Clinical considerations on the use of IgG in GBS and CIDP

Yuri Matteo Falzone, MD, PhD

IRCCS San Raffaele Scientific Institute

Neuromuscular Repair Research Unit

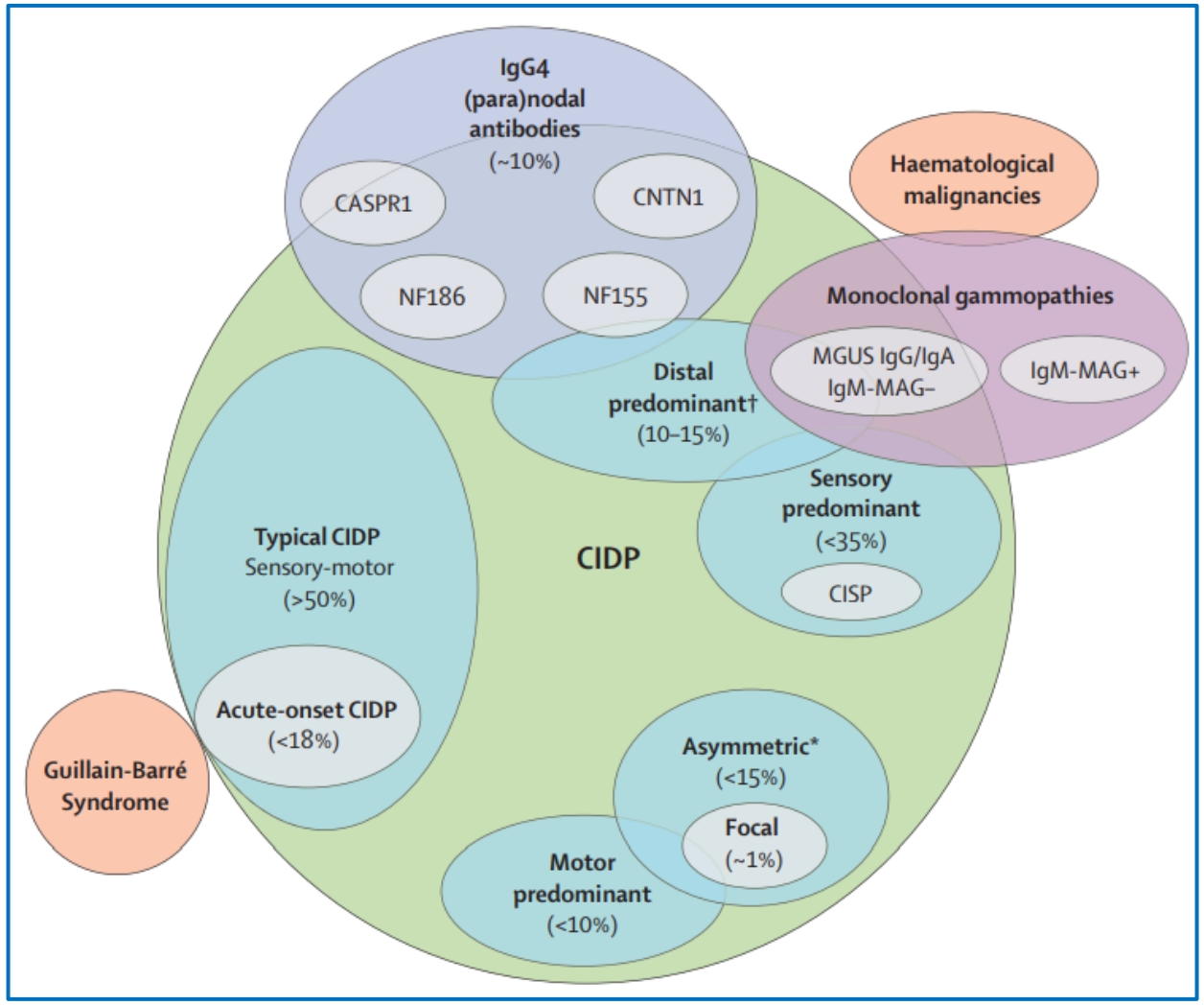
InSpe and Division of Neuroscience

Conflicts of Interest

I do not declare any competing interests related to this presentation

I participate in advisory boards for the following companies: Argenx, Takeda and Alnylam.
I have received travel grants from Alexion, Alnylam, and Kedrion."

