Identification and management of Guillain-Barré syndrome in the context of Zika virus

Interim guidance update

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1. Introduction

1.1 Background

On 1 February 2016, the Director-General of the World Health Organization (WHO) declared the recent clusters of microcephaly cases, Guillain-Barré syndrome (GBS) and other neurological conditions in some areas affected by Zika virus, a Public Health Emergency of International Concern.[1] As of 07 July 2016, fifteen countries and territories worldwide have reported increased GBS incidence and/or laboratory confirmation of Zika virus infection among people with GBS.[2] Other neurological manifestations, including myelitis (inflammation of the spinal cord), meningoencephalitis (inflammation of the brain and meninges) and acute disseminated encephalomyelitis (ADEM) have been identified in patients with Zika virus infection, however, further work is required to understand the spectrum and impact of such manifestations in the context of Zika virus infection.[3-4]

1.2 Rationale and objectives

This guidance provides an overview of current knowledge pertaining to the clinical assessment and management of patients with GBS in the context of Zika virus infection. This document updates the WHO interim guidance *Identification and management of Guillain-Barré syndrome in the context of Zika virus* published on 25 February 2016. It includes narrative summaries of recent evidence underpinning the recommendations for assessment and management of GBS and provides remarks concerning implementation.

1.3 Scope of the guidance

This guidance is relevant to all children and adults with GBS in areas with Zika virus transmission. It is not intended to provide a comprehensive guide for the prevention and management of GBS.

1.4 Target audience

The primary audience for this guidance is health care professionals providing care to GBS patients including general practitioners, emergency and intensive care providers, neurologists and paediatricians. This guidance may also be used by local and national policy-makers and those responsible for implementing care guidelines in regions affected by Zika virus transmission.

2. GBS in the context of Zika virus infection

GBS is an acute immune-mediated neuropathy that affects nerves controlling muscle strength and nerves transmitting pain, temperature and touch sensations. This can result in weakness and loss of sensation in the legs and/or arms. The worldwide incidence of GBS is estimated as 0.8–1.9 (median 1.1) cases per 100 000 people per year among all ages.[5] The annual incidence of GBS increases with age (0.6 per 100 000 per year in children and 2.7 per 100 000 per year in people aged 80 years and over) and the condition is slightly more frequent in males than in females.[5]

Most patients with typical GBS present with rapidly progressive bilateral leg weakness with hypo/areflexia in the affected limbs. In rare cases, patients can present with facial, oculomotor, bulbar (i.e. difficulty with swallowing and speaking) weakness, or primary sensory symptoms.

GBS is potentially life-threatening, with 20–30% of patients developing respiratory failure requiring ventilation and intensive care support.[6] Up to 70% of patients have some degree of autonomic instability (i.e. arrhythmias and extremes in blood pressure), with 20% developing serious and potentially fatal autonomic dysfunction. There is a 5% mortality rate, despite optimal care.[6]

Approximately two thirds of GBS cases are preceded by an infection. Possible triggers are infections including bacteria (e.g. campylobacter jejuni) and viruses (e.g. dengue, chikungunya, cytomegalovirus, human immunodeficiency virus (HIV)).[6] GBS may also be triggered by vaccine administration or surgery. GBS has a progressive, monophasic disease course, usually without relapse.

During a Zika virus outbreak in French Polynesia between October 2013 and April 2014, a 20-fold increase in GBS incidence was observed compared with the previous four years. A case-control study[7] showed a strong association between Zika infection and GBS during the outbreak. 41 patients (98%) with GBS had anti-Zika virus IgM or IgG. Thirty-seven patients (88%) experienced a transient illness

lasting a median of 6 days (interquartile range 4–10) before the onset of neurological symptoms, suggesting recent Zika virus infection. Past dengue virus history did not differ significantly between patients with GBS and those in the control groups. Based on a 66% attack rate of Zika virus infection in the general population, the risk of GBS was estimated to be 0.24 per 1000 Zika virus infections.

