MANAGEMENT, MORBIDITY AND MORTALITY OF GUILLAIN BARRÉ SYNDROME PATIENTS ADMITTED TO ICU AT UNIVERSITAS ACADEMIC HOSPITAL.

Dr Mamonokane Innocentia Diale

Student no: 2017560539

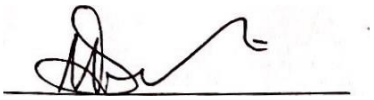
Submitted in fulfilment of the requirements in respect of the Master's Degree MMed in the Department of Neurology in the Faculty of Health Sciences at the University of the Free State.

Submission date: 21 April 2021

Supervisor: Professor AA Moodley

DECLARATION:

I, Dr Mamonokane I Diale, declare that the coursework Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree Qualification in Neurology at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of Higher Education.



Dr Ml Diale

ACKNOWLEDGEMENTS:

I would like to thank my supervisor Prof Moodley and my biostatistician Prof G Joubert for all the help and the guidance they provided in conducting this research, analysing the data and the writing up of this manuscript.

I would also like to thank the neurophysiology team at Universitas Academic Hospital for all the help in retrieving the nerve conduction studies and to thank the neurology team for their support.

TABLE OF CONTENTS:

ABSTRACT:

Background.

Guillain Barré Syndrome is the commonest cause of acute flaccid paralysis. It is an autoimmune post-infectious disorder that is monophasic and has good prognosis. However, a third of hospitalised patients with GBS are admitted to ICU with respiratory failure or dysautonomia. ICU mortality and morbidity has been associated with prolonged ICU stay of more than nine days and mechanical ventilation.

Objective.

The main aim of the study was to describe the clinical presentation, ICU management, complications and outcome of patients with Guillain Barré Syndrome requiring ICU management at the Universitas Academic Hospital, Free State Province of South Africa.

Methods.

The study was a retrospective observational study. A medical audit was carried out in all patients above the age of 13 years admitted to ICU at UAH with a diagnosis of GBS or AIDP. Telephonic interviews were also conducted to follow up on disease progression post discharge from hospital.

Results.

Twenty-six patients were included in the study. The median age was 30 years (range 13-77 years), males were predominant (65.8%) and black ethnicity comprised 83.3% of the patients. The median length of ICU stay was 9 days (range 1-140 days). The main indicator for ICU admission was respiratory monitoring (73%) followed by both respiratory monitoring and dysautonomia (26%) and dysautonomia (4%). Seventeen of the 25 (68%) patients were intubated and 11/17 (65%) had a tracheostomy for prolonged intubation. All patients were treated with intravenous immunoglobulin and four patients had additional immunosuppressive therapy. Eighteen patients (69,2%) had comorbidities with HIV infection being the commonest. Nineteen patients (73%) had complications that included prolonged ICU stay of more than nine days, mechanical ventilation, electrolyte imbalance, hypoalbuminaemia, anaemia, ventilator associated pneumonia and sepsis. The median ICU stay for patients with complications was 14 days (range 3-140 days) and for patients without complications was 3 days (range 1-7 days) ($p<0.01$). The serious complication rate was 88.9% in HIV infected patients versus 64.7% in

HIV non-infected patients (p = 0.357). The use of traditional medicine was associated with a high complication rate, especially hepatic and multi-organ failure. Four ICU managed patients died.

Conclusion.

Prolonged ICU stay was associated with multiple complications. There was no significant difference between patients with co-morbidities and those without co-morbidities in terms of length of ICU stay and complications.

KEYWORDS

- Guillain Barré Syndrome
- ICU management
- ICU complications
- Comorbidities
- Acute inflammatory demyelinating polyneuropathy

LIST OF ABBREVIATIONS

- AIDP → Acute Inflammatory Demyelinating Polyneuropathy
- AMAN → Acute Motor Axonal Neuropathy
- AMSAN → Acute Motor and Sensory Axonal neuropathy
- CIDP → Chronic Inflammatory Demyelinating Polyneuropathy
- CMV→ Cytomegalovirus
- COPD → Chronic Obstructive Pulmonary Disease
- CSF→ Cerebrospinal Fluid
- DM → Diabetes Mellitus
- EBV → Epstein Barr Virus
- EGRIS → Erasmus GBS Respiratory Insufficiency Score
- EGOS → Erasmus GBS Outcome Score
- GBS → Guillain Barré Syndrome
- HAART → Highly Active Antiretroviral Therapy
- HIV→ Human Immunodeficiency Virus
- HPT→ Hypertension
- ICU → Intensive Care Unit
- IRIS → Immune Reconstitution Inflammatory Syndrome
- IVIG → Intravenous Immunoglobulin
- MFS → Miller Fisher Syndrome
- MRC → Medical Research Council
- NCS → Nerve Conduction Studies
- NHLS → National Health Laboratory Service
- NINCDS → National Institute of Neurological and Communicative Disorders and Stroke
- PCP → Pneumocystis pneumonia
- PLEX → Plasma Exchange
- SA → South Africa
- TB → Tuberculosis
- UAH → Universitas Academic Hospital
- URTI → Upper Respiratory Tract Infection
- VAP → Ventilator Associated Pneumonia

LIST OF FIGURES AND TABLES

APPENDICES:

A. Letter of approval from the Research Ethics Committee.
B. Permission from the HOD of Neurology.
C. Permission from the Department of Health.
D. Research information leaflet.
E. Consent form.
F. Questionnaire.
G. Copy of the research protocol.
H. Cover letter.
I. Journal guidelines to authors.
J. Turnitin Plagiarism Search Engine report.
K. Supplementary tables.
    - Diagnostic criteria for GBS.
    - EGRIS score.
    - Hughes scale

MANAGEMENT, MORBIDITY AND MORTALITY OF GUILLAIN BARRÉ SYNDROME PATIENTS ADMITTED TO ICU AT UNIVERSITAS ACADEMIC HOSPITAL

10. CHAPTER 1: LITERATURE REVIEW

10. 1 BACKGROUND

10. 1.1 Introduction.

Guillain-Barré syndrome (GBS) is very uncommon disorder but potentially fatal. It is an inflammatory disorder that affects the peripheral nervous system and is the commonest cause of acute hypotonic weakness with areflexia. [(1),(2)] It is a monophasic disorder with maximum weakness being reached between 2 to 4 weeks. The disease plateaus thereafter for a couple weeks then improves in the majority of cases. [(1)(3)(4)]

GBS tends to affect males more than females and the frequency goes higher with age although all age groups can be affected. [(1)] The diagnosis of GBS is made clinically. Examination of cerebrospinal fluid (CSF) and nerve conduction studies (NCS) are supplementary to the diagnosis. [(1)(5) (6)]

Approximately a third of patients with GBS are admitted to the intensive care unit (ICU) and many require respiratory support, usually for an extended period of time. [(7)] Patients requiring ICU management are those who present with weakness of the bulbar muscles resulting in an incapacity to protect their airway, those with impending respiratory failure due to respiratory muscle weakness, and those with autonomic instability.

ICU complications in patients with GBS have been associated with mechanical ventilation, long duration of immobility or distinct treatments. [(8)] Most common complications include pneumonia, hyponatraemia, urinary tract infection, autonomic dysfunction, confusion and impairment of cognition. [(8)] Other complications that occur less frequently include infection at the site of the tracheostomy, thrombosis of the deep veins, myocardial infarction, heart block and abnormalities of liver and renal function. [(8)]

10.1.2 Epidemiology

GBS is a rare disorder. The worldwide incidence of GBS is approximately 1-2 per 100,000 person-years. [(1) (6)] The worldwide incidence is variable.

The low rate of 0.40 per 100,000 people–years observed in Brazil, differs to the high rate of 2.5 per 100,000 people–years reported in Curaçao and Bangladesh. [6] The incidence has been found to increase with advancing age in Europe and North America, whilst in China the incidence is much less in adults compared to elsewhere, and similar in children. [5]

GBS is more common in males than females with a ratio of 3:2. [6] Some studies have suggested a bimodal presentation in the young and the elderly. [2][5]

The incidence of GBS in South Africa is not well known and there are very limited data in Africa.

10.1.3 Pathophysiology

GBS is an acute immune-mediated polyneuropathy with antibodies cross-reacting with epitopes on peripheral nerves and roots leading to demyelination or axonal damage. GBS often follows an infection but is not always a post-infective process. [9] There has been some association with immunisation, although the link is not strong [9], and in other cases no causal factor is noted.

In two-thirds of patients who develop GBS, it is preceded by an upper respiratory tract infection or gastro-intestinal infection [1]. The immune response generates antibodies that cross-react with gangliosides at nerve membranes. The preceding infection triggers an autoimmune response through 'molecular mimicry' in which the host generates antibodies against the pathogen that shares epitopes with the peripheral nerves. The immune response is both cell mediated and humoral.

An inflammatory demyelinating process with perivascular and endoneurial inflammatory infiltrates occurs throughout the nerve. Segmental demyelination occurs in some areas associated with lymphoid cells and macrophages. [10] The peripheral nerves may be affected at any level, from the nerve roots to the intramuscular nerve terminals. Damage to the nerve or functional blockade may ensue. [5][6] The nature of preceding infection and the distinct antiganglioside antibodies affected, largely determine the subtype and disease progression. [6]

The most common infections resulting in GBS are gastro-enteritis and upper respiratory tract infection in at least two thirds of cases. [5][6][9] In about half of patients with GBS, a particular type of preceding infection can be identified. *Campylobacter jejuni (C. jejuni)* is responsible for at least one-third of these infections. The *C. jejuni* bacterium is a gram-negative rod and responsible for most bacterial enteritis worldwide. *C.jejuni* is also associated more commonly

with the axonal subtypes. [2] some of the other pathogens implicated in GBS include cytomegalovirus (CMV), Epstein– Barr virus (EBV), *Mycoplasma pneumonia*, *Haemophilus influenza*, and the influenza A virus. [6] [11]

10.1.4 Clinical presentation and subtypes

In general, the clinical presentation is that of acute onset of symmetrical weakness of the limbs. The weakness usually starts distally and ascends. It may be preceded by paraesthesia. Severe pain of radicular or neuropathic type occurs in majority of the patients. [3] The weakness is associated with hyporeflexia or areflexia with or without a glove and stocking distribution sensory loss. The weakness may also affect the cranial nerves. In 70% of the patients, facial weakness occurs, and dysphagia in 40% of the cases. In some rare cases the patients develop ophthalmoplegia, vocal cord paralysis and ptosis. [2] Dysautonomia is also a common feature of GBS. It can vary from blood pressure and heart rate instabilities, bladder involvement and pupillary dysfunction. [1] Other rare presentations may occur such as papilloedema and hearing loss.

The onset is acute and progression is rapid. Maximal weakness is usually reached within 2 weeks in 50% of the patients but may progress up to 4 weeks in about 90% of the cases. [3] Cases that progress beyond 4 weeks are suggestive of the subacute variant of the disease and if beyond 8 weeks is considered to be chronic demyelinating inflammatory polyneuropathy (CIDP). [3] Diagnostic difficulties are usually experienced with atypical presentation especially with the rare variants. Some patients get a less severe form of the disease and some may progress within hours to days requiring mechanical ventilatory support. [3]

The differentiation between subtypes relies on both clinical presentation and electrophysiological studies. Although the diagnosis of GBS is predominantly clinical, mimics of GBS should still be excluded.

COMMON SUBTYPES

1. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)

AIDP is the commonest subtype of GBS especially in Europe and North America. [1][4][6] [12] The myelin sheath is targeted with evidence of lymphocytic infiltration and macrophage-mediated demyelination. On NCS there are features of demyelination which include slow

conduction, conduction blockade and prolonged distal latencies. Motor, sensory and autonomic fibres may be involved. In most cases remyelination results in resolution of symptoms.

2. Acute motor axonal neuropathy (AMAN)

AMAN is a common subtype in Asia. [12] It is associated with *C-jejuni* infection with at least 64% of patients being seropositive. [12] The target in the pathogenesis of AMAN is the ganglioside antigens on the axolemma. The nodes of Ranvier are invaded by the macrophages which insert between the axon and the surrounding axolemma and leave the myelin sheath intact. [4] In severe cases where axons are damaged in the ventral root, the degeneration of the entire axon may occur. [4]

AMAN presents as a motor neuropathy with no sensory involvement. The pattern of weakness may be similar to AIDP. On NCS, there are features of axonal motor neuropathy evidenced by decreased or absent compound muscle action potentials (CMAP).

The antibodies associated with AMAN include GM1, GM1b, GD1a, GD1b and GalNAc-GD1a. [10] [13] [14]

3. Acute motor and sensory axonal neuropathy (AMSAN)

AMSAN occurs more commonly in adults. The pathogenesis is similar to AMAN, with the addition of the sensory fibres and/or roots also affected. [4]

4. Miller Fisher Syndrome (MFS)

This variant consists of ophthalmoplegia, ataxia and hypo-/areflexia with no weakness. [3] The description of this variant was first made by C Miller Fisher in 1956. The neurophysiological studies suggest an axonal injury with decreased sensory action potential without any slowing of conduction. CSF findings are similar to those of other variants and the prognosis is usually good. [13] Patients with MFS usually have a less aggressive disease and may recover completely within 6 months without any treatment. Some patients with MFS may still develop limb weakness and bulbar weakness (MFS/GBS overlap) and may require immunomodulatory treatment. [1] Even though MFS patients have a milder form of the disease they still need monitoring for progression to MFS/GBS overlap. The Miller Fisher variant is associated with GQ1b antibodies. [10]

5. Other variants (rare)

5.1 Acute panautonomic neuropathy.

This is the rarest of the GBS variants and involves purely the sympathetic and parasympathetic systems. Patients present with severe orthostatic hypotension, urinary retention, anhidrosis, pupillary abnormalities and decreased salivation and lacrimation. Arrhythmias are common and usually the cause of death in these patients.