Inflammatory Neuropathies – General overview



- Heterogenous disease spectrum embracing several **autoimmune neuropathies**

Guillain–Barrè syndrome (**GBS**)

Most common **acute** variant

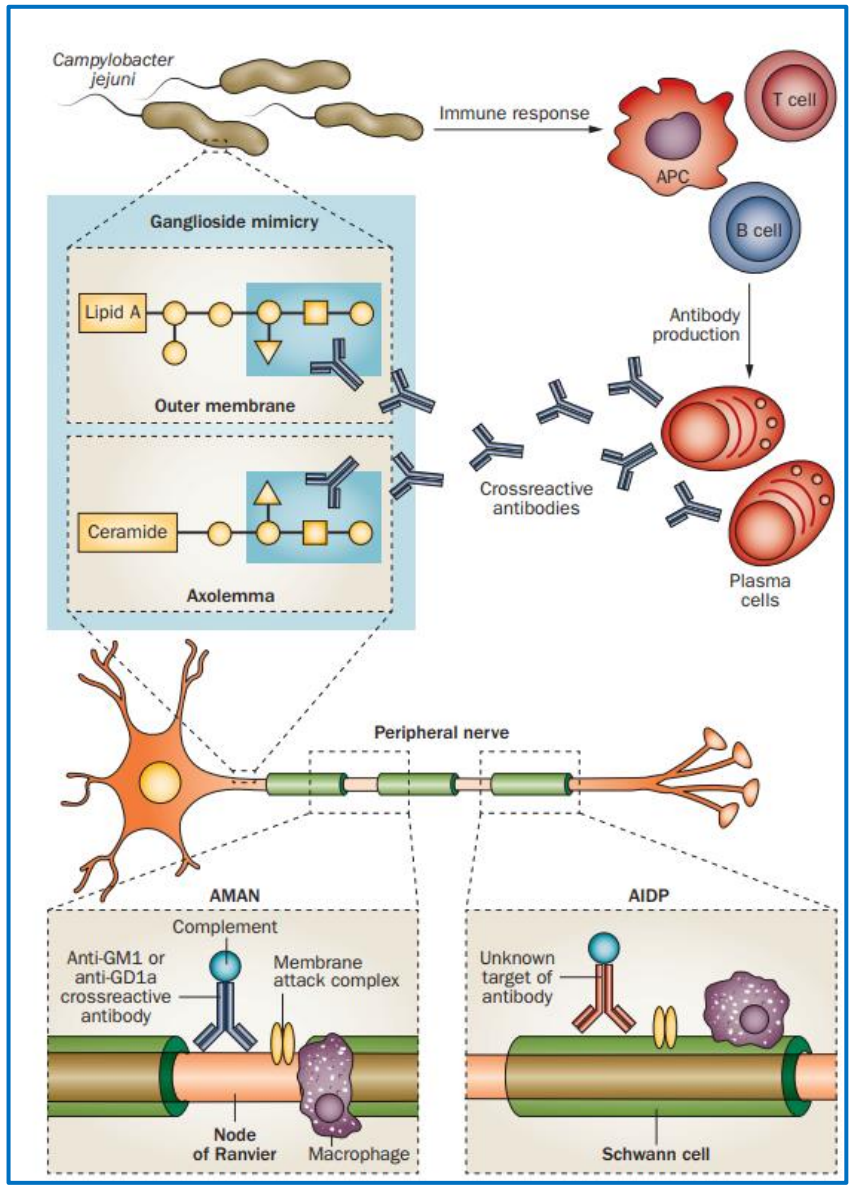
Chronic Inflammatory Demyelinating Polyradiculopathy (**CIDP**)

Most common **chronic** variant

- Timely **immunomodulatory** treatment required to reduce mortality and long-term disability
- **Rare diseases** with an incidence of 1-2 cases per 100'000 people per year

Image from Bunschoten C, et al. Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. Lancet Neurology, 2019

GBS – Pathogenesis



Two patients out of three report symptoms of a respiratory or gastrointestinal tract **infection** before the onset of GBS

↓

Molecular mimicry between microbial and nerve antigens plays a key role in the development of GBS