In 2015 in the Brazilian state of Bahia, 42 GBS cases were reported, including 26 (62%) with a history of symptoms consistent with Zika virus infection.[6] A total of 1708 cases of GBS was registered nationwide, representing a 19% increase of GBS cases from 2014 (total 1439 cases), although not all states reported an increase in incidence. As of June 16th 2016, in the context of Zika virus circulation, 13 countries and territories worldwide have reported an increased incidence of Guillain-Barré syndrome (GBS) and/or laboratory confirmation of Zika virus infection in people with GBS cases.[2] GBS has been reported in children as well as adults in the affected countries. Polio surveillance reports have indicated an increased incidence in cases of acute flaccid paralysis in children under 15 years in some countries with ongoing Zika virus transmission. These cases are currently under investigation.

3. Evidence and recommendations

3.1 Assessment of GBS

3.1.1 Clinical assessment

Summary of evidence

In 2011, the Brighton Collaboration developed case definitions for GBS aimed at improving epidemiological surveillance in response to concerns about a possible association between GBS and the H1N1 swine flu vaccine.[8] The Brighton criteria were developed by expert consensus and are based on clinical findings and results of ancillary testing, including neurophysiology and lumbar puncture. Four validation studies have been performed on the use of the Brighton criteria for epidemiological purposes.[9-12]While two of these studies are limited by their small sample size and patient selection, the remaining two provide stronger evidence, including one study in a resource-limited setting.[10-11] Three other diagnostic criteria, based on expert opinion (Asbury et al, Wakerley et al, Van der Meche et al), exist for GBS, [13-15] however, there are no studies validating these three sets of diagnostic criteria.

All of the above four criteria include limb weakness and absent or decreased deep tendon reflexes in the affected limbs as mandatory features for diagnosis. Temporal association of symptoms, findings from lumbar puncture and neurophysiology testing are supporting characteristics.

Recommendations

A detailed history and neurological examination should be carried out on all patients presenting with neurological symptoms. A person with progressive symmetric limb weakness and decreased or absent deep tendon reflexes in the weak limbs is a **suspected case** of GBS and should be evaluated by a health-care provider with expertise in neurological examination, if available.

A **clinical case** of GBS, evaluated by a health care professional with expertise in neurological examination, should meet the following criteria: bilateral and symmetric weakness of the limbs; decreased or absent deep tendon reflexes in the weak limbs; monophasic illness pattern; interval between the onset and nadir of weakness ranging from 12 hours to 28 days with a subsequent clinical plateau; and absence of an identified alternative cause for the weakness.

Remarks

- A suspected case of GBS should be promptly evaluated and early supportive care provided. Treatment should be initiated in all suspected cases according to these guidelines.
- Verification of the GBS diagnosis should be done by a health-care professional with expertise in performing neurological examinations.
- A clinical case meets ***level 3 of diagnostic certainty of Brighton criteria*** for surveillance and reporting purposes (see Annex 1 for Brighton criteria).

3.1.2 Cerebrospinal fluid (CSF) examination

Summary of evidence

Cerebrospinal fluid (CSF) albuminocytological dissociation (CSF protein level above laboratory normative value and CSF total white blood cell count <50 cells/ul) provides supporting evidence for GBS in the appropriate clinical context. Albuminocytological dissociation is present in 50-66% of patients with GBS in the first week after symptom onset and in over 75% of patients in the third week.[16] However, a lumbar puncture performed within one week of symptom onset may show normal results.

Recommendations

CSF examination is not needed to make a clinical diagnosis of GBS and should not delay treatment. If there is clinical suspicion of GBS, CSF examination for evaluation of albuminocytological dissociation should be performed as this test provides important supporting data. A repeat CSF examination may be performed one to two weeks after symptom onset if the initial results are normal and the diagnosis of GBS remains uncertain.

Remarks

- Patients meeting the clinical case definition for GBS and who have CSF albuminocytological dissociation should be categorized as ***level 2 of diagnostic***

certainty** of **Brighton criteria for surveillance and reporting purposes.

- Patients with a questionable clinical diagnosis of GBS must have a lumbar puncture to evaluate whether there is CSF cytoalbuminological dissociation

3.1.3 Neurophysiology studies

Summary of evidence

Neurophysiology studies support the diagnosis of GBS and discriminate between GBS subtypes.[17-18] Abnormalities in neurophysiology testing are most pronounced at least two weeks after the start of weakness, when over 85% of patients have findings consistent with GBS.[17] Nerve conduction studies enable clinicians to categorize GBS into different types such as acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, or acute motor and sensory axonal neuropathy.[18-19]

Recommendations

Neurophysiology studies are not required to make a clinical diagnosis of GBS and should not delay treatment. Neurophysiology studies provide important supporting data when there is clinical suspicion of GBS. Thus if facilities are available, neurophysiology studies may be done at the time of initial presentation to increase the diagnostic certainty of GBS. Neurophysiology studies may be repeated two weeks after symptom onset if initially normal.

