GUILLAIN-BARRÉ SYNDROME

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OBJECTIVES

- Define Guillain-Barré Syndrome (GBS)
- Review the incidence of GBS
- Understand the role of molecular mimicry in GBS pathogenesis
- Recognize classical presentation of GBS and differential diagnoses
- Recommend disease modifying therapies
- Identify supportive care measures as necessary

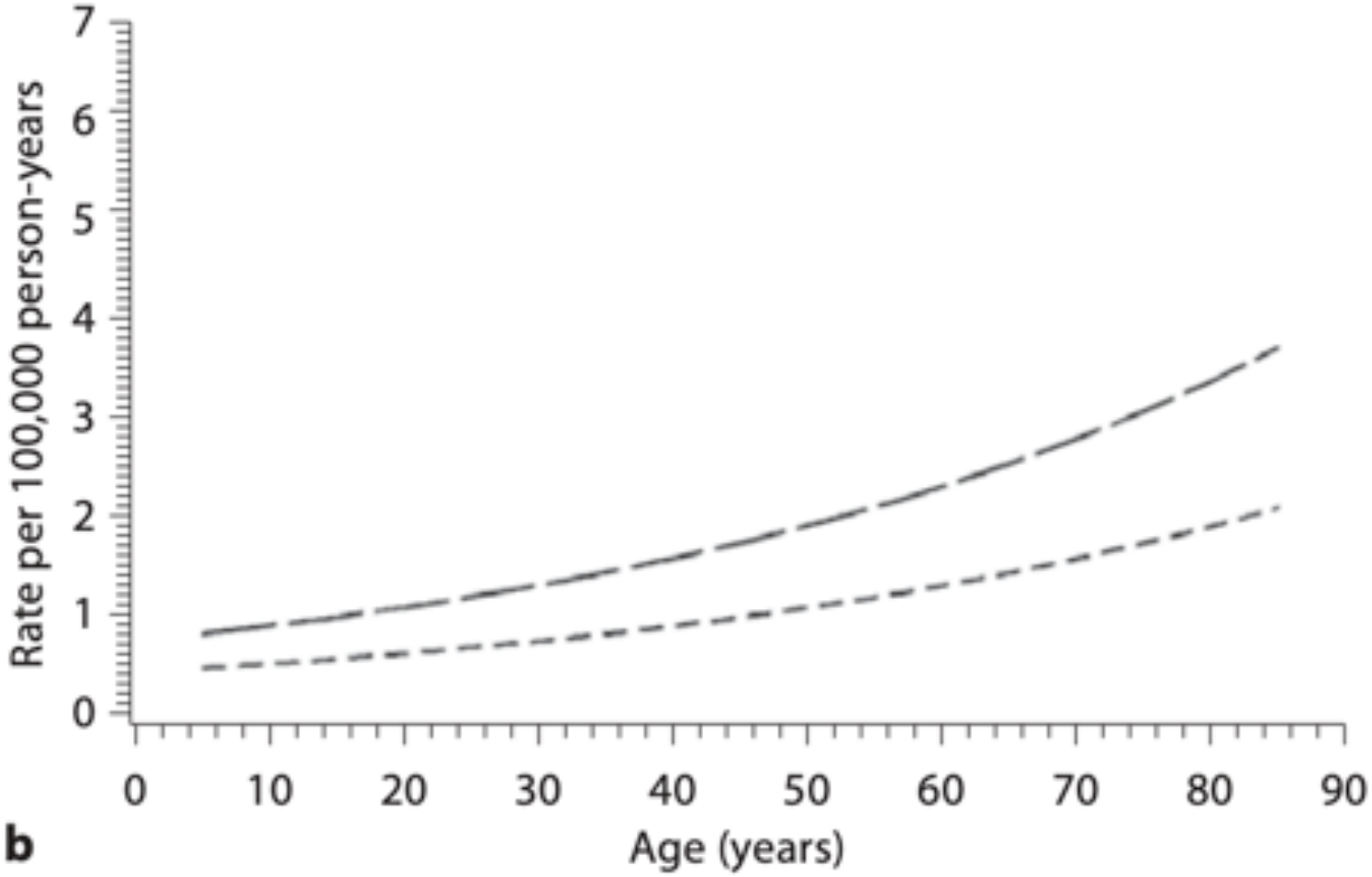
BACKGROUND

- Guillain-Barré Syndrome (GBS) is a severe acute paralytic neuropathy
  - Most common cause of acute flaccid paralysis worldwide
- Autoimmune attack on myelin sheath or Schwann cells of sensory and motor neurons, resulting in impairment/destruction