↓

Humoral immune and **cellular** autoimmune responses

↓

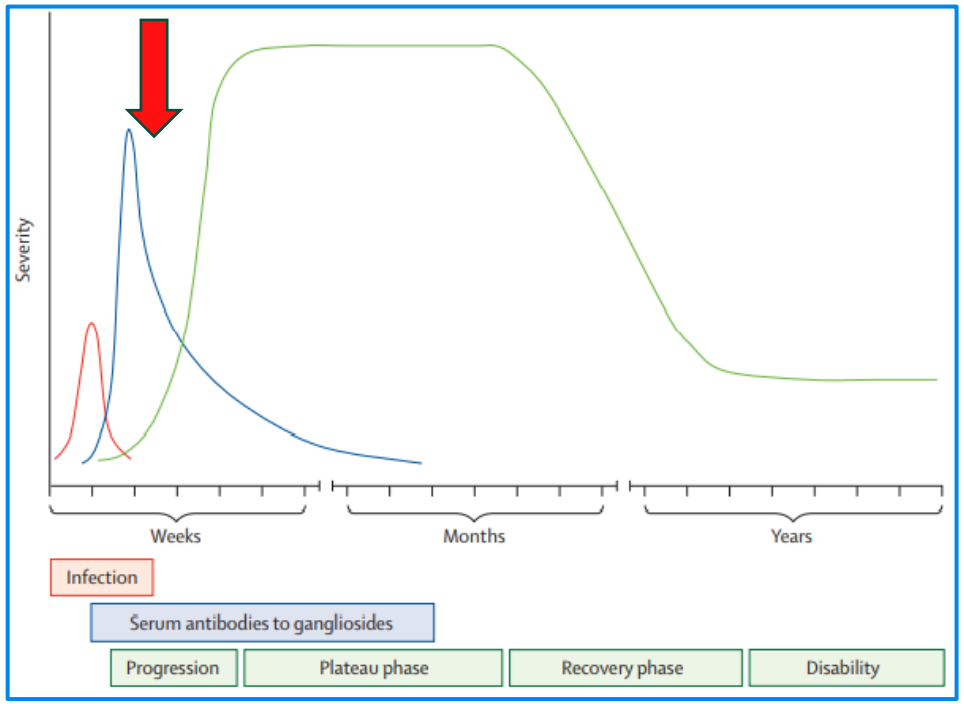
Autoantibodies and **autoreactive T-cells** that crossreact with myelin and axon antigens

↓

Macrophagic invasion leading to axonal (AMAN) or demyelinating (AIDP) GBS variant

Image from Van den Bergh B, et al. Guillain–Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. *Nature reviews 2014*

GBS – Clinical Overview



- Clinical manifestation characterized by **subacute progressive muscle paralysis**, which may progress to respiratory failure

- **Monophasic** disease → after reaching the nadir (typically within 2-3 weeks from symptom onset) recovery phase follows

Timely **immunomodulatory** interventions are required to reduce mortality and disability

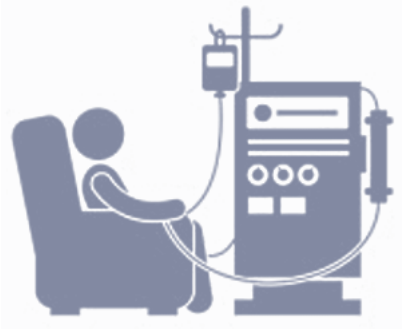
- **Mortality** ranges from 3.5% to 12%[1]

- Significant residual **disability** occurs in 12% of cases[1]

Image from Willison H et al. Guillain-Barrè syndrome. Lancet Neurology, 2016

1. Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. Cochrane Database of Systematic Reviews 2014

GBS – Intravenous Immunoglobulin (IVIg)



In 1987, randomized clinical trial (RCT) established the effectiveness of Plasma Exchange (PE) in GBS[1]

IVIg 0.4g/kg daily for five days compared with PE 200–250 ml/kg in five sessions over 7 to 14 days

Non-ambulatory patients with a disease duration of less than two weeks enrolled

No difference in disability grade after 4 weeks from treatment

Intravenous immunoglobulin for Guillain-Barré syndrome (Review)

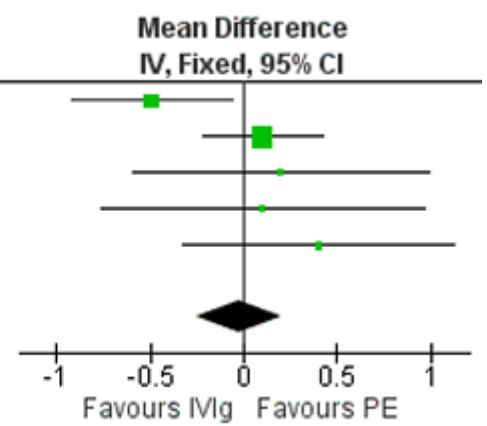
Hughes RAC, Swan AV, van Doorn PA

THE COCHRANE COLLABORATION®

Study or Subgroup	IVIg Mean	IVIg SD	IVIg Total	PE Mean	PE SD	PE Total	Weight	Mean Difference IV, Fixed, 95% CI
Van der Meché 1992	-0.86	1.32	74	-0.37	1.33	73	27.3%	-0.49 [-0.92, -0.06]
PSGBS Study Group 1997	-0.8	1.3	130	-0.9	1.3	121	48.4%	0.10 [-0.22, 0.42]
Bril 1996	-1	1.32	26	-1.2	1.5	24	8.1%	0.20 [-0.59, 0.99]
Diener 2001	-1.2	1.32	20	-1.3	1.5	21	6.7%	0.10 [-0.76, 0.96]
Nomura 2001	-1	1	23	-1.4	1.5	24	9.5%	0.40 [-0.33, 1.13]
Total (95% CI)			**273**			**263**	**100.0%**	**-0.02 [-0.25, 0.20]**

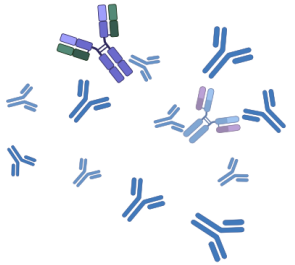
Heterogeneity: Chi² = 6.82, df = 4 (P = 0.15); I² = 41%

Test for overall effect: Z = 0.21 (P = 0.83)



Having demonstrated IVIg efficacy and safety in the treatment of GBS

IVIg recognised as therapeutic indication in GBS



1.*Efficiency of plasma exchange in Guillain-Barré syndrome:: French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome. Ann Neurol. 1987*

GBS – Clinical considerations

Treatment to add to IVIg?

