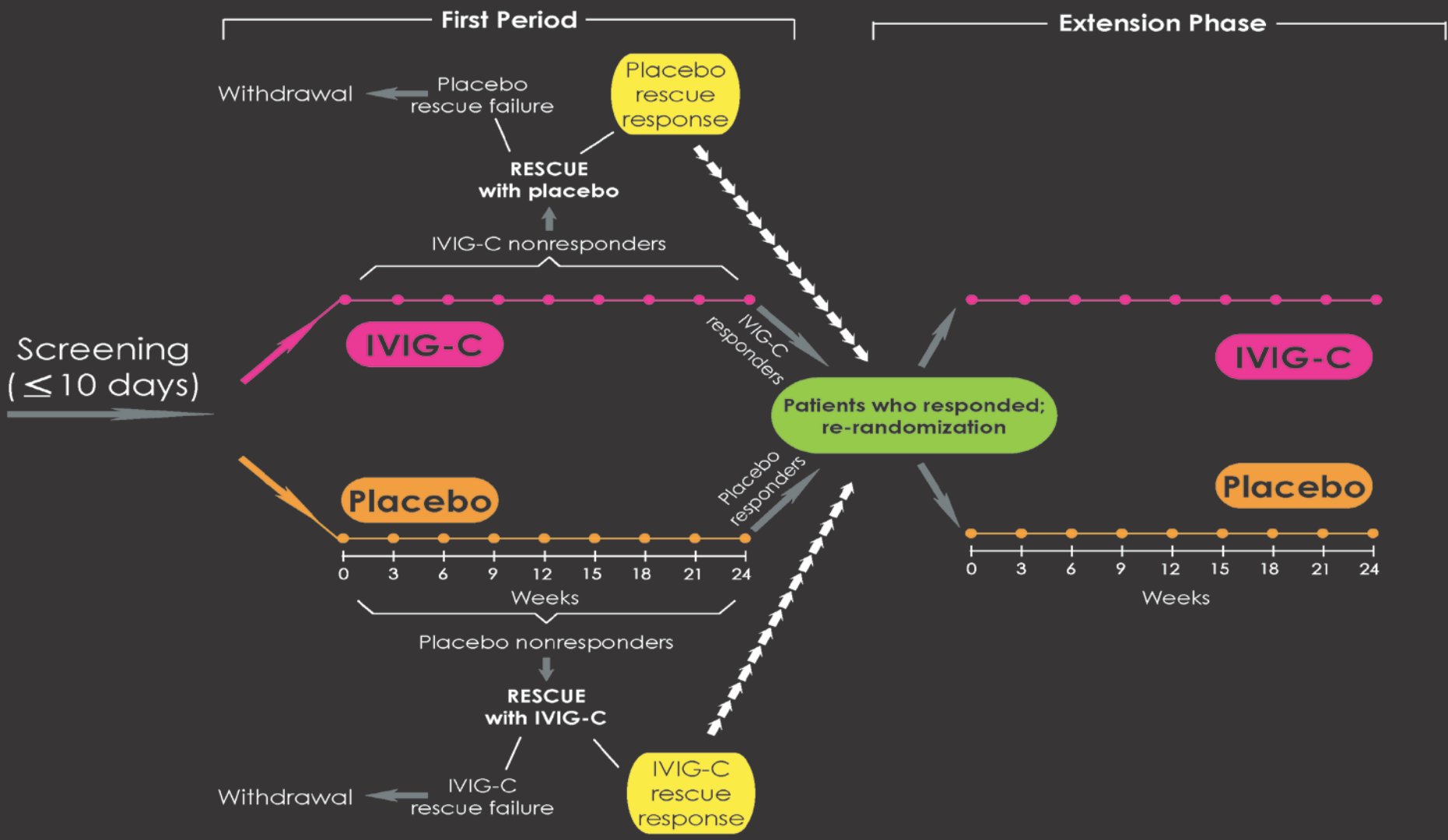
Koski CL et al. *J Neurol Sci.* 2009;277:1-8.