5.2 Pure sensory variant.

The pure sensory variant has been described in the literature. Patients typically present with purely sensory complaints that are rapidly progressive and have areflexia with an albumin-cytologic dissociation on CSF examination. The prognosis is good. It is also associated with anti-GQ1 antibodies. [1]

5.3 Pharyngeal-cervical-brachial

This is distinguished by isolated facial, oropharyngeal, cervical and upper limb weakness. It is less common compared to the other variants [1] accounting for less than 5% of GBS cases.

Other variants include pure paraplegia, Bickerstaff encephalitis and bilateral facial palsy with paraesthesia.

10.1.5 Diagnosis

The diagnosis of GBS is clinical, on the basis of history and clinical evaluation with supportive special investigations such as NCS and CSF analysis. [1]

In 1978 the standard criteria for the diagnosis of GBS was first published by the National Institute of Neurological and Communicative Diseases (NINCDS) committee. It was later revised in 1990 and again in 2011.The criteria included clinical progression, relative symmetry and mild sensory symptoms or signs also protein-cell-dissociation in cerebrospinal fluid and electro-diagnostic features such as conduction block or slowing of the nerve. [2]

Further guidelines for the diagnosis of GBS were released in November 2019 by Sonja E Leonhard et al. [1] These guidelines were an adaptation of the NINCDS (supplementary table1)

10.1. 6 Supportive Investigations

As mentioned above, the diagnosis of GBS is mainly clinical. Further investigations are done as supportive for the diagnosis or to rule out mimics.

1. LABORATORY TESTS

Basic investigation such as a full blood count, renal function, liver function tests and electrolytes can be done to rule out infections, metabolic and electrolytes abnormalities as cause of an acute paralysis. Serum anti-gangliosides are not a routine part of the investigation. Negative antibodies do not rule the diagnosis of GBS but they can be supportive especially in cases of atypical presentation. [1]

2. CSF

The typical findings in CSF are elevated protein without pleocytosis (albumin-cytological dissociation). In 30-50% of cases the CSF is normal in first seven days of the disease and it is normal in 10-30% of cases in the second week of the disease. [1] A normal CSF study does not rule out GBS. A pleocytosis >50 cells is suggestive of other diseases such as malignancies or infection. Pleocytosis of 10-50 cells should alert the physician to look for other causes. [1]

3. NCS

NCS are also not required for the diagnosis of GBS. When done in the first week of the disease they may be normal. It may be helpful in repeating studies in 2-3weeks. [1] In cases where the diagnosis is uncertain, especially in atypical presentation, NCS may be helpful.

NCS is also important in providing the subtype and the type of injury i.e. demyelination vs axonal injury. AIDP, AMAN and AMSAN can be readily classified on NCS. In other subtypes such as MFS, the conduction studies may be normal.

4. IMAGING

Imaging is not a routine investigation of GBS and it is only indicated when ruling out other diseases. The occurrence of nerve root enhancement with contrast is not specific, but it is a sensitive feature in GBS and can support the diagnosis of GBS. [1] This may be useful in cases where NCS and clinical examination may be difficult especially in children. Ultrasound of the nerve roots has been recently used to assess for inflammation of the roots.

10.1.7 Management

GBS is a monophasic disease and patients usually recover with or without treatment. But in patients with severe disease immunomodulatory treatment is recommended.

There are only 2 treatment modalities proven to be effective in GBS, intravenous immunoglobulins (IVIG) and plasma exchange (PLEX). [1][2]

Treatment is indicated in patients who present with an inability to walk more than 10m independently, autonomic instability or rapid disease progression with bulbar or respiratory insufficiency [1]. Any patient that is an ICU candidate requires treatment.

The recommended dosage for IVIG is 0.4g/kg body weight daily for 5 days and for PLEX it is 200-250ml plasma/kg body weight in five sessions. [1]

Efficacy in both modalities is similar and the indication will depend on cost, contraindication or the most easily accessible modality. IVIG has been shown to be more preferential due to less complications compared to PLEX and probably shorter stay in hospital. [2] IVIG is also more easily accessible than PLEX, especially in low socio-economic countries.

10.1.8 Prognosis

The prognosis of GBS is generally good. Most of the patients even those with tetraplegia on admission or requiring ventilator support for a prolonged duration good prognosis, especially within the first twelve months of disease onset. Approximately 80% of patients regain the ability to walk independently at 6 months after onset of the disease. [1][4]
The Erasmus GBS Outcome Scale (EGOS), a prognostic tool, has been constructed and validated to predict outcome at 6 months. [11]

Mortality in GBS can still occur in 3-10% of cases, usually related to cardiac and pulmonary complications which can occur in both the first few weeks and later in the recovery stages of the disease. [1]

10.1.9 ICU admission

As stated above, at least a 3rd of hospitalised patients with GBS require ICU admission and some will require mechanical ventilation. ICU management is indicated for patients with autonomic instability, bulbar weakness, respiratory insufficiency and rapid progression. [1] [11]
Respiratory insufficiency refers to signs of respiratory distress which will include the following [1]:

- Shortness of breath at rest or when speaking.
- Unable to count to 15 in one single breath.
- Using accessory respiratory muscles.
- Tachypnoea and/or tachycardia.

- Vital capacity of <15-20ml/kg or less than 1 litre.
- Abnormal arterial blood gas (ABG) or decreased oxygen saturation on pulse oximeter testing.

An Erasmus GBS Respiratory Insufficiency Scale (EGRIS) was established to assist in predicting patients that may need ICU or ventilator support on admission. [1] [11]

The scale is based on the clinical examination. The main predictors for mechanical ventilation were days between onset of weakness and admission, Medical Research Council (MRC) sum score, and the presence of facial and/or bulbar weakness. [11] Major independent risk factors for mechanical ventilation include decreased forced vital capacity and shorter time interval between the onset of weakness and admission. [2]

In patients where prolonged intubation is anticipated early tracheostomy is advised.

10.1.10 ICU complications

Mortality of patients with GBS in the ICU occurs in the setting of severe illness with co-existing medical problems especially in the older patients. General prognosis in patients with GBS is good, also encompassing those requiring mechanical ventilation if they do not succumb to medical complications. [15]

ICU complications in patients with GBS have been associated with mechanical ventilation, long duration of immobility or some treatments. [8] Most common complications include pneumonia, hyponatraemia, urinary tract infection, autonomic dysfunction, confusion and impairment of cognition. [8] Other less frequent complications include tracheostomy site infection, deep vein thrombosis, myocardial infarction, heart block and abnormalities of liver and renal function. [8]

A study done by Netto et al on complications of GBS patients on mechanical ventilation however found that tracheobronchitis, hypokalaemia and hyponatraemia were much higher complications in their patients compared to other studies. [16] This was however attributed to the dilutional effects from PLEX that was the treatment modality in the majority of the patients.

In a study by Ancona et al, the overall ICU and hospital mortality was 3,9% and 6,9% respectively, but increased to 9.7% and 14,3% in the mechanically ventilated (MV) group.

Patients in the MV group had a significantly longer stay in ICU of 25 days (range 12.8-47.2 days) and in hospital of 42.2 days (range 28.3-81 days). [9] In another study done by Dhar et al, the mean ICU stay was found to be 41 days (median 21 days, range 6-335 days) and the hospital stay averaged 71 days (median 49 days). [7] Only 13% of the patients were discharged home, and the remainder returned to the referring hospital or rehabilitation facility. GBS patients suffering serious ICU complications while in ICU had significantly longer ICU stays and were much less likely to be discharged home. [7]

The study done by Henderson et al found that prolonged ICU stay was associated with increased chances of sepsis, although it was not commonly associated with mortality. [15]
Complications related to dysautonomia occur in major systems such as gastrointestinal, genitourinary, cardiovascular and endocrine. [17]
Gastrointestinal bleeding was also a complication in about 5% of the patients. [15]

10.2 STUDY RATIONALE

There are very limited data/studies regarding GBS in South Africa and also fewer studies regarding the presentation, incidence and ICU complication.

Co-morbidities may affect the length of ICU stay and recovery. [15] With the high prevalence of HIV in SA it is unclear if this has a different impact on the GBS presentation or prognosis in ICU compared to other countries.

10.3 METHODOLOGY.

A retrospective analytic observational study was done. Patients that were admitted to the Multi-ICU at Universitas Academic Hospital (UAH) with a diagnosis of GBS or AIDP between January 2014 and June 2020 were included in the study. Medical records were retrieved from the electronic hospital records on Meditech, from hospital archives, from the UAH neurophysiology lab for NCS and also from the National Health Laboratory Services (NHLS) online system trakcare for CSF and blood tests.

Telephonic interviews were conducted to follow up on patients' functional status post discharge and to supplement medical records. A questionnaire was used for the interviews and the assessment of functional status was based on Hughes GBS scale.

Patients below the age of 13 were excluded from the study and those whose diagnoses changed during admission or on discharge were also excluded.

10.4 AIMS AND OBJECTIVES.

The main aim of the study was to describe the clinical presentation, ICU management, complications and outcome of patients with Guillain Barré Syndrome requiring ICU management at the UAH, Free State Province of South Africa.

Objectives of the study

1. To describe the demographic profile of patients with GBS requiring ICU management.
2. To describe the clinical presentation, investigation, co-morbidities and preceding illnesses in patients with GBS admitted to ICU.
3. To describe the duration of ICU care, immunomodulatory treatment and complications experienced by GBS patients admitted to ICU.
4. To assess the functional outcomes of patients with GBS managed in ICU immediately post ICU discharge and their current functioning.

By relating the outcome measures to demographic, clinical, electrophysiological and ICU factors (if the numbers permit), red flags would be identified and thereby guide us in improving the intensive care of these patients.

10.5 REFERENCES

1. Leonhard SE, Mandarakas MR, Gondim FAA, Bateman K, Ferreira MLB, Cornblath DR, et al. Diagnosis and management of Guillain–Barré syndrome in ten steps. Nat Rev Neurol [Internet]. 2019;15(11):671–83. Available from: http://dx.doi.org/10.1038/s41582-019-0250-9
2. McGrogan A, Madle GC, Seaman HE, De Vries CS. The epidemiology of Guillain-Barré syndrome worldwide: A systematic literature review. Neuroepidemiology. 2009;32(2):150–63.
3. Mazen M. Dimachkie, M.DRichard J. Barohn M. GBS and Variants. NIH Public Access. 2014;31(2):491–510.
4. Hughes RAC, Cornblath DR. Guillain-Barré syndrome. Lancet. 2005;366(9497):1653–

66.

5. González P, García X, Guerra A, Arango JC, Delgado H, Uribe CS, et al. Experience with Guillain-Barré syndrome in a neurological Intensive Care Unit. Neurol (English Ed [Internet]. 2016;31(6):389–94. Available from: http://dx.doi.org/10.1016/j.nrleng.2014.09.003

6. Van Den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, Van Doorn PA. Guillain-Barré syndrome: Pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol [Internet]. 2014;10(8):469–82. Available from: http://dx.doi.org/10.1038/nrneurol.2014.121

7. Dhar R, Stitt L, Hahn AF. The morbidity and outcome of patients with Guillain-Barre syndrome admitted to the intensive care unit. J Neurol Sci. 2008;264:121–8.

8. Taylor CJ, Hirsch NP, Kullmann DM, Howard RS. Changes in the severity and subtype of Guillain-Barré syndrome admitted to a specialist Neuromedical ICU over a 25 year period. J Neurol. 2017;264(3):564–9.

9. Ancona P, Bailey M, Bellomo R. Characteristics, incidence and outcome of patients admitted to intensive care unit with Guillain-Barre syndrome in Australia and New Zealand. J Crit Care [Internet]. 2018;45:58–64. Available from: https://doi.org/10.1016/j.jcrc.2018.01.016

10. Dalakas MC. Pathophysiology of autoimmune polyneuropathies. Press Medicale [Internet]. 2013;42(6 PART2):e181–92. Available from: http://dx.doi.org/10.1016/j.lpm.2013.01.058

11. van Doorn PA. Diagnosis, treatment and prognosis of Guillain-Barré syndrome (GBS). Press Medicale [Internet]. 2013;42(6 PART2):e193–201. Available from: http://dx.doi.org/10.1016/j.lpm.2013.02.328

12. López-Hernández JC, Colunga-Lozano LE, Garcia-Trejo S, Gomez-Figueroa E, Delgado-Garcia G, Bazán-Rodríguez L, et al. Electrophysiological subtypes and associated prognosis factors of Mexican adults diagnosed with Guillain-Barré syndrome, a single center experience. J Clin Neurosci. 2020;80(xxxx):292–7.

13. Winer JB. Guillain-Barré syndrome: Clinical variants and their pathogenesis. J Neuroimmunol [Internet]. 2011;231(1–2):70–2. Available from:

http://dx.doi.org/10.1016/j.jneuroim.2010.09.017

14. Uncini A, Kuwabara S. Nodopathies of the peripheral nerve: An emerging concept. J Neurol Neurosurg Psychiatry. 2015;86(11):1186–95.

15. Henderson RD, Lawn ND, Fletcher DD, McClelland RL, Wiljdicks EFM. the morbidity of Guillain-Barre syndrome admitted to intensive care unit. Neurology 2003; 60:17-21

16. Netto AB, Taly AB, Kulkarni GB, Uma Maheshwara Rao GS, Rao S. Complications in mechanically ventilated patients of Guillain-Barre syndrome and their prognostic value. J Neurosci Rural Pract. 2017;8(1):68–73.

17. Pfeiffer G, Schiller B, Kruse J, Netzer J. Indicators of dysantonomia in severe Guillain-Barre syndrome. J Neurol. 1999;246(11):1015–22.

MANAGEMENT, MORBIDITY AND MORTALITY OF GUILLAIN BARRÉ SYNDROME PATIENTS ADMITTED TO ICU AT UNIVERSITAS ACADEMIC HOSPITAL

11. Chapter 2. Publishable ready manuscript

11.1 ABSTRACT:

Background.