- Combination of PE and IVIg

No demonstrated superiority compared to single treatments[2]

- Second course of IVIg

No superiority in efficacy found when compared a single administration[3]

Which treatment to choose?

IVIg and PE equally effective, but…

IVIg

- Fewer adverse events and less likely to be discontinued
- Readily available in most hospitals

PE

- Specialized facilities and reliable intravenous access required
- Higher risk of adverse events

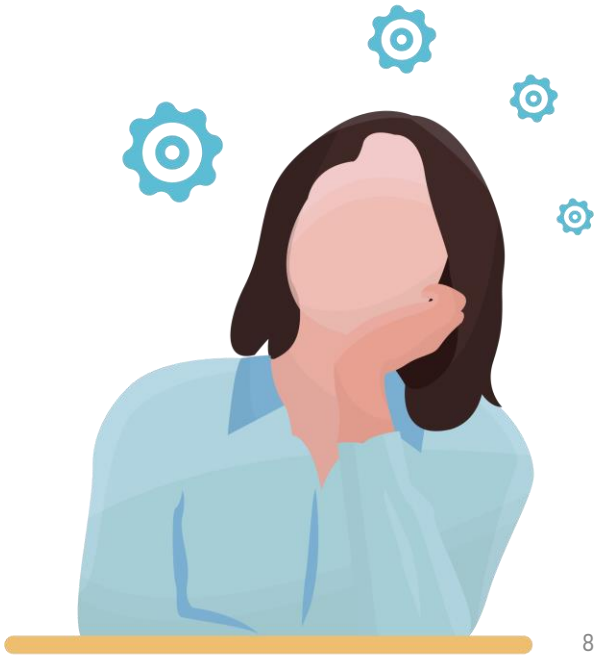
1. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in GBS. Plasma Exchange/Sandoglobulin GBS Trial Group. Lancet. 1997*; 2. Waalgard et al.* Second intravenous immunoglobulin dose in patients with Guillain-Barré syndrome with poor prognosis (SID-GBS): a double-blind, randomised, placebo-controlled trial. Lancet Neurol. 2021

GBS – Clinical perspectives

No data on treatment for **milder phenotypes** or administration **after two weeks from onset**

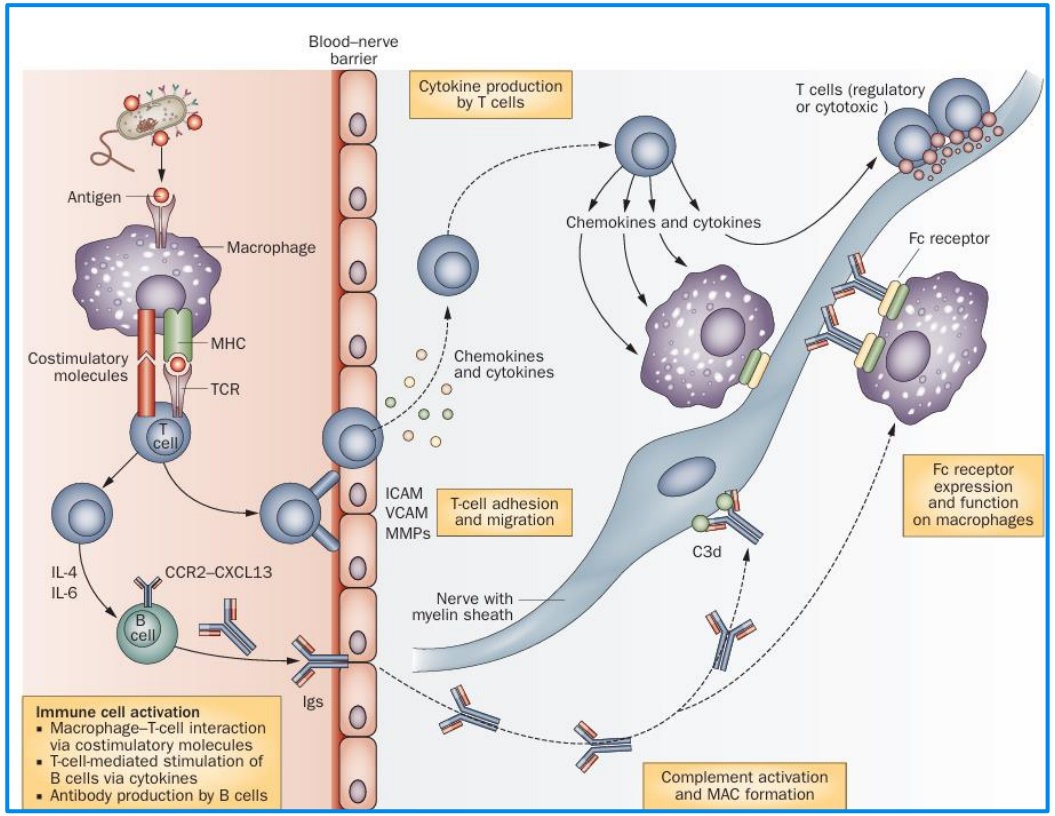
Treat patients with rapid progression, even if able to walk unaided[1]

