Treatment of Acute Immune-Mediated Neuropathies

Pieter A van Doorn
Erasmus MC
Rotterdam, the Netherlands

WCN 22 September 2013

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- Diagnosis and course of disease
- General medical treatment
- Admission and EGRIS prognostic model
- Immunological treatment
- Pain
- Fatigue
- Transition to CIDP?
- Recent developments and international studies

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- Diagnosis and course of disease

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Guillain-Barré syndrome (GBS)

- AIDP = acute inflammatory demyelinating polyneuropathy
- AMAN = acute motor axonal neuropathy
- AMSAN = acute motor and sensory axonal neuropathy

- MFS = Miller Fisher syndrome

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Guillain-Barré syndrome (GBS)

- Most frequent cause of acute neuromuscular paralysis
- About 7000 pat/year in European Union

- 2/3 post-infectious (Campylobacter, URTI, other)
- Rapidly progressive
- Monophasic
- Severe
  - 25% artificial ventilation,
  - 20% unable to walk after 6 months;
  - 3-5% die
  - often: long-term pain and fatigue

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Epidemiology

1.1-1.6/100.000 persons/year

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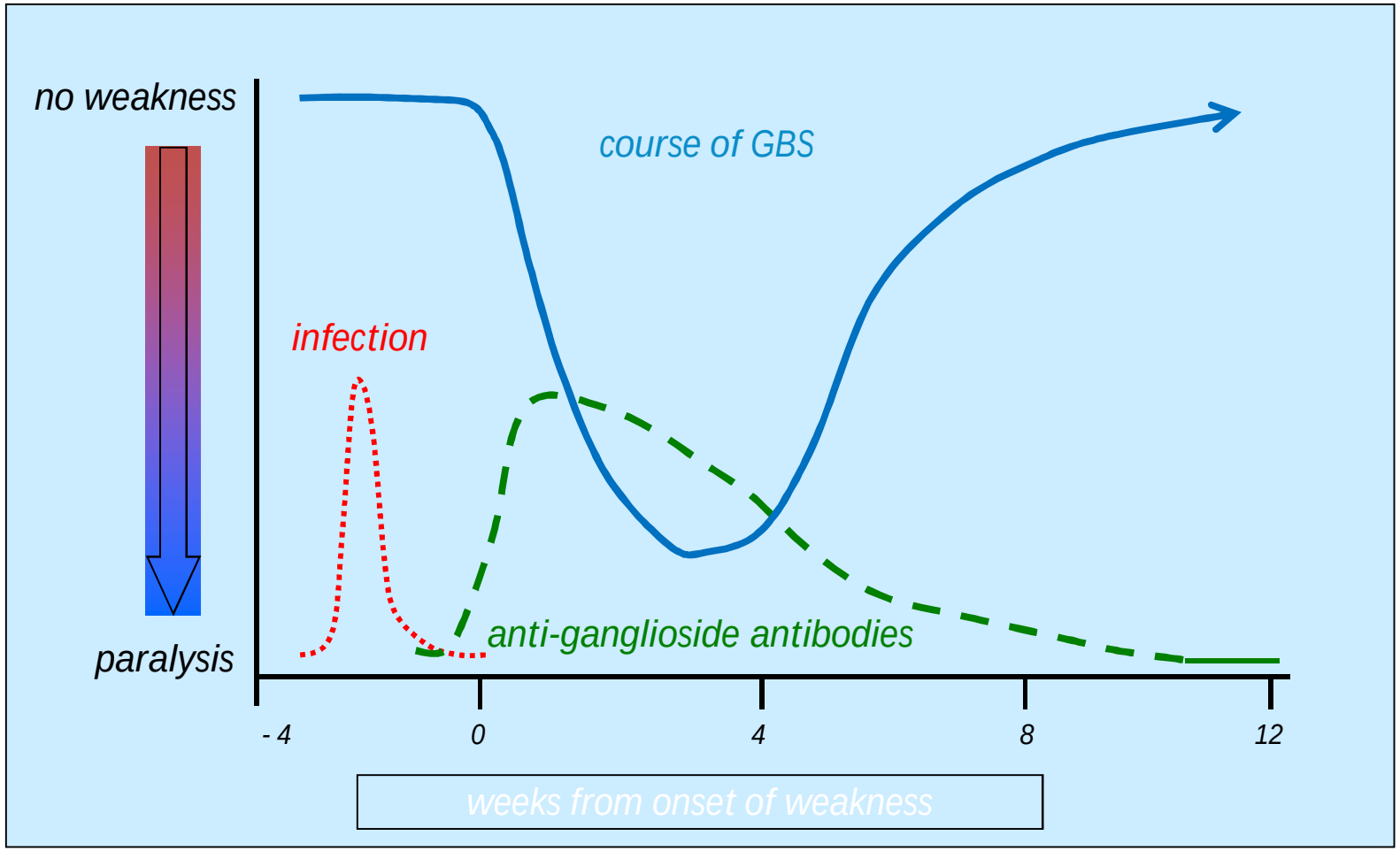
Preceding infections, anti-ganglioside antibodies and course of disease in GBS



Diagnostic criteria for GBS

- Asbury and Cornblath. Ann Neurol 1990
- Sejvar et al. Brighton criteria for GBS. Vaccine 2011

New information:

- Fokke et al. Brain in press

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Diagnostic criteria	Asbury & Cornblath (1990)		Brighton collaboration criteria for GBS (2011)
Bilateral and flaccid weakness of limbs	?Ø	*Required*	?Ø
Decreased or absent deep tendon reflexes in weak limbs	?â		?â
Monophasic course and time between onset-nadir 12 hr-28 days	?ì	*Supportive*	?ì
Mild sensory symptoms and signs	?E		?E
Cranial nerve involvement	?æ		?æ
Several other clinical features	?B		?B
CSF cell count <50/µl	?		?
CSF protein level > normal value	?^		?^
EMG findings consistent with GBS	?º		?º
Absence of identified alternative diagnosis for weakness	?æ	*Rule out*	?æ

Levels of certainty

Brighton collaboration criteria for GBS

Sejvar et al. Vaccine 2011

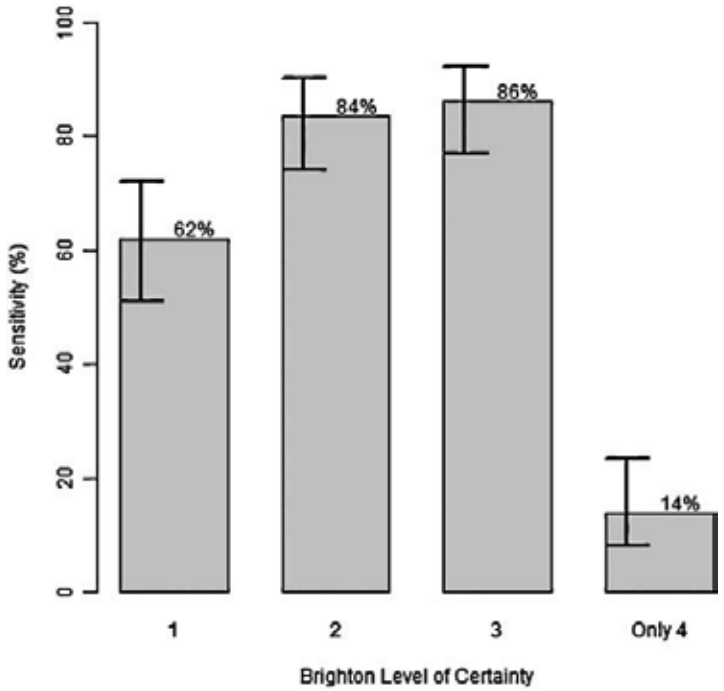
Diagnostic criteria	Level of diagnostic certainty 1	2	3	4
Bilateral and flaccid weakness of limbs	+	+	+	+/-
Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+/-
Monophasic course and time between onset-nadir 12 hr-28 days	+	+	+	+/-
CSF cell count <50/µl	+	+	-	+/-
CSF protein level > normal value	+	+/-	-	+/-
EMG findings consistent with GBS	+	+/-	-	+/-
Absence of identified alternative diagnosis for weakness	+	+	+	+

Guillain–Barré Syndrome in India: Population-based validation of the Brighton criteria

FJ Mateena, DR Cornblath, H Jafari, RT Shinohara , D Khandit, B Ahuja, S Bahl, RW Sutter

Vaccine 2011

Casefiles of 718 patients considered to have GBS



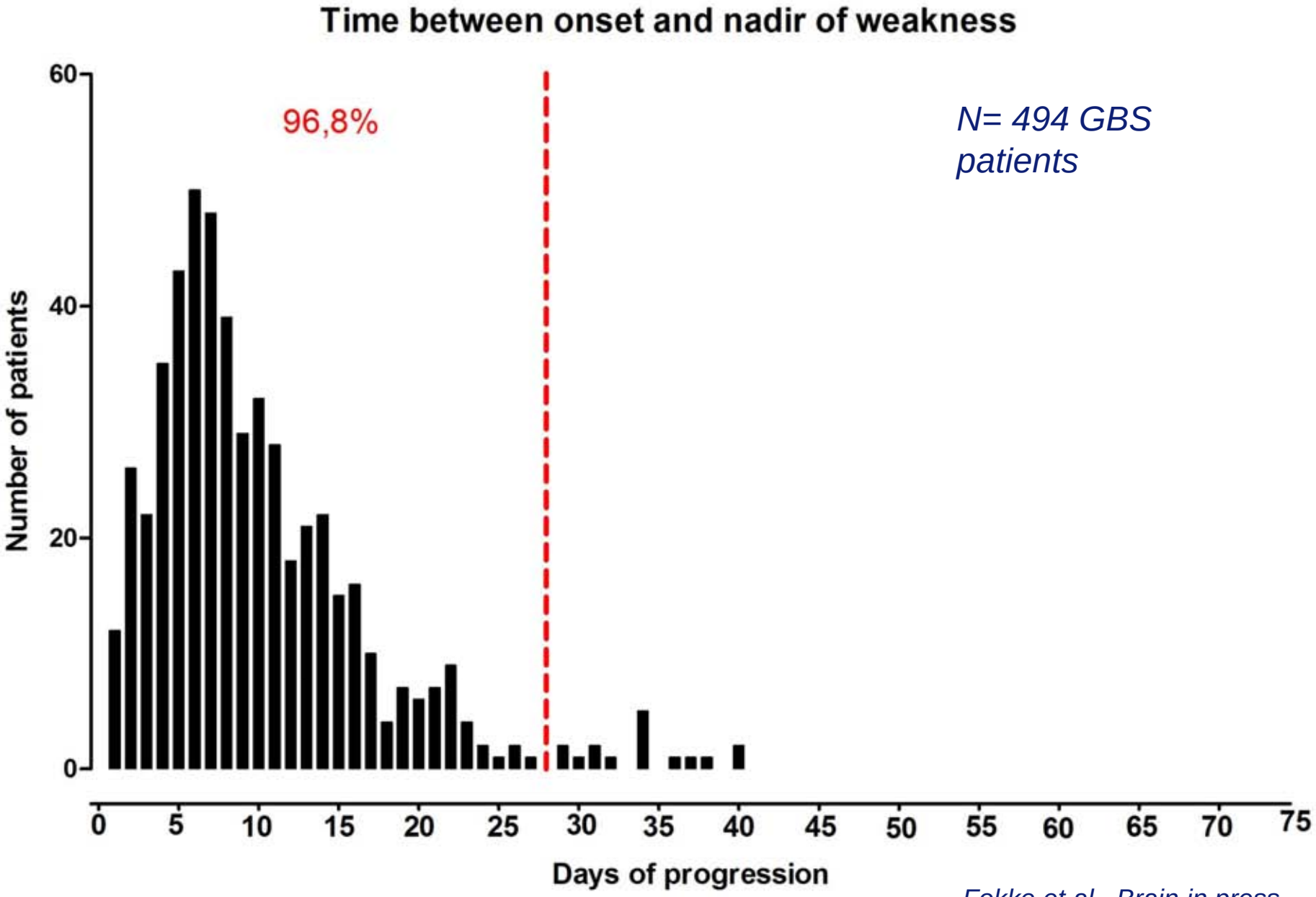
Using Brighton criteria: diagnosis GBS can be made in India with moderate to high sensitivity.

Brighton case definitions are a plausible standard for capturing a majority of cases of GBS in field operations in low income settings during AFP surveillance.

Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria

Fokke et al., Brain in press

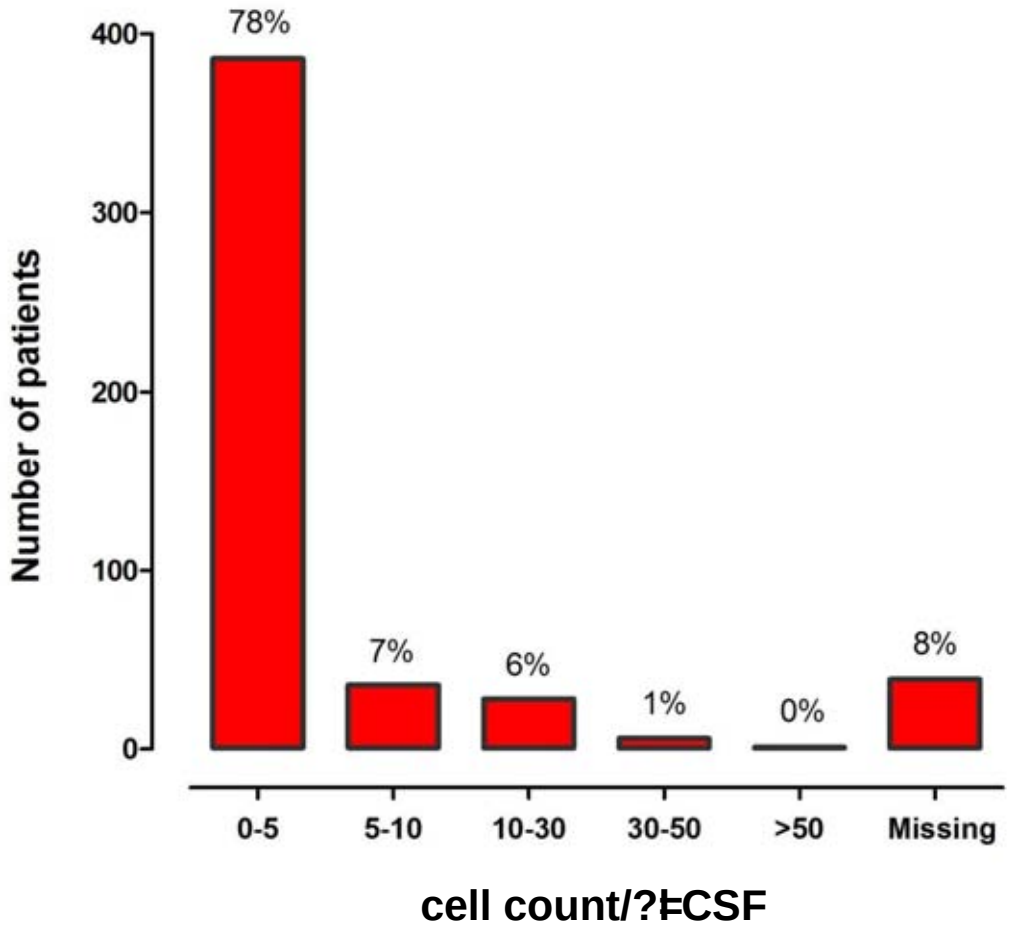
- Duration of progressive weakness
- CSF cell count
- CSF protein



Fokke et al., Brain in press

Cell counts in cerebrospinal fluid of GBS patients

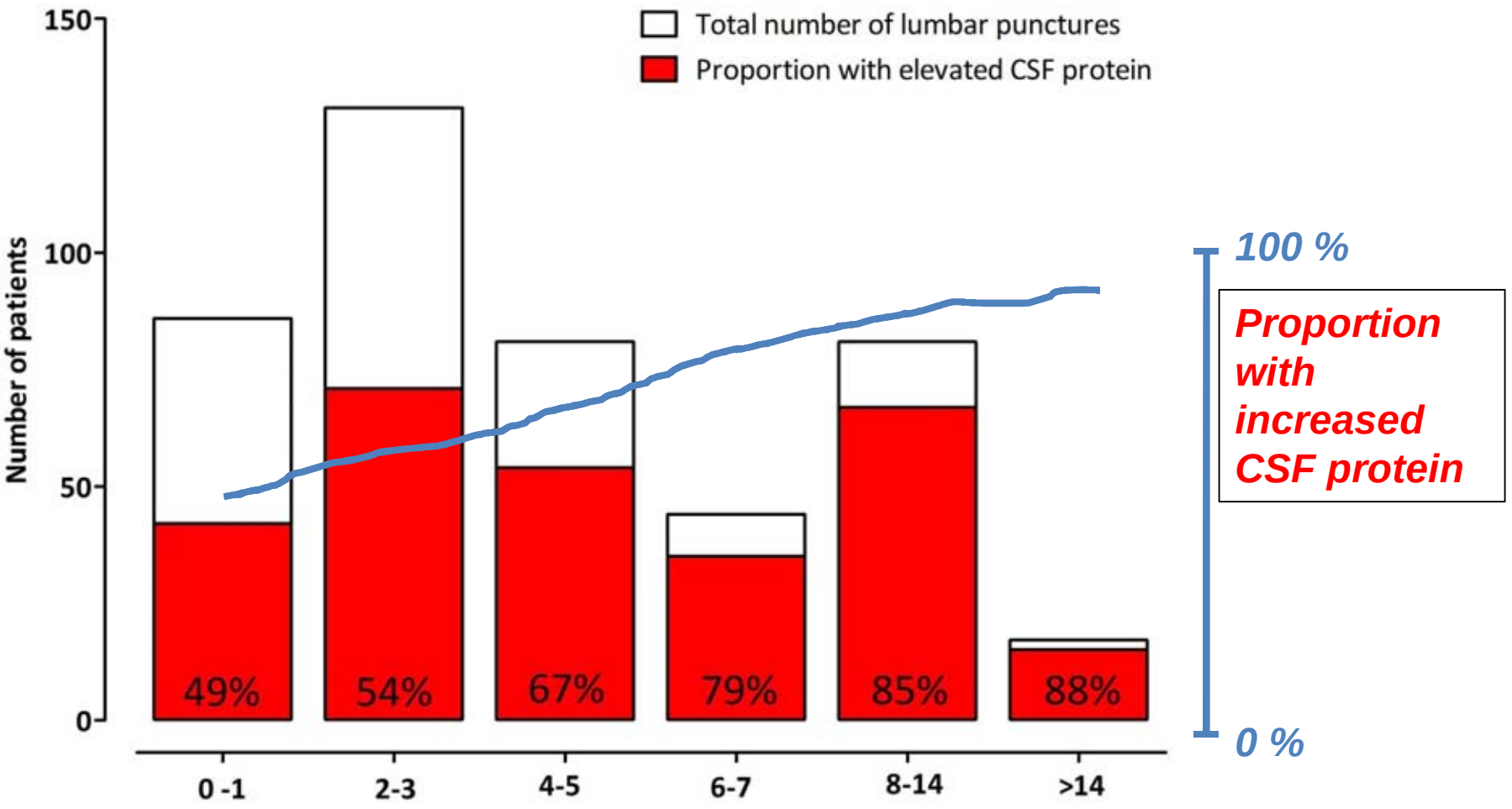
(N=494)



Fokke et al., Brain in press

Elevated protein levels in CSF of GBS patients

(N=494)



Fokke et al., Brain in press

- Asbury & Cornblath criteria (1990) are useful for clinical practise
- No specific EMG criteria for GBS available
- Brighton criteria (2011) seem predomiantly useful for epidemiological/field studies, especially when the diagnosis requires a high level of certainty
- There is a need for an evidence based international GBS guideline. Such a guideline is currently under construction: EFNS/PNS 'GBS Guideline'

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- General medical treatment

CME

Practice parameter: Immunotherapy for Guillain–Barré syndrome

Report of the Quality Standards Subcommittee of the American Academy of Neurology

R.A.C. Hughes, MD; E.F.M. Wijdicks, MD; R. Barohn, MD; E. Benson; D.R. Cornblath, MD; A.F. Hahn, MD; J.M. Meythaler, MD; R.G. Miller, MD; J.T. Sladky, MD; and J.C. Stevens, MD

Neurology 2003

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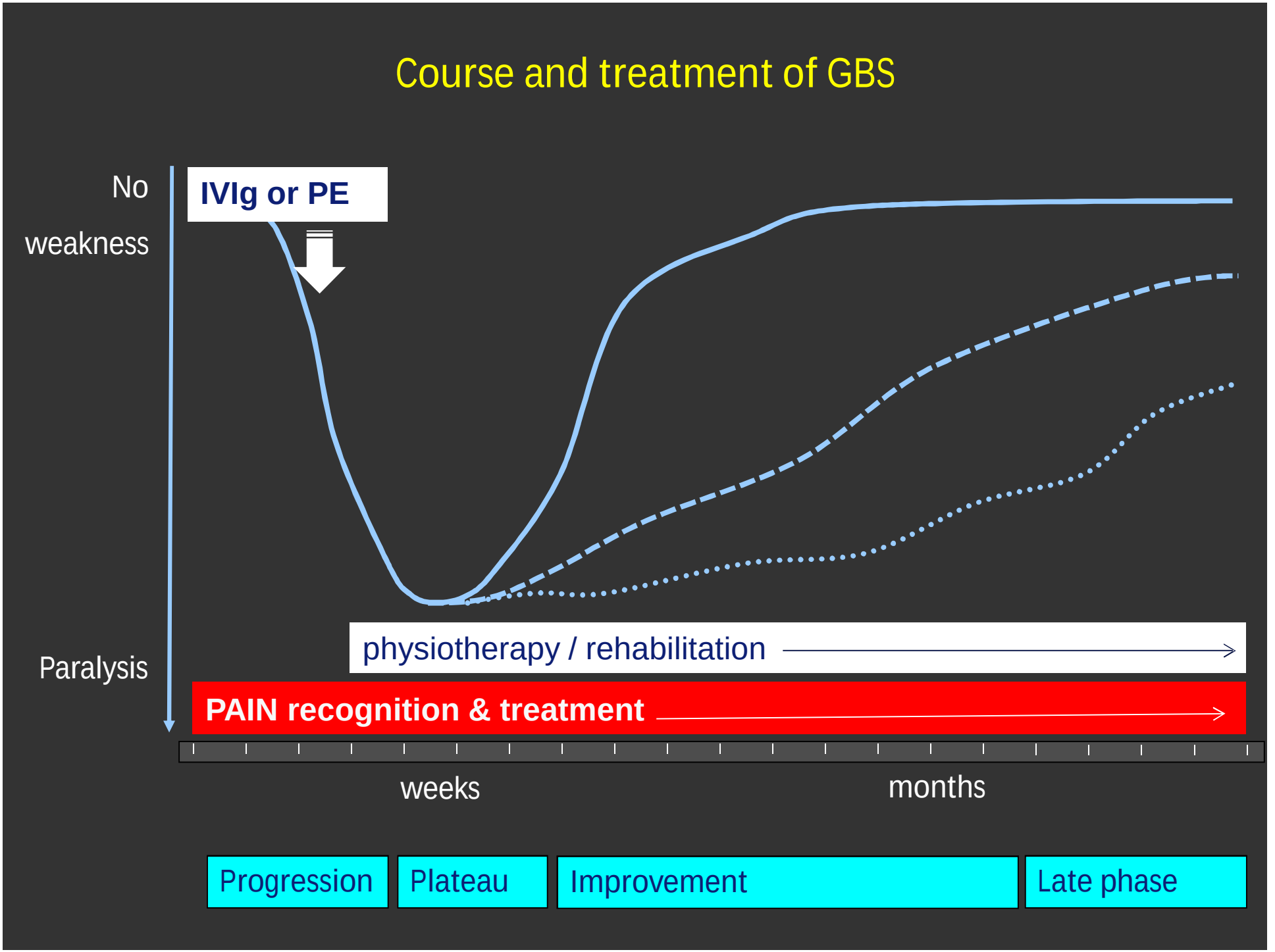
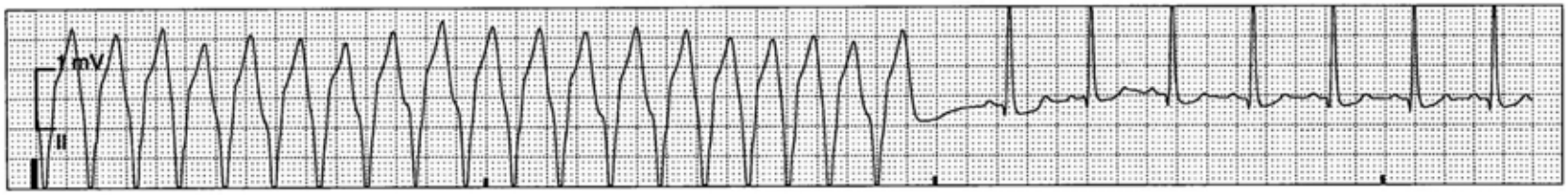
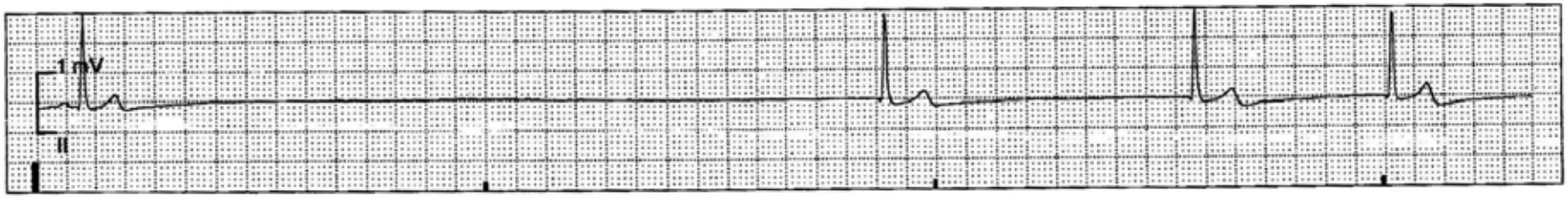
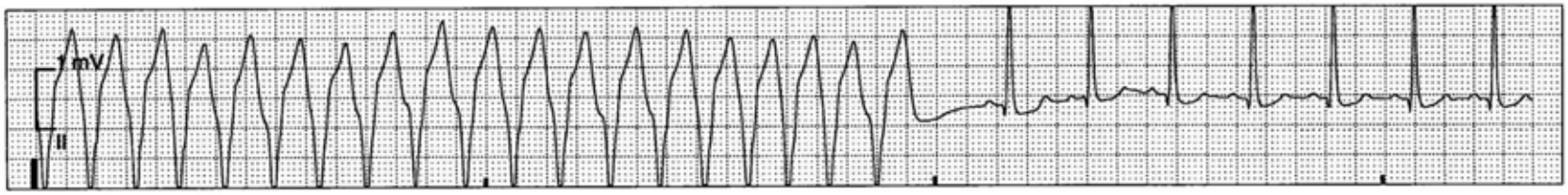
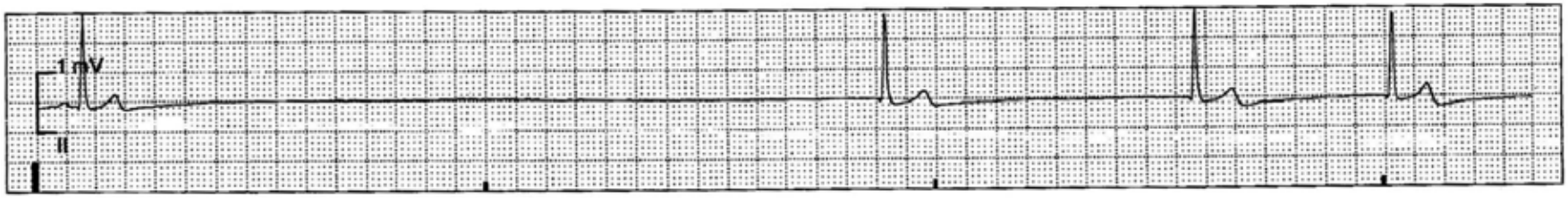
Course and treatment of GBS