- Prognosis is variable

Yuki N, et al. *N Engl J Med*. 2012.

INCIDENCE OF GUILLAIN-BARRÉ SYNDROME

- Median 1.11 cases per 100,000 person-years
- Increases with age
  - ↑ 20% per 10 years of life
- Male predominance
  - Ratio: 1.78
  - 95% CI: 1.36 to 2.33

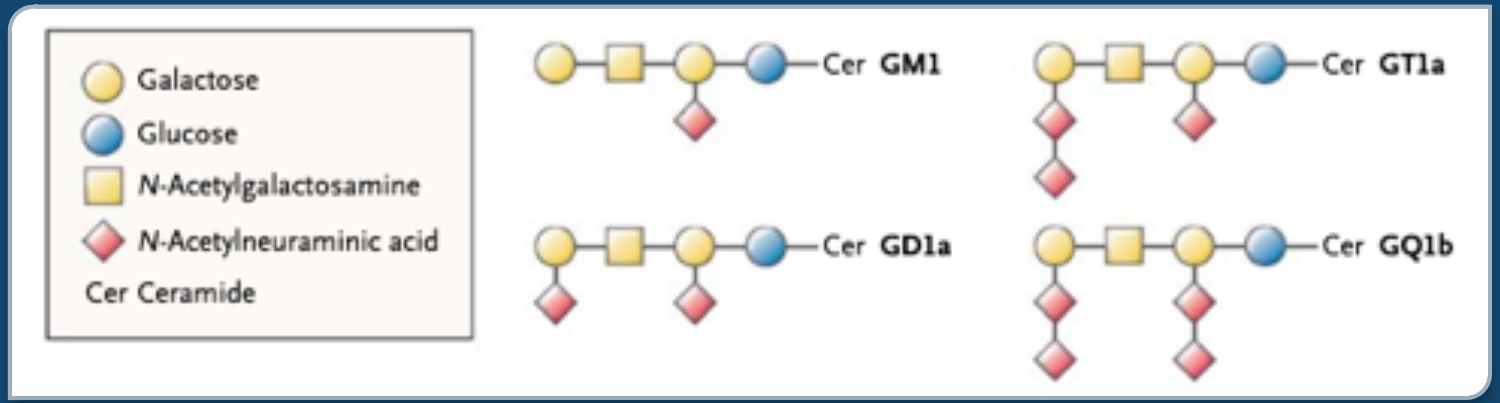


Yuki N, et al. *N Engl J Med*. 2012.
Sejvar JJ, et al. *Neuroepidemiology*. 2011.

PROPOSED MECHANISMS OF PATHOGENESIS

Molecular Mimicry

- Most cases are preceded by infection
- Immune response can generate antibodies that cross-react to gangliosides or other neuronal components
- Target of immune response determines myelin versus axonal damage



