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THE MANAGEMENT OF GUILLAIN-BARRÉ SYNDROME

OVERVIEW

Guillain-Barré syndrome (GBS) is clinically characterized by an acute flaccid paralysis that can affect all four (4) limbs, with or without cranial nerve impairment. GBS is considered a heterogeneous group of autoimmune diseases, which includes the Miller Fisher syndrome and the motor, sensory, sensorimotor, and pure dysautonomic variants.

The Miller Fisher syndrome is characterized by:

- Ophthalmoplegia
- Ataxia
- Areflexia

Other asymmetrical or focal variants have been reported, such as:

- Paraparetic
- Pharyngeal-cervical-brachial
- Bulbar

In the typical form, weakness begins distally in the lower limbs, with difficulty walking, climbing stairs, or rising from a seated position. GBS can sometimes progress to affect the facial nerves, and may produce bulbar involvement and affect the respiratory muscles.

CLINICAL PRESENTATION

The syndrome usually manifests as a rapidly evolving areflexic motor paralysis with or without sensory deficits. The usual pattern is of an ascending paralysis accompanied by absent or decreased deep tendon reflexes. The lower extremities are usually more affected than the upper extremities. Patients initially present with difficulty walking, climbing stairs, or rising from a seated position. Subsequently, motor weakness may spread to involve the arms. Sensory changes may develop, such as paresthesia,

dysesthesias, or hypoesthesia. Pain (neuropathic, radicular, or musculoskeletal) is common. The lower cranial nerves may be involved, causing facial nerve palsy and bulbar palsy.

As the paralysis ascends, respiratory muscle involvement may occur, leading to respiratory complications and failure. Autonomic dysfunction may complicate GBS causing tachycardia, bradycardia, other arrhythmias, hypertension alternating with hypotension, orthostatic hypotension, urinary retention, ileus, and anhidrosis / hypohidrosis. Recovery may occur over many months to a year. Most cases of GBS are preceded by an infection.

A significant percentage of patients, up to 30%, will require intensive care unit admission due to respiratory complications and dysautonomia including cardiac arrhythmia or blood pressure changes.

It is critical to be able to screen for possible Acute Flaccid Paralysis. The following key clinical features have been noted in suspected GBS cases by the Jamaican medical community since January 2016:

- Bilateral facial weakness, often profound
- Prominent sensory symptoms and signs particularly vibratory impairment often to thoracic level
- Areflexia
- Limb weakness, prominently proximal
- Bulbar symptoms , especially dysphonia and dysarthria
- Diminished chest expansion indicative of respiratory muscle weakness and potential for respiratory failure

GBS is primarily a clinical diagnosis. Cerebrospinal fluid (CSF) analysis and electrophysiology may aid in its definitive diagnosis. CSF albuminocytologic dissociation which is an increase in proteins in the absence of pleocytosis (>50 leucocytes per microliter) and electrophysiological studies characterizing the subtypes of GBS such as acute demyelinating polyradiculoneuritis, motor axonal form and other variants may be conclusive.

CASE DEFINITION

The Brighton criteria (see table 1) is recommended for use as the case definition of GBS. It is based on presenting clinical findings and ancillary testing including neurophysiology and lumbar puncture findings. Patients are categorized as level 1 (the highest level of diagnostic certainty) to level 3 (the lowest level of diagnostic certainty). Although potentially applicable in a clinical setting, the level of diagnostic certainty is primarily intended for epidemiologic purposes and not as a criterion for treatment.