CIDP—Evidence-Based Treatments

- IVIG: 2 g/kg as induction therapy
- Plasma exchange: 5–6 treatments
- Prednisone: 60–100 mg per day, followed by taper

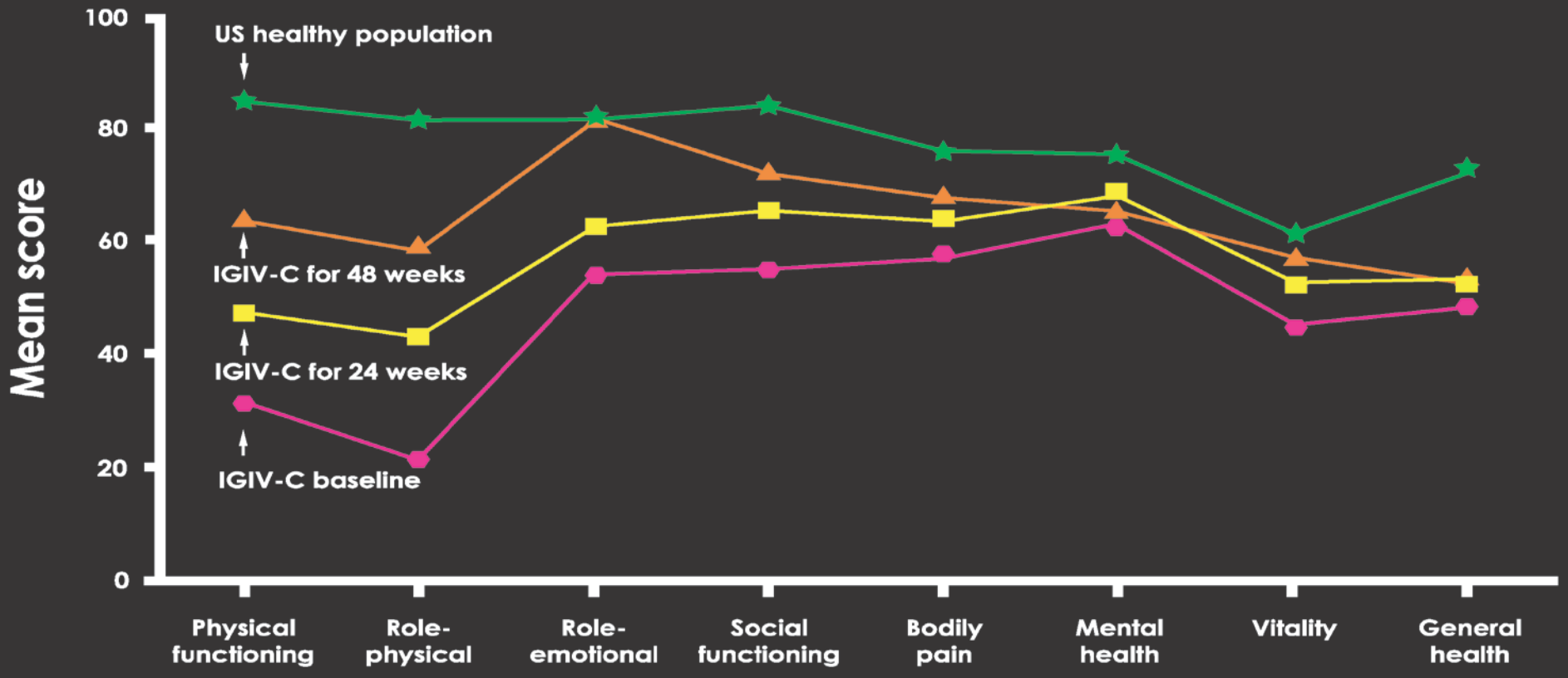
Hughes RA et al. *Cochrane Database Syst Rev*. 2004;(4):CD003280. Mehndiratta MM et al. *Cochrane Database Syst Rev*. 2004;(3):CD003906. van Schaik IN et al. *Cochrane Database Syst Rev*. 2002;(2):CD001797.

