GBS
Life After Diagnosis

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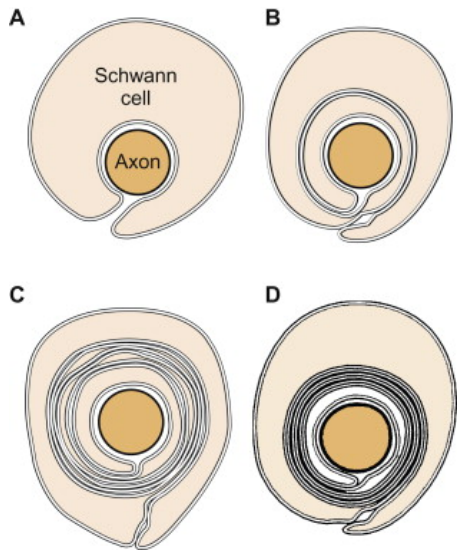
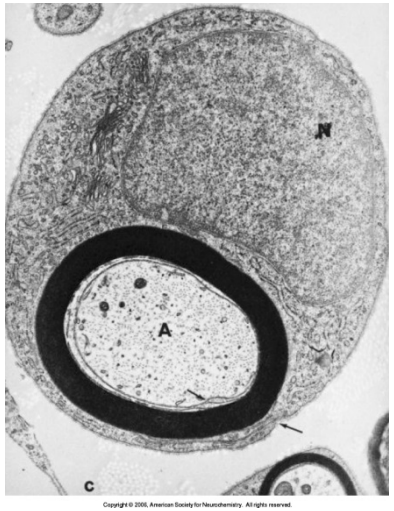
DISCLOSURES

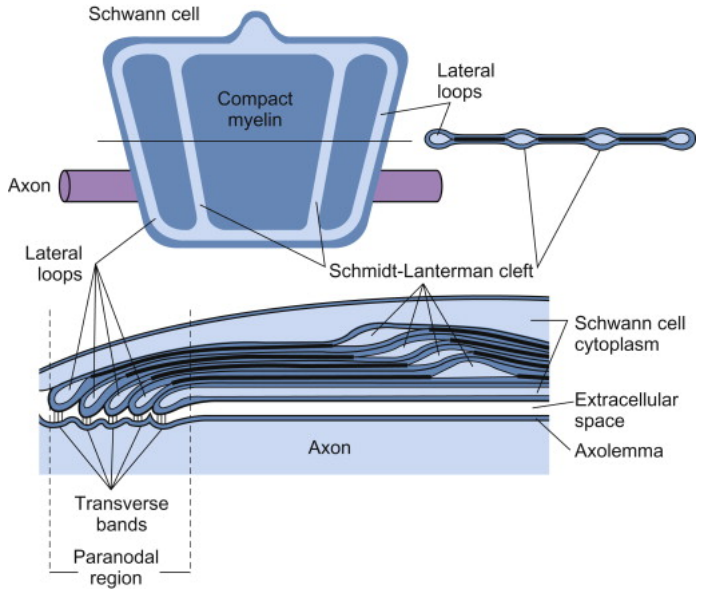
- **Robert P Lisak over the past 2 years has been funded for research support by the National Institutes of Health, National Multiple Sclerosis Society (USA), Genentech, Teva Pharmaceuticals, Novartis, Medimmune, Ra Pharmaceuticals, Argenx and Chugai. He has served as a consultant to Argenx, Novartis, Mallinckrodt GLG, Syntimmune, Alexion, Argenx, Alpha Sites, Insights Consulting, Informa Pharma Consulting, Slingshot Consulting, Schlesinger Group Consulting, Health xxxx. He has served on speakers bureau for Teva Pharmaceuticals (non-branded talks only)**

Guillain-Barre *Syndrome*

- Guillain-Barre syndrome is a syndrome, not a single disease
  - Commonality of symptoms and signs
  - Not all cases are identical in pathogenesis; how the disease develops at in the tissues but again have some commonality
  - A syndrome that affects the peripheral nervous system (PNS) which includes the peripheral nerves, the nerve roots (the part of the nerve inside the spinal canal) and the nerve plexus (area outside the spinal canal) where roots are organized into the nerves themselves.
  - Preceding illness or ‘event’
  - CSF findings
  - EMG/NCS can be very different in different variants