Table1: Brighton criteria for case definition of Guillain-Barré syndrome

Level 1 of diagnostic certainty	Level 2 of diagnostic certainty	Level 3 of diagnostic certainty
Bilateral and flaccid weakness of the limbs; AND	Bilateral and flaccid weakness of the limbs; AND	Bilateral and flaccid weakness of the limbs; AND
Decreased or absent deep tendon reflexes in weak limbs; AND	Decreased or absent deep tendon reflexes in weak limbs; AND	Decreased or absent deep tendon reflexes in weak limbs; AND
Monophasic illness pattern; and interval between onset and nadir of weakness between 12h and 28 days; and subsequent clinical plateau; AND	Monophasic illness pattern; and interval between onset and nadir of weakness between 12h and 28 days; and subsequent clinical plateau; AND	Monophasic illness pattern; and interval between onset and nadir of weakness between 12h and 28 days; and subsequent clinical plateau; AND
Absence of identified alternative diagnosis for weakness; AND	Absence of identified alternative diagnosis for weakness; AND	Absence of identified alternative diagnosis for weakness
Cytoalbuminologic dissociation (i.e. elevation of CSF* protein level above laboratory normal value and CSF total white cell count <50 cells/μl); AND	CSF total white cell count <50 cells/μl (with or without CSF protein elevation above laboratory normal value); OR	
Electrophysiologic findings consistent with GBS	Electrophysiologic studies consistent with GBS if CSF not collected or results not available	

Suspected case of Zika virus associated GBS

A suspected case of Zika virus associated with GBS is one who:

- lives in or visited an area with current Zika virus circulation OR
- has had unprotected sex with someone who was previously infected with Zika virus

AND;

presents with the following signs and symptoms (level 3 Brighton "criteria"):

- Bilateral and flaccid weakness of the limbs; AND
- Decreased or absent deep tendon reflexes in the weak limbs; AND
- Monophasic illness pattern; and interval between onset and nadir of weakness between 12 hours and 28 days; and subsequent clinical plateau; AND
- Absence of identified alternative diagnosis for weakness

Confirmed case of Zika-virus-associated GBS

- Patient with laboratory confirmation of recent infection with the Zika virus infection

LABORATORY DIAGNOSIS

The laboratory diagnosis of ZIKV infection in a patient with GBS is done according to the protocol described for the detection of viral infection.

SAMPLES

Required Samples

- Serum (5 to 8 mls in a Red Top Tube)
- Urine (3 ml to 10 mls in a sterile Universal Container)
- Stool:
 - (10 to 15 grams of Solid Stool – in a sterile Universal Container) or
 - (15 to 30 ml of Liquid Stool in a sterile Universal Container) or
 - at a minimum a heavily inoculated Rectal Swab sample in Viral Transport Medium

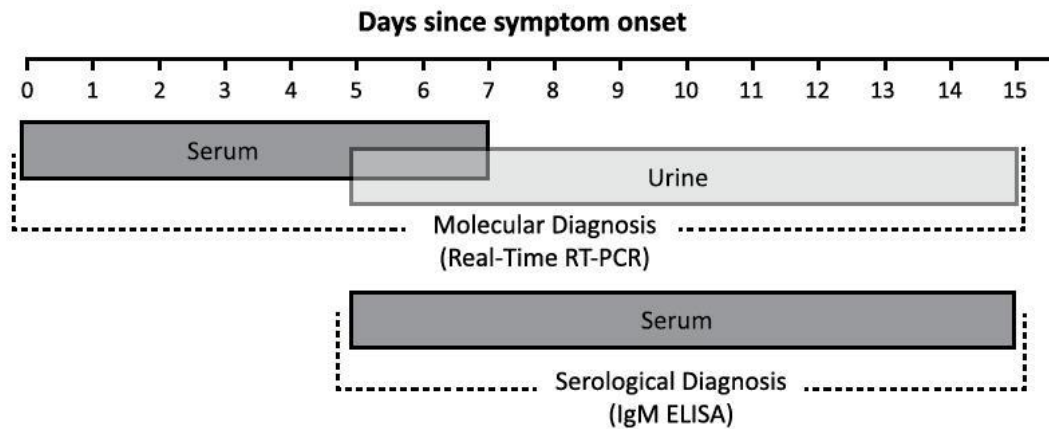
Additional Samples

- Cerebrospinal Fluid (CSF) can also be tested. This must be collected in a sterile red-top tube.