Remarks

- Patients who meet the clinical case definition for GBS, and who have evidence of CSF albuminocytological dissociation and neurophysiology testing findings consistent with GBS, should be categorized as ***level 1 of diagnostic certainty of Brighton criteria*** for surveillance and reporting purposes.
- Where possible, neurophysiology testing should be carried out on patients in whom a clinical diagnosis of GBS is in question.

3.2 Laboratory evaluation

Summary of evidence

Two thirds of GBS cases are preceded by infection.[6] There are several potential triggers of GBS including viral (e.g. chikungunya, dengue, HIV) and bacterial (e.g. campylobacter jejuni) infections.

Recommendations

Laboratory testing to identify an underlying GBS trigger is not required to make the diagnosis of GBS and should not delay treatment. Laboratory testing to identify a potential trigger should be performed in the context of local epidemiology. Serological testing for HIV infection should be carried out in all patients with GBS.

Laboratory testing to identify Zika virus infection as an infectious trigger of GBS should be done according to WHO interim guidance on *Laboratory testing for Zika virus infection*.[20] Testing for GBS should follow the proposed testing algorithm for suspected cases of arbovirus infection as per the above guidance. This includes reverse-transcription polymerase chain reaction (RT-PCR) testing of blood and urine samples and flavivirus IgM testing. Additional testing of CSF samples, including RT-PCR and serological testing (e.g. IgM, IgG, neutralizing antibodies or antibody index) should be considered.

Remarks

- Any testing for the presence of Zika virus should be performed in appropriately equipped laboratories by staff trained in the relevant technical and safety procedures.
- National guidelines on laboratory biosafety should be followed in all circumstances. Protocols for standardized sample handling and storage are required.

3.3 Management of GBS

GBS is a potentially life-threatening illness. Supportive medical care and monitoring and evaluation of the need for immunotherapy should be performed rapidly and concurrently.

3.3.1 Immunotherapy

Summary of evidence

A meta-analysis of six randomized controlled trials, published in 2012, showed that treatment with therapeutic plasma exchange was superior to supportive care.[21] A meta-analysis published in 2014 on the use of intravenous immunoglobulin in GBS showed moderate quality evidence that, in severe disease, intravenous immunoglobulin started within two weeks of onset hastens recovery as much as therapeutic plasma exchange.[22, 25] In five trials with 536 participants, for whom outcomes were available, there were no significant differences in benefits and harms between the two treatments. Giving intravenous immunoglobulin after therapeutic plasma exchange did not confer any significant added benefit.[22] There are no existing large randomized controlled trials in children regarding the use of immunotherapy in GBS.

In a review that included six trials, corticosteroids used as monotherapy did not significantly hasten recovery from GBS or affect long-term outcomes.[23] One randomized controlled trial found that combined treatment with intravenous methylprednisolone and intravenous immunoglobulin showed no significant benefit compared with intravenous immunoglobulin alone for patients with GBS.[24]

Recommendations

Intravenous immunoglobulin or therapeutic plasma exchange should be used for the treatment of GBS. Corticosteroids should not be used in the treatment of GBS.

Remarks

- Intravenous immunoglobulin and therapeutic plasma exchange are equally efficacious and treatment selection should be based on availability, cost and feasibility of administration.
- Training in the appropriate administration of intravenous immunoglobulin and therapeutic plasma exchange is required.
- Blood sampling for Zika virus and other flaviviruses should be performed prior to intravenous immunoglobulin administration.

3.3.2 Clinical indications for immunotherapy

Summary of evidence

Immunotherapy confers a benefit within the first four weeks from onset of symptoms in patients with GBS who are unable to walk unaided (GBS disability score >2).[25, 34] It appears to be most effective when started within the first 2 weeks after symptom onset. There is poor quality evidence showing a lack of benefit in immunomodulatory treatment in mild GBS (GBS disability score<2).[26]See Annex 2 for the GBS disability scale).