The ICE Trial–Study Design



Adapted from: Hughes RA et al. *Lancet Neurol*. 2008;7:136-144.

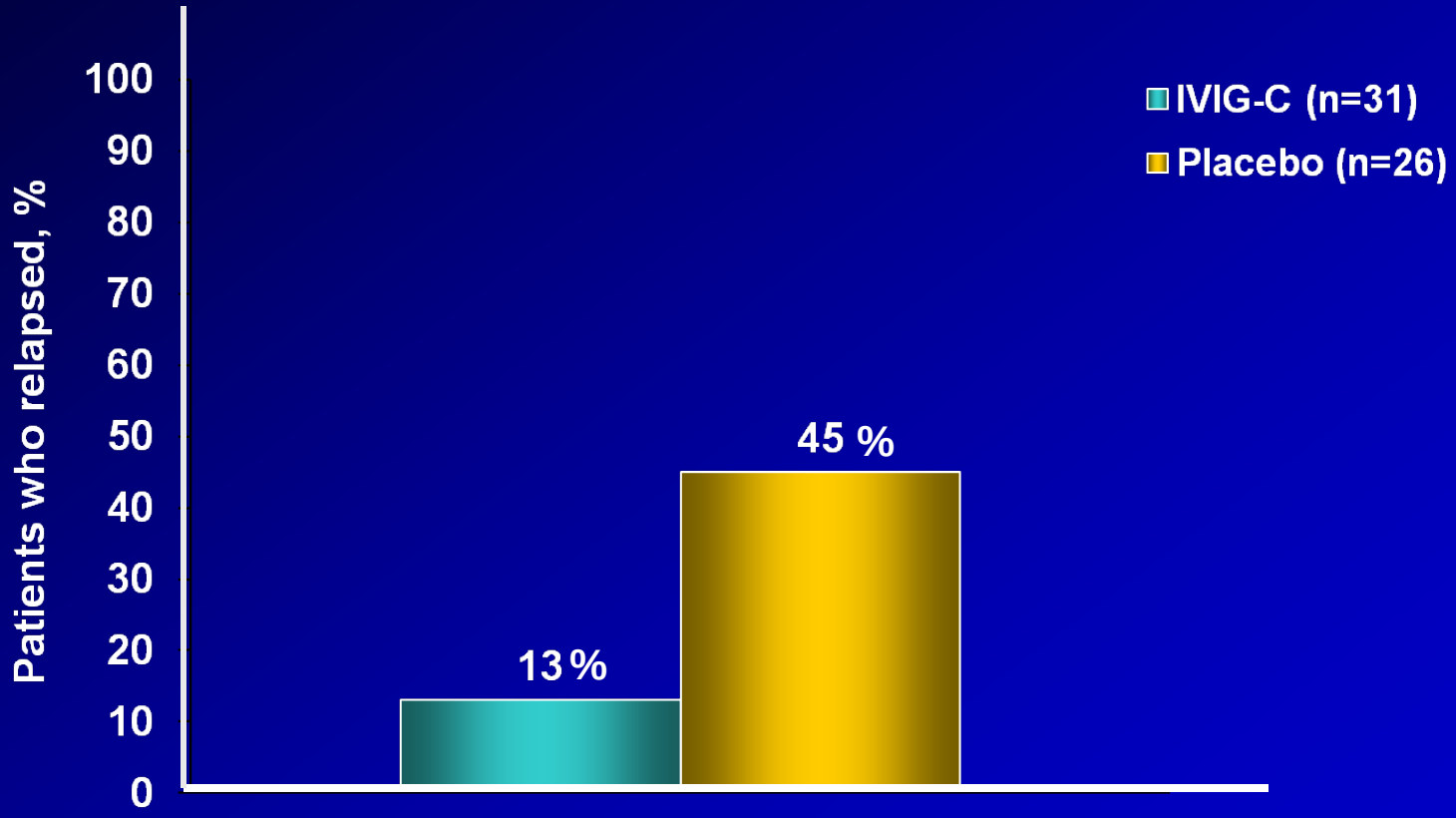
The ICE Trial—Effect of IVIG on QoL Scores



Adapted from: Merkies IS et al. *Neurology*. 2009; 72:1337-1344.