Macklin and Rasband, Chapter 31, Basic Neurochemistry 8th edition, 2011

TYPES/FORMS OF GBS

- **Acute inflammatory demyelinating polyneuropathy (AIDP)**
  - **Varying degrees of secondary axonal degeneration**
- **Acute motor axonal neuropathy (AMAN)**
  - **Most common form in China, *C. jejuni* association**
- **Acute motor sensory axonal neuropathy (AMSAN)**
- **Fisher syndrome**
  - **EOM, ataxia and hypo-areflexia**
- **Acute multifocal motor axonopathy ?**
- **Cervical-Pharyngeal-Brachial Neuropathy**
- **Bickerstaff's Brainstem Encephalitis**

- **Different forms likely have different pathogenic mechanisms and likely different target autoantigens**

Antecedent events: GBS

Viruses

- CMV-
- EBV, VZV, CMV
- HIV
- Others

Vaccines

- Swine flu (1976)
- Other influenza??
- Hepatitis B?
- Rabies
  - Suckling mouse CNS
  - Semple rabbit CNS
- Vaccinia

Bacteria

- C. jejuni- GM1, GD1A, GQ1b, GT1A
- M. pneumoniae- GalC
- H. influenza

Surgery

GBS:Presentation

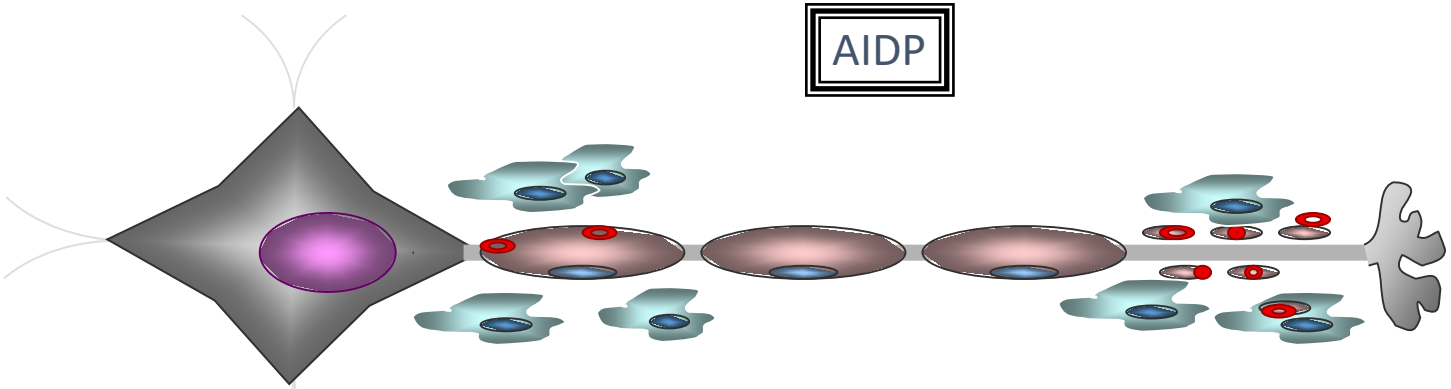
- **Pain**
  - **Diffuse ache of back or neck, sometimes limbs**
- **Paresthesias**
  - **May be minor**
- **Weakness**
  - **Bilateral and basically symmetric; proximal and distal**
  - **Can begin in arms or legs or face**

GBS: Clinical Features

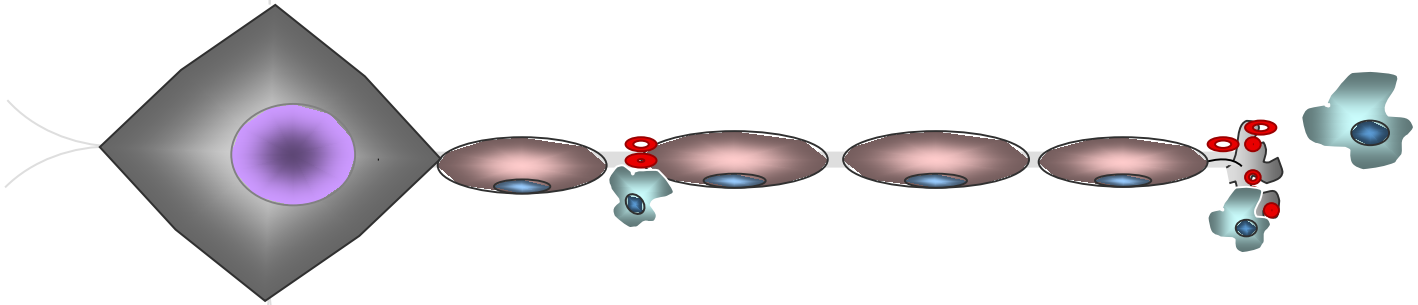
- **Cranial nerves**
  - **Facial nerves ~ 50%**
  - **Bulbar nerves (IX, X, XII) with dysphagia**
  - **Ocular motor (III, IV, VI) ~ 10%**