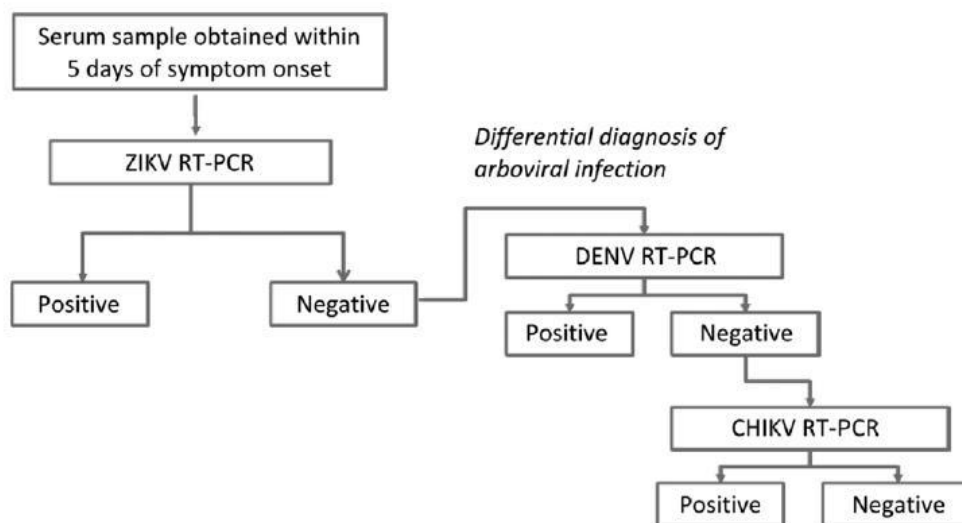
SAMPLE TRANSPORT & HANDLING

- All Samples should be transported on ice or with ice packs to the National Public Health Laboratory (NPHL), immediately
- The sample(s) may be refrigerated at 2 to 8°C for 48 hours while awaiting referral to the NPHL
- Samples should be frozen at -10 to -20° C if they have to be kept longer than 48 hours or within a week following collection while awaiting referral to the NPHL

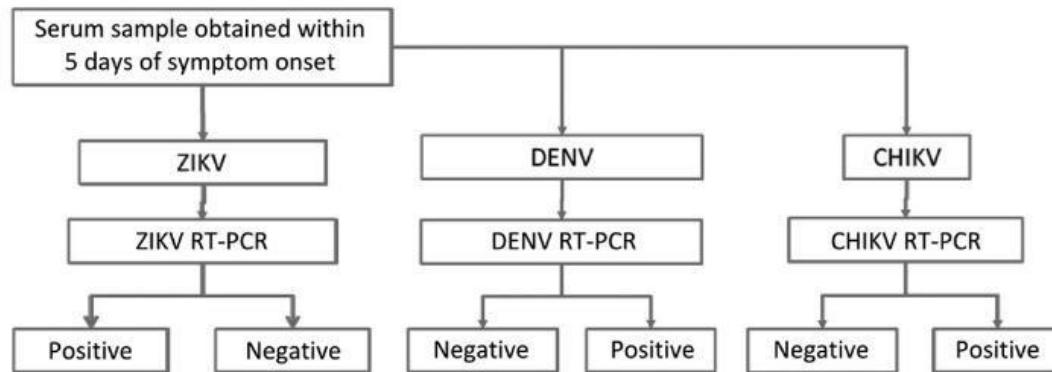
Figure 1. Diagnostic indications, according to day of symptom onset and sample type.