Lower Probability of Relapse With Continued IVIG-C Maintenance Therapy

Hazard ratio=0.19; 95% CI=0.05–0.70



CI=confidence interval.

Adapted from: Hughes et al. *Lancet Neurol.* 2008;7:136-144.

Acute CIDP–Need to Distinguish From Fluctuating GBS

- 16% of CIDP patients have rapidly progressive course, reaching nadir within 8 weeks
- 8%–16% of GBS patients have one or more deteriorations after initial treatment (treatment-related fluctuation [TRF])
- Treatment decisions differ: a patient with GBS-TRF requires repeat IVIG or plasmapheresis (PEx), whereas a patient with acute CIDP requires long-term maintenance with immunotherapies, including steroids

Ruts L et al. *Neurology*. 2010;74:1680-1686.

Acute CIDP vs Fluctuating GBS–Criteria

- Patients thought to have GBS should be considered to have acute CIDP if:
  - They deteriorate again after 8 weeks from onset or have more than 3 TRFs
  - They have no CN involvement
  - They have no autonomic symptoms
  - NCV is more compatible with CIDP

Ruts L et al. *Neurology*. 2010;74:1680-1686.

CIDP—Long-term Prognosis

- n=38 seen at Chiba University Hospital 1990−2000
  - Evaluated at least q2 mo; NCS at least annually
  - Hughes Grade 0–6
- Follow-up 5 yrs after therapy initiation
  - 89% corticosteroids
  - 45% IVIG
  - 34% PE
  - 5% AZA, 5% CTX
  - 58% combined therapy
- Outcomes
  - 26% complete remission (Hughes 0 >2 yrs)
  - 61% partial remission (Hughes 1 or 2; all ambulatory)
  - 13% nonambulatory or relapsing course (Hughes Grade ≥3; 1 death)

Kuwabara S et al. *J Neurol Neurosurg Psychiatry.* 2006;77:66-70.

CIDP—Long-term Prognosis (cont)

- Hughes improvement ≥1 within 2 mo of initiation
  - 70% corticosteroids
  - 82% IVIG
  - 58% PE
- Complete remission, treatment (n=10)
  - 9 on corticosteroids
  - 1 on IVIG
- Ongoing treatment
  - 39% dependent on immunotherapies

Kuwabara S et al. *J Neurol Neurosurg Psychiatry.* 2006;77:66-70.

CIDP—Long-term Prognosis (cont)

- Prognostic factors predicting complete remission
  - Subacute onset (Rx within 6 mo)
  - Symmetric symptoms
  - No atrophy
  - Distal nerve NCS abnormalities
  - Initial corticosteroid response

- Poor prognostic factors
  - Insidious onset
  - Asymmetric symptoms
  - CB or TD in intermediate segments (forearm or lower leg)
  - Absence of sural sparing

Kuwabara S et al. *J Neurol Neurosurg Psychiatry.* 2006;77:66-70.

MMN–Clinical Features

- Male > female, 3:1
- Pattern of nerve involvement
- Upper extremity > lower extremity
- Motor conduction block in clinically involved nerves with normal SCV over the same segments
- May have some degree of abnormal temporal dispersion,
- GM1 antibodies in some patients (60%)
- Focal motor conduction block (40%–50%) in 2 or more nerves, excluding common sites of nerve entrapment
- Normal sensory conduction across area of block

MMN—Treatment

- IVIG
  - Randomized controlled trials: positive effect
  - Effect is temporary and follow-up infusions needed
  - Frequency of monthly IVIG is individualized and quite predictable in a given patient
  - IVIG is the only drug that helps MMN
- Other immunomodulating drugs
  - Corticosteroids: ineffective
  - Plasma exchange: not effective
  - Mycophenolate: not effective
  - Cyclophosphamide: inconsistent responses
  - Rituximab: variable response

van Schaik IN et al. *Cochrane Database Syst Rev*. 2005;(2):CD004429; Umapathi T et al. *Cochrane Database Syst Rev*. 2005;(3):CD003217.