Recommendations

Patients who have a rapidly progressive illness and are unable to walk unaided (GBS disability score>2)[26, 34] or those who develop progressive bulbar weakness, should receive immediate treatment with immunotherapy.

Remarks

- Treatment should be administered in patients presenting within four weeks of symptom onset, preferably within two weeks.

3.3.3 Inpatient hospital monitoring and supportive care

Summary of evidence

GBS continues to progress for one to three weeks after the onset of symptoms in the majority of patients. Two thirds of patients are unable to walk unaided when maximum weakness is reached. Up to 70% of patients have some degree of autonomic instability during their course of GBS, with 20% developing serious and potentially fatal autonomic dysfunction such as arrhythmias and extremes in blood pressure. 20-30% of patients develop respiratory insufficiency requiring mechanical ventilation. Major complications occur in 60% of intubated patients and include pneumonia, sepsis and pulmonary embolism. Clinical signs requiring a higher level of care include rapid progression of neurological symptoms, signs of respiratory distress, bulbar weakness and signs of severe autonomic dysfunction.[6,28]

Recommendations

GBS is a potentially life-threatening condition. All patients clinically diagnosed with GBS should be admitted to hospital (inpatient care) and monitored closely. Given the high risk of clinical deterioration, patients should be monitored in an inpatient setting until clinically stable for at least five days.

Close monitoring for complications should be carried out in all patients with GBS. Complications may include worsening neurological status, respiratory and autonomic dysfunction including marked fluctuations in blood pressure and heart rate, paralytic ileus, and other complications.

Any patient with rapid progression of motor weakness, signs of respiratory distress, bulbar symptoms (i.e. difficulty swallowing or trouble speaking) or signs of autonomic dysfunction (marked fluctuations in blood pressure and/or heart rate) should be admitted to a higher level of care (intensive care unit) where continuous cardiac monitoring and ventilator support is available.

Supportive care should be provided to all patients throughout their hospital stay, including deep vein thrombosis prophylaxis, pain monitoring and treatment, nutritional support, prevention of bed sores, bowel and bladder care, prevention of corneal ulceration if facial weakness is present, early initiation of a multidisciplinary rehabilitation programme, and psychosocial support (refer to existing WHO guidance on *Psychosocial support for pregnant women and for families with microcephaly and other neurological complications in the context of Zika virus*).[28]

Remarks

- The total length of time spent in inpatient care should be based on clinical evaluation and include factors such as clinical course, severity of symptoms, complications, and availability of follow-up care.
    - Frequent monitoring of vital signs (blood pressure, heart rate, and respiratory rate) and bedside pulmonary function testing should be performed in all patients. If pulmonary function testing is not available, bedside clinical testing such as assessment of inability to lift the head or inability to cough can be used to predict the need for intubation.
- Trained staff and strengthened hospital systems and infrastructure are required to provide appropriate inpatient hospital monitoring and supportive care.

3.3.4 Outpatient supportive care

Summary of evidence

Based on a Cochrane review, GBS is a significant cause of long-term disability. Low quality evidence provides some support for the use of high intensity and multi-disciplinary inpatient rehabilitation to reduce disability in the short term (less than six months) and to improve quality of life, as measured by a reduction in handicap.[29]

Recommendations

Patients should be followed for sequelae and multidisciplinary rehabilitation therapy should be provided (refer to WHO resource material on community-based rehabilitation, access to assistive devices, and psychosocial support).[35-37]

Remarks

- Patients should receive nutritional and psychosocial support.
- Development of acute and chronic rehabilitation services with an emphasis on neuromuscular rehabilitation is required.

3.4 Prevention

Preventing GBS associated with Zika virus infection requires preventing any infection with Zika virus. Vector control and personal protection measures should be emphasized. Recommendations to prevent Zika virus transmission provided in WHO guidance on *Prevention of sexual transmission of Zika virus*[30] and *Maintaining a safe and adequate blood supply during Zika virus outbreaks*[31] should also be followed.

4. Implications

4.1 Implications for health systems

4.1.1 Clinical assessment

Clinical evaluation of GBS requires expertise in neurological examination. In areas experiencing Zika virus outbreaks, the neurological examination capacity of the primary care workforce should be evaluated and training provided if additional skills are required. Health service managers may consider increasing access to local neurology specialists. In areas with little or no local neurological expertise, alternatives such as remote consultation (telemedicine) and appropriate referral mechanisms may be established.