- **Respiratory involvement**
  - **Occurs in at least 25%**
  - **Ventilator in over 15%**

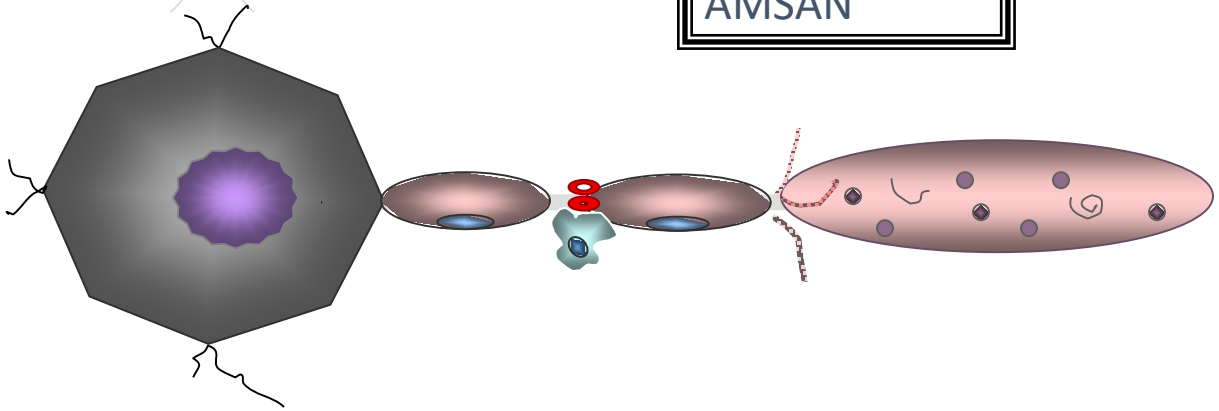
AIDP



AMAN

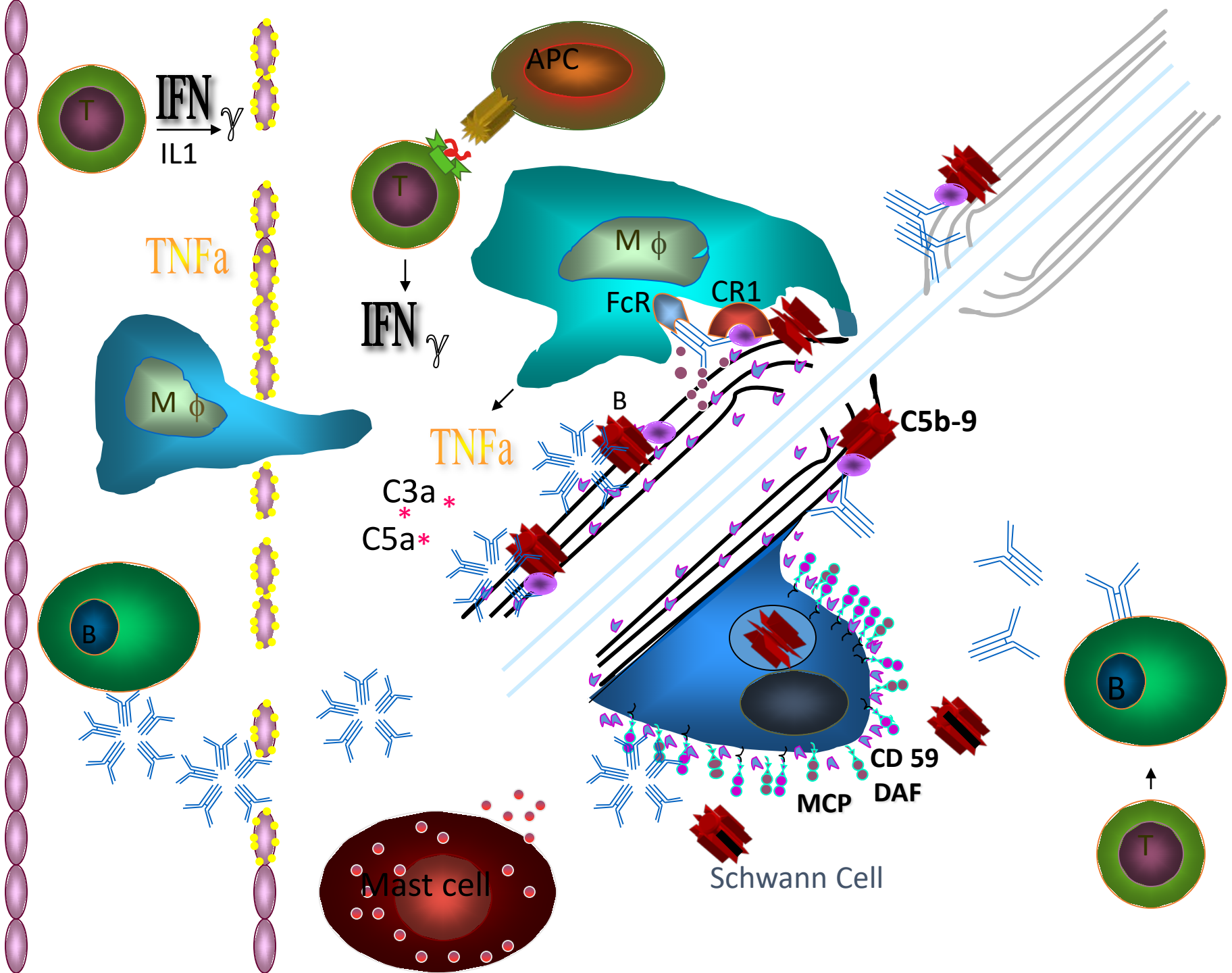


AMSAN



Pathology and Immunopathologenesis of AIDP

- **Multifocal perivascular inflammation with lymphs and monocytes**
- **Segmental demyelination**
- **Varying degrees of axonal damage**
- **Similarity of pathology to EAN induced with P2 myelin protein, PMP22 and P0**
  - **Cells and cytokines open BNB and also lead to SC and myelin damage**
  - **Open BNB (ordinarily less tight than BBB) allows for passage of humoral factors including antibodies to SC/myelin; complement**
- **AIDP likely a combination of cell-mediated immunity and antibodies to constituents of PNS myelin**
- **Triggering factors may work via molecular mimicry**
  - **Evidence better in axonal and Fisher forms**