Guillain Barré Syndrome is the commonest cause of acute flaccid paralysis. It is an autoimmune post-infectious disorder that is monophasic and has good prognosis. However, a third of hospitalised patients with GBS are admitted to ICU with respiratory failure or dysautonomia. ICU mortality and morbidity has been associated with prolonged ICU stay and mechanical ventilation.

Objective:

The main aim of the study was to describe the clinical presentation, ICU management, complications and outcome of patients with Guillain Barré Syndrome requiring ICU management at the Universitas Academic Hospital, Free State Province of South Africa

Methods:

The study was a retrospective analytic observational study. A medical audit was carried out in all patients above the age of 13 years admitted to ICU at UAH with a diagnosis of GBS or AIDP. Telephonic interviews were also conducted to follow up on disease progression post discharge from hospital.

Results:

Twenty-six patients were included in the study. The median age was 30 years (range 13-77 years), males were predominant (65.8%) and black ethnicity comprised 83.3% of the patients. The median length of ICU stay was 9 days (range 1-140 days). The main indicator for ICU admission was respiratory monitoring (73%) followed by both respiratory monitoring and dysautonomia (26%) and dysautonomia (4%). Seventeen of the 25 (68%) patients were intubated and 11/17 (65%) had a tracheostomy for prolonged intubation. All patients were treated with intravenous immunoglobulin and four patients had additional immunosuppressive

therapy. Eighteen patients (69.2%) had comorbidities with HIV infection being the commonest. Nineteen patients (73%) had complications that included prolonged ICU stay, mechanical ventilation, electrolyte imbalance, hypoalbuminaemia, anaemia, ventilator associated pneumonia and sepsis. The median ICU stay for patients with complications was 14 days (range 3-140 days) and for patients without complications was 3 days (range 1-7 days) ($p<0.01$). The serious complication rate was 88.9% in HIV infected patients versus 64.7% in HIV non-infected patients ($p = 0.357$). The use of traditional medicine was associated with a high complication rate, especially hepatic and multi-organ failure. Four ICU managed patients died.

Conclusion.

Prolonged ICU stay was associated with multiple complications. There was no significant difference between patients with co-morbidities and those without co-morbidities in terms of length of ICU stay and complications.

11.2 INTRODUCTION

Guillain-Barré syndrome (GBS) is one of the commonest causes of acute onset paralytic quadriparesis. It affects approximately 0.4 to 4 people per 100, 000 per year. [1,2] Although it generally follows a monophasic course, up to 20% of patients remain disabled and approximately 5% die despite immunotherapy. [3] It is an autoimmune disorder resulting from cross reaction by antibodies against microbial agents and neuronal antigens. GBS may present with motor, sensory, sensorimotor and/or autonomic signs.

Approximately one third of patients with GBS are admitted to the intensive care unit (ICU) and many require respiratory support, most often for a prolonged period.[1] Patients requiring ICU are those who present with autonomic instability and respiratory compromise. ICU complications in patients with GBS have been described in association with mechanical ventilation, prolonged immobilization or specific treatments. Mortality has also been associated with prolonged ICU stay and mechanical ventilation.

Multiple studies have been done regarding the ICU stay and ICU complications in patient with GBS, but there is limited data from South Africa (SA) and no studies done in the Free State Province.

With human immunodeficiency virus (HIV), tuberculosis (TB), diabetes mellitus (DM) and hypertension (HPT) being of high prevalence in SA, it is unclear if these affect the presentation and the outcome of GBS patients.

The aim of this study was to describe the clinical presentation, ICU management, complications and outcome of patients with GBS requiring ICU management at the Universitas Academic Hospital (UAH), Free State Province in South Africa. Further objectives included investigating the co-morbidities and their association with morbidity and mortality in GBS patients admitted to ICU.

All patients above the age of 13 years who were admitted to Multi-ICU at UAH with a diagnosis of GBS or acute inflammatory demyelinating polyneuropathy (AIDP) between January 2014 and June 2020 were included. The terms are used interchangeably by clinicians.

11.3 METHODOLOGY

This was a retrospective analytic observational study conducted at UAH. There were two parts to the study; audit of medical records and telephonic interview of patients.

UAH is a state run tertiary hospital in the Free State Province of South Africa (SA) which receives referrals from regional hospitals in the Free State Province. It also offers neurological services to the Northern Cape Province and the neighbouring country of Lesotho.

The study population consisted of all patients aged 13 years and older, who were admitted to the UAH intensive care unit (ICU), multi-ICU, from the period of January 2014 to June 2020 with the diagnosis of GBS or AIDP. A list of the patients admitted to ICU between January 2014 and June 2020 was obtained from the multi-ICU database and all patients with a diagnosis of GBS or acute inflammatory demyelinating polyneuropathy (AIDP) were included in the study. Patients names, date of birth or identity number, and hospital numbers were obtained to retrieve medical records.

Medical records were retrieved from the hospital medical archives, from the medical electronic site, Meditec, and from the multi-ICU database. The neuro-electrophysiology unit was also consulted for nerve conduction study (NCS) reports that were not available in patients' records. The National Health System Laboratory (NHLS) online system, trakcare, was perused for blood and cerebrospinal fluid test results that were not available in other records.

Patients' telephone numbers were retrieved from their demographic data in records and telephonic consent was obtained for interviews regarding their illness and prognosis post discharge.

Telephonic interviews were conducted to follow up on patients' functional status post discharge and to supplement medical records. A questionnaire was used for the interviews and the assessment of functional status was based on Hughes' GBS scale. Telephonic consent to participate in the interview for the study was obtained.

Exclusion criteria from the study included patients with a different diagnosis on discharge or those whose medical records were not available.

The data analysis was done by the department of biostatistics. Descriptive statistics, namely means and standard deviation or medians and percentiles, were be calculated for continuous data. Researcher entered data into Excel spreadsheet for analysis.

Ethical approved was obtained from the Free State Health Sciences Research Ethics Committee (HSREC). The ethics approval reference no is UFS-HSD2020/0291/2508

11.4 RESULTS

A total of 31 patients were admitted to ICU with a diagnosis of GBS and/or AIDP between January 2014 and June 2020. Five patients were excluded from the study as their diagnosis changed after further investigations. The diagnoses of the excluded patients included: pontine infarct, TB arachnoiditis, porphyria and two patients with hypokalaemic myopathy.

Demographics

Male patients accounted for 65.4% of the recruited patients. Eighty-three percent were of black ethnicity and 16% were white. In two of the patients' ethnicity was not specified. The median age was 30 years (range 13-77 years) (figure1)

Antecedent infection

Data was missing with regards to preceding illness in 10 patients. Of the remaining 16 patients, three (18.8%) had upper respiratory tract infection, three (18.8%) had acute gastro enteritis and 10 (62.5%) had no prior illness specified.

Data for duration of illness prior to admission was available for 21 patients. The median duration of illness prior to admission was 5 days (range 1-35 days).

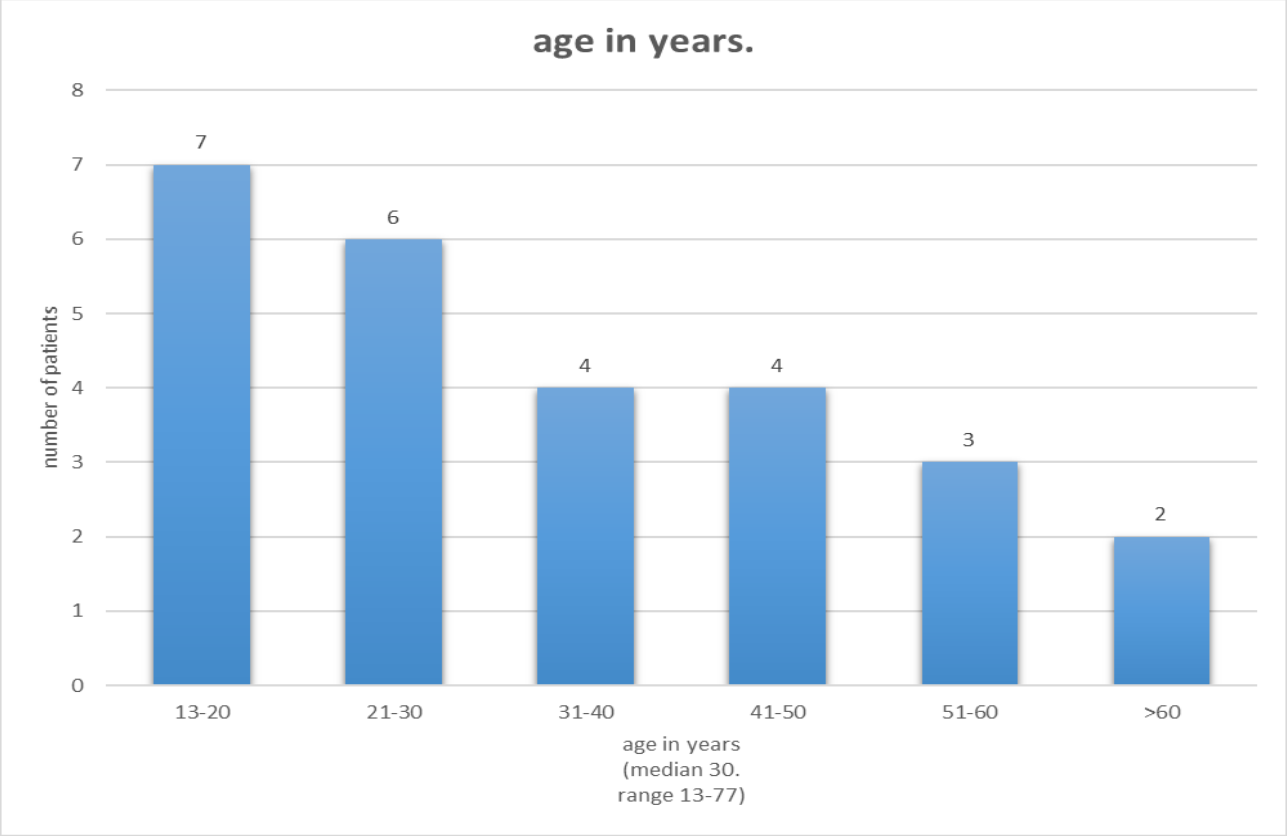


Figure1. Age distribution of patients admitted to ICU for management of Guillain Barré Syndrome

Indication for ICU admission

In 19 (73%) of the ICU admitted patients, the indication was for respiratory monitoring. In six (26%) of the patients the indication for ICU admission included both respiratory monitoring and dysautonomia. Only one patient had dysautonomia as the sole indication for ICU admission, with elevated blood pressure. Seventeen (68%) of the patients who needed respiratory monitoring were ventilated, of whom 11 (64.7%) had a tracheostomy for prolonged intubation. In one of the patients, tracheostomy was attempted but failed.

Investigations

Blood results were missing for seven of the patients. Anti-ganglioside antibodies were not done in any of the patients. Twelve of the patients had electrolyte disturbance, of which

hyponatraemia was present in seven of the patients. Eleven patients had anaemia and 10 had hypoalbuminea.

CSF results were available for 17 of the patients and 10 (58.8%) showed a protein-cell dissociation while the others were normal. In one patient Epstein Barr Virus (EBV) was isolated in the CSF.

Nerve conduction studies were available in 13 of the patients. In seven of the patients (53.9%), NCS showed acute motor axonal neuropathy (AMAN), in three (23%)demyelinating neuropathy (AIDP) was noted, in two (15.4%) acute motor and sensory axonal neuropathy (AMSAN) and one of the patients had normal NCS.

Treatment modalities

All patients were treated with intravenous immunoglobulins (IVIG) at a total dose of 2g/kg divided daily over five days. Four patients had additional immunosuppressive treatment. In one of the patients, plasma exchange (PLEX) was given after four weeks of no improvement with IVIG. A 27 weeks' pregnant patient received dexamethasone which was prescribed by the obstetricians for foetal lung maturation in preparation for possible early delivery. Another patient received methylprednisolone after she deteriorated two weeks post IVIG. The fourth patient was receiving oral prednisone as treatment for haemolytic anaemia which was diagnosed on admission.

Length of ICU stay, co-morbidities and complications.

The average length of ICU stay was 26.4 days, median was 9 days and range was from 1 to 140 days. (figure2)

Eighteen (69.2%) of the patients had comorbidities. (figure 3) Thirteen of the patients with co-morbidities had complications. Eight patients had no comorbidities but complications were still experienced by six (75%) of these cases. There was no significant statistical difference between the patients with comorbidities and those without comorbidities in terms of complications (p value 1.00). The majority of patients (9/18) with co-morbidities were living with HIV infection. Traditional herbal medicine use and respiratory illnesses were also common. When comparing patients with HIV infection to those without HIV infection, 88.9% of the HIV group had significant complications and only 64.7% of the non-HIV group had complications, but this was not statistically significant ($p = 0.357$). Patients who were pregnant, had respiratory illnesses or used traditional herbal medicines all had complications.

Still, there was no significant statistical difference (p values 0. 5396, 0.1456 and 0.5463 respectively) compared to other patients without these comorbidities.