MMN—Long-term IVIG Issues

- Increased conduction block and axonal degeneration in prior IVIG studies with follow-up to 8 yrs
  - Van den Berg-Vos et al. *Brain* 2002;125:1875-1886
- n=10 pts with conduction block
- Mean age at onset 46 8 yrs
- IVIG 2g/kg q4 wks x 3 mos followed by maintenance infusions
  - If no functional decline, monthly dose decreased by 0.4 gm/kg
  - If functional decline, monthly dose increased by 0.4 gm/kg
  - Over time, IVIG dose “gradually adjusted,” so no functional decline between infusions
  - Average maintenance IVIG dose: 1.63 g/kg
- Follow-up mean 7.25 yrs (3.5−12)

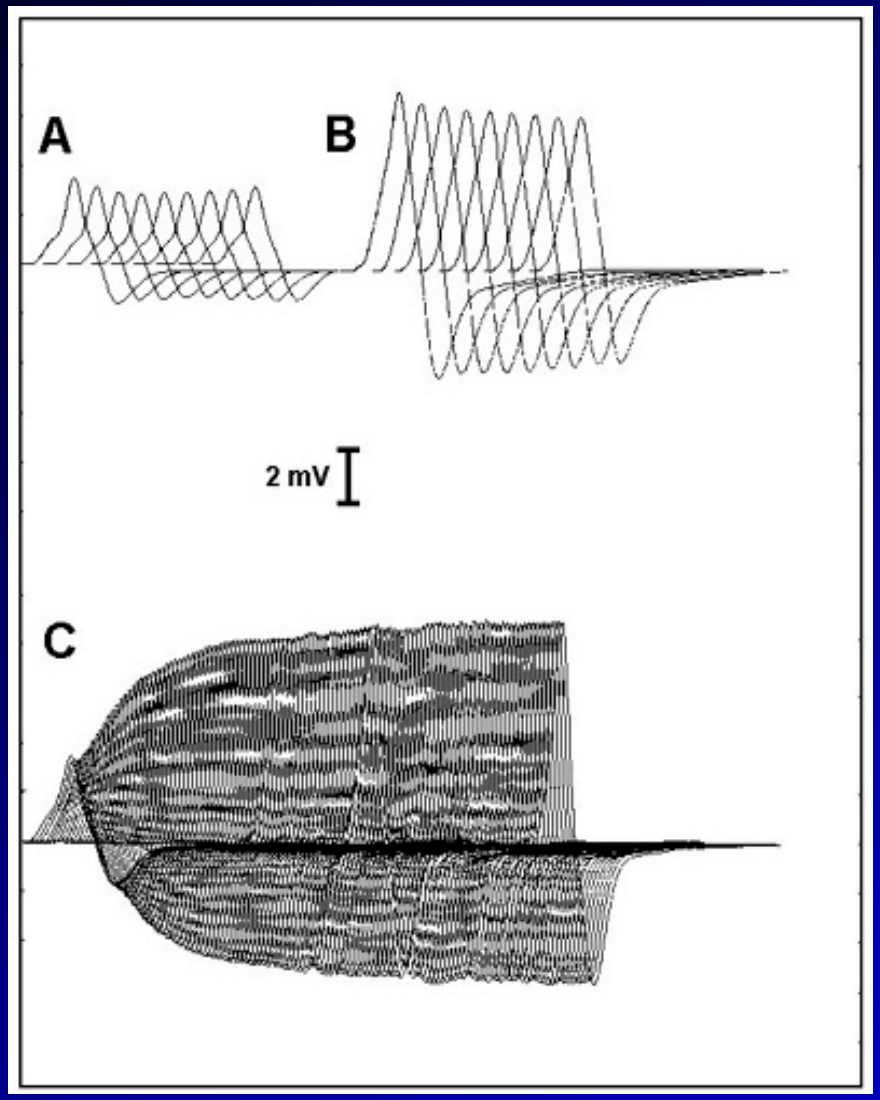
Vucic S et al. *Neurology* 2004;63:1264-1269.