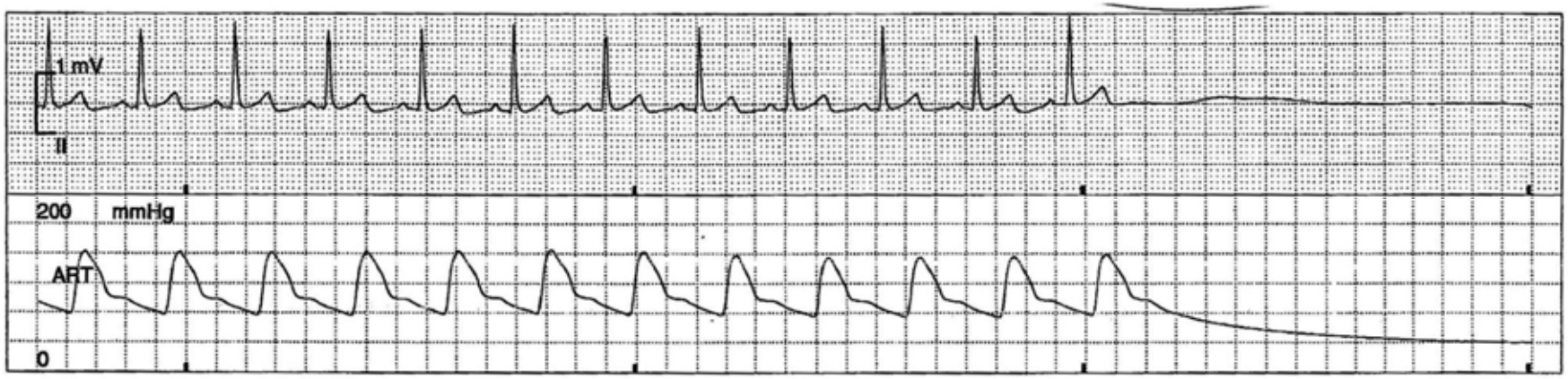



1 mV
II


1 mV
II


1 mV
II


1 mV
II


1 mV
II
200 mmHg
ART
0

Treatment

General medical care

- prevention and treatment of complications
- swallowing problems (pneumonia)
- autonomic dysfunction
- thrombosis
- pain

Decision making at admission:

Neurology ward or ICU?

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- Admission and EGRIS prognostic model

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Prediction of respiratory insufficiency at admission!

Erasmus **G**BS **R**espiratory **I**nsufficiency **S**core = EGRIS

	Categories	**Score**
Days between onset of weakness and inclusion	?å8 days 4 – 7 days < 3 days	0 1 2
Facial and/or bulbar weakness	Absence Presence	0 1
MRC sum score (0-60)	60 – 51 50 – 41 40 – 31 30 – 21 ?á20	0 1 2 3 4
EGRIS		**0 – 7**

Walgaard, Ann Neurol 2010

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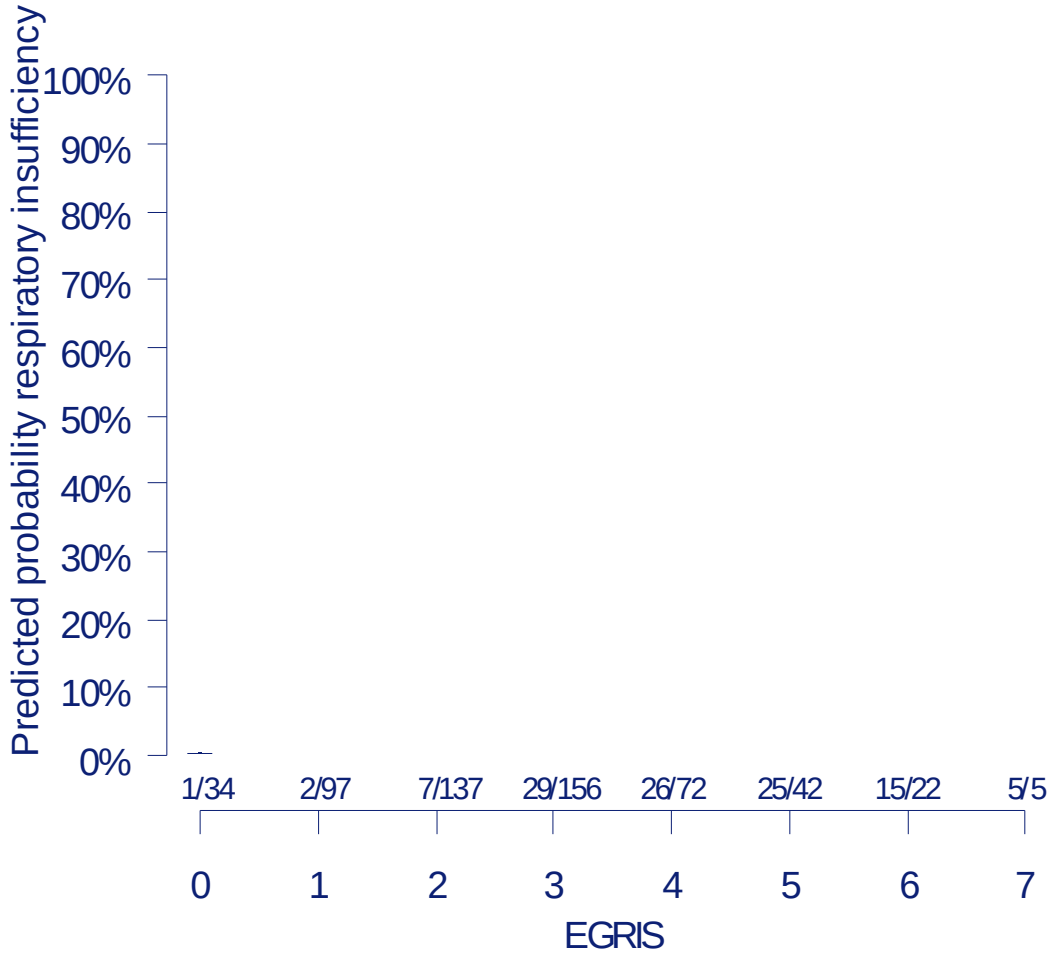
Prediction of respiratory insufficiency

Erasmus **G**BS **R**espiratory **I**nsufficiency **S**core = EGRIS



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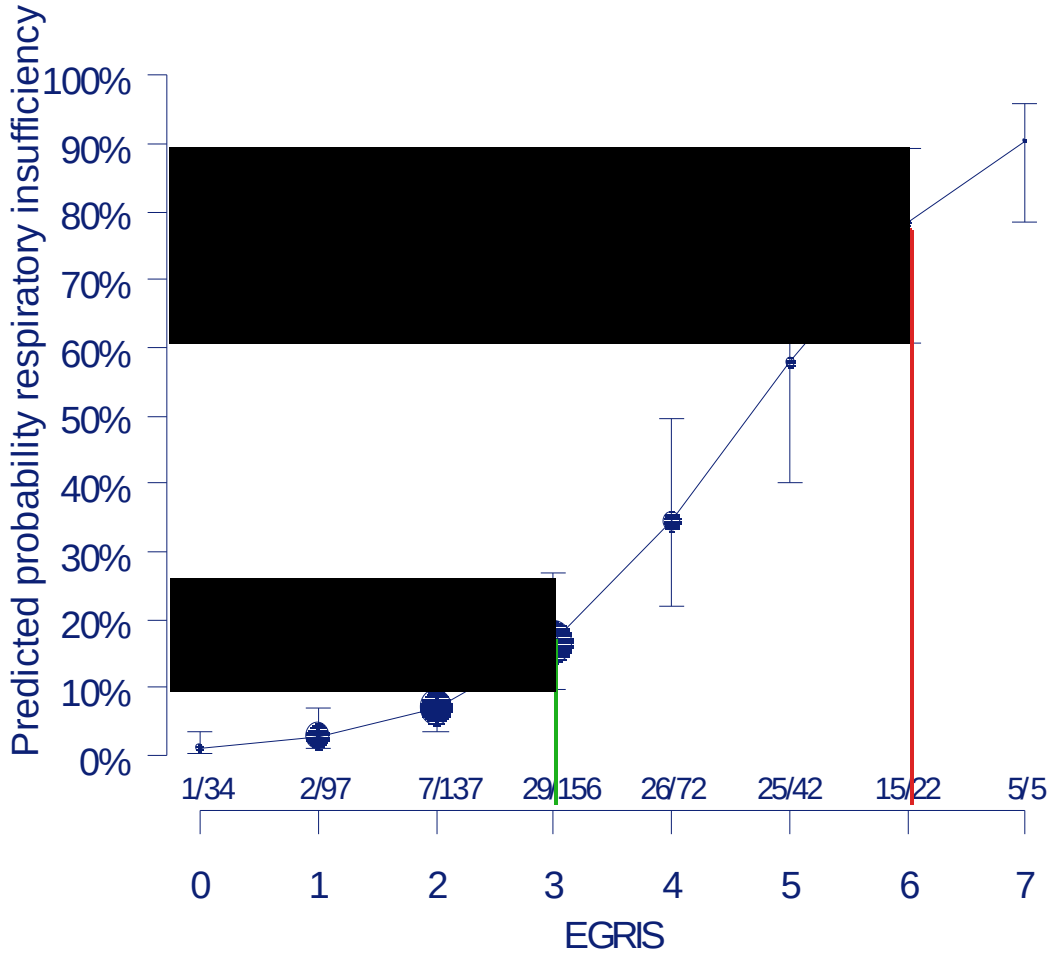
Prediction of respiratory insufficiency

Erasmus **G**BS **R**espiratory **I**nsufficiency **S**core = EGRIS



2 patients with similar MRC sumscore of 25/60 (3 points)

Patient 1:

- *Weakness for 1 day (2 points)*
- *Facial weakness (1 point)*

Total EGRIS = 6

Patient 2:

- *Weakness for 10 days (0 points)*
- *No facial or bulbar weakness (0 points)*

Total EGRIS = 3

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Mortality of GBS

Literature: 3-15%

autonomic dysfunction
respiratory insufficiency
infections (pneumonia etc)
thrombosis
other complications

When during the course of disease?

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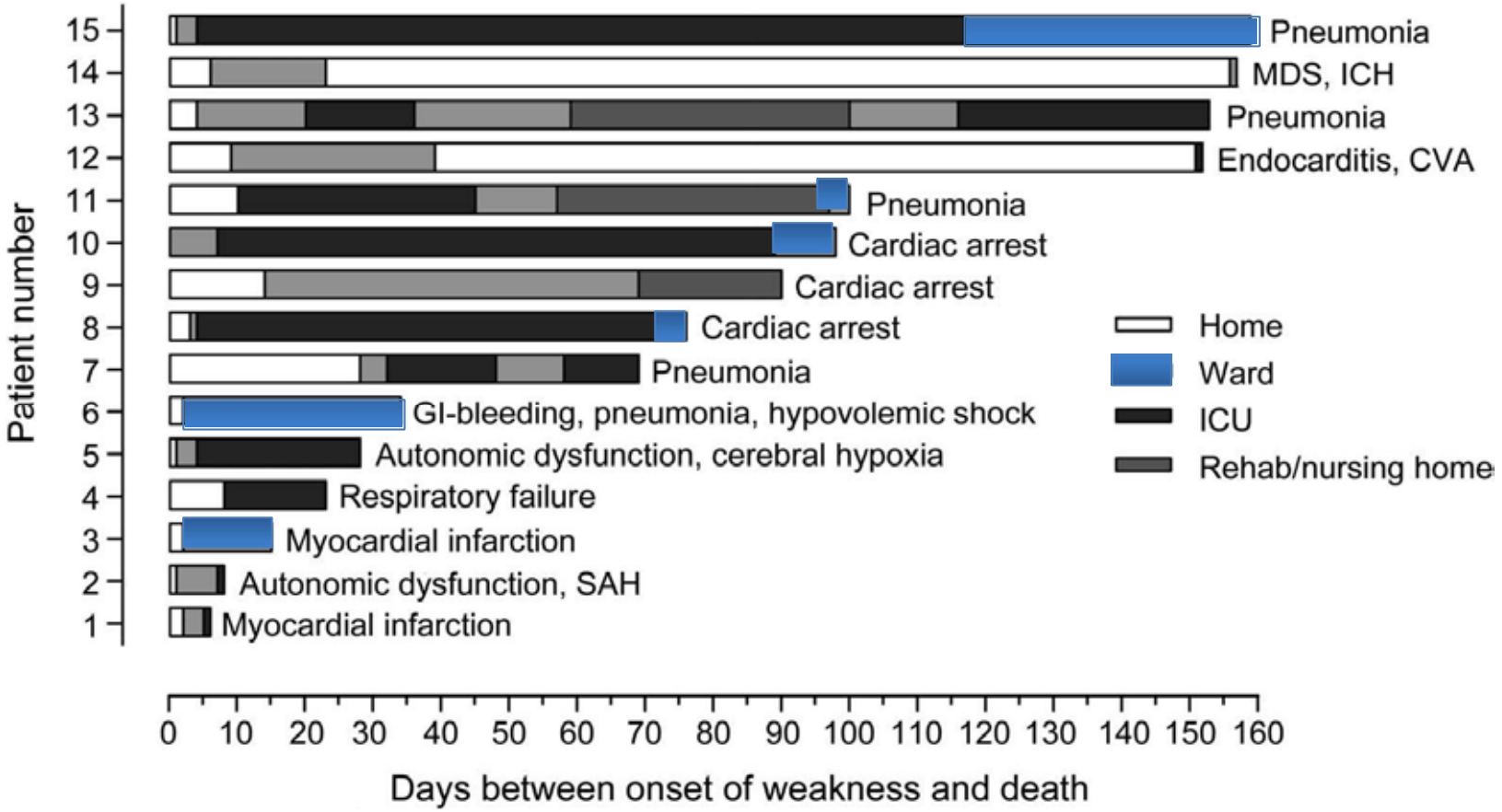
15 fatal cases of GBS in cohort of 528 patients (2.8%)

van den Berg et al., Neurology 2013

NEUROLOGY



10/15 (67%) died during the recovery phase

6/15 (40%) died at the ward (mostly after ICU admission)

- Immunological treatment

Cochrane reviews (2012)

- *Intravenous immunoglobulin for Guillain-Barré syndro*
  Hughes RA, Swan AV, van Doorn PA