Intensive care unit staff should be trained to manage GBS patients. Ventilation support equipment and telemetry monitors should be made available. Lumbar puncture tool kits and training in their use should be made available, as well as equipment and training in neurophysiological testing and interpretation.

4.1.2 Laboratory evaluation

Access to laboratories able to perform diagnostic testing should be enhanced in areas affected by Zika virus. These laboratories should implement standardized protocols for Zika virus testing on quality standards, appropriate sample testing (e.g. urine, CSF, serum), handling, storage, and shipping.

Laboratory staff should be trained in appropriate Zika virus testing procedures, and clinicians should educated on appropriate laboratory tests for GBS patients in the context of Zika virus infection.

4.1.3 Management

Health system managers in areas affected by Zika virus should prepare access to primary, secondary and tertiary care (including intensive care units) and psychosocial and family support services to manage complications associated with Zika virus infection.

Availability, affordability and access to intravenous immunoglobulin and therapeutic plasma exchange should be enhanced. Health care workers may require further training in a range of functions including: appropriate administration of intravenous immunoglobulin and therapeutic plasma exchange; use of the GBS disability score; performance of pulmonary function tests; neurorehabilitation; and psychosocial support and community engagement.

4.2 Implications for surveillance

4.2.1 Clinical assessment

Countries with potential Zika virus transmission should consider enhancing surveillance systems for neurological disorders including GBS and developing prospective surveillance systems for GBS. Existing acute flaccid paralysis surveillance systems for polio surveillance may be enhanced or adapted to detect GBS in the context of Zika virus. Surveillance systems may be facilitated by platforms such as mobile telecommunications and internet-based registries.

4.2.2 Laboratory evaluation

Protocols to report laboratory findings in GBS patients should be developed and implemented in areas affected by Zika virus.

4.2.3 Management

Surveillance systems should be established to report on the clinical progress of GBS patients including immunotherapy and supportive care, hospital data (length of hospital stay, intensive care unit admission, intubation requirements, outcome on hospital discharge etc.) and short- and long-term follow-up.

4.3 Implications for research

4.3.1 Clinical assessment

Further work is required to identify the clinical features of GBS in the context of Zika virus infection (including atypical forms) as well as the wider spectrum of neurological disorders associated with Zika virus infection. Studies should seek to establish the time from acute viraemia to the onset of neurological symptoms and the contribution of the patient's baseline immune status to the development of neurological symptoms.

Research is needed to determine the age distribution of GBS cases, the number of patients who have prodromal symptoms prior to GBS, and the contribution of axonal and demyelinating damage to the pathophysiology of GBS in the context of Zika virus infection.

4.3.2 Laboratory evaluation

Global research and development efforts should aim to enhance the sensitivity and specificity of Zika virus testing in GBS patients and to develop laboratory repositories of samples for future testing.

Scientific investigation is needed to determine whether the development of GBS and other neurological manifestations is related to prior or concurrent arboviral infection or to the phylogeny of the virus; to determine how Zika virus affects the neuroaxis (i.e. direct peripheral nerve injury or post-infectious immune phenomenon); and to determine the role of immunity and antiganglioside antibodies in GBS cases associated with Zika virus.

4.3.3 Management

Critical knowledge gaps should be addressed in a number of areas affecting the management of GBS associated with Zika virus infection, including risk factors for developing GBS as a complication of Zika virus infection; the associated morbidity and mortality; and the natural history of GBS cases associated with Zika virus.

4.3.4 General

At a global level, there is a need to coordinate and standardize research protocols and data gathering methods for GBS associated with Zika virus. In addition, large cohort studies on GBS across international sites with controls are needed to further our understanding of GBS and its relationship to Zika virus infection.

5. Guidance development

5.1 Methods

5.1.1 Evidence retrieval, assessment and synthesis

A systematic search of the evidence was undertaken using search terms chosen to reflect the scope of the guidelines. No date or language limits were set.