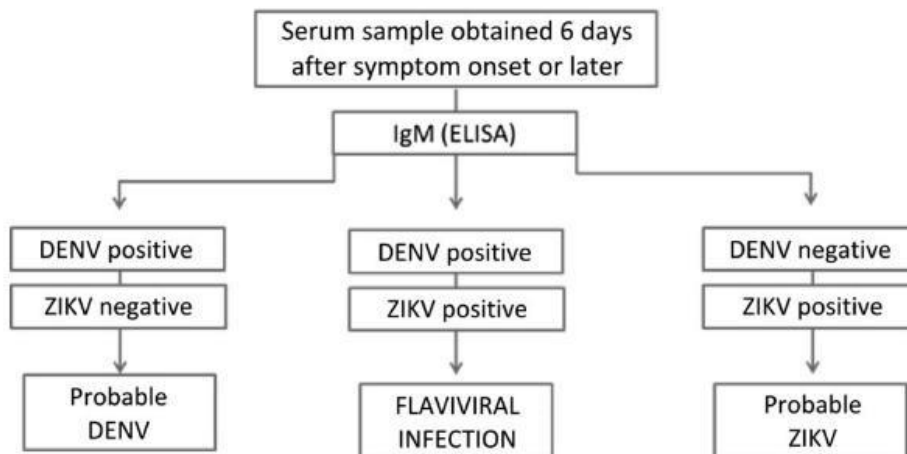
A. Algorithm for virological confirmation of suspected cases of ZIKV infection in areas where other arboviruses are in circulation



B. Algorithm for virological confirmation of suspected cases of ZIKV infection in areas where other arboviruses are in circulation (multiplex PCR).



C. Algorithm for serological detection in suspected cases of ZIKV infection in areas where other arboviruses are in circulation.



The suspicion of a neurological syndrome associated with Zika virus often occurs outside the viraemic period, however, it is recommended that viral detection be attempted through RT-PCR in both serum and urine collected from the patient under investigation.

Virologic (RT-PCR) analysis and the detection of anti-Zika virus IgM antibodies by ELISA can also be performed using a cerebrospinal fluid (CSF) sample.

In a case of GBS with a positive Flavivirus screening test result: (i.e. positive DENV and ZIKV IgM – both of which must be done together, as per Algorithm C), the result is suggestive of ZIKV infection since GBS after dengue infection is a rare occurrence.

For serological IgM detection, paired serum specimens should be collected. Serological detection of anti-Zika IgM and IgG antibodies, should also be performed using Enzyme-Linked Immunosorbent Assay (ELISA). ELISA and immunofluorescence assays may be performed on blood samples collected after six (6) days following the onset of symptoms.

ZIKV-specific IgM antibodies can be detected by ELISA or immunofluorescence assays in serum specimens. Since a single serum in the acute phase is only presumptive, it is recommended that a second sample be taken two (2) to three (3) weeks after the first sample to demonstrate seroconversion or a four-fold increase in the antibody titer be collected.

The first serum specimen should ideally be collected during the first seven (7) days of illness. Positive Zika IgM antibodies AND Plaque reduction neutralization (PRNT 90) for Zika virus titers > 20 and four (4) or more times greater than the titers for other flaviviruses; AND exclusion of other flavivirus is confirmatory.

Virologic (RT-PCR) analysis and the detection of anti-Zika virus IgM antibodies by ELISA can also be performed using a cerebrospinal fluid (CSF) sample.

MANAGEMENT OF GBS

- Careful history of possible Zika symptomatology with accurate estimation of days from onset of symptoms
- Neurological examination for facial weakness, speech, (proximal) weakness, areflexia
- Chest expansion at bedside but optimally spirometry for proper assessment of anyone with neurological presentation; Pulse Oximetry and Arterial Blood Gas to assess for respiratory impairment or failure