- *Plasma exchange for Guillain-Barré syndrome.*
  Raphael JC, Chevret S, Hughes RA, Annane D

- *Corticosteroids for Guillain-Barré syndrome .*
  Hughes RA, van Doorn PA

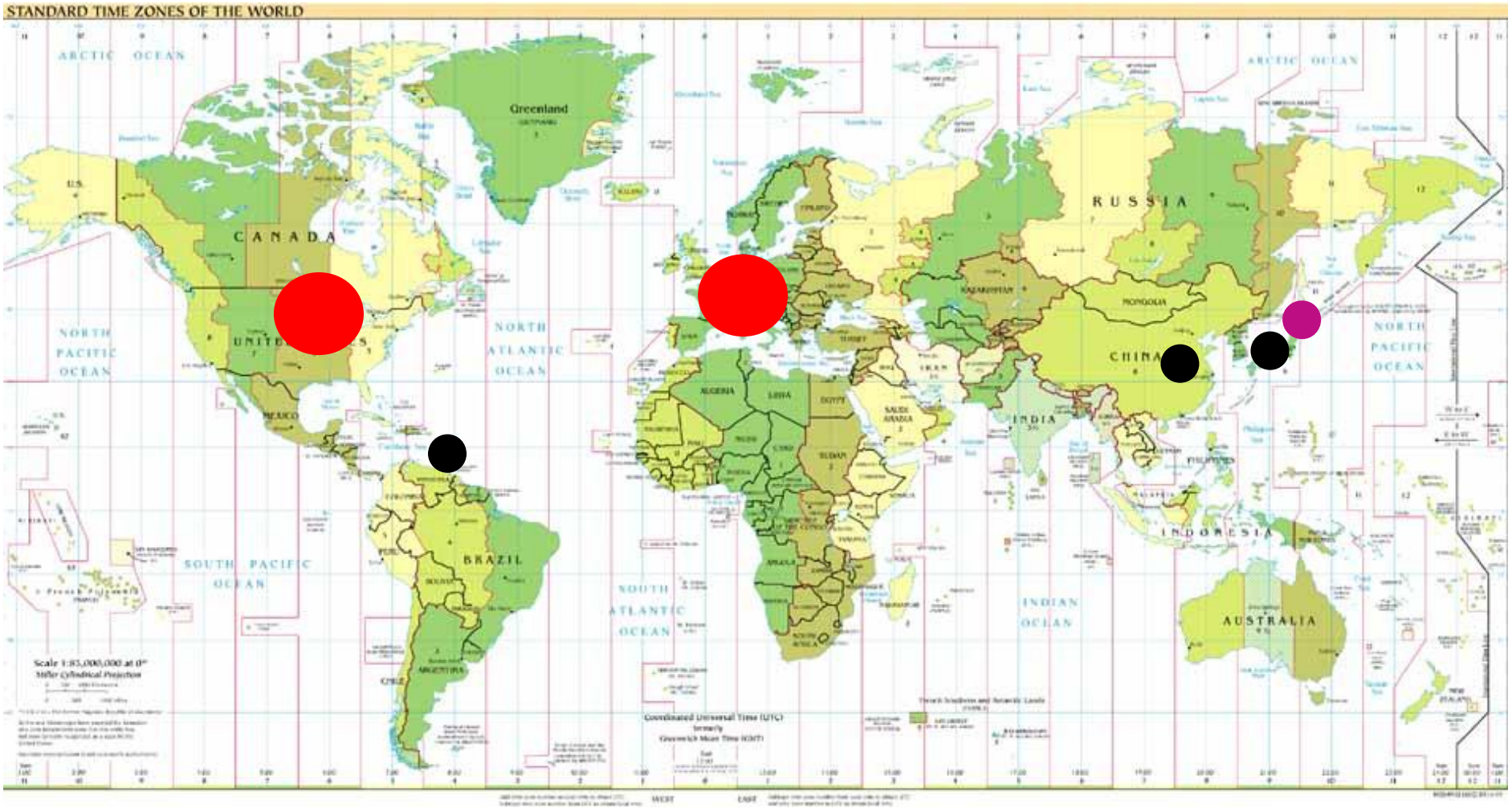
doi:10.1093/brain/awm004 *Brain* (2007), **130**, 2245–2257

REVIEW ARTICLE

Immunotherapy for Guillain-Barré syndrome: a systematic review

Richard A. C. Hughes,[1] Anthony V. Swan,[1] Jean-Claude Raphaël,[2] Djillali Annane,[2] Rinske van Koningsveld[3] and Pieter A. van Doorn[3]

GBS around the world



● = high incidence of AMAN

● = high incidence of MFS

● = AIDP (RCT's)

Published randomized controlled trials in GBS

Year	Group	N=	Outcome
1985	N-American	245	PE effective
1987	French	220	PE effective
1992	Dutch	150	IVIg = PE
1993	Int. Steroid	242	Mpred not effective
1994	Int. PE/Sando	383	IVIg = PE = PE+IVIg
1997	French	556	limited PE effective in mild pat
2004	Dutch	225	IVIg = IVIg + Mpred

- PE and IVIg are effective
- PE + IVIg is not superior
- Steroids alone are not effective

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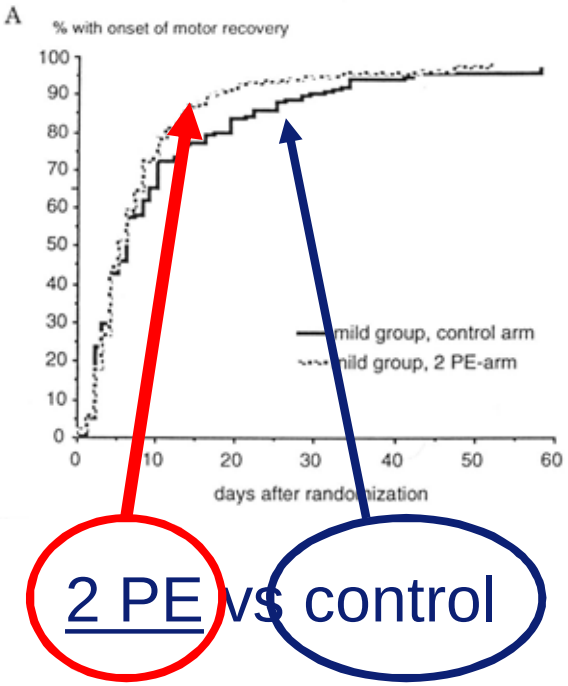
Appropriate number of Plasma exchanges in GBS

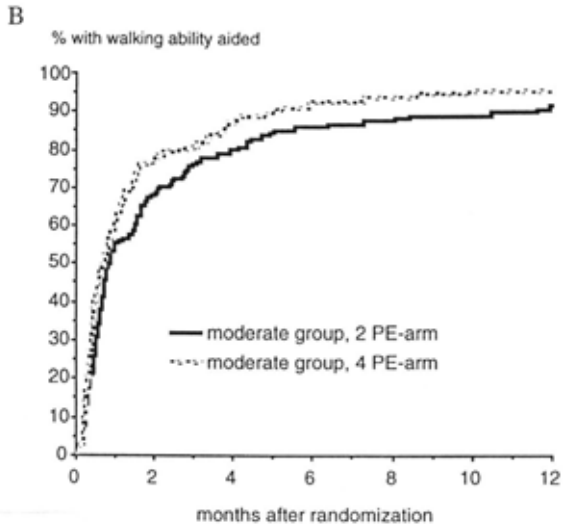
French Cooperative Group. Ann Neurol 1997

Mild



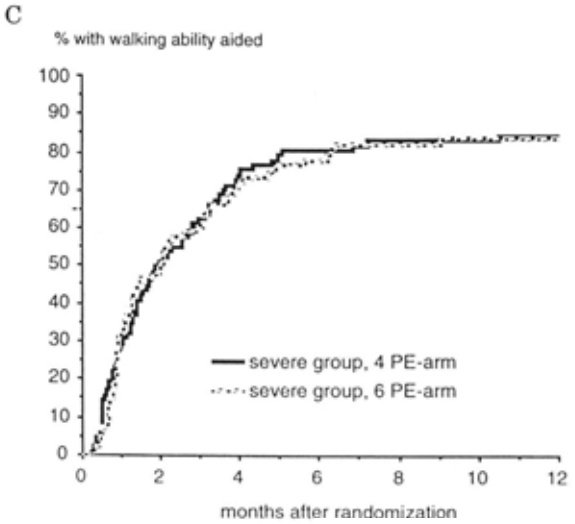
2 PE vs control

Moderate



2 PE vs 4 PE

Severe



4 PE vs 6 PE

→ mild GBS favours from 2x PE

Conclusions

- IVIg ?ˆPE
- 'limited PE' (2x) more effective than no PE in mildly affacted patients

- IVIg 'effective' if started < 2 weeks in non-ambulant patients
- combination PE + IVIg is not superior
- Steroids alone are ineffective
- IVIg + MP not significantly better

→ IVIg (2 g/kg bodyweight) is often first choise:

→ easy, no special equipment, less side-effects than PE, expensive

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Timing IVIg or PE

Timing (IVIg or PE)

In principle: as soon as possible, when unable to walk

Or when there is rapid progressive weakness (in still ambulant patient)

PE: likely effective in mildly affected patients

Dosage

0.4 g/kg for 5 days days

PE: 5 x 2-2.5 liter plasma over 2 weeks

Duration

One course, repeat IVIg when treatment related fluctuation (TRF)

Prospective ‘limited PE study’ from India presented at PNS/INC 2010 meeting

by Prof Sarada (India)

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What to do if a GBS patient initially improves after IVIg and than has a secondary deterioration?

‘ treatment related fluctuation’ or TRF

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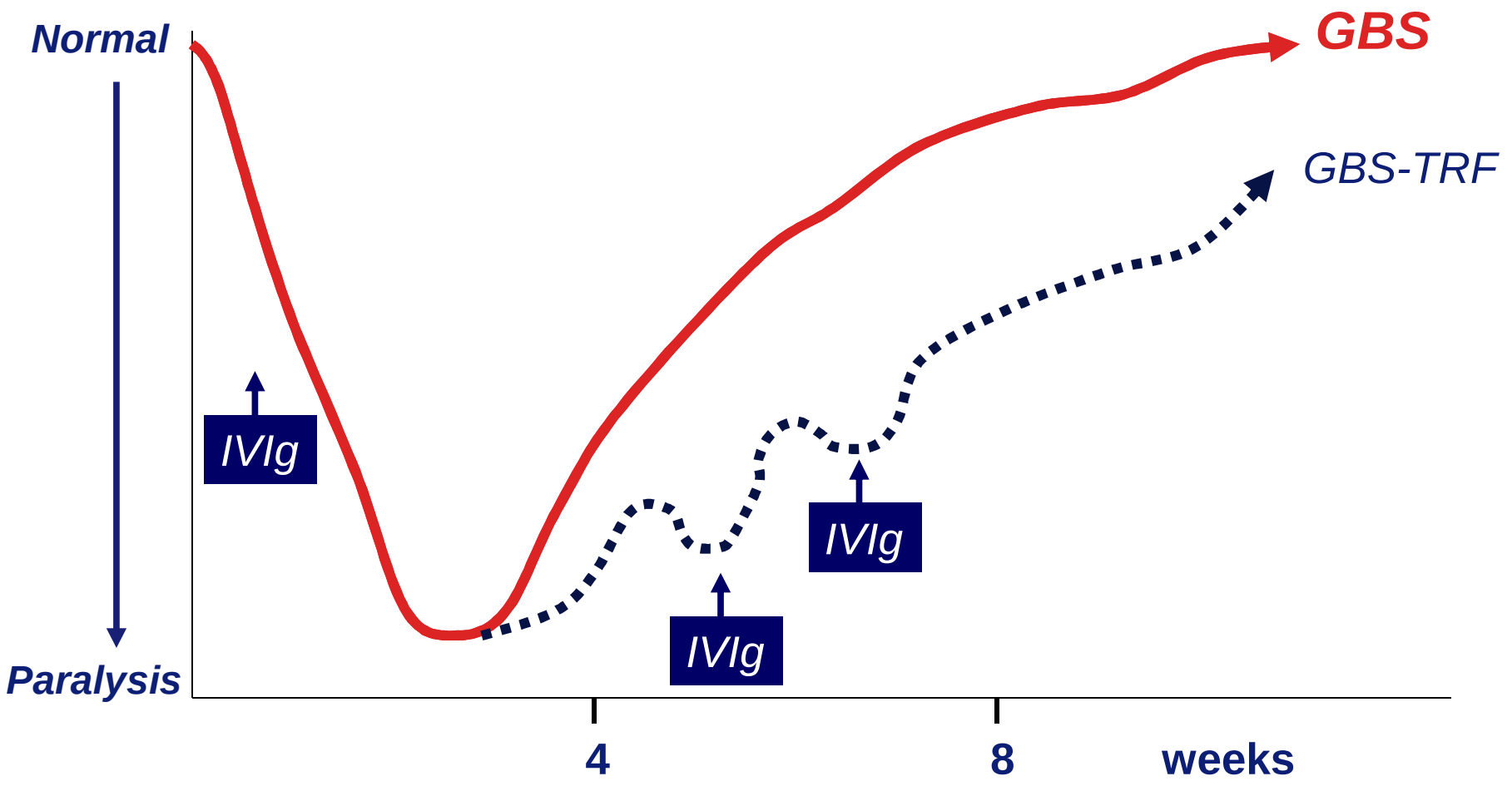
Treatment related fluctuations (TRF)