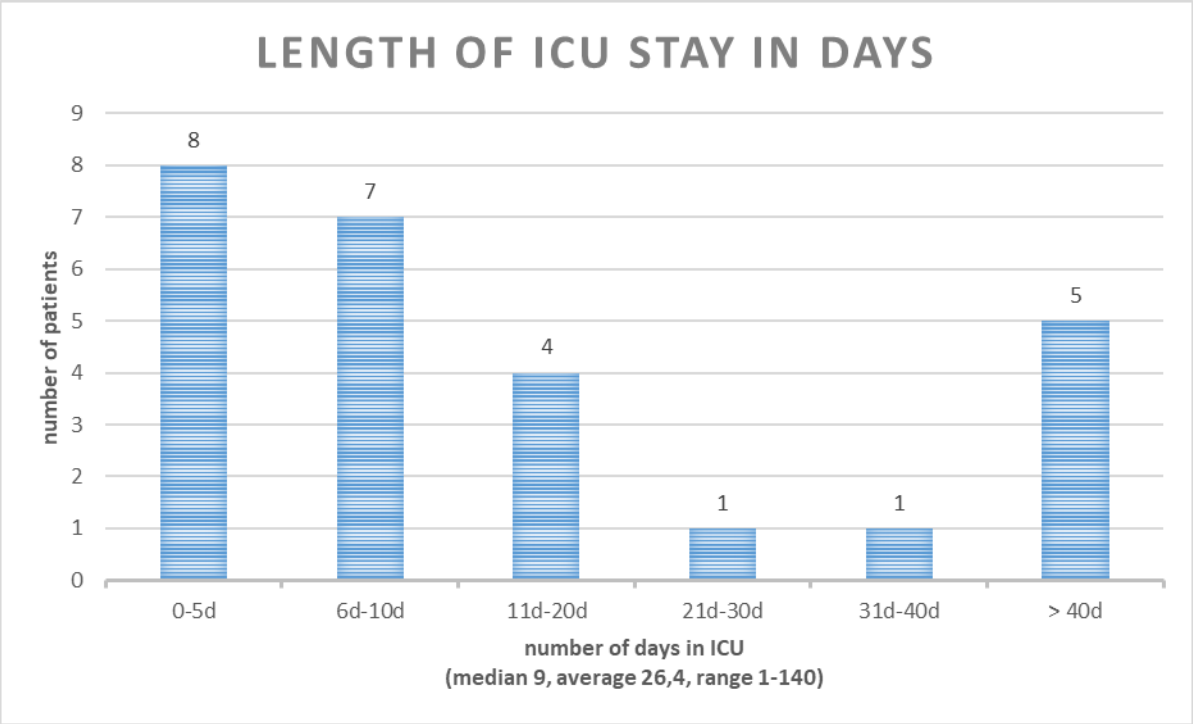


Figure 2: Length of ICU stay in days

Patients with respiratory co-morbidities who were ventilated had a much more prolonged stay. Of the six patients with respiratory co-morbidities, three of them had chronic obstructive pulmonary disease (COPD). One patient with COPD stayed for six days but was not ventilated. Two of the patients with respiratory co-morbidities (Pneumocystis pneumonia (PCP) and COPD died. The other three patients with respiratory co-morbidities (Asthma, COPD and TB) had ICU stay of longer than 90 days with recurrent ventilator associated pneumonias (VAP).

Nineteen patients had complications while in ICU (figure 4). Electrolyte imbalance, anaemia and hypoalbuminea were the commonest. Ventilator associated pneumonia (VAP) and sepsis were also common being present in 9 of the patients. None of the patients had any deep vein thrombosis (DVT) and only one had tracheostomy associated complications.

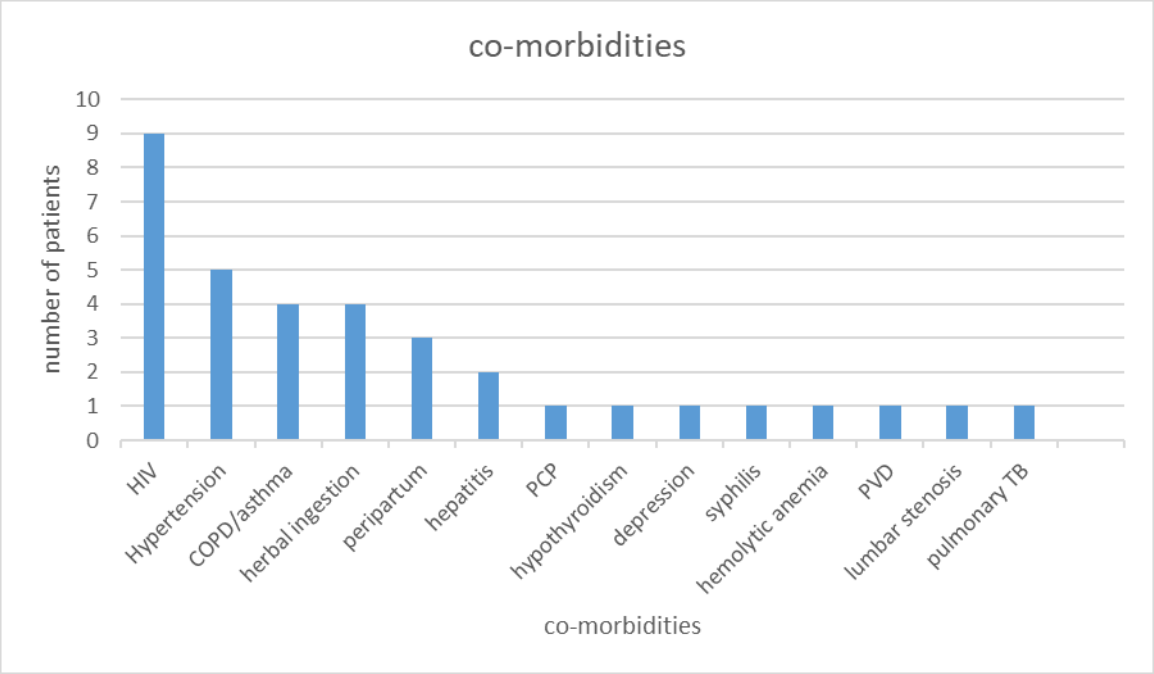


Figure3. Comorbidities/ pre-existing conditions of patients admitted to ICU for GBS complications. HIV-human immunodeficiency virus, COPD-chronic obstructive pulmonary disease, PCP-pneumocystis pneumonia, PVD-peripheral vascular disease, TB-tuberculosis

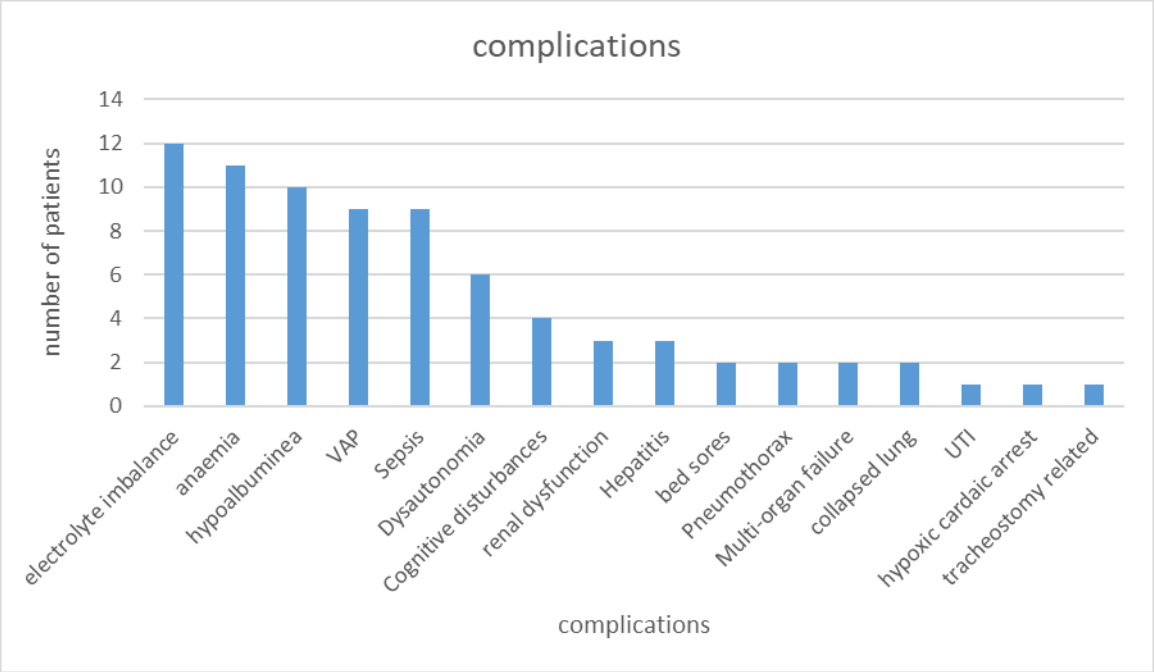


Figure 4. Complications experienced by patients admitted to ICU. VAP-ventilator associated pneumonia, UTI-urinary tract infection

Prolonged ICU stay and mechanical ventilation were associated with multiple serious complications. The median ICU stay for patients with complications was 14 days (range 3-140 days). Of the 19 patients who had complications, only three were not ventilated.

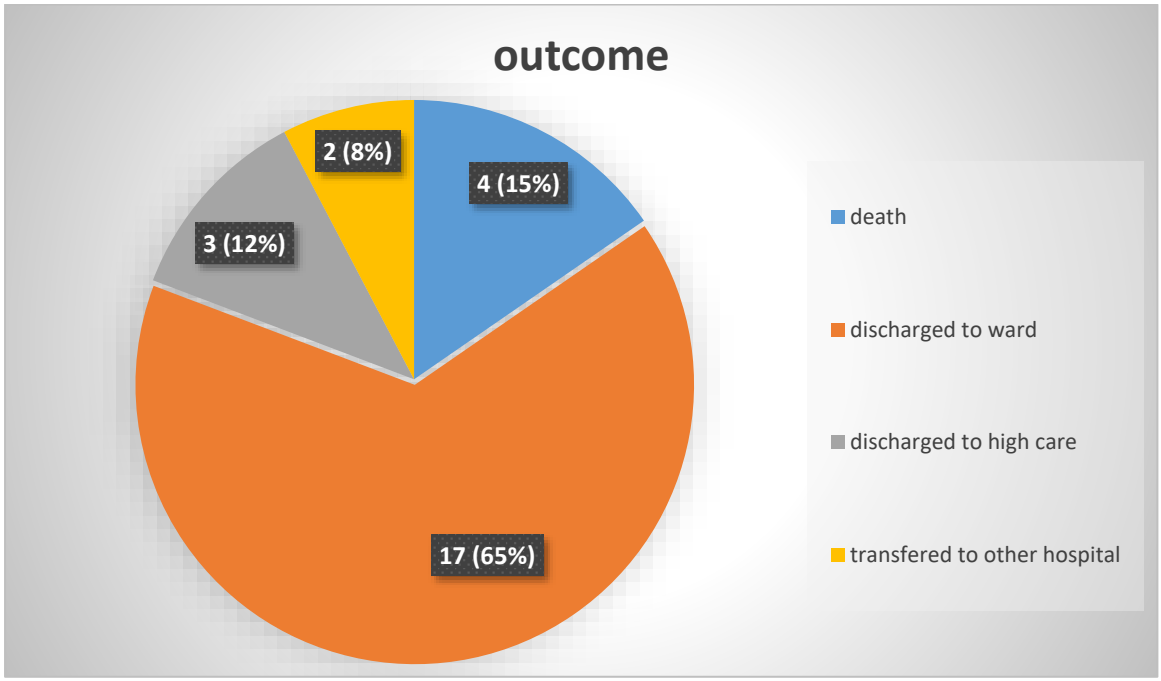
Patients without complications had a much shorter ICU stay with a median of 3 days (range 1-7 days). None of the patients without complications were ventilated.

The median ICU stay for patients with complications (14 days) was significantly longer than those without complications (3 days) ($p < 0.01$)

Outcome

In terms of the outcome (figure 5), a higher percentage of the patients were discharged to the ward and 4 patients died.

Figure 5: Outcome of patients admitted to ICU with GBS.



Causes of mortality are outlined in the table below:

Table no 1: Causes of mortality.

Patient	Cause of death	Other complications	Co-morbidities	Length of ICU stay in days
No.3	Septic shock	• Multi organ failure • Pre-eclampsia	• HIV • Herbal medication • PCP • 27 weeks gestation	20
NO. 6	Dysautonomia	• VAP	• HIV • COPD • Alcohol use	8
No. 13	Dysautonomia	• Multi-organ failure	• HIV	13
No. 14	Dysautonomia	• Acute renal failure • Sepsis	• Hypertension • Herbal medication	3

HIV (human immunodeficiency virus), PCP (pneumocystis pneumonia), VAP (ventilator associated pneumonia), COPD (chronic obstructive pulmonary disease)

The average ICU stay for the patients who demised was 11 days (Range 3-20 days). All patients who demised were ventilated.

The patients without complications were all discharged to the ward and 21% of the patients with complications died.

Telephonic interviews.

We were only able to contact 6/26 patients for telephonic interviews. Four of the patients had demised, four of the patients had wrong contact details in their records, five of the patients had

no contact details and for the remaining number we received no answer even after multiple attempts.

The results from the telephonic interview were therefore not included in the study as the number had no significant value and the results did not have much impact on the main aim of the study.

11.5 DISCUSSION

1. Demographics.

The majority of the patients that were admitted were Black African, which makes up the largest ethnic group in SA. Studies have shown that there are variations in clinical presentation and outcome depending on geographical location and ethnicity. In a study done by Doets et al, they noted that patients from Bangladesh tend to have a worse outcome compared to Asian and Europe/American patients. [4] Studies done in Black African patients are still very few.

In Europe and North America the incidence of GBS increases with age. [5] In our study the majority of the patients were of younger age. A study done in India by Bhagat et al found similar results. They attributed their findings to the increase risk of CMV and campylobacter infections in young adults. [6]

A higher percentage of the patients below the age of 30 years in our study were living with HIV infection which is implicated in GBS. [7,8] The higher incidence of GBS in younger patients in our study may be attributed to the high incidence of HIV in the younger population or may reflect the ICU policy of accepting younger patients. Schleicher et al also found that the patients in their study were younger in the HIV infected group compared to HIV negative patients. [9]

The male to female ratio was 1.8:1 which is slightly higher compared to other studies of ratio 1.5:1. [10] HIV co-infection cannot account for this difference as epidemiological studies in South Africa show a higher prevalence of HIV infection in females. [11] Perhaps later presentations by males after onset of the HIV infection may account for this.