Other Triggering Events

- Immunization, Trauma, Surgery, Bone-Marrow Transplantation

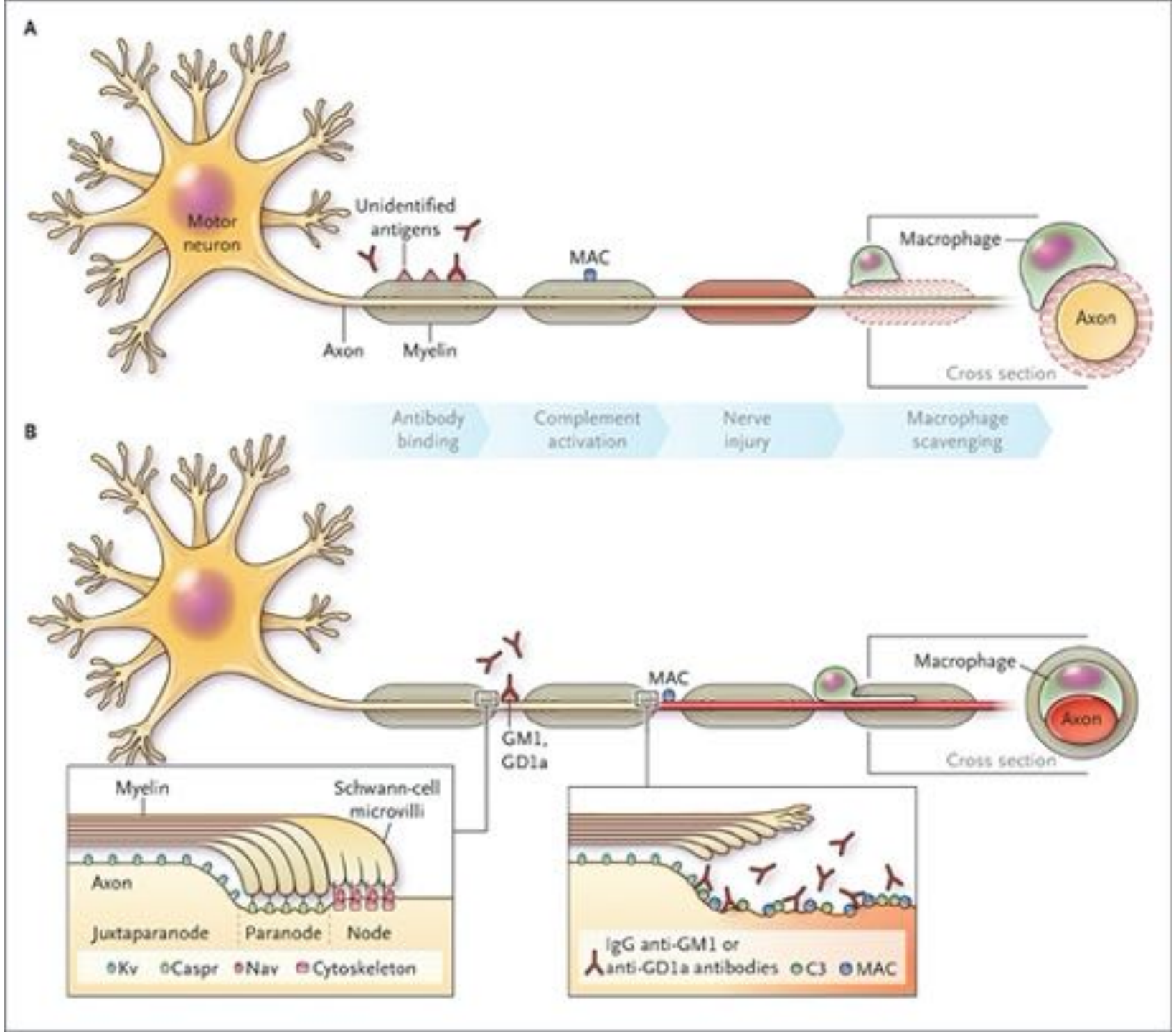
Yuki N, et al. *N Engl J Med*. 2012.
Willison HJ, et al. *Lancet*. 2016.
Winer JB. *BMJ*. 2008.