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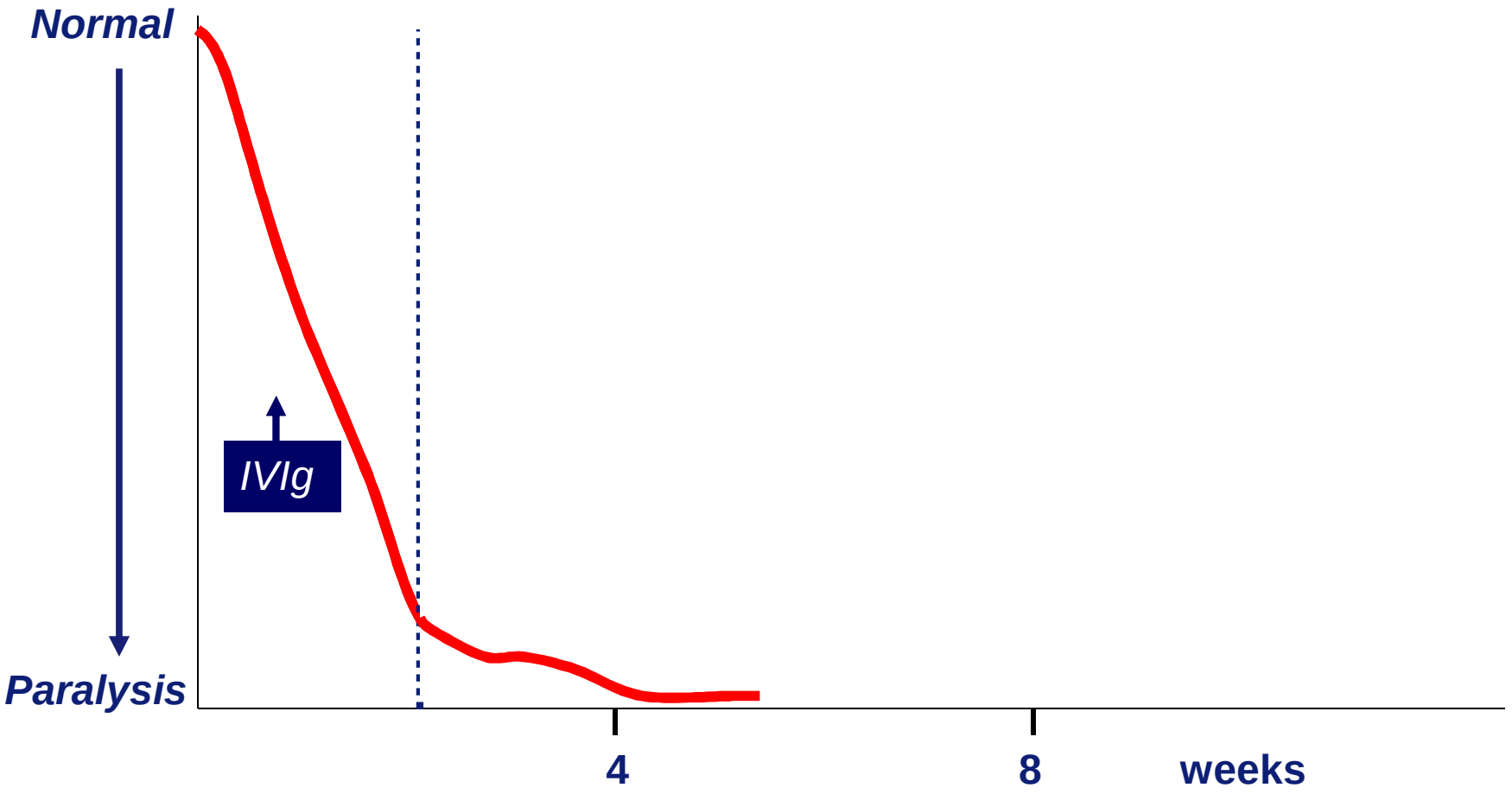
What to do if a patient continues to deteriorate after treatment?



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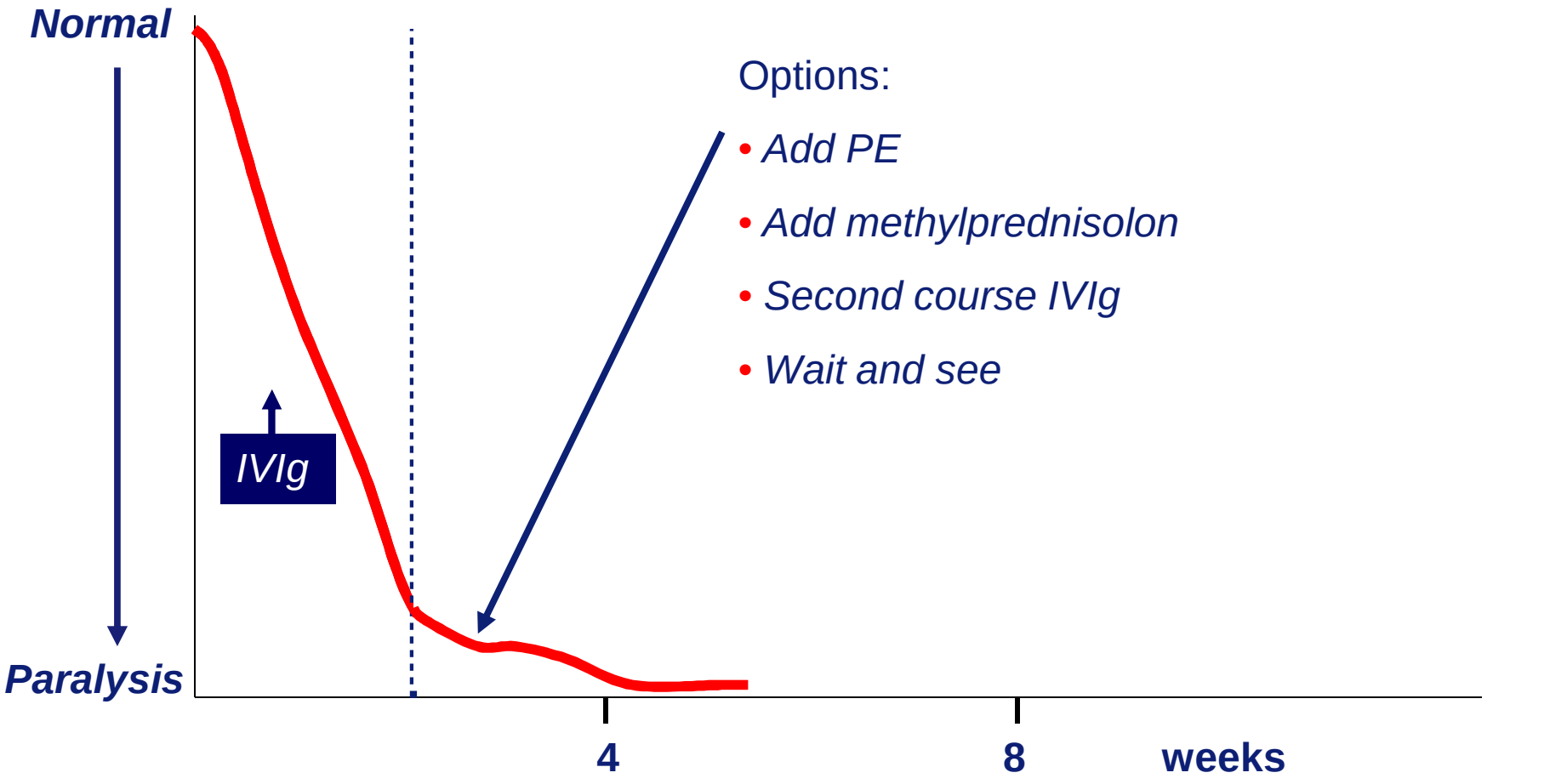
What to do if a patient continues to deteriorate after treatment?



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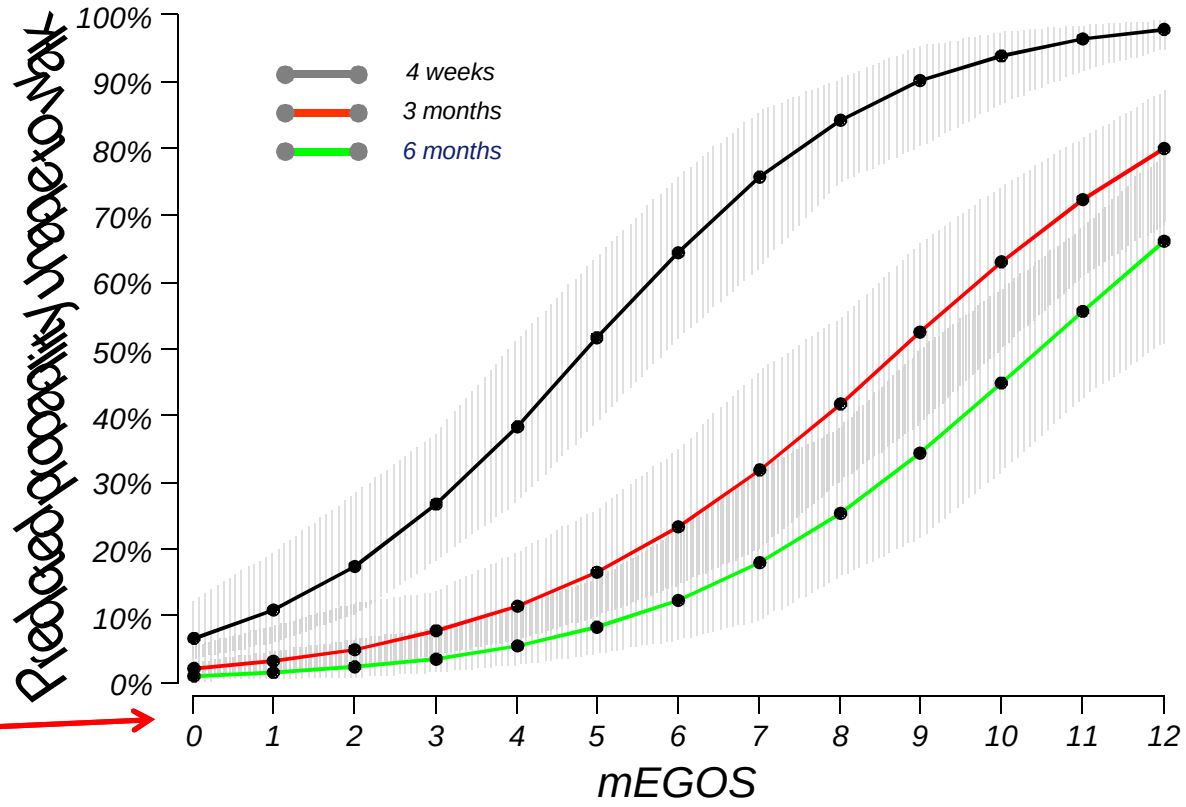
Early recognition of poor prognosis in Guillain-Barré syndrome

Neurology® 2011;76:968-975

C. Walgaard, MD
H.F. Lingsma, PhD
L. Ruts, MD
P.A. van Doorn, MD
E.W. Steyerberg, PhD
B.C. Jacobs, MD



Age
Diarrhea
MRC sumscore

AUC 0.87

Good prognosis *Poor prognosis*

- Pain

Pain can be horror for the patient.

Pain can also induce confusion by mimicking other disorders and may cause a delay in making the diagnosis

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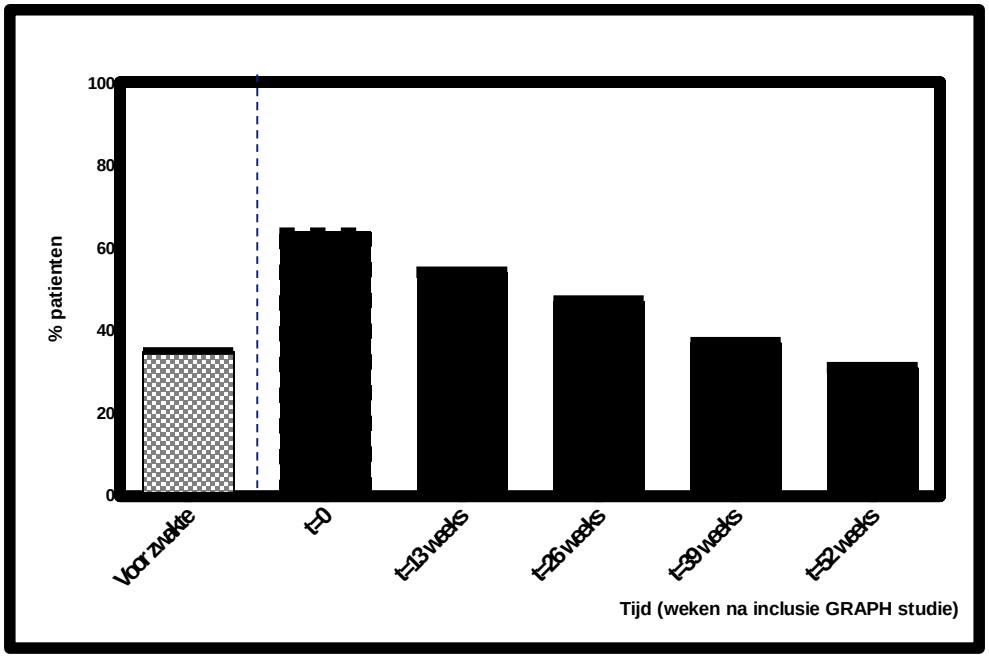
Pain in Guillain-Barré syndrome

A long-term follow-up study

Neurology® 2010;75:1439-1447

L. Ruts, PhD, MD
J. Drenthen, MD
J.L.M. Jongen, PhD, MD
W.C.J. Hop, PhD
G.H. Visser, PhD, MD
B.C. Jacobs, PhD, MD
P.A. van Doorn, PhD, MD
On behalf of the Dutch GBS Study Group

156 patients with GBS (including 18 MFS)
Prospective follow-up study for 1 year (GRAPH study)



- Pain may persist over long period of time, can be very severe!
- Often pain before onset of weakness!