- CSF examination after CT brain in all patients suspected of GBS; CSF done 48 hours after symptom onset should usually demonstrate cytoalbuminologic dissociation which is a classic diagnostic finding in GBS
- Nerve conduction studies (NCS) may not be feasible in all patients in the setting of an epidemic. Neither is it necessary for many in whom diagnosis can be otherwise safely established by a focused history, physical examination for the key clinical features, CSF examination for cytoalbumin dissociation and evidence of recent Zika infection. Nerve conduction studies would be indicated in the following situations:
 - Rapidly evolving GBS-like syndrome
 - All patients:
 - >50 years of age with neurological presentations
 - with respiratory compromise to confirm diagnosis, ascertain prognosis and establish a neurophysiological baseline
 - in whom there is diagnostic uncertainty when typical clinical picture not complete

TREATMENT

In hospital supportive care is recommended. Intravenous immunoglobulin therapy or therapeutic plasma exchange should be provided to GBS patients who are unable to walk or who have rapidly progressive symptoms.

Not all patients with GBS require Intensive Care support. Approximately one third (1/3) of patients do experience deterioration of respiratory muscle strength during the course of the disease, eventually leading to respiratory failure requiring Intensive Care. Admission to the Intensive Care Unit (ICU) may also be required because of dysautonomia associated with GBS or for other medical or iatrogenic complications occurring with the syndrome.

While in the ICU along with respiratory support when necessary, attention is paid to positioning, fluid and electrolyte balance, nutrition, analgesia and psychological support. All patients should be given subcutaneous fractionated or unfractionated heparin and support stockings until they are able to walk independently to prevent deep vein thrombosis.

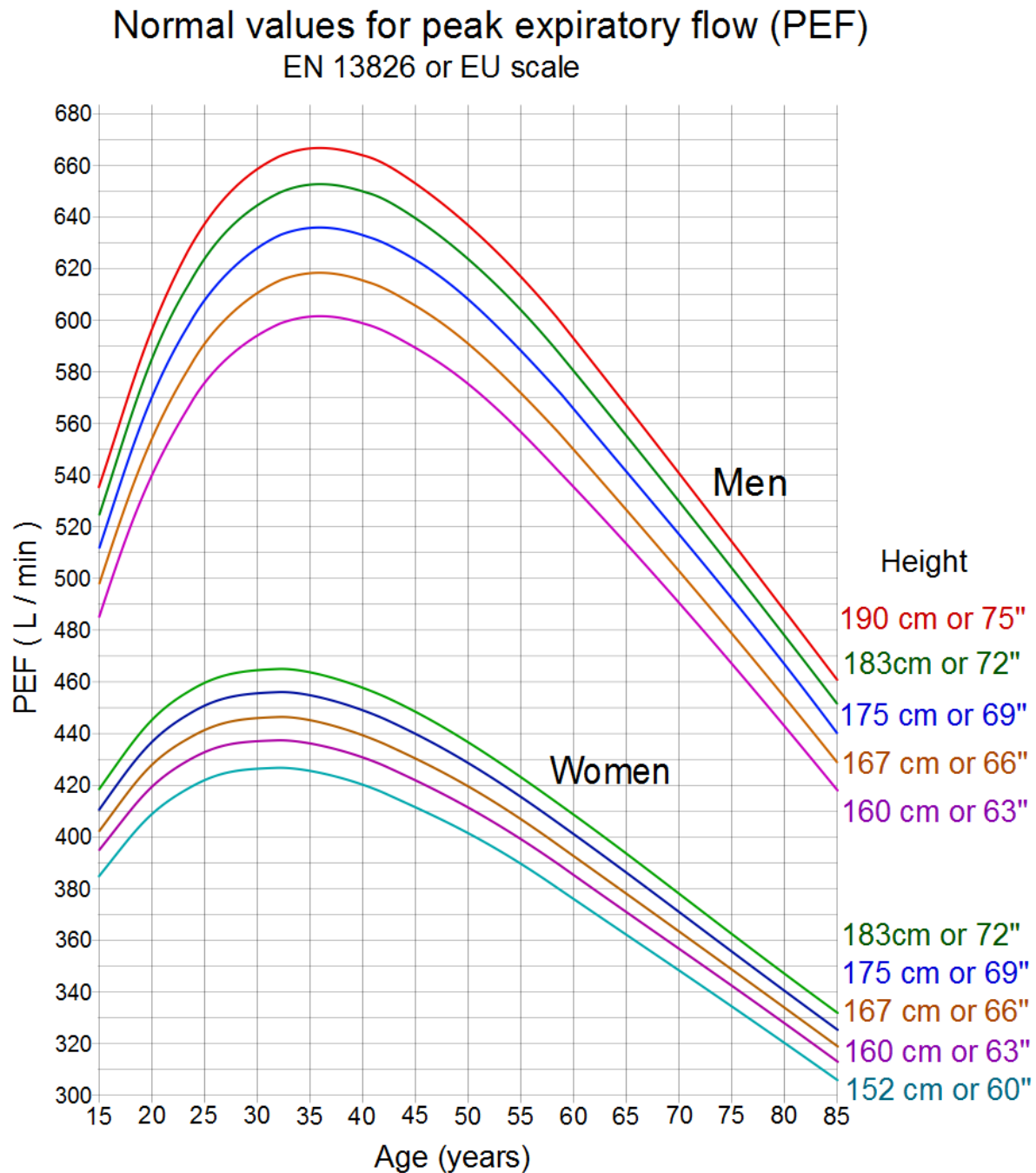
INDICATORS FOR INTUBATION AND MECHANICAL VENTILATION