ETIOLOGY: PRECEDING INFECTIONS

Campylobacter jejuni	Cytomegalovirus (CMV)	Epstein-Barr Virus (EBV)	Human Immunodeficiecny Virus (HIV)
Zika Virus	*Mycoplasma pneumoniae*	Herpes zoster	Influenza Virus

PATHOGENESIS

1. Complement Activation
2. Membrane Attack Complex
3. Neuronal Damage
4. Macrophage invasion



PRESENTATION

- Progressive, symmetrical muscle weakness with absent or depressed deep tendon reflexes
- Patients most commonly present a few days to a week after onset
- History of upper respiratory infection or diarrhea up to 6 weeks prior
- Symptoms are generally non-specific and may be confused with a variety of other diseases
- Albuminocytologic Dissociation

Leonhard SE, et al. *Nature*. 2019

DIAGNOSIS OF GUILLAIN-BARRÉ

Willison HJ, et al. *Lancet*. 2016.

NINDS Criteria

Required Features

- Progressive weakness of the legs and arms
- Areflexia or decreased reflexes in weak limbs

Supportive Features

- Progression of symptoms
- Relative symmetry
- Cranial nerve involvement
- Albuminocytologic Dissociation
  - Elevated protein in CSP with cell count $\leq 50/mm^3$
- Pain
- No fever at onset
- Electrodiagnositic abnormalities consistent with GBS
- Autonomic dysfunction
- Recovery starting two to four weeks after progression halts

DIFFERENTIAL DIAGNOSIS

- Electrolyte Disturbances
- Acute Myopathy
- Spinal Injury
- Infection
- Malignancy
- Toxic Neuropathy
- Myasthenia Gravis
- Stroke

DISEASE PROGRESSION AND COMPLICATIONS

Progressive Weakening/Paralysis

- Complications include permanent disability, aspiration, thromboembolic events

Respiratory Failure (15-30%)

- Paralysis of the diaphragm requiring intubation and mechanical ventilation

Autonomic Dysfunction (70%)

- Arrhythmias (tachycardia, bradycardia), hypertension alternating with hypotension, Tachycardia, urinary retention, ileus, loss of sweating
- 20% of patients experience severe autonomic disturbances