2. Antecedent infection

GBS is an autoimmune disorder that often follows an infective process, but it is not always post-infective. [12]

At least 2/3 of patients with GBS report an antecedent infection, either gastro-enteritis or upper respiratory tract infection (URTI). In our study 10/26 patients had missing data regarding preceding illness and the same number reported no illness. One of the patients that reported no illness was diagnosed with cytomegalovirus (CMV) hepatitis on admission. CMV has been associated with GBS [10,13] and was attributed to be the probable para-infectious cause. This patient was HIV negative. CMV was not tested in the CSF but the CSF showed protein-cell dissociation.

Two of the patients that reported no illness were diagnosed with HIV infection. One of the patients was initiated on highly active antiretroviral therapy (HAART) six weeks before presenting to UAH. The CD4 count was 78 cells/µL and the CD4 count on initiation of HAART was unknown. The association between HIV and GBS has been described as early as 1986 by L Hagberg et al where they describe two separate cases of patients developing GBS during the seroconversion phase of the disease. [8] In other case studies [7,14], patients also presented with GBS secondary to an immune reconstitution inflammatory syndrome (IRIS). It is possible that our patient had IRIS presenting as GBS given the very low CD4 count. However, in the other patient, Epstein Barr Virus (EBV), which has been associated with GBS [15] was later detected in CSF.

Most of the patients in the study presented within two weeks of onset of symptoms (median 5 days). At least 50% of patients with GBS reach maximum weakness within two weeks and 90% in four weeks which was in keeping with the patients in our study.[16] The one exception was the patient, discussed above, who presented after 35 days of onset of weakness and newly diagnosed with HIV infection, with CD4 count of 78 cells/µL and an unknown viral load. He initially presented to his local hospital with paraesthesia and was diagnosed with HIV infection and started on treatment. A week later he developed ascending weakness which was treated with IVIG at a local hospital and he was discharged home. He presented to UAH four weeks after being discharged from the local hospital with worsening weakness involving the respiratory muscles. A subacute presentation, worsening and recurrence of GBS have been described in people living with HIV infection. Some may even progress to having chronic inflammatory demyelinating neuropathy (CIDP). [7, 17] Another possibility in this patient is treatment related fluctuation which is a phenomenon whereby patients may initially improve or stabilize on treatment then later deteriorate. [18, 19] This deterioration may occur within 8 weeks of treatment. [19] The patient was initially given IVIG and discharged home five weeks prior to presenting to UAH. We presume that he either improved or stabilized before deteriorating.

3. Indication for ICU management

A third of patients with GBS require ICU admission for autonomic instability, bulbar weakness, respiratory insufficiency and rapid progression of the disease. [13, 18]

The biggest indicator for ICU admission in our study was respiratory compromise. Only one of the 26 patients in our study had no respiratory weakness.

The Erasmus GBS Respiratory Insufficiency Scale (EGRIS) was established to assist in predicting patients that may need ICU or ventilator support on admission. The main predictors for mechanical ventilation were days between onset of weakness and admission, Medical Research Council (MRC) sum score, and the presence of facial and/or bulbar weakness. [13, 18]

The patients in our study were not scored according to the EGRIS and the decisions were based solely on the opinion of the admitting physician. ICU admission indicators for respiratory monitoring included bulbar and/or respiratory muscle weakness, signs of respiratory distress, abnormal arterial blood gas or abnormal oxygen saturation.

4. Investigations

a. <u>CSF results.</u>

The typical findings in the CSF of patients with GBS is an albumin-cytological dissociation (elevated protein without elevation in cell count). CSF is normal in 30-50% of the cases in the first week of the disease and normal in 10-30% of the cases in the second week of the disease. [18]

In our study, 7/17 (41.2%) of the patients in whom CSF was done was normal. It was not mentioned in the records on which day the CSF was done, but four of the patients had presented within the first week of the disease, one of the patients presented in the second week and in two patients the day of presentation was unknown.

Of the 10/17 (58.8%) patients with albumin-cytological dissociation, four of the patients presented within the second week of the disease and five in the first week. These CSF findings are in keeping with other studies and the diagnostic guidelines of GBS. [18]

b. Electrophysiological studies.

Nerve conduction studies are supportive for GBS and are often done to exclude GBS mimics. Three main types of GBS variants can be identified on NC viz, AIDP, AMAN and AMSAN. AIDP is commonest in the USA and Europe and AMAN is more common in the Mexican population and in China. [20]

In our study the commonest NCS finding were consistent with AMAN (7/13 (53.9%), followed by AIDP 3/13 (23%) and AMSAN in 2/13 (15.4%) of the patients.

Both patients with AMSAN were HIV positive and needed ventilator support. Three of the seven patients with AMAN were HIV positive and only one did not require ventilator support.

There is limited data about the histological patterns in South Africa and in sub-Saharan Africa. A non-published study done in Cape Town, South Africa found that the commonest variant was AIDP. [21]

Lopez-Hernández et al from Mexico showed that patients with AMAN tend to have a poorer short-term outcome (at 3 months) compared to patients with AIDP even though there was no difference at admission. [20] Although the numbers in our study are too small to be of significant statistical value, the patients with axonal variants had much longer ICU stay compared to the patients with the demyelinating variant.

Kalita et al also mentioned that patients with AMAN have more respiratory paralysis compared to other variants. [22]

Treatment modalities.

There are two treatment modalities recommended for GBS viz IVIG and PLEX. [18,23] Both modalities have been found to be equally effective. In our study all patients received IVIG. IVIG is readily available in our centre compared to PLEX and much easier to administer. Therefore, IVIG is the preferred method of treatment and PLEX is reserved for patients with contraindications to IVIG. The choice of treatment modalities is in keeping with worldwide trends where IVIG is chosen more frequently than PLEX. [23]

Four patients had additional immunosuppressive treatment. One patient received PLEX four weeks after IVIG was given without clinical improvement noted. There is no evidence to support the use of IVIG in combination with PLEX. [18] In patients with poor outcome or patients with treatment related fluctuations, there is no consensus on further treatment modalities. [24]

Another study compared patients on IVIG, PLEX, PLEX +IVIG or neither to include the cost effectiveness of giving a second course of treatment in patients with poor response and there was no significant improvement noted in giving a second course of treatment. [25]

Three of the patients received additional steroids. Steroids have been shown to have no significant impact on GBS and patients on oral prednisone may have a negative outcome. [18]

One patient who received oral prednisone had a much longer stay in ICU of 140 days. She was receiving prednisone for haemolytic anaemia and it was noted that she relapsed regarding the haemolytic anaemia every time her prednisone was reduced.

Association between duration of ICU stay, complications, co-morbidities and outcome.

Previous studies have shown that prolonged ICU stay and mechanical ventilation is associated with serious complications and poor prognosis. Co-existing medical conditions and increased age have also been associated with poor outcome. [26]

The average ICU stay in our study was 26.4 days with a median of 9 days (range 1-140 days). The patients who had a shorter ICU stay had less complications and better outcome compared to those with longer ICU stay. This was in keeping with other studies. [1]

The majority of patients with prolonged ICU stay had significant co-morbidities and serious complications. HIV infection was the commonest co-morbidity. We found a higher number of patients with HIV infection (8/9, 88%) had a prolonged ICU stay. In patients that were HIV negative the rate of complications was lower (11/17 patients (64.7%). However, these results were not statistically significant ($p = 0.357$).

Schleider et al did a study in 2003 on the effect of HIV on ICU outcome in patients with GBS. They found that there was no significant difference in the outcome between the HIV infected group and the non HIV infected group. [9] Another study done by Chetty in Cape Town, SA, found that there was no significant outcome between patients living with HIV and HIV negative patients admitted with GBS. [21] The findings in both these studies were similar to ours.

In a review article on the impact of co-morbidities on critical illness, patients that failed non-invasive mechanical ventilation, those of older age and those with multiple co-morbidities had increased risk of mortality. [27]

The practice of traditional herbal medicinal use seemed to have a great impact on the ICU outcome and stay. All four patients with a history of herbal ingestion had serious complications and two died. However, there was no statistical difference when compared to patients with no history of herbal ingestion (p = 0.5463). In an article written in 2003 on herbal medication toxicity in SA, Scott mentioned that black indigenous healers, who use mainly indigenous medical herbs, still provide health care to at least 60%-75% of the SA population. Also, these herbs can be bought in marketplaces and some are readily available in the "wilderness". [28] Traditional herbal medicine was also found to have a higher mortality rate in all causes of poisoning. [28] Organ specific toxicity may occur with some herbal medication but the commonest toxicity is hepatic. In severe cases of herbal toxicity, multi-organ failure may occur. [29]

The spectrum of ICU complications in GBS in our study is in keeping with other studies. Of note is that none of the patients in our study had any deep vein thrombosis which has been found to be common in other studies. Patients admitted to Multi-ICU are all put on prophylactic anti-coagulation, usually a low molecular weight heparin (LMWH) and compression stockings. Tracheostomy related complications were very few. No tracheostomy site infection or bleeding occurred**.**

Electrolyte disturbances, anaemia and hypoalbuminaemia were the commonest complications in our group. Hyponatraemia was the commonest electrolyte disorder, present in seven patients. It is found to be the commonest encountered electrolyte abnormality in both ICU patients and in GBS in general. [30] Proposed causes of hyponatraemia in GBS include post IVIG dilutional phenomena, inappropriate secretion of antidiuretic hormone and also the renal salt wasting syndrome as part of the dysautonomia. [30]

Ventilator associated pneumonia and sepsis are common complications and they are associated with high risk of mortality. This was also evidenced in our study. Although the cause of death was attributed to dysautonomia in 3 of the 4 patients, VAP and sepsis were present in 3 of the 4 patients.

The outcome of GBS varies widely, and the mortality ranges between 1% and 18%. This percentage increases up to 15-30% in patients that require mechanical ventilation. [6]

The mortality in our study was 15%. Dhar et al found that mortality in their ICU patients was not significantly increased compared to hospital patients. Increased age and significant comorbidities increased the risk of mortality in ICU and hospital admissions. [1]

Three of the four patients that died were HIV positive with other co-morbidities and the fourth patient was hypertensive with a history of herbal medication use. Dysautonomia was the cause of death in three patients.

Dysautonomia has been reported to be the cause of death in GBS. [31] It presents as arrhythmias, labile blood pressure, pupil abnormalities, ileus and urinary retention. However, it is difficult to state if the dysautonomia was purely from GBS or secondary to other complications such as multi-organ failure and sepsis in our patients.

11.6 LIMITATIONS.

The study population was very small and participants were recruited from one hospital in the province. This may affect the statistical significance of the results.

This being a retrospective study, data was missing in a lot of patients which may affect the results. Only patients with a diagnosis of GBS or AIDP were included in the study. Wrong entry of diagnosis on admission or on discharge in the ICU database may affect number recruited.

Long term follow-up of these patients would be good in providing long term data on recovery. Telephonic interviews were unhelpful as patients provided wrong numbers on admission and were unavailable for the follow up part of the study.

11.7 CONCLUSION

Hospital records of GBS patients at the UAH are scanty and therefore open to litigation. A good database is paramount both for clinical service delivery, clinical audits and research purposes.

There were more males than females in our study in keeping with worldwide trends, however we had younger patients in our study. This may be due to the high prevalence of HIV in the younger population in SA. HIV infection as expected was the commonest co-morbidity in our study group followed by hypertension. Our study did not show a statistical difference between the rate of complications between seropositive and seronegative HIV infected patients. These findings are similar to other studies. There was no significant difference in terms of complication rate between patients with comorbidities and those without comorbidities. The

use of traditional herbal medicine carried a high complication rate in ICU. Prolonged ICU stay was associated with significant ICU complications.

11.8 RECOMMENDATIONS

A prospective multicentre study with a larger sample size, with follow up at 3 months, 6 months and probably 12 months will help in assessing the long term effect of ICU complications. A prospective study will also eliminate the issue of missing data. However good clinical record keeping is essential including a reliable computerised database. Other complications to consider that were not highlighted in our study include neuropathic pain, critical illness myopathy/neuropathy and nutritional complications. Regulation of the traditional medicine industry in South Africa needs re-evaluation.

11.9 REFERENCES

1. Dhar R, Stitt L, Hahn AF. The morbidity and outcome of patients with Guillain-Barré syndrome admitted to the intensive care unit. J Neurol Sci. 2008;264(1–2):121–8.
2. González P, García X, Guerra A, Arango JC, Delgado H, Uribe CS, et al. Experience with Guillain-Barré syndrome in a neurological Intensive Care Unit. Neurol (English Ed [Internet]. 2016;31(6):389–94. Available from: http://dx.doi.org/10.1016/j.nrleng.2014.09.003
3. Netto AB, Taly AB, Kulkarni GB, Uma Maheshwara Rao GS, Rao S. Complications in mechanically ventilated patients of Guillain-Barre syndrome and their prognostic value. J Neurosci Rural Pract. 2017;8(1):68–73.
4. Doets AY, Verboon C, van den Berg B, Harbo T, Cornblath DR, Willison HJ, et al. Regional variation of Guillain-Barré syndrome. Brain. 2018;141(10):2866–77.
5. Hughes RAC, Cornblath DR. Guillain-Barré syndrome. Lancet. 2005;366(9497):1653–66.
6. Bhagat H, Dash H, Chauhan R, Khanna P, Bithal P. Intensive care management of Guillain-Barre syndrome: A retrospective outcome study and review of literature. J Neuroanaesth Crit Care. 2014;01(03):188–97.
7. Piliero PJ, Fish DG, Preston S, Cunningham D, Kinchelow T, Salgo M, et al. Guillain-

Barré syndrome associated with immune reconstitution. Clin Infect Dis. 2003;36(9):111–4.