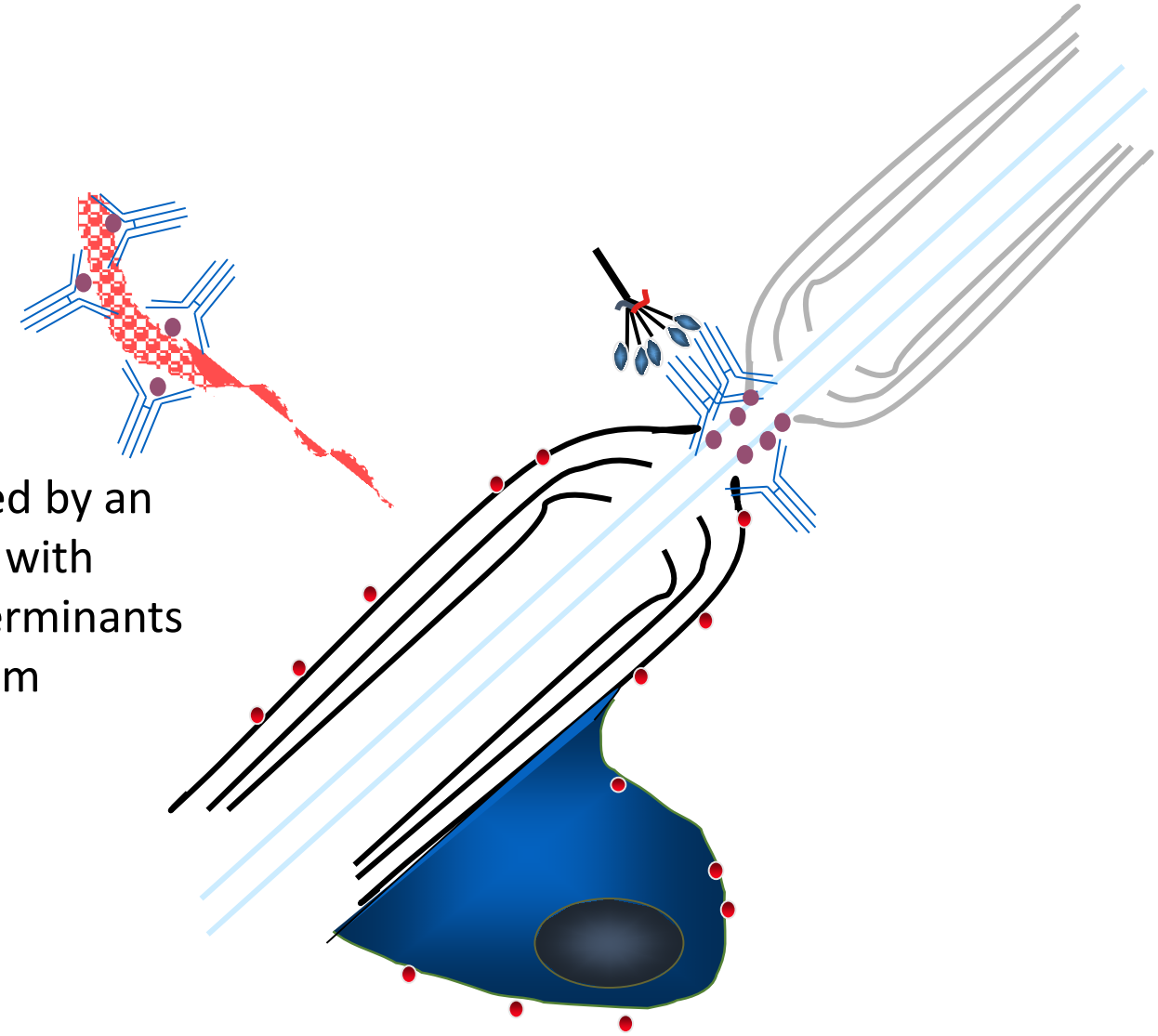

T
IFN γ
IL1
APC
T
TNFa
M ϕ
IFN γ
M ϕ
FcR
CR1
B
C5b-9
TNFa
C3a *
*
C5a*
B
CD 59
DAF
MCP
Mast cell
Schwann Cell
B
T

Pathology and Immunopathogenesis of AMAN/AMSAN

- **Infiltration of macrophages at the internode and/or presynapic area along with Ig and complement activation**
- **Varying degrees of axonal damage**
- **IgG antibodies to one of several gangliosides likely targeted against the axons (GM1, GM1b, GD1a, GalNAc-GD1a)**
- **Anti-ganglioside antibodies may also act presynaptically to inhibit neurotransmission (terminal axonopathy)**
- **The reason that some AMAN/AMSAM patients recover relatively quickly is not understood, perhaps those with more distal lesions**
- **Strong evidence for molecular mimicry between gangliosides and components of certain strains of *C. jejuni***