Lack of Data or **Low-Quality Evidence** Comparing Different Doses and Administration Schemes



1. *European Academy of Neurology/Peripheral Nerve Society Guideline on diagnosis and treatment of Guillain-Barré syndrome. Eur J Neurol. 2023*

CIDP - Pathogenesis



Unknown antigens are presented by macrophages to T-cells

↓

Clonal expansion of T-cells and activation of **B-cells**, which produce **autoantibodies** targeting self-antigens

↓

Transmigration of T cells across the blood–nerve barrier

↓

Chemokines and cytokines produced by T-cells, along with autoantibodies, **activate resident macrophages**

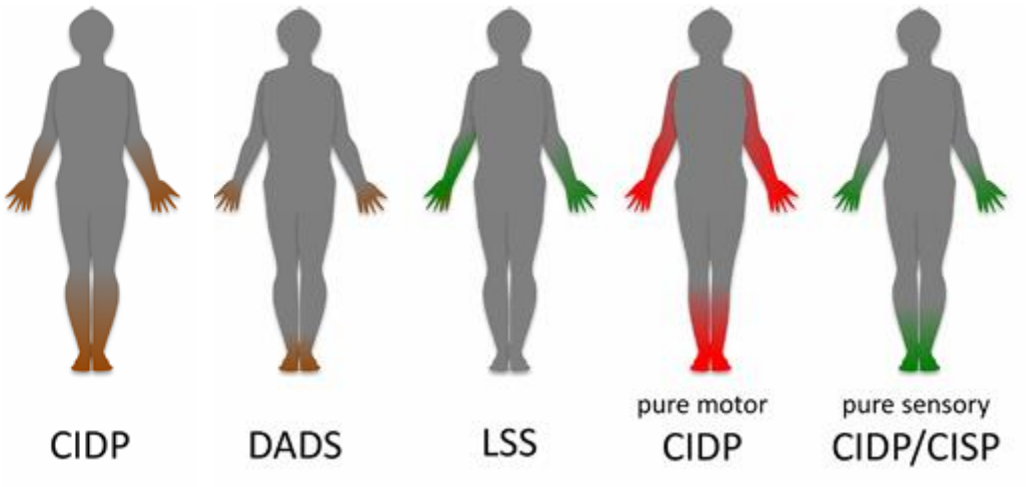
↓

Myelin damage caused by macrophage activation and **complement activation**

Image from Dalakas M. Advances in the diagnosis, pathogenesis and treatment of CIDP. *Nature reviews 2011*

CIDP – Clinical Overview

Typical CIDP
Progressive Weakness of Proximal and Distal Limbs with Sensory Disturbances



Several phenotypes have been described, involving either motor or sensory dysfunction, reflecting the wide clinical **heterogeneity** of **CIDP**

If left untreated or inadequately treated, it can lead to severe **disability**

IVIg and corticosteroids (CS) are the **first-line treatments** for **CIDP**

Image from Lehmann, et al. Chronic inflammatory demyelinating polyneuropathy: update on diagnosis, immunopathogenesis and treatment. Neurology, 2019

CIDP – Treatment, use of corticosteroids

What about corticosteroids?

- No RCTs comparing CS with placebo
- One RCT comparing corticosteroids with no treatment had a small sample size and a high risk of bias (Dyck 1982)
- Pulsed intravenous corticosteroids have similar efficacy compared to oral steroids (Van Schaik 2010)

↓

Corticosteroids are widely used in clinical practice, but **low-quality** evidence from RCTs