8. Hagberg L, Malmvall BE, Svennerholm L, Alestig K, Norkrans G. Guillain-Barré syndrome as an early manifestation of HIV central nervous system infection. Scand J Infect Dis. 1986;18(6):591–2.

9. Schleicher GK, Black A, Mochan A, Richards GA. Effect of human immunodeficiency virus on intensive care unit outcome of patients with Guillain-Barré syndrome. Crit Care Med. 2003;31(6):1848–50.

10. Van Den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, Van Doorn PA. Guillain-Barré syndrome: Pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol [Internet]. 2014;10(8):469–82. Available from: http://dx.doi.org/10.1038/nrneurol.2014.121

11. Mabaso M, Makola L, Naidoo I, Mlangeni L, Jooste S, Simbayi L. HIV prevalence in South Africa through gender and racial lenses: results from the 2012 population-based national household survey. Internation Journal for Equity in Health 2019; 18:167

12. Ancona P, Bailey M, Bellomo R. Characteristics, incidence and outcome of patients admitted to intensive care unit with Guillain-Barre syndrome in Australia and New Zealand. J Crit Care [Internet]. 2018;45:58–64. Available from: https://doi.org/10.1016/j.jcrc.2018.01.016

13. van Doorn PA. Diagnosis, treatment and prognosis of Guillain-Barré syndrome (GBS). Press Medicale [Internet]. 2013;42(6 PART2):e193–201. Available from: http://dx.doi.org/10.1016/j.lpm.2013.02.328

14. Teo ECY, Azwra A, Jones R, Gazzard BG, Nelson M. Guillain-Barré syndrome following immune reconstitution after antiretroviral therapy for primary HIV infection. J HIV Ther. 2007;12(3):62–3.

15. Donofrio PD. Guillain-Barré Syndrome. Contin Lifelong Learn Neurol. 2017;23(5, Peripheral Nerve and Motor Neuron Disorders):1295–309.

16. Mazen M. Dimachkie, M.DRichard J. Barohn M. GBS and Variants. NIH Public Access. 2014;31(2):491–510.

17. Brannagan TH, Zhou Y. HIV-associated Guillain-Barré syndrome. J Neurol Sci.

2003;208(1–2):39–42.

18. Leonhard SE, Mandarakas MR, Gondim FAA, Bateman K, Ferreira MLB, Cornblath DR, et al. Diagnosis and management of Guillain–Barré syndrome in ten steps. Nat Rev Neurol [Internet]. 2019;15(11):671–83. Available from: http://dx.doi.org/10.1038/s41582-019-0250-9

19. Fokke C, Van Den Berg B, Drenthen J, Walgaard C, Van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barré syndrome and validation of Brighton criteria. Brain. 2014;137(1):33–43.

20. López-Hernández JC, Colunga-Lozano LE, Garcia-Trejo S, Gomez-Figueroa E, Delgado-Garcia G, Bazán-Rodríguez L, et al. Electrophysiological subtypes and associated prognosis factors of Mexican adults diagnosed with Guillain-Barré syndrome, a single center experience. J Clin Neurosci. 2020;80(xxxx):292–7.

21. S. Chetty. Guillain Barre Syndrome (GBS) in Cape Town, South Africa: a descriptive outcome cohort study. (MMed thesis, unpublished)

22. Kalita J, Ranjan A, Misra UK. Outcome of guillain-barre syndrome patients with respiratory paralysis. Qjm. 2016;109(5):319–23.

23. Barnes SL, Herkes GK. Guillain–Barré syndrome: clinical features, treatment choices and outcomes in an Australian cohort. Intern Med J. 2020;50(12):1500–4.

24. Alboudi AM, Sarathchandran P, Geblawi SS, Kayed DM, Inshasi J, Purayil SP, et al. Rescue treatment in patients with poorly responsive Guillain–Barre syndrome. SAGE Open Med. 2019;7:205031211984019.

25. Oczko-Walker M, Manousakis G, Wang S, Malter JS, Waclawik AJ. Plasma exchange after initial intravenous immunoglobulin treatment in Guillain-Barré syndrome: Critical reassessment of effectiveness and cost-efficiency. J Clin Neuromuscul Dis. 2010;12(2):55–61.

26. henderson RD, Lawn ND, Fletcher DD, McClelland RL, Wijdicks EFM. The morbidity of Guillain-Barre syndrome admitted to intensive care unit. Neurology 2003; 60:17-21

27. Esper AM, Martin GS. The impact of cormorbid conditions on critical illness. Crit Care Med. 2011;39(12):2728–35.

28. Bateman J, Chapman RD, Simpson D. Possible toxicity of herbal remedies. Scott Med J. 1998;43(1):7–15.

29. Scot G. Acute toxicity associated with the use of South African traditional medicinal herbs. Trans R Soc South Africa. 2003;58(1):83–92.

30. Hiew FL, Winer JB, Rajabally YA. Hyponatraemia in Guillain-Barré syndrome revisited. Acta Neurol Scand. 2016;133(4):295–301.

31. Pfeiffer G, Schiller B, Kruse J, Netzer J. Indicators of dysantonomia in severe Guillain-Barre syndrome. J Neurol. 1999;246(11):1015–22.

APPENDIX

A. LETTER OF APPROVAL FROM THE RESEARCH ETHICS COMMITTEE.

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

24-Jul-2020

Dear **Dr Mamonokane Diale**

Ethics Clearance: **CLINICAL PRESENTATION, ICU MANAGEMENT, MORBIDITY AND MORTALITY OF PATIENTS WITH GUILLIAN BARRE SYNDROME ADMITTED TO ICU AT UNIVERSITAS ACADEMIC HOSPITAL FROM 2014 TO 2019.**

Principal Investigator: **Dr Mamonokane Diale**

Department: **Neurology Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2020/0291/2508**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00011992, REC 230408-011; IORG 0010096; FWA 00027947

B. LETTER OF PERMISSION FROM HOD

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES

DEPARTMENT OF NEUROLOGY

18 February 2020

Health sciences research ethics committee
University of the Free State

Principal investigator: Dr Innocentia Diale
Study title: Clinical presentation, ICU management, morbidity and mortality of patients with Guillain Barre Syndrome admitted to ICU at Universitas Academic Hospital from 2014 TO 2019.

Dr Diale has presented her study protocol to the department of neurology research committee and was given approval for continuation of the study after various corrections and modifications were suggested. She has in addition discussed her study with the statistician, Prof Gina Joubert.

I hereby grant Dr Diale full permission and support for her study as head of neurology.

Kind regards

Anand Moodley
Associate professor and head of neurology
Universitas Academic Hospital and University of the Free State
moodleyAA@ufs.ac.za

Department of Neurology: School of Medicine/Departement Neurologie: Skool vir Geneeskunde
T: +27 (0)51 4053550 | F: +27(0)51 401 9804 | E: dupreezac@ufs.ac.za
205 Nelson Mandela Drive/Rylaan |Parkwes | Bloemfontein 9301 | South Africa / Suid Afrika
PO Box /Posbus 339 (G63) | Bloemfontein 9300 | South Africa/Suid-Afrika | www.ufs.ac.za

C. LETTER OF APPROVAL FROM THE DEPARTMENT OF HEALTH

health
Department of Health
FREE STATE PROVINCE

08 July 2020

Dr M Diale
Dept. of Neurology
UFS

Dear Dr M Diale

Subject: Clinical presentation, ICU management, morbidity and mortality of patients with guillian barre syndrome admitted to ICU at Universitas Academic Hospital from 2014 to 2019.

- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary
- A written consent by each participant must be obtained.
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeco.ats@fshealth.gov.za / makenanm@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day**

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 24 | 07 | 2020

Head : Health
PO Box 227, Bloemfontein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and Harvey Road, Bloemfontein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail: [illegible]@fshealth.gov.za@fshealth.gov.za/[illegible]@fshealth.gov.za

www.fs.gov.za

D.

PARTICIPANT INFORMATION LEAFLET

TITLE: CLINICAL PRESENTATION, ICU MANAGEMENT, MORBIDITY AND MORTALITY OF PATIENTS WITH GUILLAIN-BARRÉ SYNDROME ADMITTED TO ICU AT UNIVERSITAS ACADEMIC HOSPITAL FROM JANUARY 2014 TO JUNE 2020

Principal investigator: Dr MI Diale

Address: Neurology Department: Universitas Academic Hospital (UAH)

Contact numbers: 051 405 3003 / 051 405 3911 / 076 702 5560

Supervisor: Prof A Moodley, 051 405 3550

Dear Participant

My name is Dr MI Diale and I am a Neurology registrar at the UAH. I would like to invite you to participate in a research project that aims to investigate the clinical presentation, intensive care unit (ICU) management and ICU complications in patients admitted to the UAH multi-ICU with a diagnosis of Guillain-Barré Syndrome (GBS) between January 2014 and June 2020.

You were admitted to the ICU at Universitas Academic Hospital for a period of time. I would like to get more information from you regarding your physical complaints at admission to ICU, at discharge and how you are currently coping physically. Your participation is entirely voluntary and you are free to decline to participate. If you decline, this will not affect you negatively in any way. You are also free to withdraw from the study at any point, even if you initially agreed to take part.

This study has been approved by the Health Sciences Research Ethics Committee (HSREC) at the University of the Free State, and will be conducted according to accepted and applicable national and international ethical guidelines and principles, including those of the international Declaration of Helsinki.

In this study we are looking at the patients who presented to UAH with a diagnosis of Guillain-Barré Syndrome (GBS) and were admitted to the ICU between January 2014 and June 2020.

We will be looking at the reasons why patients were admitted to ICU and how long they stayed in ICU. We will also be looking at all the complications they had in ICU. Other information that we are going to look at include any illnesses you had prior to having GBS, and what type of treatment you received in ICU. Most of this information will be retrieved from the medical records in the hospital archives.

As one of the participants you will be asked questions about your illness. Questions will centre around your symptoms and your recovery. We would like to know your functional status when you were discharged from ICU, and your current functional status. If you have fully recovered, we would also like to know how long it took you to recover.

As the principal investigator who will be responsible for conducting the interview, I will be the only person who will know your name. Your information will be recorded with a coded number on the study records to ensure your confidentiality and privacy. Your name, hospital number and any other identifying information will not appear on any of the research papers and you will remain anonymous.

By agreeing to participate you are providing consent.

Thank you most sincerely for your assistance and participation in this study.

Dr MI Diale

DECLARATION BY PARTICIPANT

By signing, I _____ agree to take part in a research study entitled Clinical presentation, ICU management, morbidity and mortality of patients with Guillain-Barré Syndrome admitted to ICU at Universitas Academic Hospital (UAH) from January 2014 to December 2019.

I declare that:

- I have read the attached information leaflet and it is written in a language in which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.

- I understand that taking part in this study is voluntary and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced for this in any way.
- I may be asked to leave the study before it has finished, if the researcher feels that this is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (place) _____ On (date) _____ 20___

Signature of participant: _____

E. INFORMED CONSENT

TITLE: CLINICAL PRESENTATION, ICU MANAGEMENT, MORBIDITY AND MORTALITY OF PATIENTS WITH GUILLAIN-BARRÉ SYNDROME ADMITTED TO ICU AT UNIVERSITAS ACADEMIC HOSPITAL FROM JANUARY 2014 TO JUNE 2020

Principal investigator: Dr MI Diale

Reference number: UFS-HSD202/0291

Address: Neurology Department: Universitas Academic Hospital (UAH)

Contact number: 051 405 3003 / 051 405 3911 / 076 702 5560

Dear participant

You are invited to take part in a research project. Please ask the doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied, that you clearly understand what this research entails and how you will be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way. You are also free to withdraw from the study at any point, even if you initially agreed to take part.

This study has been approved by the Health Sciences Research Ethics Committee (HSREC) at the University of the Free State and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, the South African Good Clinical Practice Guidelines and the Medical Research Council (MRC) Ethical Guidelines and Research.

The study will be conducted at the UAH and approximately 30 participants will be recruited. The participants will include all the patients who were admitted to UAH multi-ICU between January 2014 and June 2020 with a diagnosis of Guillain-Barré Syndrome (GBS).

The reason we are doing this study is to see how patients that are admitted to ICU with GBS initially present to hospital. We would also like to evaluate the type of complications that may develop while patients are in ICU, and the length of their ICU stay. We will also evaluate if chronic illnesses such as HIV, hypertension and others contribute to the complications of patients in ICU.

The procedure for this study will involve the investigator going through the ICU admission statistics for the mentioned dates and selecting all the patients with a diagnosis of GBS. Medical records from the hospital archives and the Meditech system will then be evaluated. Telephone numbers will be retrieved from patient records by the principal investigator, who will call all the patients and invite them for a telephonic interview.

You have been invited to participate in the study as you were admitted to ICU with GBS during the mentioned period. The aim of the interview is to record the clinical history regarding your initial presentation to the hospital that may augment the information we have from your medical records. We would also like to evaluate your progress post-discharge, if you have fully recovered from the illness, and if so how long it took you to recover.

Your responsibility during the study is to complete a standardised questionnaire during an interview that will be conducted by the investigator via telephonic consultation. There are no personal benefits for you by participating in the study, however the study will assist the doctors in noting complications related to GBS patient in ICU and will help in the future management of GBS in ICU.

There are no risks involved in your taking part in this research. There will be no physical/medical harm towards you by participating in the study. You will not be paid to take part in the study and there will be no costs involved for you. You may inform your relatives that you are involved in a study.

You may contact the HSREC at 051 401 7794/5 if you have any concerns or complaints that have not been adequately addressed by the investigator.