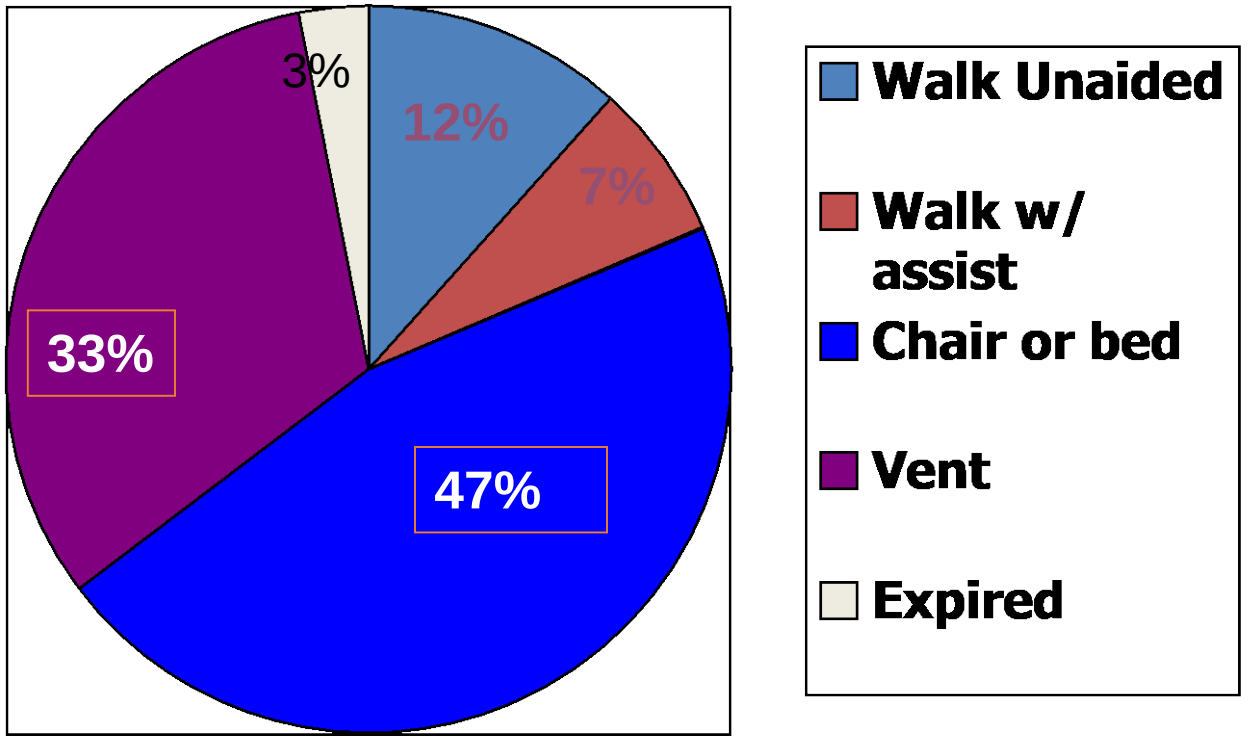
AMAN

Immune responses stimulated by an an infectious organism react with shared foreign and host determinants expressed in the endoneurium



Schwann Cell

GBS: Severity at Peak

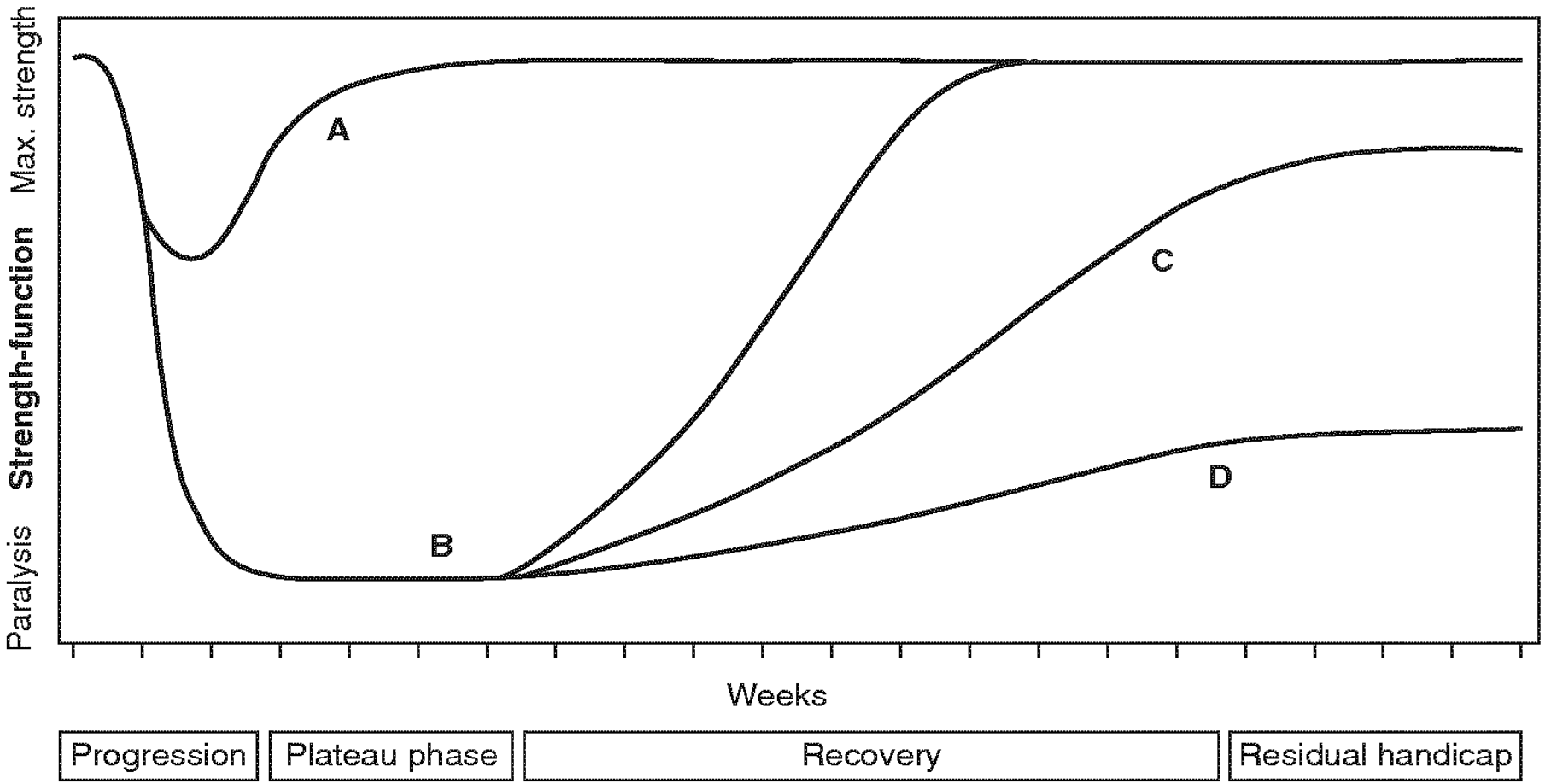


GBS: Clinical Course

- Variable Progression: Nadir

- A few patients will progress to quadriplegia in 24 hours

Variable Disease Course



Measure	Categories	Score
Days between onset of weakness and hospital admission	>7 days	0
	4–7 days	1
	≤3 days	2
Facial and/or bulbar weakness at hospital admission	Absence	0
	Presence	1
MRC sum score at hospital admission	60–51	0
	50–41	1
	40–31	2
	30–21	3
	≤20	4
EGRIS		0–7