CIDP – Treatment, use of IVIg

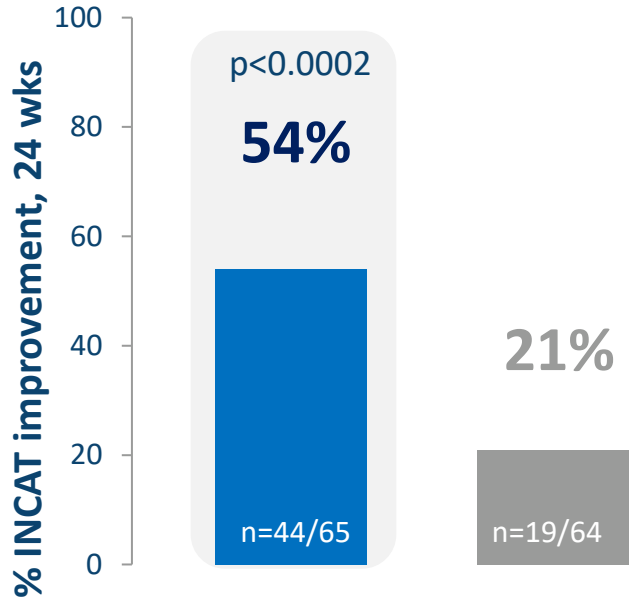
First large RCT (117 CIDP patients) proving the **long-term efficacy of IVIg compared** to **Placebo** (ICE study)

Loading dose
of 2 g/kg

+

Maintenance infusion
of 1 g/kg every 3 weeks
for up to 24 weeks

Primary outcome = percentage of patients who had maintained an improvement from baseline in INCAT disability score through to week 24



Primary endpoint

Secondary outcomes

	First period				Crossover (rescue) period			
	Change from baseline* Mean (SD)		LSM difference† (95% CI)	p†	Change from baseline* Mean (SD)		LSM difference† (95% CI)	p†
	IGIV-C (n=59)	Placebo (n=58)			IGIV-C (n=45)	Placebo (n=23)		
Adjusted INCAT disability score	−1·1 (1·8)	−0·3 (1·3)	−0·7 (−1·3 to −0·2)	0·010	−1·2 (1·5)	−0·3 (1·8)	−0·9 (−1·7 to −0·1)	0·022
Amplitude (mV)‡	0·69 (1·86)	0·47 (2·29)	0·24 (−0·53 to 1·00)	0·542	0·28 (1·71)§	−0·23 (0·82)¶	0·49 (−0·32 to 1·30)	0·230
Grip strength (kPa)								
Dominant hand	13·2 (19·3)††	1·5 (15·6)	10·9 (4·6 to 17·2)	0·0008	15·5 (26·8)	−1·0 (11·7)	16·1 (4·5 to 27·7)	0·007
Non-dominant hand	13·3 (17·4)‡‡	4·3 (14·9)	8·6 (2·6 to 14·6)	0·005	14·6 (23·1)	−2·9 (11·6)	17·6 (7·0 to 28·1)	0·001
MRC sum score	3·3 (5·6)	0·2 (4·5)	3·1 (1·3 to 4·9)	0·001	4·4 (6·5)	−0·6 (5·4)	4·7 (1·6 to 7·8)	0·004
ISS score	−1·2 (3·4)††	0·2 (3·9)††	−1·5 (−2·7 to −0·2)	0·021	−1·7 (3·8)	−0·5 (3·1)	−0·6 (−2·4 to 1·2)	0·499

Serious adverse events were similar in the two study groups
Most common adverse events were **headache**, pyrexia, and hypertension

Treatment response sometimes may **only** be observed **after 3–5 infusions** of 1 g/kg every 3 weeks,
as according to PRIMA (Leger 2013) and PRISM (Nobile-Orazio 2021) studies

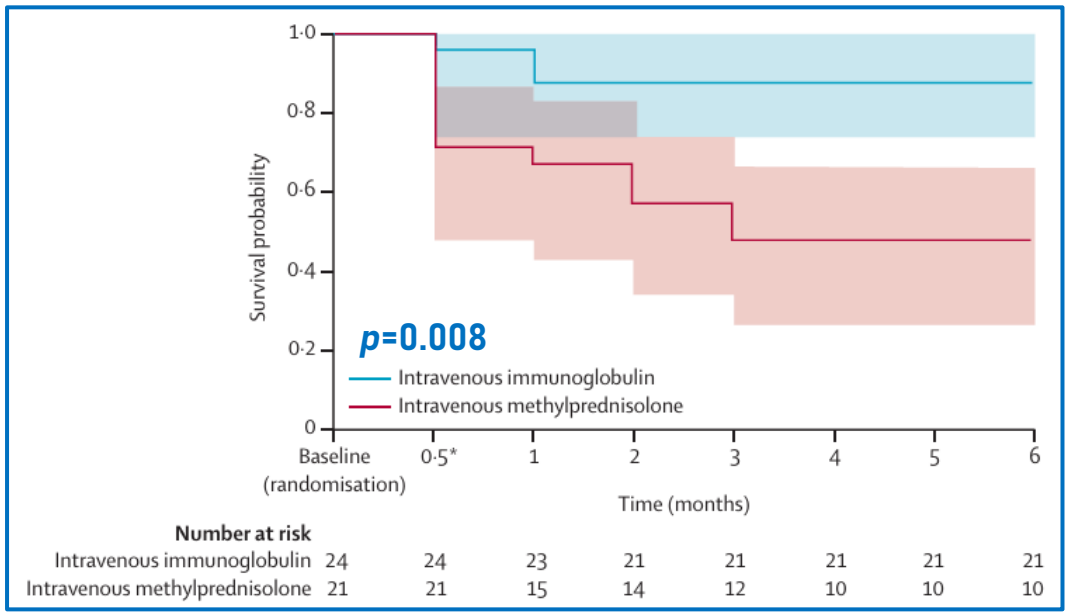
Hughes et al. Intravenous immune globulin (10% caprylate chromatography purifi ed) for the treatment of chronic infl ammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurology, 2008