DECLARATION BY PARTICIPANT

I (name) _____ agree to take part in a research study entitled Clinical presentation, ICU management, morbidity and mortality of patients with Guillain-Barré Syndrome admitted to ICU at Universitas Academic Hospital from January 2014 December 2019.

I declare that:

- I have read or had read to me this information and consent form and it is written in a language in which I am fluent and comfortable.

- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is voluntary and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced for this in any way.
- I may be asked to leave the study before it has finished if the study doctor or the researcher feels that this is in my best interest, or if I do not follow the study plan, as agreed to.

Signed at (place) _____ On (date) _____ 20_____

Participant signature: _____ Witness signature: _____

DECLARATION BY INVESTIGATOR

I explained the information in this document to _____.

I encouraged him/her to ask questions and took adequate time to answer them. I am satisfied that he/she adequately understands all aspects of the research as discussed above. I did/did not use an interpreter.

Signed at (place) _____ On (date) _____ 20____

Investigator signature: _____ Witness signature: _____

DECLAREATION BY INTERPRETER

I _____ declare that:

- I assisted the investigator _____ to explain the information in this document to participant _____ using the language medium of Afrikaans/SeSotho.
- We encouraged him/her to ask questions and took adequate time to answer them.

- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Interpreter signature: _____ Witness signature: _____

F. QUESTIONAIRE

TITLE: CLINICAL PRESENTATION, ICU MANAGEMENT, MORBIDITY AND MORTALITY OF PATIENTS WITH GUILLAIN-BARRÉ SYNDROME ADMITTED TO ICU AT UNIVERSITAS ACADEMIC HOSPITAL FROM JANUARY 2014 TO JUNE 2020

Principal investigator: Dr MI Diale

Person study no:

Date of interview:

1. When were you diagnosed with Guillain-Barré Syndrome (weakness of your arms and legs requiring hospital treatment)?

_____

2. What were the initial symptoms of your disease?

_____

3. Functional status on admission to ICU:
    a. Did you have minor symptoms, were you able to run?

_____

    b. Were you able to walk 5 meters independently (without any support)?

_____

    c. Were you able to walk 5 meters with a walker or support?

_____

    d. Were you bed or chair-bound?

_____

    e. Were you requiring oxygen, CPAP machine or have a tube in your throat for breathing?

_____

    f. When were you discharged from ICU?

_____

4. Functional status on discharge

    a. Were you completely recovered?

_____

    b. Did you have minor symptoms, were you able to run?

_____

    c. Were you able to walk 5 meters independently?

_____

    d. Were you able to walk 5 meters with a walker or support?

_____

    e. Were you bed or chair-bound?

_____

    f. Were you still requiring oxygen, CPAP machine or a tube in your throat for breathing?

_____

5. Current functional status

    a. Have you recovered completely?

_____

    b. Do you have minor symptoms, are you able to run?

_____

    c. Are you able to walk 5 meters independently?

_____

    d. Are you able to walk 5 meters with a walker or support?

_____

    e. Are you bed or chair-bound?

_____

f. Are you still requiring oxygen, CPAP machine or a tube in your throat for breathing?

_____

6. Are you still having regular follow ups at a hospital, clinic, physiotherapist, occupational therapist or doctor for this problem?

    a. If yes, which one (clinic, rehabilitation centre, hospital by general physician or neurologist) and how often do you go for review?

_____

G. PROTOCOL

UNIVERSITY OF THE FREE STATE

TITLE: CLINICAL PRESENTATION, ICU MANAGEMENT, MORBIDITY AND MORTALITY OF PATIENTS WITH GUILLAIN BARRÉ SYNDROME ADMITTED TO ICU AT UNIVERSITAS ACADEMIC HOSPITAL FROM JANUARY 2014 TO JUNE 2020.

RESEARCHER:

Dr MI Diale (Registrar in Neurology Department Universitas Academic Hospital)

Degree: MBChB

HPCSA: MP0733156

Student No: 2017560539

SUPERVISOR:

Prof AA Moodley (senior Consultant in Neurology and Head of department in Neurology)

BIOSTATISCTICS

Prof Gina Joubert (Biostatistics)

University of the Free State.

Tel: 051 401 3117

TABLE OF CONTENTS

1. INTRODUCTION

Guillain-Barré Syndrome (GBS) is one of the commonest causes of an acute onset paralytic quadriparesis and may also involve the bulbar, respiratory muscles and also the autonomic nervous system. (1) It affects approximately 0.4 to 4 people per 100 000 per year and it has a bimodal distribution, seen more frequently in the young adults and elderly patients. (2) Although it generally follows a monophasic course, up to 20% of patients remain severely disabled and approximately 5% die, despite immunotherapy (3).

The disorder is preceded by an infection, most commonly gastro-enteritis or upper respiratory tract infection, in at least two thirds of the cases (2,4). The pathophysiology is suggested to be autoimmune damage from the cross-reaction between the antibodies against microbial antigens and neuronal molecules (2). This affects the conduction of the nerves, resulting in dysfunction of the motor, sensory and/ or autonomic systems. (2) The diagnosis of GBS is essentially clinical in addition, protein-cell dissociation in the CSF, as well as nerve conduction studies (NCS) support the diagnosis (2).

The histological features of GBS support a distinction between acute inflammatory demyelinating polyneuropathy(AIDP), acute motor axonal polyneuropathy(AMAN) and acute motor and sensory polyneuropathy(AMSAN). This is evidenced on nerve conduction studies (NCS). However, electrical abnormalities may not be widespread in the first two weeks, and therefore the diagnosis has to be made clinically as it is important to start treatment early. (5,6)

Approximately one third of patients with GBS are admitted to intensive care unit (ICU) and many require respiratory support, most often for a prolonged period. (1) Patients requiring ICU are those who present with bulbar weakness resulting in an inability to protect their airway, those with impending respiratory failure due to respiratory muscle weakness, and those with autonomic instability.

ICU complications in patients with GBS have been described in association with mechanical ventilation, prolonged immobilization or specific treatments. (7) Most common complications include pneumonia, hyponatraemia, urinary tract infection, dysautonomia, confusion and cognitive disturbances (7). Other less frequent complications include

tracheostomy site infection, deep vein thrombosis, myocardial infarction, heart block and abnormalities of liver and renal function. (7)

In one study, the overall ICU and hospital mortality was 3,9% and 6,9% respectively, but increased to 9.7% and 14,3% in the mechanically ventilated (MV) group. Patients in the MV group had a significantly longer stay in ICU of close to a month and in hospital of close to 40 days (8). In another study the mean ICU stay was found to be 41 days (median 21 days, range 6-335) and the hospital stay averaged 71 days (median 49 days). Only 13% of the patients were discharged home, and the remainder returned to the referring hospital or rehabilitation facility. GBS patients suffering serious ICU complications while in ICU had significantly longer ICU stays and were much less likely to be discharged home. (1)

There is limited data in South Africa, especially the Free State regarding mortality and morbidity of patients with GBS admitted in ICU and their NCS findings.

2. AIMS AND OBJECTIONS

a. Aim

To describe the clinical presentation, ICU management, complications and outcome of patients with Guillain Barré Syndrome requiring ICU management at the Universitas Academic Hospital (UAH), Free State Province.

b. Objectives:

5. To describe the demographic profile of patients with GBS requiring ICU management.
6. To describe the clinical presentation, investigation, co-morbidities and preceding illnesses in patients with GBS admitted to ICU.
7. To describe the duration of ICU care, immunomodulatory treatment and complications experienced by GBS patients admitted to ICU.
8. To present the functional outcomes of patients with GBS managed in ICU immediately post ICU discharge and their current functioning.

9. By relating the outcome measures to demographic, clinical, electrophysiological and ICU factors (if the numbers permit), red flags will be identified and thereby guide us in improving the intensive care of these patients.
10. To compare the clinical presentation between children and adults with GBS and the ICU outcome in both groups, if there are adequate numbers for comparison.

3. METHODOLOGY

a. Study design

This is a retrospective analytic observational study, with in addition a survey of cohorts post discharge administered by a telephonic interview.

b. Sampling

All patients admitted in the Multi-ICU in UAH with a diagnosis of GBS or AIDP will be included in the study by a convenience sampling method. The data will be obtained from January 2014 to June 2020, estimated number of patients is 30 over the 6.5 year period. Records will be retrieved on Meditech, hospital archives, National Health Laboratory Services (NHLS) online tracking care system for blood results and CSF results and the neurophysiology lab for NCS reports. The department of critical care will be approached for access to ICU notes for the study. Formal approval from the department of health will be obtained for access to patient files and access to patients.

Patients will also be interviewed with regards to their initial presentation to supplement the clinical notes from records and also to assess their functional status post discharge from hospital and their current functional status.

Interviews will be done telephonically by the principal investigator who is proficient in English, Sotho and Afrikaans. Telephone numbers will be retrieved from the demographic records listed on the hospital records.

With regards to children, interviews will be conducted both with the care-giver and the child if the child is able to give some history

Exclusion criteria: patients whose diagnosis have changed and patients below the age of 13 years. Patient below the age of 13years are managed by the Department of Paediatrics.

c. Measurements

1. Demographics.

   Age, gender and ethnicity.

2. Preceding illness and co-morbidities.
3. Clinical presentation prior to ICU admission.
4. Length of ICU stay.
5. Complications in ICU.
6. Immunotherapy.
7. Morbidity and mortality
8. Nerve conduction studies (where available).
9. Functional outcome after ICU stay and at present, which will be assessed telephonically. This will be done using the Hughes Scale.

4. DATA ANALYSIS

Support for statistics will be provided by the department of biostatistics. Descriptive statistics, namely means and standard deviation or medians and percentiles, will be calculated for continuous data. Frequencies and percentages will be calculated for categorical data. The principal investigator will enter data into Excel spreadsheet for analysis.

5. IMPLEMENTATION OF FINDINGS

Results will be used for academic and publication purposes.

The results will be used to identify ICU complications in GBS patients admitted to ICU and to implement preventative measures where needed.

6. PILOT STUDY

A pilot study will be conducted looking at the first 3 cases of ICU admission from the year 2014.

7. TIME SCHEDULE

1. Protocol submission and Ethics approval.

June-July 2020.

2. Free State Department of Health approval.

August 2020

3. Collection of data.

September 2020

4. Analysis and interpretation.

October 2020

5. Writing up of study.

November 2020- January 2021

8. BUDGET

	amount
1. Printing of medical data	R 500
2. Copying of medical data	R 500
3. Binding of documents	R 500
4. Airtime for telephonic interviews: (Estimate number of patients (30) 1page per patient, estimated 15minutes of interview per patient = R15 airtime)	R 450
5. Language editing	R 2000
Total	**R 3950**

9. ETHICAL ASPECTS

Application to the Health Sciences Research Ethics Committee (HSREC), University of Free State will be done for ethics approval to conduct this study.

There will be no identifying data such as patient name or hospital number present on the excel sheet. Each patient will be allocated a case number to aid with confidentiality. The case number and the patients name will be stored separately and be password protected by the principal investigator.

Patient information such as case number, age, gender, ethnicity, clinical assessment, outcome etc. will be recorded on the Microsoft excel data form and will only be seen by the investigator, supervisor and statistician.

All hard copy paper/documents used for data collection and rough drafting will be transferred to electronic format that will be password protected, on a read-only file and subsequently the raw data and hard copy paper/documentation will be destroyed by means of shredding.

The Free State DoH will be approached for consent to review or recover data from Meditech or the Archives.

Verbal consent will be requested for telephonic interviews from those patients that have already been discharged from the Neurology department. In cases of children/minors, consent will be requested from the parents or guardian. Their current functional assessment will be done using the Hughes scale.

There is no conflict of interest expected in this study.

10. LIMITATIONS OF STUDY

1. Problems accessing data.

This is a retrospective study. There might be difficulties accessing some data which might be missing from the archives or Meditech. When records cannot be retrieved from either archives or Meditech, those patients will be excluded from the study.

2. Missing NCS reports from neurophysiology laboratory

The neurophysiology laboratory was not functioning well between 2014 and 2016. Some of the patients admitted during that time may not have had NCS done. As NCS are not a

requirement for diagnosis of GBS and does not generally affect the management of the disease, patients with missing NCS reports will still be included.

3. **Incomplete investigations.**

Investigations for each patient are dependent on the physician caring for the patient. Some patients may not have CSF done, especially if they presented too early in the disease. These patients will be included in the study, as GBS is a clinical diagnosis, and CSF findings are merely supportive rather than diagnostic.

4. **Telephonic interviews.**

There might be difficulties getting a hold of all patients for telephonic interviews. There is a possibility that some of the patients contact details have been changed since last being seen in UAH. If there is no response, the number will be tried at least three more times. In cases where there are alternative numbers listed, they will also be tried if there is no response from the main number.

The aim of the telephonic consult is to supplement the clinical history on presentation of the disease and to follow up improvement. Patients that are not available for interviews will still be included in the study as it is unlikely that the interview will affect the main aim and objective of the study, which is ICU complications in GBS.

11. Bibliography

1. Dhar R, Stitt L, Hahn AF. The morbidity and outcome of patients with Guillain-Barre syndrome admitted to the intensive care unit. J Neurol Sci. 2008;264:121–8.

2. González P, García X, Guerra A, Arango JC, Delgado H, Uribe CS, et al. Experience with Guillain-Barré syndrome in a neurological Intensive Care Unit. Neurol (English Ed [Internet]. 2016;31(6):389–94. Available from: http://dx.doi.org/10.1016/j.nrleng.2014.09.003

3. Netto AB, Taly AB, Kulkarni GB, Uma Maheshwara Rao GS, Rao S. Complications in mechanically ventilated patients of Guillain-Barre syndrome and their prognostic value. J Neurosci Rural Pract. 2017;8(1):68–73.