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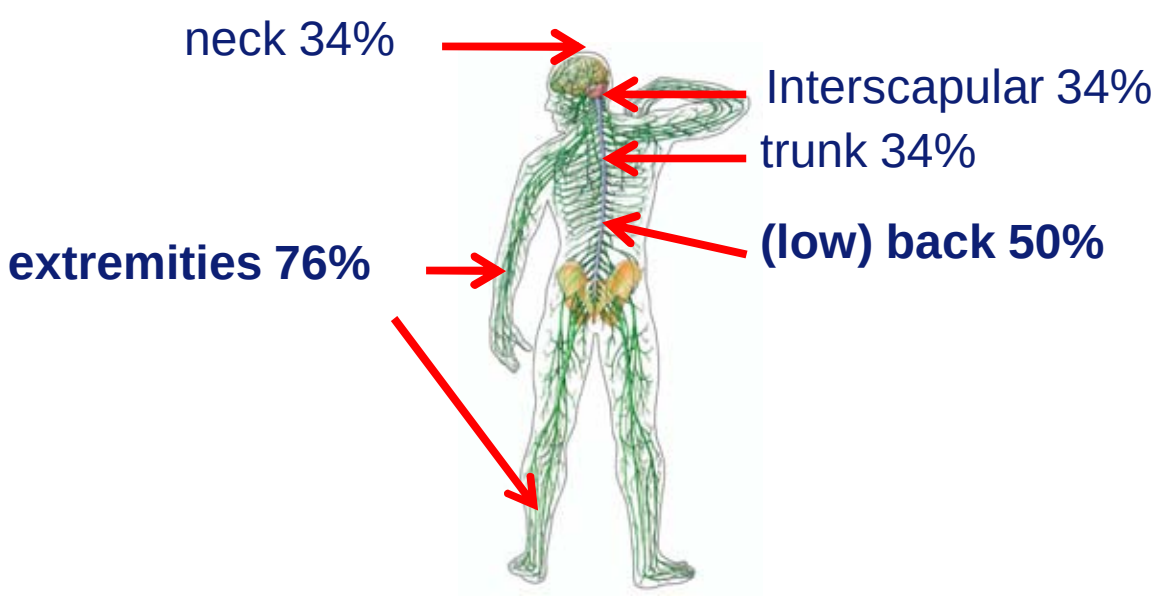
What location and type of pain in ACUTE phase



Type of pain:	**ACUTE**	**CHRONIC** (6mth)
• muscle pain	62%	43%
• painful paresthesias and dysesthesias	43%	31%
• radicular pain	31%	7%
• joint pain	14%	22%
• other type of pain	7%	
• meningism	4%	

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PAIN GBS children

Recognizing Guillain-Barré syndrome in preschool children

Neurology® 2011;76:807-810

J. Roodbol, MSc
M.C.Y. de Wit, MD, PhD
C. Walgaard, MD
M. de Hoog, MD, PhD
C.E. Catsman-Berrevoets, MD, PhD
B.C. Jacobs, MD, PhD

Table 2 Difference between the preschool children and the older children

	Preschool children (n = 23)	Older children (n = 32)	p Value
Patient delay, d, mean (IQR)[a]	5 (3–7)	5 (3–7)	NS
Doctor delay, d, mean (IQR)[b]	3 (0–8)	0 (0)	<0.001
Misdiagnosis, n (%)	15 (68)	6/29 (21)	0.001
Pain, n (%)	16 (70)	19/31 (61)	NS
Autonomic dysfunction, n (%)	7 (30)	4/31 (13)	NS

…pain initially suggested myositis, meningitis, tonsilitis, discitis, coxitis, and rheumatoid disorder..

…examination is more difficult in under 6-year-olds, especially when painful or irritable, and weakness may be missed…..

Conclusions - Pain

1. Pain is a frequent problem in GBS
2. Pain can be very severe: ask for it, also when patients are ventilated
3. It can preceed GBS, and may cause delay to diagnose GBS
4. Treat with drugs also used in other forms of neuropathic pain:

   amitriptyline, (pre)gabaline, anti-epileptic drugs, opiods etc
   sodium channel blockers?
5. Real steps forward need to be made.

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- Fatigue

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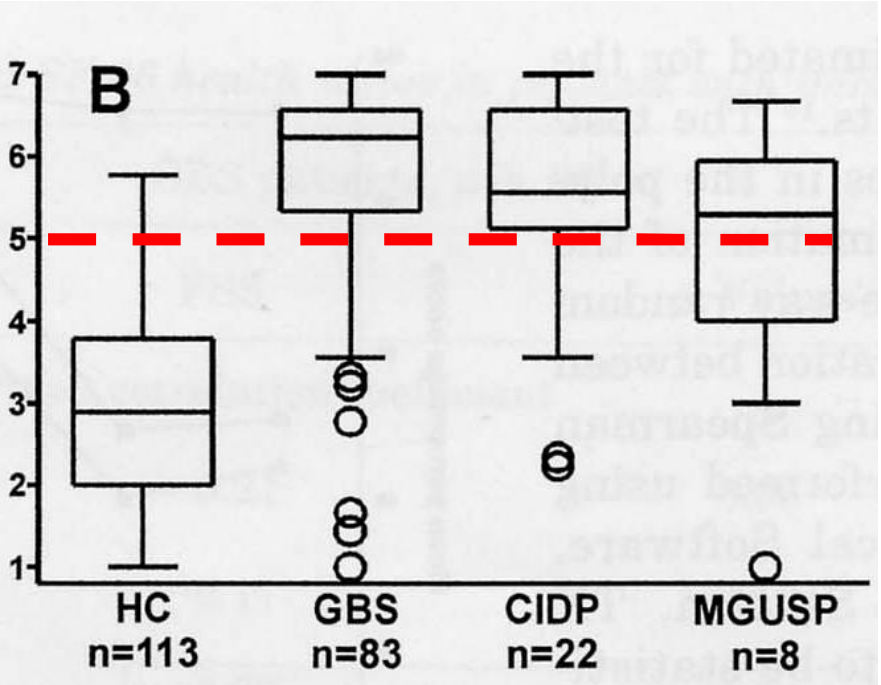
Fatigue in immune-mediated polyneuropathies

Merkies et al. Neurology 1999

most disabling fatigue è

Fatigue severity scale

no fatigue è



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Fatigue

is a frequent and important issue in GBS and CIDP

How to deal with it?

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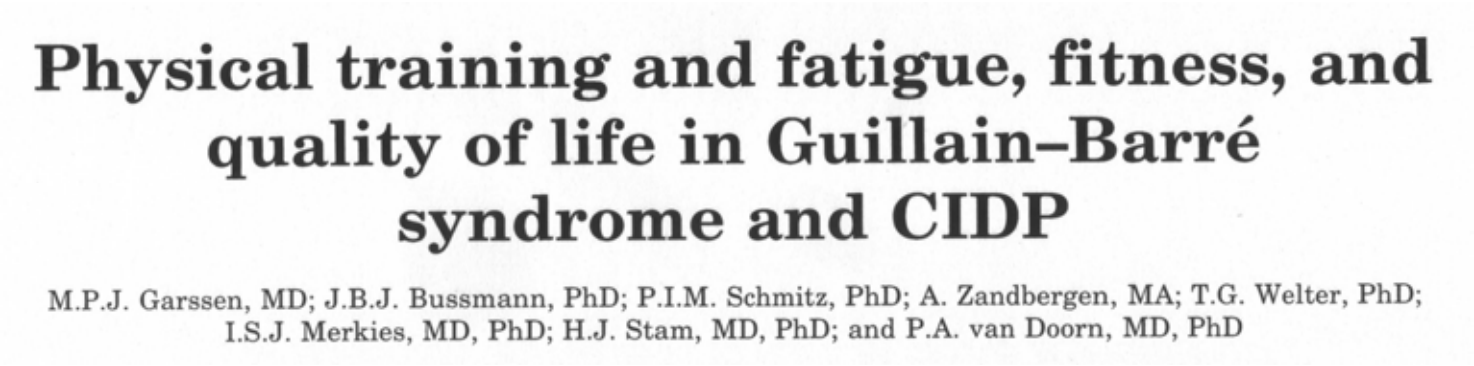
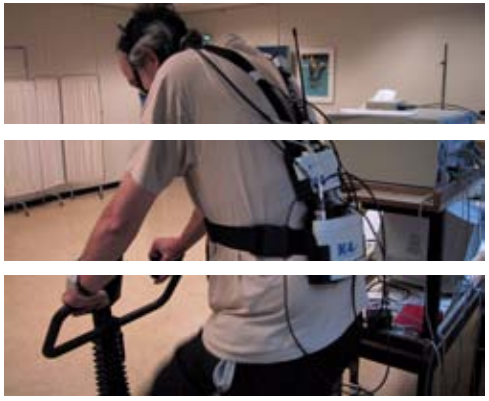
Large proportion of GBS and CIDP patients remain severely fatigued



Physical training and fatigue, fitness, and quality of life in Guillain–Barré syndrome and CIDP

M.P.J. Garssen, MD; J.B.J. Bussmann, PhD; P.I.M. Schmitz, PhD; A. Zandbergen, MA; T.G. Welter, PhD; I.S.J. Merkies, MD, PhD; H.J. Stam, MD, PhD; and P.A. van Doorn, MD, PhD



12 week cycle training (3x/wk):

- significantly reduces severe fatigue
- increases fitness and Q of life

- Effect remains present 2 years after training intervention!

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- Transition to CIDP?

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What to do if a patient deteriorates several times after initial improvement?

Is this course still compatible with GBS or is it CIDP?

Should treatment for CIDP be started?

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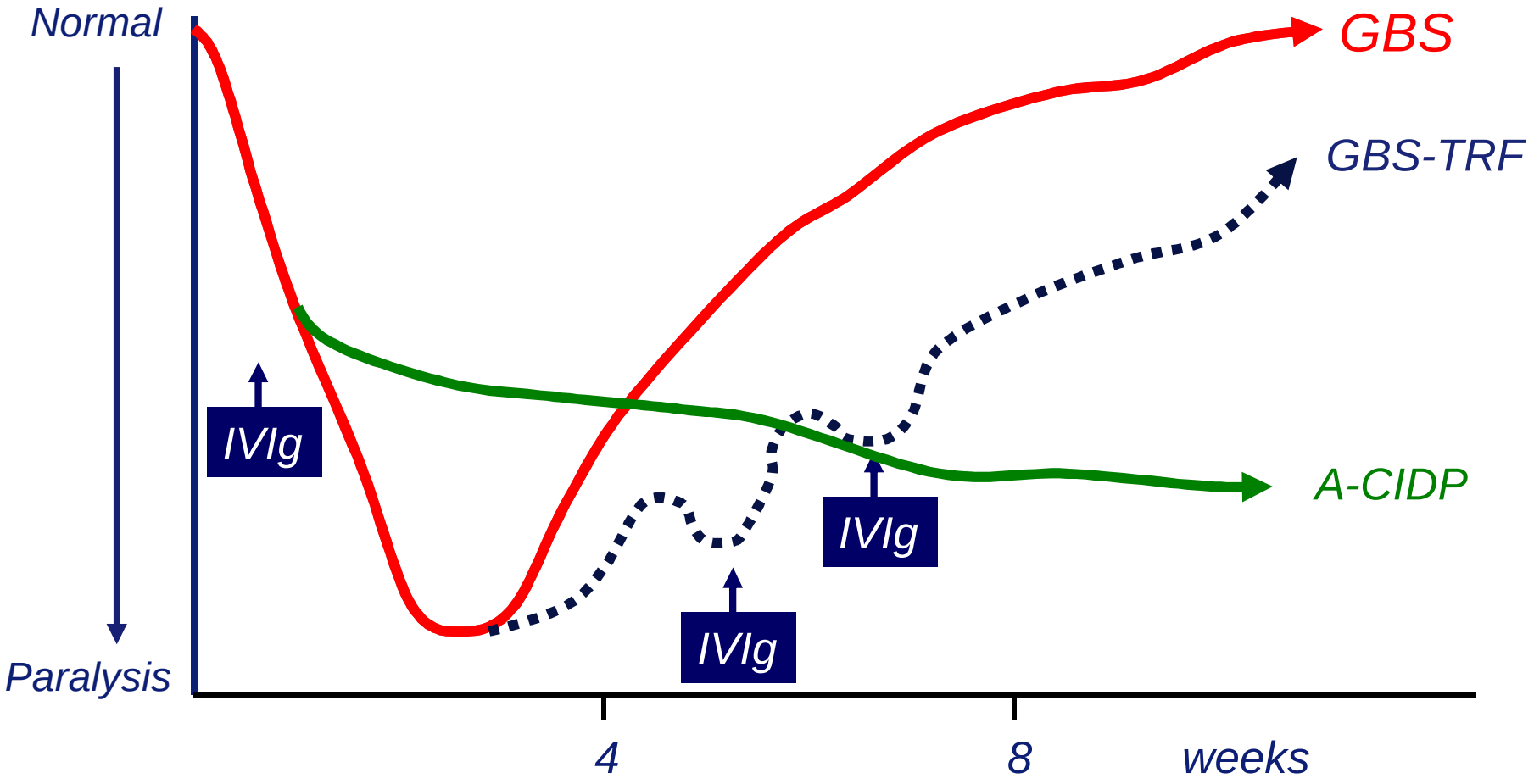

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Distinguishing Acute onset CIDP from Guillain-Barré Syndrome with treatment related fluctuations, a prospective study

Ruts et al. Neurology 2010

	GBS-TRF	A-CIDP
	10%	5%
• Deteriorations	1-2	3 or more
• Deteriorates	<8 weeks	after 8 weeks
• Remains able to walk at nadir	sometimes	often
• Artificial ventilation	25%	no (rare!)
• Cranial nerve dysfunction	often	no
• EMG	axon/demyel	demyelination
• Prominent sensory signs	-	yes

(A. Dionne, Muscle & Nerve 2010)

- Recent developments and international studies

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Clinical studies currently going on:

1. Second-dose IVIg in GBS patients with poor prognosis (RCT)
   Dutch GBS study group (van Doorn et al.)

2. International Second-dose IVIg in GBS (I-SID) within IGOS
   embedded within IGOS (consortium study)

3. International GBS outcome study (IGOS)
   Inflammatory Neuropathy Consortium (Jacobs et al).

Start end 2013:

4. Eculizumab in GBS (RCT)
   Scotland (Willison et al.)

Clinical studies currently going on:

1. Second-dose IVIg in GBS patients with poor prognosis (RCT)
   Dutch GBS study group (van Doorn et al.)

2. International Second-dose IVIg in GBS (I-SID) within IGOS
   embedded within IGOS (consortium study)

Modified EGOS (mEGOS) is a simple, easy to use and accurate bedside model to predict outcome of GBS

Can be applied 7 days after admission/start IVIg

Modified EGOS at day 7 to predict ability to walk unaided

Walgaard et al. Neurology 2011

Modified Erasmus GBS outcome score (mEGOS)