CIDP – Treatment, use of IVIg

RCT (45 CIDP patients) comparing the **long-term effects** of IVIg with intravenous corticosteroids → Patient randomization

- **IVIg** 2 g/kg in five days
- **IV methylprednisolone** (IVMP) 500 mg x 4 days

every 28 days for six months



Primary outcome = difference in the proportion of patients discontinuing treatment with IVIg or intravenous methylprednisolone during the 6 months

A higher percentage of patients **stopped IV methylprednisolone** (11/21 pt, 52%) compared to IVIg (3/24 pt, 24%)

Reasons for stopping IVMP	Reasons for stopping IVIg
• 5 clinical worsening • 3 no clinical improvement • 3 side effects	• 2 clinical worsening • 1 no clinical improvement

A trial (Hughes 2001) compared IVIg and oral prednisone, showing no difference in efficacy.

Limitations
- small sample size
- 2-week observation period

→ European guidelines **do not recommend** an overall treatment preference

Image from Nobile-Orazio et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. Lancet Neurology, 2012

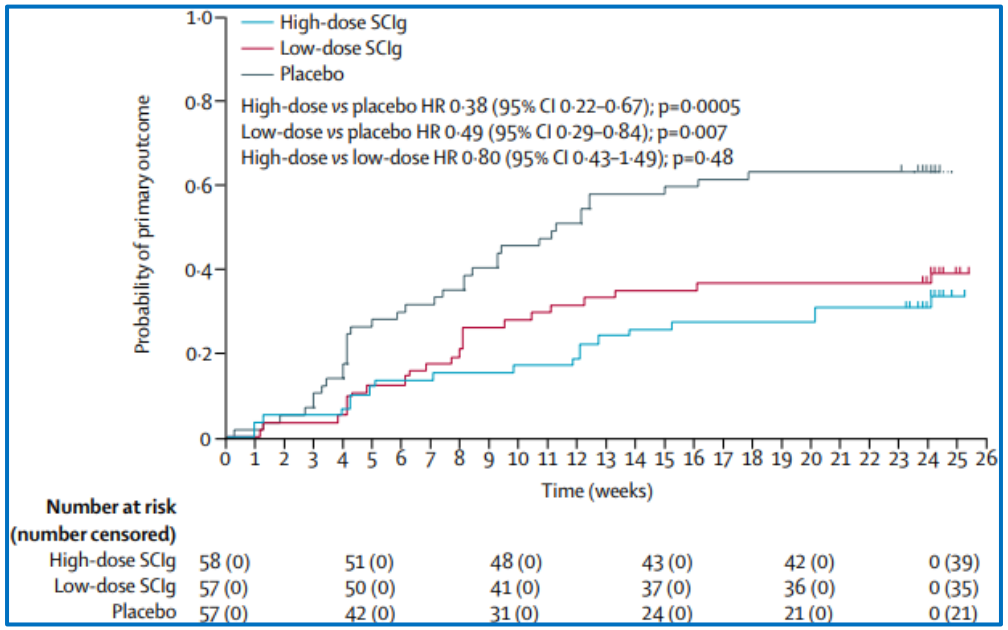
1. *Van Den Bergh et al.* European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision. EJN, 2021

CIDP – Treatment, use of SCIg

RCT (172 CIDP patients, IVIg dependent) comparing the **efficacy** of SCIg with placebo (PATH study)

Patient randomization

- High-dose SCIg (0.4 g/kg weekly)
- Low-dose SCIg (0.2 g/kg weekly)
- Placebo



Primary outcome = proportion of patients with a CIDP relapse or who were withdrawn for any other reason during 24 weeks of treatment

Probability of reaching the primary endpoint → significantly **lower** in both SCIg groups than in the placebo group

Adverse events were more frequent in the SCIg groups, with the most common being local site reactions

European guidelines **strongly** recommended using SCIg for maintenance treatment in **CIDP**[1]

Image from Nobile-Orazio et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. Lancet Neurology, 2012

1. *Van Den Bergh et al.* European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision. EJN, 2021