EGRIS = Erasmus GBS Respiratory Insufficiency Score; MRC = Medical Research Counsel.

MRC SUM SCORE
(0-5)
6 muscles bilaterally:
(1) upper arm abductors,
(2) elbow flexors,
(3) wrist extensors,
(4) hip flexors,
(5) knee extensors,
(6) foot dorsiflexors

Low risk = 0-2; Intermediate = 3-4; High Risk = 5-7

GBS: Autonomic Dysfunction

- **Common**
  - **70%- sustained or paroxysmal hypertension**
  - **Most- sinus tachycardia**
  - **Sinus arrhythmia in 50% (vagal involvement)**
  - **Postural hypotension in 20%**
  - **Cardiac arrhythmias- Brady and tachy**
  - **EKG changes- T inversion; ST elevation**
  - **Excessive sweating in 30%**

GBS: Treatment

- **Monitor respiration: FVC and NIF**
- **Monitor swallowing and secretions**
- **Prevent DVT**
- **Plasma exchange *or* IVIG**
- **Symptom management and psych issues**
- **Rehabilitation**

TREATMENT OF GBS

- **Plasma exchange (PLEX)**
  - **6 total body exchanges done as `one qod**
- **IVIg**
  - **400mg/kg per day x5 days**
- **Combination is no more effective than either therapy by itself**
- **Improve outcome; reduce time on vent; speed recovery**
- **Hard to prove differences over the long term (studies are generally lacking)**

SYMPTOMATIC THERAPY IN GBS

- **Pain**
  - **Narcotics (acute phase only and only when necessary)**
  - **Tricyclics**
  - **AED**
- **Autonomic**
  - **Depends on what occurs**
- **Fatigue (late effects)**

Outcome at 4 weeks

- **31/72 (18%) walked with aids**
- **35/172 (20%) walked without aids**
- **44/308 (14%) still on ventilator**

Outcome at 6 months

100/122 (82%) walked unaided

Outcome at 1 year

- **312/515 (61%) recover full strength**
- **292/347 (84%) walk unaided**
- **188/1349 (14%) have persistent severe weakness**
- **31/82 (38%) had to change jobs**
- **61/1391 (4%) died**
- **24/624 (4%) relapse**

Predictors of prognosis in Guillain-Barre´syndrome: derived from findings of prospective literature of studies including a majority of treated patients

Category	Predictor
Clinical	Age >40 or 50 years
	Reduced vital capacity
	Need for mechanical ventilation
	Preceding diarrhoea
	Low MRC Sum Score at admission
	Low MRC Sum Score at day 7 postadmission
	Short interval between onset and admission
	Facial and/or bulbar weakness
Electrophysiological	Inexcitable nerves
	Low summated distal CMAP <20% of LLN
Biological	None of definite value
	More confirmatory studies required

GBS Disability Score for EGOS

- 0 = normal
- 1 = minor symptoms, capable of running
- 2 = able to walk 10 m unassisted, but unable to run
- 3 = able to walk 10 m with help
- 4 = bedridden or chair bound
- 5 = needs ventilator

Erasmus GBS Outcome Scale (EGOS) Can Predict Outcome

- **Ability to walk at 6 months predicted**
  - **Scale of 0-7**
- **Age at onset**
  - **< 40= 0 40-60 = 0.5 >60 = 1**
- **Diarrhea**
  - **No = 0 Present = 1**
- **GBS Disability Scale at 2 weeks**
  - **0-1 = 1 2=2 3=3 4 = 4 5= 5**