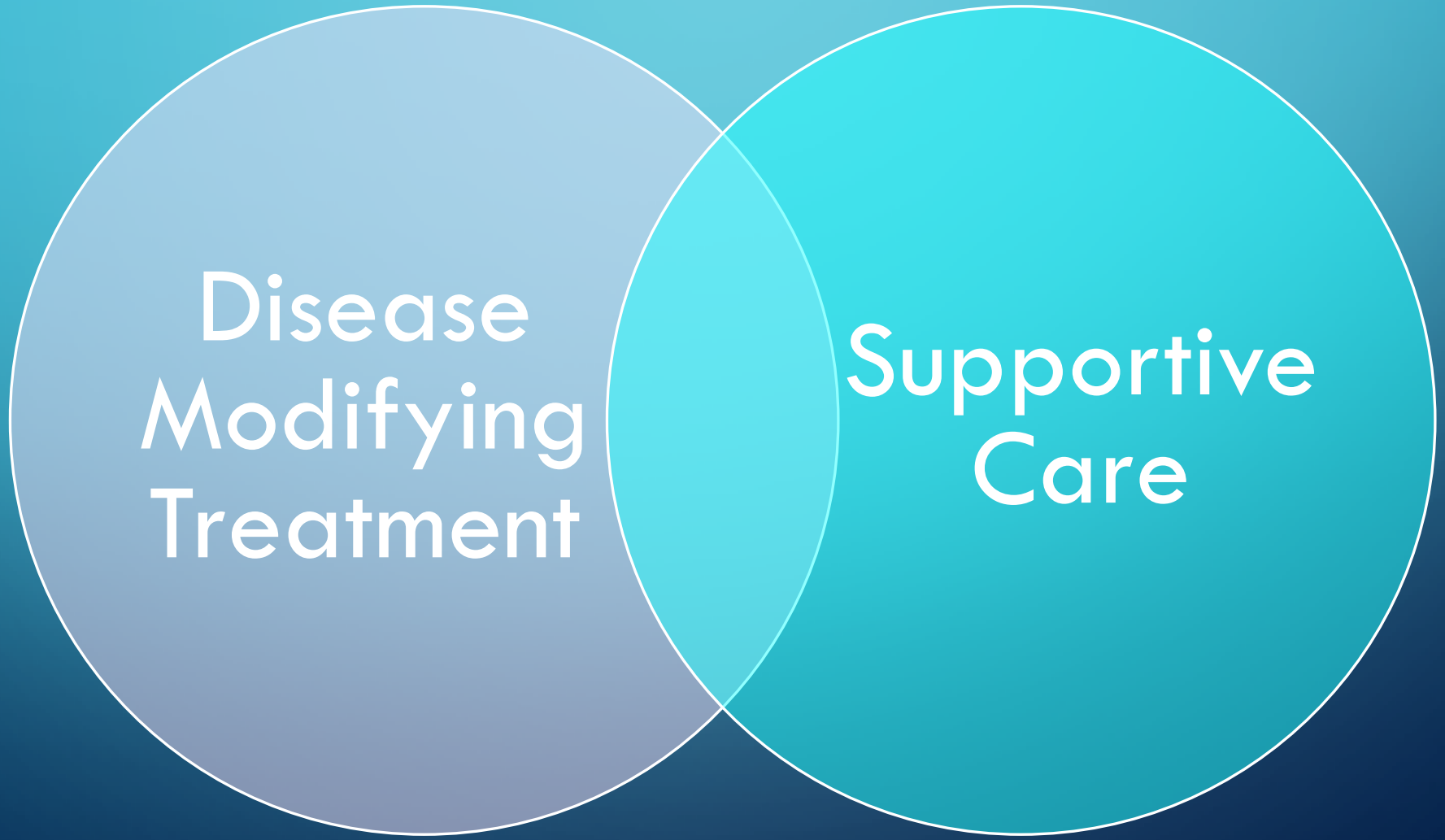
Yuki N, et al. *N Engl J Med*. 2012.
Willison HJ, et al. *Lancet*. 2016.
Winer JB. *BMJ*. 2008.

STARTING TREATMENT

- Treatment should be initiated if any of the following are present:
  - Inability to walk > 10 m independently
  - Rapid progression of weakness
  - Severe autonomic dysfunction
  - Respiratory insufficiency

Leonhard SE, et al. *Nature*. 2019

TREATMENT MODALITIES



DISEASE MODIFYING TREATMENTS (IMMUNOTHERAPY)

- Plasma Exchange (Plasmapharesis)
- Intravenous Immune Globulin (IVIG)