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

→ **Chance being unable to walk unaided at 4 weeks, 3 and 6 months**

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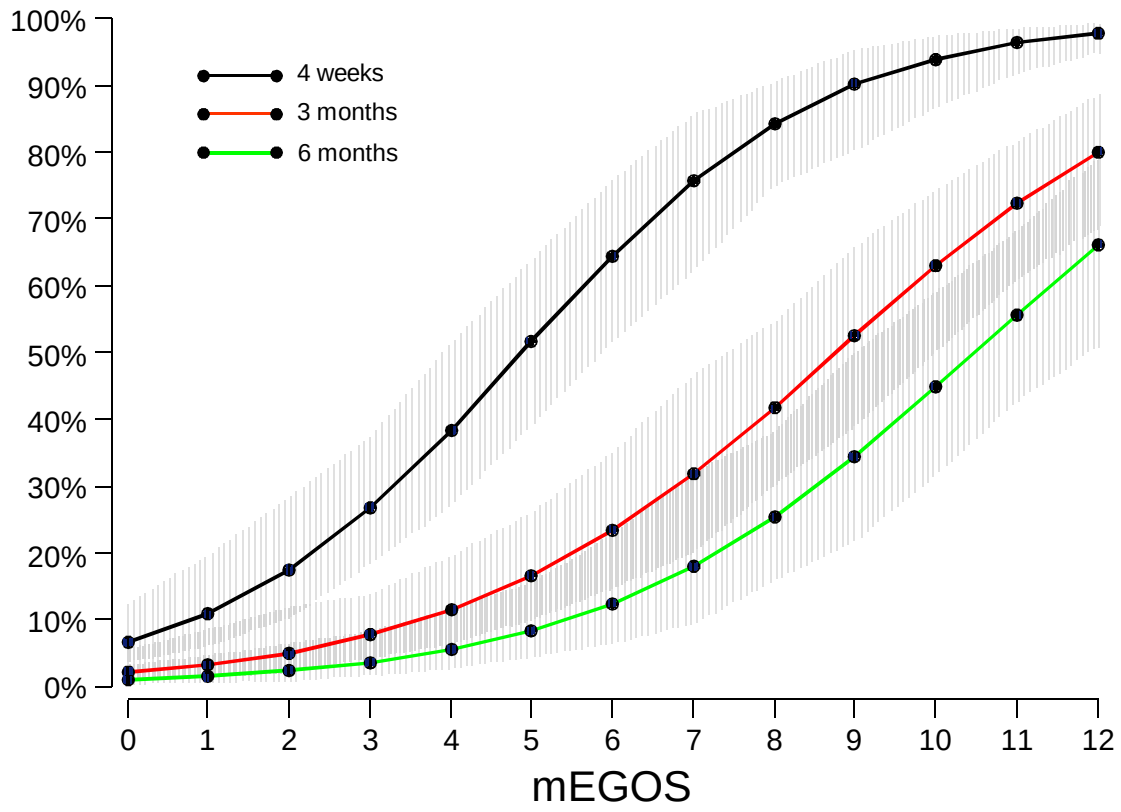
Chance being unable to walk at 4 weeks, 3 and 6 months according to mEGOS (n= 394)

Predicted probability unable to walk



AUC 0.87

Good prognosis *Poor prognosis*

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A more effective treatment for GBS patients with a poor prognosis?

Second dose IVIg?

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Select patients with poor prognosis
Why a second IVIg dosage in selected patients?

- Second IVIg dosage effective in GBS patients having secondary progression of weakness after initial improvement (‘treatment related fluctuations’)
- Second IVIg dosage possibly effective in a small uncontrolled series of severe ‘unresponsive’ GBS patients (Farcas, Lancet 1997)
- Patients with minor increase in serum IgG level after standard dose IVIg treatment had poorer prognosis (Kuitwaard, Ann Neurol 2009).

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Second IVIg Dose (SID-GBS) study

Only in selected patients with a poor prognosis
based upon the mEGOS

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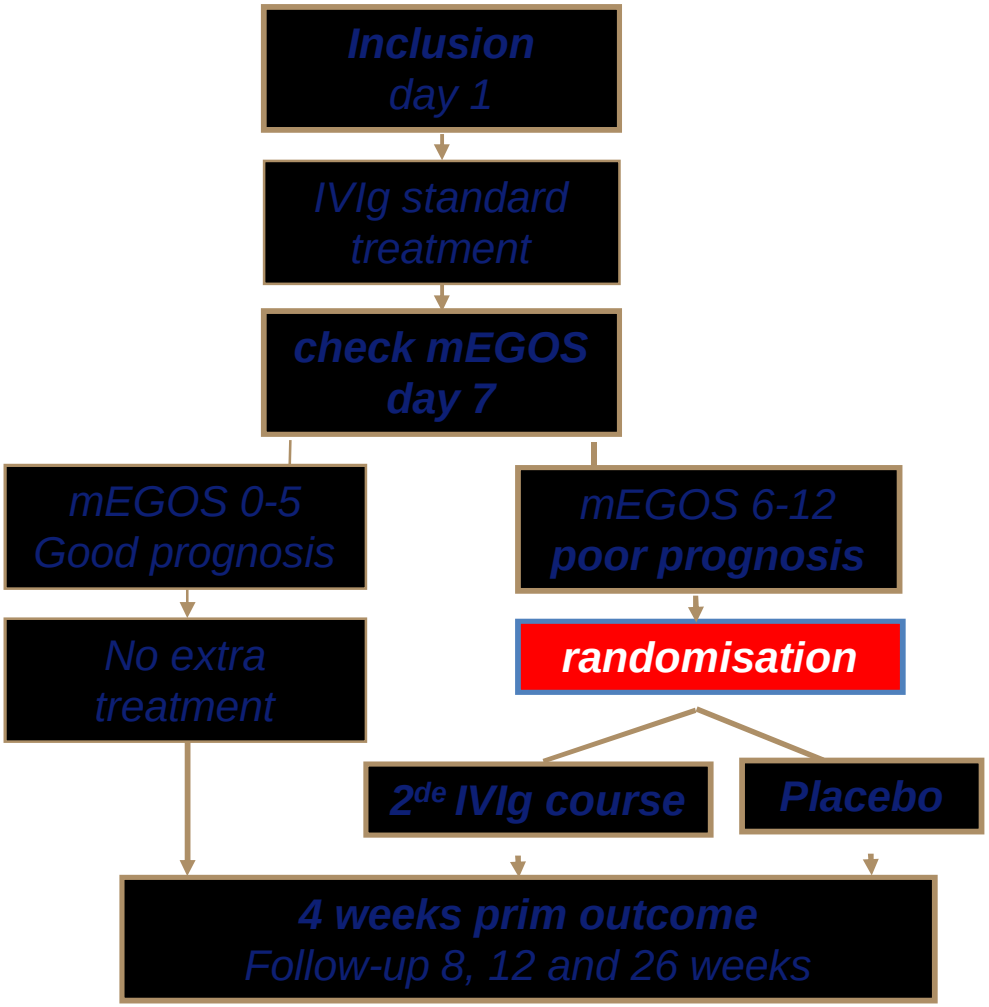
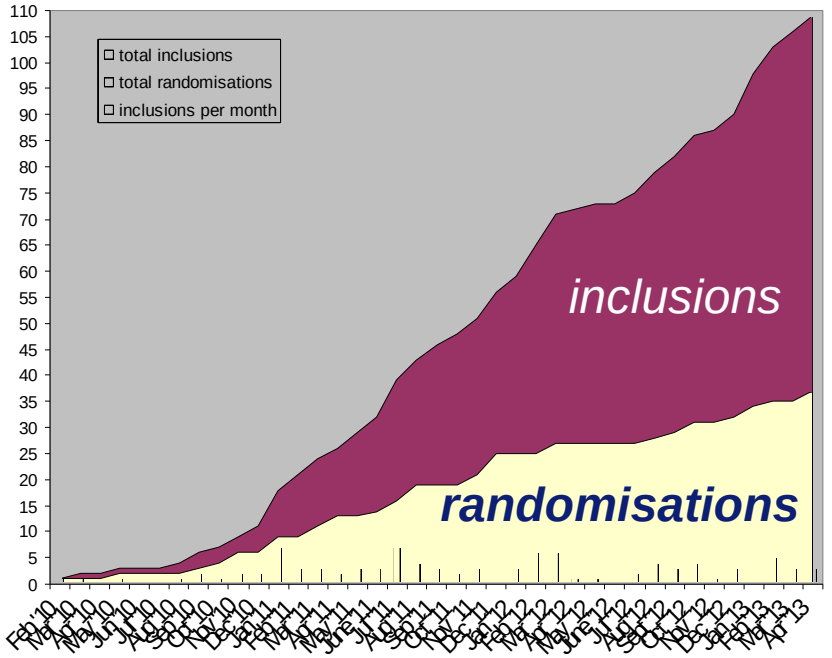
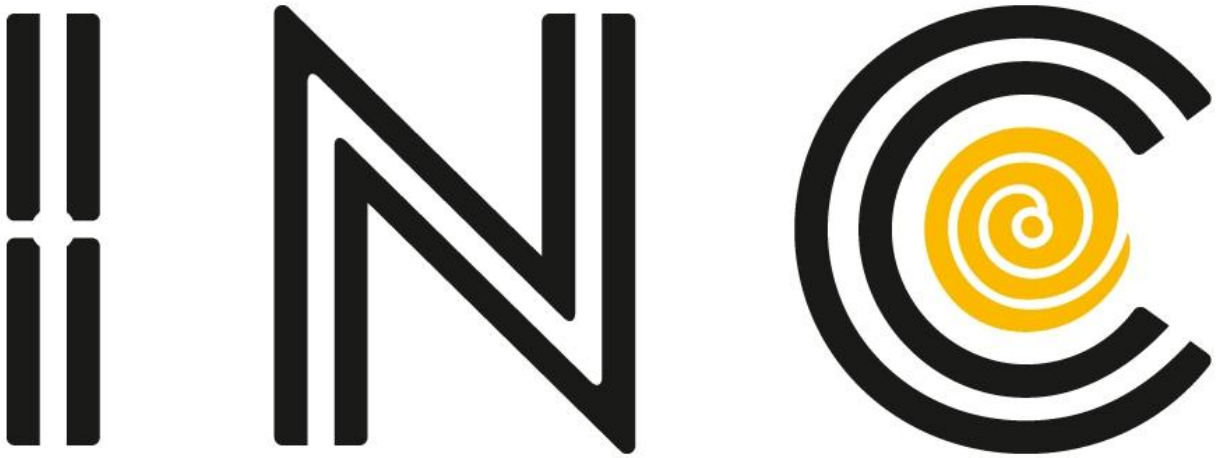
SID-GBS | Erasmus MC University Medical Center Rotterdam

- *RCT design*
- *Study started before I-SID GBS*
- *Nanogam®, Sanquin*
- *Only in the Netherlands*







Inflammatory Neuropathy Consortium

International Second IVIg Dose study in GBS patients with a poor prognosis (I-SID GBS study)

Pieter A. van Doorn, Bianca van den Berg, Bart C. Jacobs, David R. Cornblath, Christa Walgaard, Kenneth C. Gorson, Michael P. Lunn, Hans-Peter Hartung, Ewout W. Steyerberg for the I-SID study group.

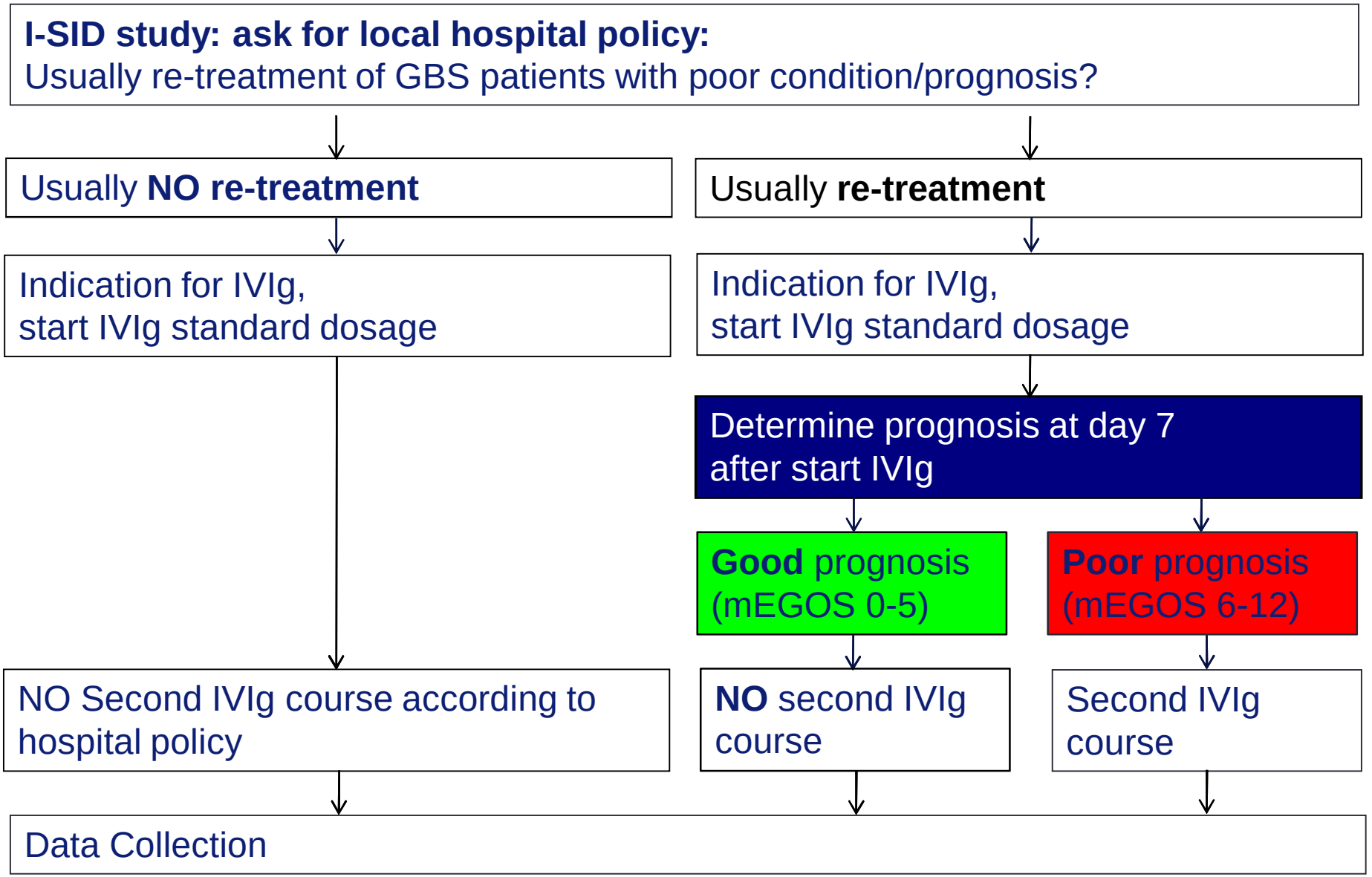
I-SID GBS study

Aim:

to determine if a second course of IVIg given to GBS patients with a poor prognosis improves functional outcome.