Indications for intubation and mechanical ventilation are based on spirometry (see figure 1):

- Forced Vital Capacity (FVC) < 20 mls/kg

- Maximal Inspiratory Pressure < 30 cmH₂O
- Maximal Expiratory Pressure < 40 cmH₂O

Peak Expiratory Flow Rate (PEFR)



Peak Expiratory Flow Rate below 300 -500 mls in the absence of coexisting pulmonary pathology (e.g. COPD) depending on age, height and gender as seen on chart will indicate need for respiratory support.

This is a simple measurement that can be done with only a Peak Flow Meter as the required instrument. Additional clinical predictors of indicators for mechanical ventilation include:

1. A time from onset of GBS to hospital admission of less than seven (7) days
2. Inability to lift the elbows or head above the bed
3. Ineffective cough
4. Increased liver enzyme levels

Eighty five percent (85%) of GBS patients achieve full and functional recovery in six (6) to 12 months. Recovery is maximal eighteen (18) months post onset of the disease. Seven to fifteen percent (7-15 %) of patients have permanent neurologic sequelae. Relapse may occur in a small percentage of patients (3-5%).

The following are predictors of a poor recovery during the acute phase:

- Age greater than sixty (60) years
- Severe rapidly progressive disease
- Low nerve conduction amplitude on distal stimulation which suggests axonal loss
- Prolonged mechanical ventilation for greater than one (1) month
- Preexisting Pulmonary Disease

COMPLICATIONS

Complications of GBS include:

- Residual numbness or other sensations
- Pain
- Dysfunction of bowel and bladder
- Deep Vein Thrombosis
- Pulmonary embolism
- Decubitus ulcers
- Relapse

The risk of death in patients with GBS is associated with respiratory failure, cardiac arrhythmias, and thrombo-embolism. Optimal supportive care including frequent neurological assessments, vital signs and respiratory function monitoring cannot be over emphasized.

Intravenous immunoglobulin (IVIg) or Plasmapheresis is effective when administered early, ideally within two (2) weeks of onset of GBS symptoms. Intravenous immunoglobulin (IVIg) is given for five (5) days at

0.4 gram/kg per day. Side effects of **IVIg** include: aseptic meningitis, rash, acute renal failure and rarely hyperviscosity leading to stroke. **IgA** deficiency can lead to anaphylaxis.

The aim must be for rapid diagnostic evaluation and early treatment to prevent respiratory failure with its contingent complications and expense.

References

1. WHO/PAHO. Guidelines for surveillance of Zika virus disease and its complications. May 2016