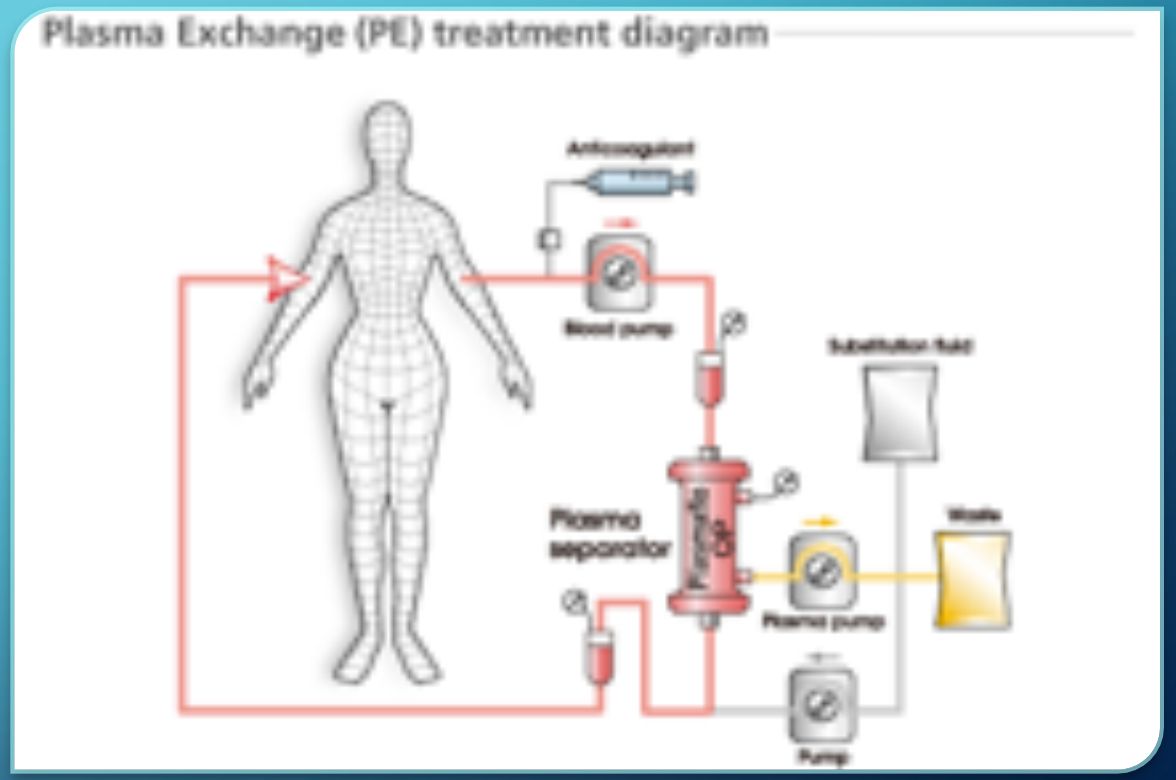
IMMUNOTHERAPY FOR GUILLAIN-BARRÉ

Recommendations from the Quality Standards Subcommittee of the American Academy of Neurology

1. Plasma Exchange (PE) is recommended for non-ambulant adult patients with GBS who seek treatment within 4 weeks of symptom onset
   - Plasma Exchange (PE) should be considered for ambulant patients examined within 2 weeks of symptom onset
2. Intravenous Immune Globulin (IVIG) is recommended for non-ambulant patients with within 2 or possibly 4 weeks of symptom onset
3. PE and IVIG are equivalent
4. Corticosteroids are not recommended
5. PE and IVIG are treatment options for children with severe GBS

CLINICAL CONSIDERATIONS FOR PLASMA EXCHANGE

- Dosing: 200-250 mL/kg for 5 sessions
- Adverse Events:
  - Fever, chills, itching, muscle cramps, thrombosis
  - Hypocalcemia (with citrate anticoagulation)
  - Infection
- Pearls:
  - Tolerability is variable, risks may outweigh benefits if IVIG available
  - Contraindicated in hemodynamic instability



http://www.asahi-kasei.co.jp/medical/en/personal/cure/cure_01.html

Hughes RAC, et al. *Cochrane Database of Systematic Reviews*. 2014.

EVIDENCE FOR THE USE OF PLASMA EXCHANGE (PLASMAPHARESIS) IN GBS

- Plasma Exchange for GBS – Cochrane Systematic Review (2012)
  - Included 6 randomized trials of plasma exchange in 649 patients

Outcome	N	Risk Ratio	95% CI
Ability to walk with assistance	349	1.60	1.19 to 2.15
Improvement by one or more grades	623	1.64	1.37 to 1.96
Time to recover walking without aid	349	172	10.6 to 2.79
Requirement for artificial ventilation	623	0.53	0.39 to 0.74
Likelihood of full muscle strength recovery	404	1.24	1.07 to 1.45
Likelihood of severe motor sequelae	649	0.65	0.44 to 0.96

Chevret S, et al. *Cochrane Database of Systematic Reviews*. 2017.