Study design:

- International prospective observational multicenter study
- The I-SID GBS study is embedded within IGOS
- Web based supported
- Funded by: GRIFOLS



Does a second IVIg course improves functional outcome in GBS patients with poor prognosis? Interested to join: GBSstudies@erasmusmc.nl

International GBS Outcome Study

IGOS
INTERNATIONAL GBS OUTCOME STUDY

HOME | ABOUT IGOS | SYNOPSIS | PARTICIPANTS | NEWS | CONTACT

"A world-wide prospective study of INC on prognosis and biomarkers in GBS"

Home

INTERNATIONAL GUILLAIN-BARRÉ SYNDROME OUTCOME STUDY (IGOS)

Welcome to the website for the International Guillain-Barré syndrome Outcome Study (IGOS). The study aims to identify clinical and biological determinants and predictors of disease course in Guillain-Barré syndrome. The study is conducted by the Inflammatory Neuropathy Consortium (INC). At this website you can acquire information about IGOS, register as IGOS participant and include patients with Guillain-Barré syndrome. For more information about IGOS, click here.

IGOS ready to go!

Recently we received the good news that the Ethical Committees gave permission to start the IGOS. The first patient can be included at May 1st, 2012. If you are interested to participate please contact gbsstudies@erasmusmc.nl.

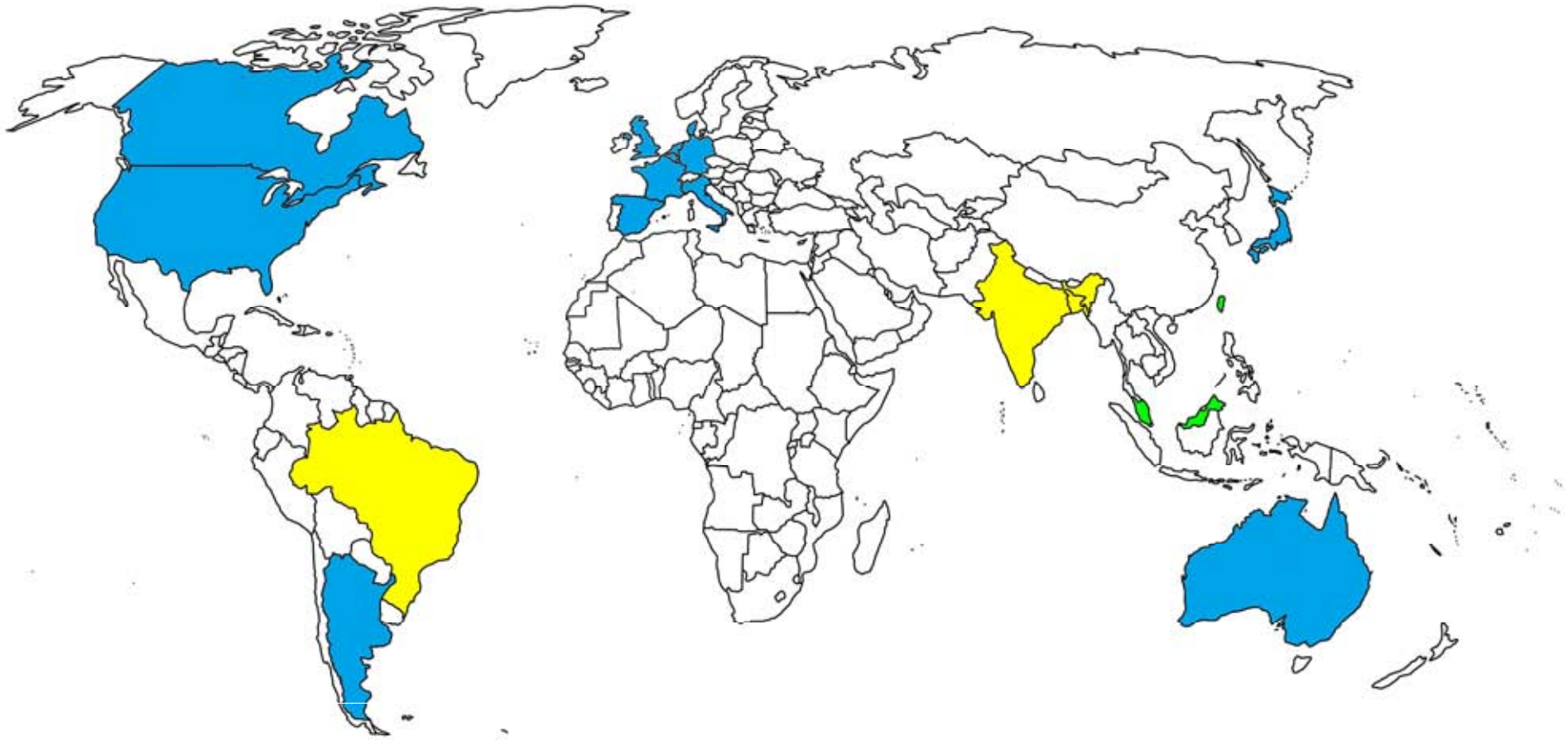
More >>

INC/PNS congress

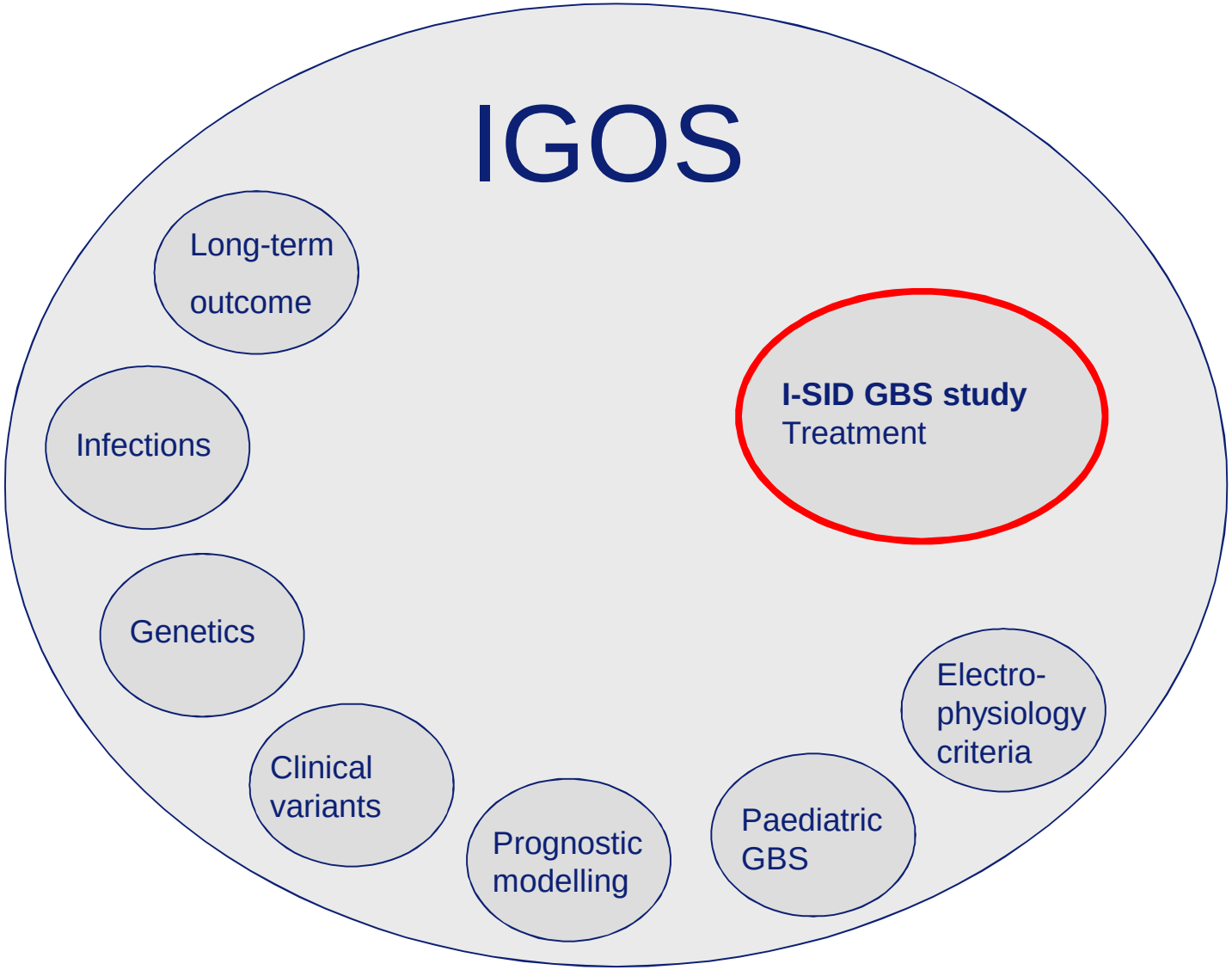
From June 24-27, 2012 the INC/PNS congress will be held in Rotterdam, The Netherlands. At the congress there will be many presentations about the International studies including IGOS. Click here for information about this congress.

More >>

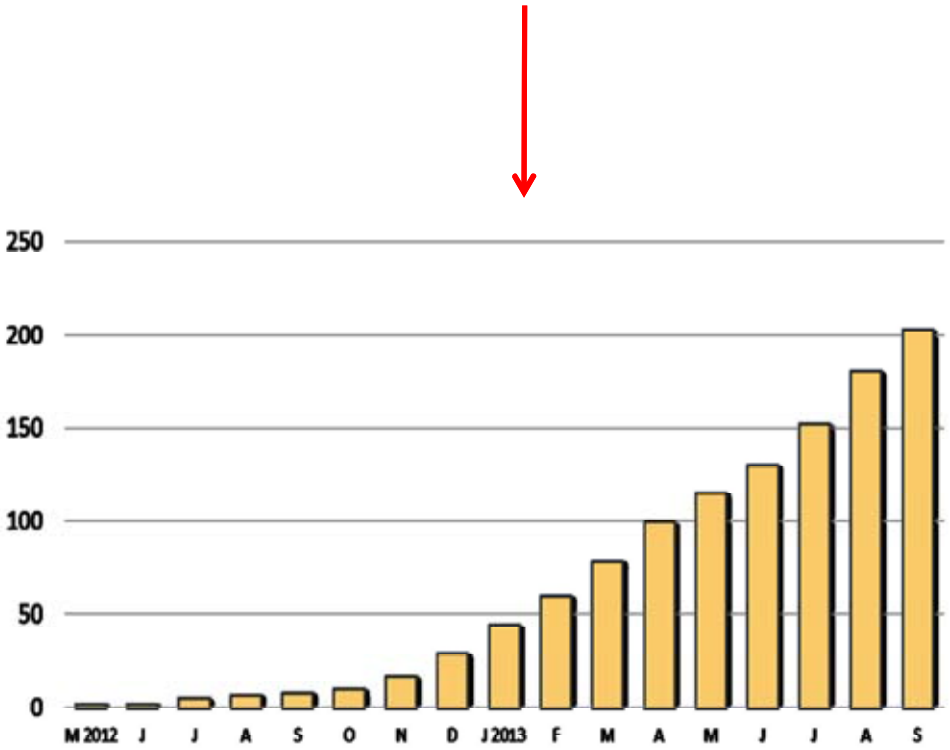
More news

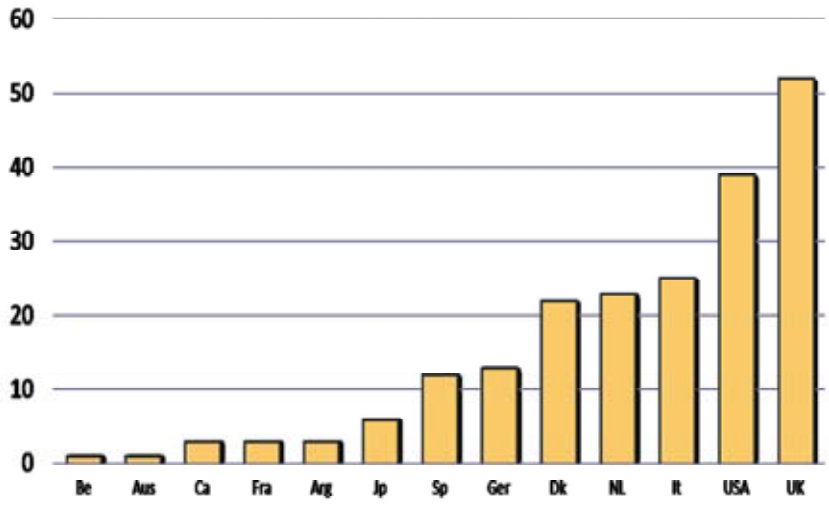


- *Inclusions*
- *IRB approval, no inclusions yet*
- *In process of IRB approval*


IGOS
Long-term outcome
Infections
Genetics
Clinical variants
Prognostic modelling
Paediatric GBS
Electro-physiology criteria
I-SID GBS study
Treatment

Number of patients included in IGOS





Inclusions per country

AIM: inclusion of ? 1.000 patients

Conclusions

- Much is now known about the pathogenesis of GBS
- New diagnostic criteria need further evaluation
- General medical treatment is very important
- Prognostic models: prediction respiration (ERGIS) and outcome (mEGOS)
- IVIg and PE are effective (Cochane reviews available)
- Need for better treatment (second dose IVIg or Eculizumab trial)
- Take care for GBS-TRF (10%) or for transition to A-CIDP (5%)
- Pain and fatigue require more attention
- New worldwide study: International GBS Outcome Study (IGOS)
- New GBS guideline (EFNS/PNS) under construction

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