The Cochrane Library, MEDLINE, and PubMed, were searched using the terms "Guillain Barre Syndrome", "Severe Guillain Barre Syndrome", "Guillain Barre Syndrome evaluation", "Guillain Barre Syndrome management", "Guillain Barre Syndrome etiologies/causes", "Guillain Barre Syndrome and IVIG", "Guillain Barre Syndrome and therapeutic plasma exchange", "Guillain Barre Syndrome and supportive care", "Guillain Barre Syndrome" and "Infections", "Myelitis" and "Infections", "encephalitis" and "infections", "Zika" and "Guillain Barre Syndrome", "Zika" and "neurological manifestations", "Zika" and "myelitis", "Zika" and "encephalitis", "Zika" and "meningitis". In addition, the grey literature was searched for "Zika and Guillain Barre Syndrome", "Zika and myelitis", "Zika and neurological manifestations".

Abstracts retrieved from the searches were screened and the full text of all potentially relevant publications reviewed. Systematic reviews, guidelines developed by national and international organizations, and Cochrane reviews published within the last five years, were identified as primary sources of information. If none existed on the topics of interest, randomized controlled trials (RCTs) and case-control studies were examined. Finally, retrospective case series and case reports were examined.

5.1.2 Guideline development group

The guideline development group (GDG) was made up of members with clinical experience and technical expertise in the areas of neurology, neuroinfection, peripheral neuropathy, neuroimmunology, epidemiology and disease surveillance. Members were drawn from affected countries as well as other regions to ensure geographic representation. The guideline development meeting was held on 17-19 March 2016 at WHO headquarters in Geneva, Switzerland. This meeting was jointly organized by the WHO Departments of Maternal, Newborn, Child and Adolescent Health; Mental Health and Substance Abuse; Nutrition for Health and Development; and Reproductive Health and Research.

5.1.3 Finalization of recommendations

Draft recommendations were prepared by the WHO secretariat. A decision-making framework was presented to guide the discussions. It included considerations such as (i) desirable and undesirable effects of the proposed intervention; (ii) available evidence; (iii) values and

preferences related to the recommended interventions in different settings; and (iv)feasibility and resource implications for programme managers in different settings. The GDG discussed the evidence on these issues to reach consensus on their final recommendations.

The draft guideline document was reviewed by GDG members to ensure there were no important omissions, contradictions or inconsistencies with scientific evidence or programmatic feasibility. The GDG also reviewed clarity of the language, especially in relation to implementation and how policymakers and programme staff may read and interpret the document. Feedback received was used to revise and finalize the document.

5.2 Acknowledgements

This guidance was developed by the WHO Department of Mental Health and Substance Abuse. The WHO Secretariat included Shekhar Saxena, Tarun Dua, Pilar Ramon Pardo and Armando Vasquez. Dr. Kiran Thakur (Assistant Professor, Department of Neurology, Columbia University College of Physicians and Surgeons, New York, New York, United States of America) was engaged as a consultant to lead the evidence review and synthesis. Final editing was performed by Qiu Yi Khut and Margaret Harris; Methodology, use of evidence reviewed by Susan Norris and Mauricio Ferri of the WHO Guidelines Review Committee secretariat.

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5.3 Declaration of interests

All GDG members completed the standard WHO declaration of interests before participating in the technical consultation or in any other activities related to the development of this guidance. Participants at the technical consultation also made a declaration of interests prior to the consultation. The forms were reviewed by the WHO secretariat and no conflicts of interest were identified.

5.4 Review date

These recommendations were produced under WHO emergency procedures and will remain valid until December 2016, unless new evidence emerges. The Department of Mental Health and Substance Abuse at WHO Geneva is responsible for reviewing this guidance and updating it as appropriate as new evidence emerges. Queries and suggestions regarding the content of this guidance are welcomed. Contact: mpa-info@who.int.

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Annex 1: Brighton criteria

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

Annex 2: Guillain-Barré syndrome disability scale

0. Healthy
1. Minor symptoms or signs of neuropathy but capable of manual work / *capable of running*
2. Able to walk without support of a stick *(5 m across an open space)* but incapable of manual work / *running*
3. Able to walk with a stick, appliance of support *(5 m across an open space)*
4. Confined to bed or chair bound
5. Requiring assisted ventilation *(for any part of the day or night)*
6. Death

The original scale is shown in regular print [38-39]. (Hughes et al., 1978) and subsequent modifications in *italics* (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group, 1997).