CLINICAL CONSIDERATIONS FOR INTRAVENOUS IMMUNOGLOBULIN

- Dosing: 0.4 g/kg daily for 5 days
- Adverse Events:
  - Headache, myalgia, fever, chills, nausea, immune reactions
  - Potential for renal failure with existing renal impairment
- Pearls:
  - Easier to administer and “more widely available”
  - Typically, treatment of choice, but currently in shortage

Hughes RAC, et al. *Cochrane Database of Systematic Reviews*. 2014.

EVIDENCE FOR THE USE OF IVIG IN GBS

Intravenous Immunoglobulin for GBS – Cochrane Systematic Review

- Included 12 trials eligible for inclusion
  - In 5 trials (n=536) comparing IVIG with PE, the mean difference in disability scale +0.02 of a grade more improvement (95% CI -0.20 to 0.25)
  - One trial of 21 mildly affected children showed mean difference of +1.42 of a grade more improvement with IVIG compared to supportive treatment alone (95% CI 0.27 to 2.57)

Hughes RAC, et al. *Cochrane Database of Systematic Reviews*. 2014.

SUPPORTIVE CARE FOR COMPLICATIONS

Mechanical Ventilation

- Stress ulcer prophylaxis
- Recognition and treatment of infection

Blood Pressure Management

- Arterial line for monitoring
- Fluid boluses for hypotension
- Short-acting antihypertensives

Arrhythmias

- Cardiac monitor
- Treat arrhythmias
- Pacing

Pain

- Gabapentin, Carbamazepine
- Avoid opioids, Avoid steroids

Paralysis and Immobility

- VTE prophylaxis
- Treatment of thromboembolism

RECOVERY

- Patients will require physical rehabilitation and management on long-term complaints
- Recovery can occur in up to 80% of patients and take years
  - 40% may require additional treatment course
  - Some patients will have recurrence of GBS (2-5%)
  - ~20% will have some permanent form of disability
- Mortality from Guillain-Barré is about 5%

Leonhard SE, et al. Nature. 2019

SUMMARY

Guillain-Barré is a rare, autoimmune-mediated cause of acute flaccid paralysis

Prior infection is suggested to cause pathogenesis through molecular mimicry and a resulting immune response to the peripheral nerves

Patients present with progressive, symmetrical weakness of the limbs with areflexia

Disease course is characterized by progressing paralysis, respiratory distress, and autonomic dysfunction

Treatment is limited to plasma exchange or intravenous immunoglobulin

Supportive care and complication management are crucial to reducing morbidity and mortality

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THE FUTURE OF GUILLAIN-BARRÉ TREATMENT

CLINICAL TRIALS

ASSOCIATION BETWEEN GBS AND IMMUNIZATION

- Guillain-Barré Syndrome has followed vaccinations, but risk is likely overemphasized
- Baxter, et al. identified cases of confirmed GBS (n=415) at Kaiser Permanente Northern California (1995-2006)
  - Influenza: OR 1.1 (0.4 to 3.1)
  - Tetanus/diptheria: OR 1.4 (0.3 to 4.5)
  - PPSV23: OR 0.7 (0.1 to 2.9)
  - Combined: OR 1.3 (0.8 to 2.3)
- Influenza Vaccination
  - an increased risk of GBS was associated with the swine influenza vaccine in 1976, although the severity of the risk has been controversial
  - Subsequent studies the small risk of GBS associated with influenza vaccination, on the order of one to two excess cases of GBS per million people vaccinated
- Infection with vaccine preventable illnesses can cause GBS

GBS SUBTYPES

ACUTE INFLAMMATORY DEMYELINATION POLYNEUROPATHY (AIDP)

- Most severe
- Causative antibodies unknown
- Commonly associated infections
  - CMV and EBV
- Neuronal damage to myelin

ACUTE MOTOR AXONAL NEUROPATHY (AMAN)

- Variable in severity
- IgG antibodies against gangliosides
- Commonly associated infections
  - Camplyobacter jejuni
- Neuronal damage to axon