CIDP – Clinical Perspectives

- Corticosteroids and IVIg are both considered first-line treatments with comparable efficacy, but → Limited available data from RCTs comparing these therapies

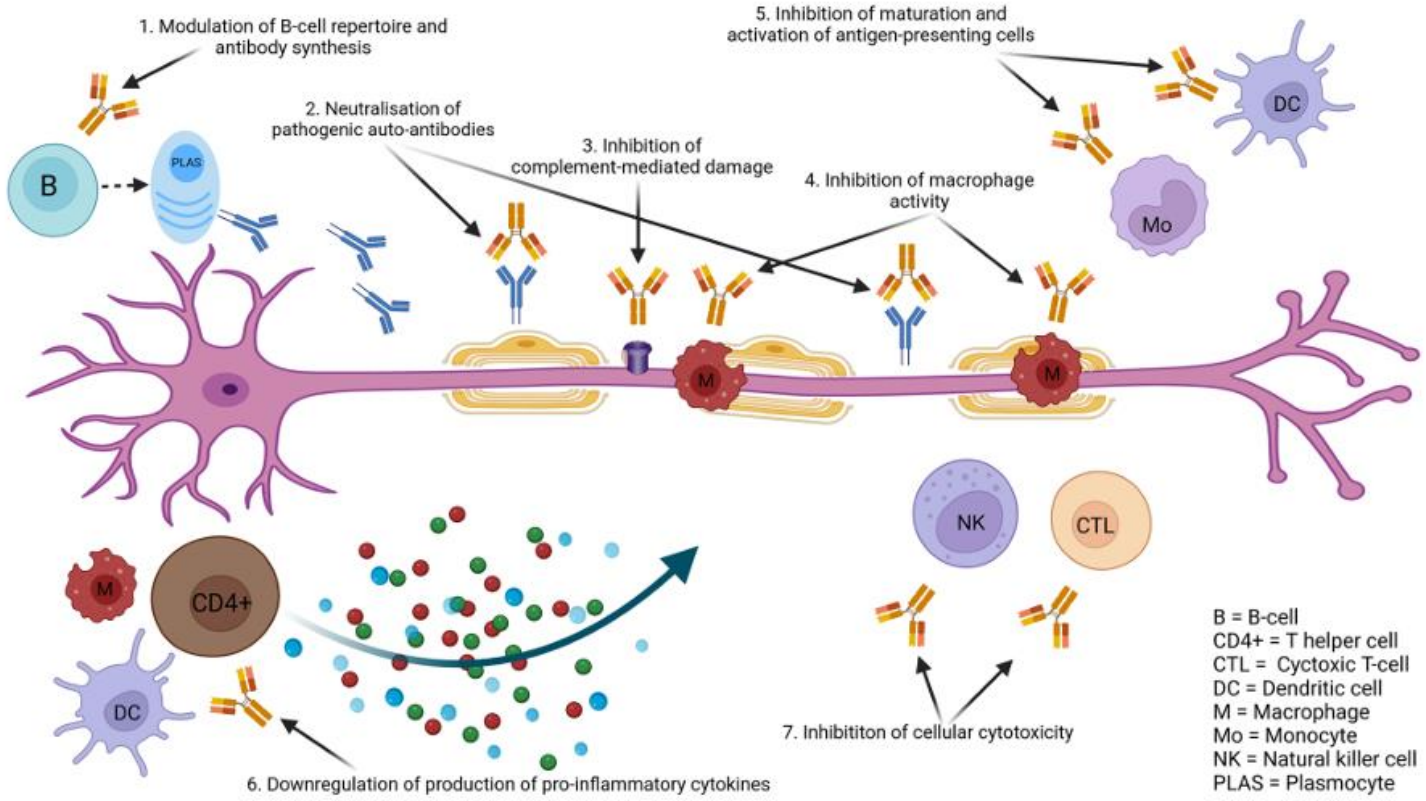
- Maintenance dose of IVIg and SCIg based on evidence from RCTs. These guidelines provide direction, but…

In clinical practice, **therapy should be tailored** to the individual patient's response

- Most RCTs enroll patients with typical forms of CIDP → Limited efficacy data for rarer phenotypes (e.g. distal or sensory variants)

- How to explain the significant variability in response to immunoglobulin therapy seen in clinical practice?
  - → IgG pharmacokinetics?
  - → Pharmacogenomics?

Ig – Immunomodulatory mechanism of action



- **Anti-Idiotypic** activity
- **Saturation** of the **FcRn** (Neonatal Fc receptor)
- **Complement inhibition**
- **Upregulation FcγRIIB** inhibiting macrophage/B.cell activation
- **Co-stimulatory** and **adhesion molecules inhibition**

Image from Rajabally Y. Immunoglobulin and Monoclonal Antibody Therapies in Guillain-Barré Syndrome. *Neurotherapeutics, 2022*

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