4. Ancona P, Bailey M, Bellomo R. Characteristics, incidence and outcome of patients admitted to intensive care unit with Guillain-Barre syndrome in Australia and New Zealand. J Crit Care [Internet]. 2018;45:58–64. Available from: https://doi.org/10.1016/j.jcrc.2018.01.016

5. Gordon PH, Wilbourn AJ. Early Electrodiagnostic Findings in Guillain-Barre ´ Syndrome. 2001;58(June).

6. Niu J, Liu M, Sun Q, Li Y, Wu S, Ding Q, et al. Motor nerve conduction block predicting outcome of Guillain-Barre syndrome. Front Neurol. 2018;9(JUN):1–4.

7. Taylor CJ, Hirsch NP, Kullmann DM, Howard RS. Changes in the severity and subtype of Guillain-Barré syndrome admitted to a specialist Neuromedical ICU over a 25 year period. J Neurol. 2017;264(3):564–9.

8. de Boisanger L. Outcomes for patients with Guillain-Barré syndrome requiring mechanical ventilation: a literature review. Ir J Med Sci. 2016;185(1):11–5.

12. INDEX

a. ABBREVIATIONS

- GBS ➔ Guillain Barré Syndrome
- AIDP ➔ Acute Inflammatory Demyelinating Polyneuropathy
- AMAN ➔ Acute Motor axonal Neuropathy
- ICU ➔ Intensive Care Unit
- UAH ➔ Universitas Academic Hospital
- NCS ➔ Nerve Conduction Studies
- DoH ➔ Department of Health

a. HUGHES SCORE (GBS score)

score	Functional status

0	**Healthy**
1	**Minor symptoms or signs, able to run**
2	**Able to walk 5 meters independently**
3	**Able to walk 5 meters with a walker or support**
4	**Bed or chair bound**
5	**Requiring assisted ventilation**
6	**Death**

H. COVER LETTER

Department of Neurology

Universitas Academic Hospital

Bloemfontein

9300

Date: 22 March 2021

Dear Editor in Chief (SAMJ)

RE: MANUSCRIPT SUBMISSION FOR CONSIDERATION OF PUBLICATION IN YOUR JOURNAL

I am sending you a manuscript titled ‘Clinical Presentation, ICU Management, Morbidity and Mortality of Patients with Guillain Barré Syndrome admitted to ICU at Universitas Academic Hospital from January 2014 to June 2020’.

We would like for the manuscript to be considered for your journal. The study was approved by the Free State University Health Science Ethics Committee (**UFS-HSD2020/0291/2508)**

This study investigated the complications in patients that were admitted to ICU with Guillain Barré Syndrome (GBS) at the Universitas Academic Hospital (UAH) over a period of five and half years (January 2014 to June 2020). We also investigated the clinical presentation, indications for ICU admission and co-morbidities and the effects on the outcome of the patients.

This was a retrospective analytic study. A list of all patients admitted to ICU over the study was requested from the ICU database. We collected data from the hospital records, from the archives, form the hospitals electronic system, from the neurophysiology unit and also from the National Health Laboratory System (NHLS).

We believe that this study will be useful as there is limited data from South Africa (SA) regarding GBS. There have been multiple studies done outside of SA regarding ICU management and complications but few in SA. The commodities in SA differ greatly from those in America, the UK and Asian countries and this study gives a perspective on the effect of comorbidities on the ICU outcomes in these patients.

I, Dr MI Diale, take full responsibility for the study conduct, the data analysis and interpretation. We confirm that this manuscript has not been published in any other journal and it is not being considered for publication in any other journal. The authors of this manuscript have agreed with and approve the submission to your journal.

We will highly appreciate your consideration for publication of this manuscript.

With Regards

Dr MI Diale

Neurology Resident

University of the Free State

I. SAMJ Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008; 17:424-433: standard human pedigree nomenclature.

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study

are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out
    - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts

J. TURNITIN REPORT

MANAGEMENT, MORBIDITY AND MORTALITY OF GUILLAIN BARRÉ SYNDROME PATIENTS ADMITTED TO ICU AT UNIVERSITAS ACADEMIC HOSPITAL: chapter 1

ORIGINALITY REPORT

18%	10%	15%	7%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

2%

1 Paolo Ancona, Michael Bailey, Rinaldo Bellomo. "Characteristics, incidence and outcome of patients admitted to intensive care unit with Guillain-Barre syndrome in Australia and New Zealand", Journal of Critical Care, 2018
Publication

2%

2 van den Berg, Bianca, Christa Walgaard, Judith Drenthen, Christiaan Fokke, Bart C. Jacobs, and Pieter A. van Doorn. "Guillain–Barré syndrome: pathogenesis, diagnosis, treatment and prognosis", Nature Reviews Neurology, 2014.
Publication

	2%
3 Dhar, R.. "The morbidity and outcome of patients with Guillain-Barre syndrome admitted to the intensive care unit", Journal of the Neurological Sciences, 20080115 Publication	
4 Ezequiel Agustin Piccione, Karim Salame, Bashar Katirji. "Chapter 28 Guillain-Barré Syndrome and Related Disorders", Springer Science and Business Media LLC, 2014 Publication	1%
5 eprints.gla.ac.uk Internet Source	1%
	1%
6 Anand B. Pithadia, Nimisha Kakadia. "Guillain-Barré syndrome (GBS)", Pharmacological Reports, 2010 Publication	
	1%
7 S. S. SINGH, S. P. MANIMUNDA, A. P. SUGUNAN, SAHINA, P. VIJAYACHARI. "Four cases of acute flaccid paralysis associated with chikungunya virus infection", Epidemiology and Infection, 2007 Publication	
8 Submitted to University of South Australia Student Paper	1%

emedicine.medscape.com 9 Internet Source	1%
www.em-consulte.com 10 Internet Source	1%
www.tandfonline.com 11 Internet Source	1%
Submitted to University of Witwatersrand Student Paper 12	1 %
	1%
Pei Shang, Jiachun Feng, Wei Wu, Hong-Liang 13 Zhang. "Intensive Care and Treatment of Severe Guillain–Barré Syndrome", Frontiers in Pharmacology, 2021 Publication	
Submitted to University of Glamorgan 14 Student Paper	1%
Prognosis of Neurological Diseases, 2015. 15 Publication	1%
appswl.elsevier.es 16 Internet Source	<1%

17	Submitted to The University of Manchester Student Paper	<1%
18	ejrnm.springeropen.com Internet Source	<1%
19	"Neuromuscular Disorders in Clinical Practice", Springer Science and Business Media LLC, 2014 Publication	<1%
20	Submitted to Jacksonville State University Student Paper	<1%
21	Bernd C. Kieseier, Emily K. Mathey, ClaudiaSommer, Hans-Peter Hartung. "Immune-mediated neuropathies", Nature Reviews Disease Primers, 2018 Publication	<1%
22	Submitted to Utica College Student Paper	<1%
23	Submitted to Weatherford College Student Paper	<1%
24	www.pubfacts.com Internet Source	<1%

25	www.thieme-connect.com Internet Source	<1%
26	preview-ccforum.biomedcentral.com Internet Source	<1%
27	www.nature.com Internet Source	<1%

MANAGEMENT, MORBIDITY AND MORTALITY OF GUILLAIN BARRÉ SYNDROME PATIENTS ADMITTED TO ICU AT UNIVERSITAS ACADEMIC HOSPITAL: chapter 2

ORIGINALITY REPORT

11%	8%	11%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	journals.sagepub.com Internet Source	1%

2	hdl.handle.net Internet Source	1%
3	"Poster Abstracts", Asia-Pacific Journal of Clinical Oncology, 2020 Publication	1%
4	Gunter K. Schleicher. "Effect of human immunodeficiency virus on intensive care unit outcome of patients with Guillain-Barr?? syndrome", Critical Care Medicine, 06/2003 Publication	1%
5	Ezequiel Agustin Piccione, Karim Salame, Bashar Katirji. "Chapter 28 Guillain-Barré Syndrome and Related Disorders", Springer Science and Business Media LLC, 2014 Publication	1%
6	scholar.ufs.ac.za Internet Source	1%
	www.som.uq.edu.au Internet Source	<1%

8	"Textbook of Neuroanesthesia and Neurocritical Care", Springer Science and Business Media LLC, 2019 Publication	<1%
9	Imran Ahmad, Farooq Azam Rathore. "Guillain-Barr é syndrome in COVID-19: A scoping review", Cold Spring Harbor Laboratory, 2020 Publication	<1%
10	appswl.elsevier.es Internet Source	<1%
11	archneur.jamanetwork.com Internet Source	<1%
12	Jingwen Niu, Mingsheng Liu, Qing Sun, Yi Li, Shuang Wu, Qingyun Ding, Yuzhou Guan, Liying Cui. "Motor Nerve Conduction Block Predicting Outcome of Guillain-Barre Syndrome", Frontiers in Neurology, 2018 Publication	<1%
13	Dhar, R.. "The morbidity and outcome of patients with Guillain-Barre syndrome admitted to the intensive care unit", Journal of the Neurological Sciences, 20080115 Publication	<1%

ejnpn.springeropen.com
Internet Source <1%

15 link.springer.com
Internet Source <1%

16 "Neuromuscular Disorders in Clinical Practice", Springer Science and Business Media LLC, 2014
Publication <1%

Critical Care Neurology and Neurosurgery, 17 2004.
Publication <1%

18 Jonas Hedlund, Lars-Olof Hansson, Åke örtqvist. "Short- and Long-Term Prognosis for Middle-Aged and Elderly Patients Hospitalized with Community-Acquired Pneumonia: Impact of Nutritional and Inflammatory Factors", Scandinavian Journal of Infectious Diseases, 2009
Publication <1%

19 Kavelin Rumalla, Adithi Y. Reddy, Vijay Letchuman, Manoj K. Mittal. "Hyponatremia in Guillain–Barré Syndrome", Journal of Clinical Neuromuscular Disease, 2017
Publication <1%

20	Submitted to University of Witwatersrand Student Paper	<1%
	Viana, Marina Verçoza, Rafael Barberena Moraes, Amanda Rodrigues Fabbrin, Manoella Freitas Santos, Vanessa Bielefeldt Leotti Torman, Silvia Regina Vieira, Jorge Luiz Gross, Luis Henrique Canani, and Fernando Gerchman. "Contrasting effects of preexisting hyperglycemia and higher body size on hospital mortality in critically ill patients: a prospective cohort study", BMC Endocrine Disorders, 2014. Publication	<1%
22	Submitted to University of Southampton Student Paper	<1%
23	Submitted to University of the Free State Student Paper	<1%
24	ikm.ku.dk Internet Source	<1%
25	www.researchgate.net Internet Source	<1%
26	www.thieme-connect.com Internet Source	<1%

27 Sasso, Milène, Elsa Chastang-Dumas, SophieBastide, Sandrine Alonso, Catherine Lechiche, <1%
Nathalie Bourgeois, and Laurence Lachaud. "Performances of four real-time PCR assays for the diagnosis of Pneumocystis jirovecii pneumonia.", Journal of Clinical Microbiology, 2015.
Publication

---

eprints.gla.ac.uk
28 Internet Source
<1%

<1%

Juan Carlos López-Hernández, Luis Enrique
29
Colunga-Lozano, Sofia Garcia-Trejo, Enrique Gomez-Figueroa et al. "Electrophysiological subtypes and associated prognosis factors of Mexican adults diagnosed with Guillain-Barré syndrome, a single center experience", Journal of Clinical Neuroscience, 2020
Publication

---

gavinpublishers.com
30 Internet Source
<1%

---

www.scielo.br
31 Internet Source
<1%

K. SUPPLEMMENTARY TABLES

1. Diagnostic criteria for Guillain–Barré syndrome

As per latest guidelines from Leohard et al article on diagnosis and management of GBS in ten step.

Features required for diagnosis

• Progressive bilateral weakness of arms and legs (initially only legs may be involved)

• Absent or decreased tendon reflexes in affected limbs (at some point in clinical course)

Features that strongly support diagnosis

• Progressive phase lasts from days to 4 weeks (usually <2 weeks)

• Relative symmetry of symptoms and signs

• Relatively mild sensory symptoms and signs (absent in pure motor variant)

• Cranial nerve involvement, especially bilateral facial palsy

• Autonomic dysfunction

• Muscular or radicular back or limb pain

• Increased protein level in cerebrospinal fluid (CSF); normal protein levels do not rule out the diagnosis

• Electrodiagnostic features of motor or sensorimotor neuropathy (normal electrophysiology in the early stages does not rule out the diagnosis)

Features that cast doubt on diagnosis

• Increased numbers of mononuclear or polymorphonuclear cells in CSF (>50 × 106/l)

• Marked, persistent asymmetry of weakness

• Bladder or bowel dysfunction at onset or persistent during disease course

• Severe respiratory dysfunction with limited limb weakness at onset

• Sensory signs with limited weakness at onset

• Fever at onset

• Nadir <24 h

• Sharp sensory level indicating spinal cord injury

• Hyper- reflexia or clonus

• Extensor plantar responses

• Abdominal pain

• Slow progression with limited weakness without respiratory involvement

• Continued progression for >4 weeks after start of symptoms

• Alteration of consciousness (except in Bickerstaff brainstem encephalitis)

2. EGRIS scale

MEASURE	**CATEGORIES**	**SCORE**
Days between onset of weakness and hospital admission	**>7days**	**0**
	4-7days	**1**
	<3days	**2**

Facial and/or bulbar weakness at hospital admission	**Absent**	**0**
	present	**1**
MRC sum score at hospital admission	**60-51**	**0**
	50-41	**1**
	40-31	**2**
	30-21	**3**
	<20	**4**
EGRIS score	**NA**	**0-7**

3. **HUGHES SCORE (GBS score)**

score	Functional status
0	**Healthy**
1	**Minor symptoms or signs, able to run**
2	**Able to walk 5 meters independently**
3	**Able to walk 5 meters with a walker or support**
4	**Bed or chair bound**
5	**Requiring assisted ventilation**
6	**Death**