MG–Diagnostic Criteria

- Characterized by fluctuating and fatiguing weakness of bulbar, ocular, and skeletal muscles
- Repetitive nerve stimulation confirms defects in neuromuscular junction typical of MG
- SFEMG
- AChR antibodies
- MuSK antibodies

van Schaik IN et al. *Cochrane Database Syst Rev*. 2005;(2):CD004429; Umapathi T et al. *Cochrane Database Syst Rev*. 2005;(3):CD003217.

MG—Differential Diagnosis



- Lambert Eaton syndrome (LEMS)—a presynaptic disorder on the NMJ associated with Ab to voltage-gated calcium channels (clinical overlap with MG)
  - Small resting CMAP (>10%) decreasing with low Hz stimulation
  - Facilitation with activation
  - Initial decrement at 20–50 Hz followed by facilitation more than 200% (small muscle of hand)
- Others
  - Myasthenic crisis
  - Botulism
  - Congenital myasthenic syndromes

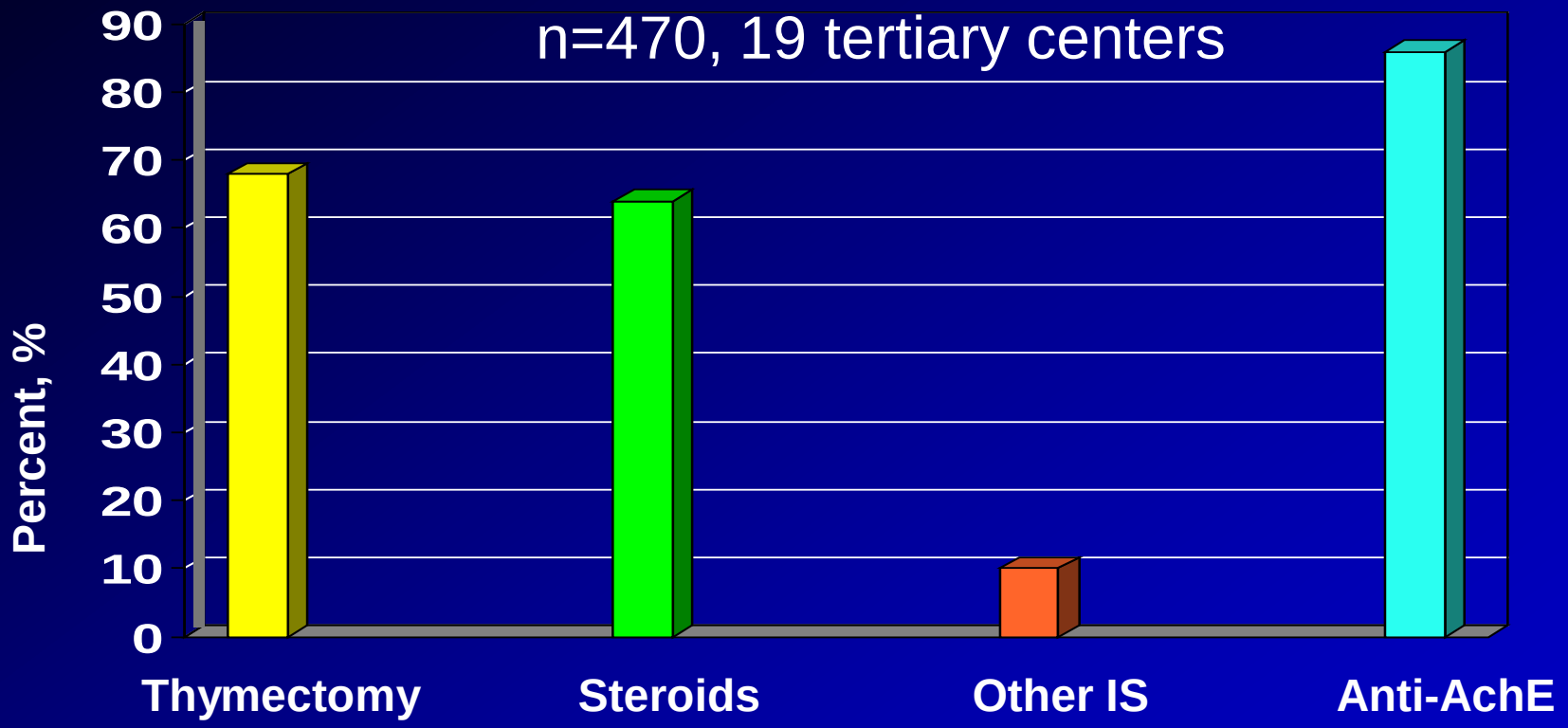
Guardia CF et al. Assessment of Neuromuscular Transmission: Multimedia. Available at http://emedicine.medscape.com/article/1140870-media. Accessed on August 1, 2010.