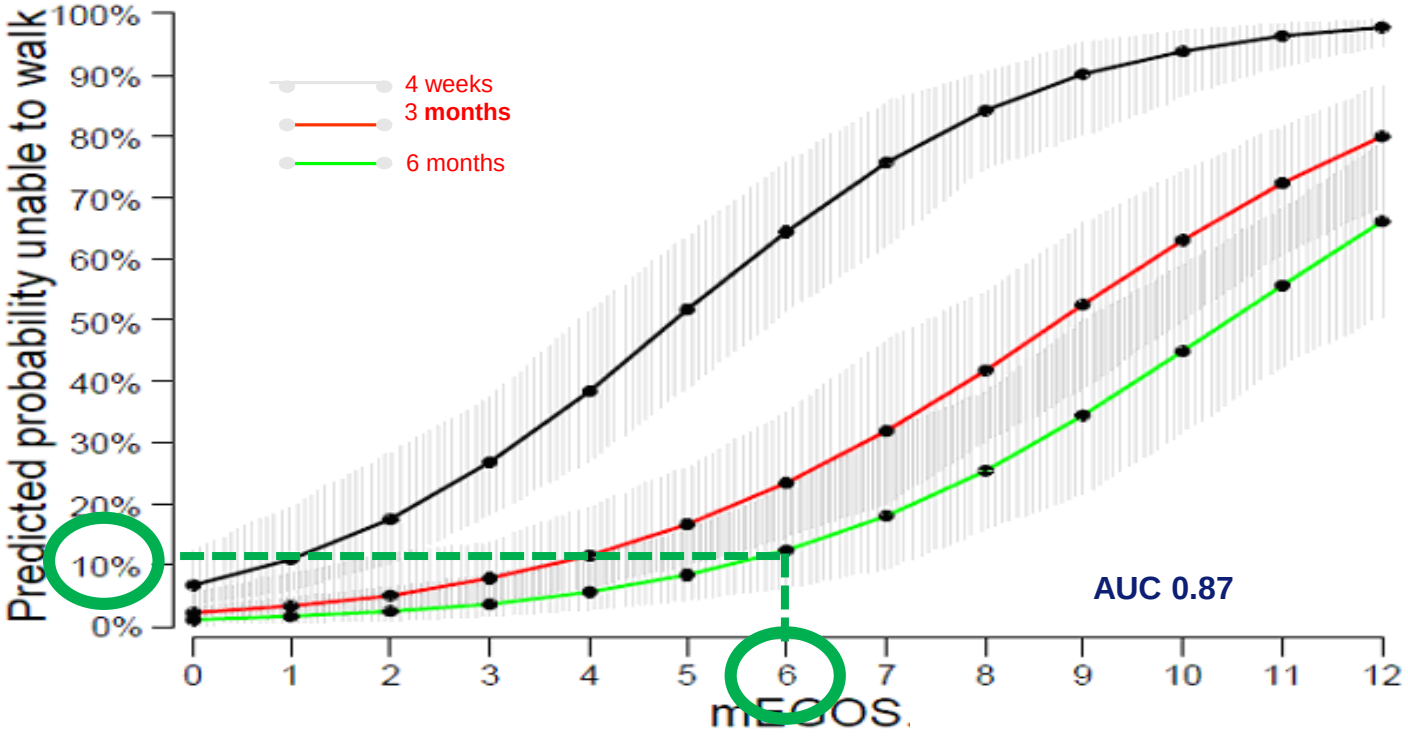
(van koningsveld R, et al. Lancet Neurol 2007)

Modified EGOS to predict clinical course in GBS *Walgaard et al., Neurology 2011*

Modified Erasmus GBS outcome score (mEGOS)

Predictors	Categories	Score
Age (years)	≤40	0
	41 – 60	1
	>60	2
Diarrhoea	absent	0
(≤ 4 weeks)	present	1
MRC sumscore	51 - 60	0
(at 1 week)	41 - 50	3
	31 - 40	6
	0 - 30	9
mEGOS.7		**0 - 12**

Chance unable to walk at 4 weeks, 3 and 6 months according to mEGOS (N=555)



Expectations in GBS

- **Muscles that are moving even just slightly at 6 months are likely to keep improving**
- **Muscles with no movement at 6 months may not improve to functional levels.**
- **The maximal degree of recovery is in the first 12-18 months but some improvement can continue for 3-5 years**

GBS: Long Term Issues

- **Ambulation, use of UEs, truncal weakness**
- **How long can you still see improvement?**
- **Fatigue (even with excellent clinical recovery)**
- **Pain**
- **Will it recur?**
  - **Rare**
- **Vaccinations**
- **FUTURE TREATMENTS**

FUTURE THERAPY IN GBS

- **Hard to do studies**
  - **Placebo controlled studies are not ethical**
  - **IRB approval**
  - **Rare disease**
  - **‘Add ons’ to IVIg, but many patients improve without/before treatment was available and with treatment most patients do well**
- **Eculizumab**
  - **Inhibits complement pathway activation**
  - **Other inhibitors of earlier stages of complement activiation**