MG–Treatment: EFNS Consensus Criteria

- Anticholinesterase agents (pyridostigmine) for symptomatic relief
- Oral prednisone
- Immunosuppressants for steroid-sparing effect (azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, rituximab)
- Plasma exchange or IVIG (both effective) for a crisis, before thymectomy, for severe exacerbations, or in patients with inadequate response to other agents
  - IVIG is more accessible
  - Plasma exchange may work faster
- Removal of thymoma
  - Effect of thymectomy is being reconsidered but remains an option

Elovaara I et al. *Eur J Neurol.* 2008;15:893-908. Hughes RA et al. AAN Practice Parameter. *Neurology.* 2003;61:736-740.

MG–Treatment and Outcomes



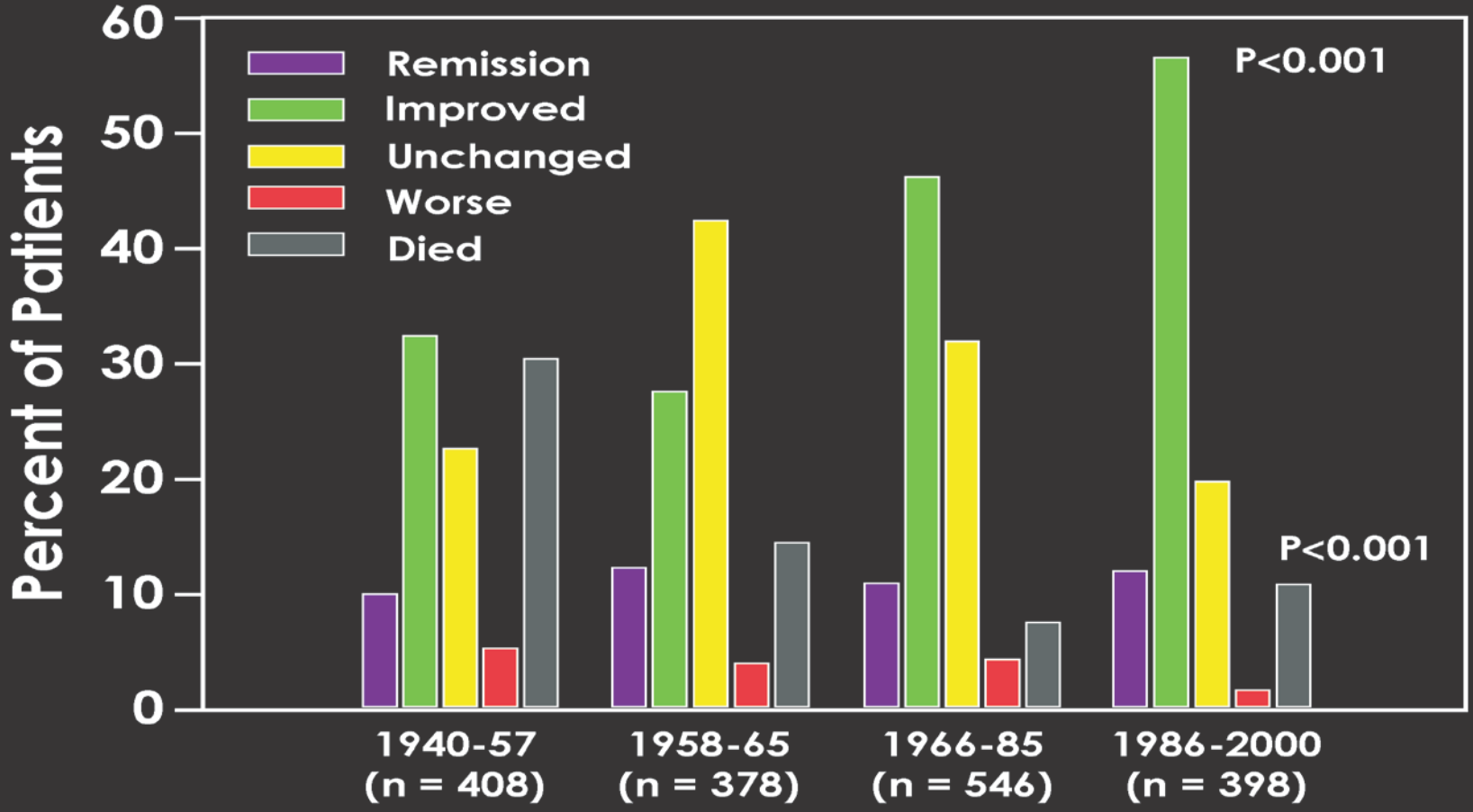
Outcomes (mean follow-up 8 yrs, minimum 1 yr)

- Remission 30%
- Ocular 35%
- Generalized 35% (only 4% with moderate to severe disability)
- MGFA 0-II increased from 78.7% to 96.7% ($p<0.01$)

IS=immunosuppressant; Anti-AchE=cholinesterase inhibitor; MGFA=Myasthenia Gravis Foundation of America.

Adapted from: Kawaguchi N et al. *J Neurol Sci.* 2004;224:43.

MG—Treatment and Outcomes (cont)



Adapted from: Grob D et al. *Muscle Nerve*. 2008;37:141.

Summary of Key Points

- We have reviewed four disorders of the neuromuscular system that cause weakness—GBS, CIDP, MMN, and MG
- Diagnosis of individual cases requires analysis of features of the history and physical as well as laboratory findings
- Electrophysiological testing and interpretation are pivotal to the diagnosis of disorders that in many cases have no known specific diagnostic test or biological marker

Summary of Key Points (cont)

- Although PEx and IVIG may work to hasten recovery in GBS, corticosteroids are ineffective in GBS
- PEx and IVIG are the only evidence-based treatments for CIDP, although prednisone is frequently used
- MMN has proven efficacy to IVIG but is not responsive to PEx, and may be exacerbated by corticosteroids

Summary of Key Points (cont)

- Evidence-based treatments for MG include anticholinesterase agents; oral prednisone; immunosuppressants for steroid-sparing; and PEx or IVIG, particularly for acute exacerbations
- Some long-term challenges in the treatment of neuromuscular disease include:
  - GBS: Physical disability (20%), emotional and general health, and QoL
  - CIDP: Treatment dependency in up to half of patients and significant physical disability in 20%
  - MMN: IVIG dependency in the majority; need to refine IVIG dosing in settings of ongoing motor decline and axonal loss

To receive CME credit, please be sure to complete the posttest and evaluation.