CONSENSUS STATEMENT

COVID-19 VACCINATION FOR PATIENTS WITH NEUROLOGICAL DISEASES IN SINGAPORE

CHAPTER OF NEUROLOGISTS
COLLEGE OF PHYSICIANS, SINGAPORE
BACKGROUND / KEY POINTS

Patients with neurological diseases are more likely vulnerable to complications arising from COVID-19.¹⁻³⁴

Vaccines are an important step in protecting the health and safety of patients with neurological diseases. The Chapter of Neurologists of the Academy of Medicine, Singapore, strongly endorses existing vaccination strategies against COVID-19.

Data to support evidence-based recommendations on the implications of vaccination for specific neurologic diseases are not yet available. This document summarises the expert opinions of the Fellows of the Chapter of Neurologists to support the safe rollout of Singapore’s vaccination programme.

The term “vaccines” is used to interchangeably refer to both mRNA and non-mRNA vaccines.

GUIDELINES

COGNITIVE IMPAIRMENT OR DEMENTIA

- Patients with cognitive impairment or dementia have higher mortality from COVID-19 infection.¹⁴
- Dementia also brings many changes in cognitive abilities, affecting a person’s memory, communication, orientation and other abilities. This makes it challenging for people living in the middle to late stages of dementia to follow pandemic safety measures such as lockdowns, quarantines and social distancing.
- No data are available to suggest an increased risk of COVID-19 vaccination in patients with cognitive impairment and dementia compared to their age peers.
- No data are available to suggest a difference in the efficacy of COVID-19 vaccination in patients with cognitive impairment and dementia compared to their age peers.
- No data are available on whether COVID-19 vaccination interferes with cognitive enhancers including donepezil, rivastigmine, galantamine and memantine.

Recommendations:

1. All patients with mild cognitive impairment and the different severity of dementia would derive a greater benefit and are recommended to receive COVID-19 vaccination. This recommendation covers patients with a diagnosis of Alzheimer disease, vascular dementia, frontotemporal dementia, dementia associated with Parkinson disease and Lewy body dementia.
2. Patients on cognitive enhancers including donepezil, rivastigmine, galantamine and memantine could receive COVID-19 vaccination.
EPILEPSY

- Patients with epilepsy are at risk of developing COVID-19. Existing data suggest that patients with epilepsy could have a slightly increased risk of dying from COVID-19.\(^5\)
- As with any vaccine, some persons may develop a fever that could lower their seizure threshold for the short-term but this does not necessarily result in a breakthrough seizure.
- No data are available to suggest an increased risk of COVID-19 vaccination in patients with chronic epilepsy.
- No data are available to suggest a difference in the efficacy of COVID-19 vaccination in patients with chronic epilepsy.
- No data are available on whether COVID-19 vaccination interferes with anti-seizure medications.

Recommendations:

1. Patients with chronic epilepsy would derive an overall benefit and are recommended to receive COVID-19 vaccination. This recommendation covers patients with primary generalised epilepsy, juvenile myoclonic epilepsy and other causes of secondary epilepsy in the setting following stroke, brain trauma and brain tumour.

2. Patients on antiepileptic medications including carbamazepine, phenytoin, valproate, topiramate, levetiracetam and lamotrigine could receive COVID-19 vaccination.

3. Patients with epilepsy are recommended to ensure adequate sleep (at least 8 hours), remain well-hydrated and excellent compliance to their medications before and after vaccination. As a febrile reaction could trigger seizures, early treatment of fever with anti-pyretic medications (e.g. paracetamol, cold sponging etc) is recommended to reduce the risk of breakthrough seizures.

MIGRAINE AND OTHER PRIMARY HEADACHE DISORDERS

- Headaches may develop as a side-effect of COVID-19 vaccine. It is generally transient, self-limiting and associated with other post-vaccination symptoms.
- In patients with migraine and other primary headache disorders, aggravation of headaches have been reported following COVID-19 vaccination.
- No data are available to suggest a difference in the efficacy of COVID-19 vaccination in patients with chronic migraine and other primary headache disorders.
- No data are available to suggest a difference in the efficacy of COVID-19 vaccination with the use of monoclonal antibodies targeting the calcitonin gene-related peptide (CGRP) pathway (Erenumab, Galcanezumab, Fremanezumab, Eptinezumab), onabotulinumtoxinA (Botox) injections, triptans and non-steroidal anti-inflammatory drugs.

Recommendations:

1. Patients with migraine and other primary headache disorders would derive an overall benefit and are recommended to receive COVID-19 vaccination.
2. Patients with migraine and other primary headache disorders should continue to adhere to their existing acute and preventive treatment before and after each vaccination. Physicians should consider and exclude secondary headache disorders for patients who develop headaches post-vaccination, especially if there are atypical features (‘red flags’) on clinical assessment.

3. In patients who develop transient headaches or experience systemic symptoms after the first dose of the COVID-19 vaccine, we do not recommend omitting or delaying the second dose of COVID-19 vaccine.

4. In patients who developed headaches or fever post-COVID-19 vaccination, administration of paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) is unlikely to alter the immunologic response to the vaccine.

5. Before vaccination, patients with migraine and other primary headache disorders are advised to pay attention to their hydration status, avoid skipping meals, ensure adequate sleep (at least 8 hours) and the avoidance of alcohol or other known headache triggers.

6. We do not recommend routine premedication with migraine-specific medications and over-the-counter analgesics to prophylactically treat potential post-vaccination headaches. However, physicians may consider the need for premedication should severe headaches are encountered following the first dose of COVID-19 vaccine.

**MOVEMENT DISORDERS**

- The approved COVID-19 vaccines and the vector vaccines under development induced immunization through mechanisms that do not interact with the neurodegenerative process in Parkinson disease.

- There is no evidence that the immune response arising from these vaccines interferes with the inflammatory mechanisms implicated in Parkinson disease.

- No data are available to suggest a difference in the efficacy of COVID-19 vaccination in patients with Parkinson’s disease.

- There is no evidence to suggest that COVID-19 vaccination interferes with existing treatment of Parkinson disease, specifically levodopa, entacapone, seligiline, rasagiline, ropinirole and pramipexole.

**Recommendations:**

1. Patients with a diagnosis of Parkinson disease, with or without being on treatment, should proceed to receive the COVID-19 vaccination.

2. We do not recommend a change in daily dose and frequency in medications in preparation for COVID-19 vaccination.

**NEUROIMMUNOLOGY**

- COVID-19 vaccines are unlikely to trigger a relapse/flare of the pre-existing central nervous system inflammatory demyelinating diseases (CNSIDD). The risk of COVID-19 infection exceeds the risk of having a relapse/flare due to COVID-19 vaccination.\(^6,7\)
• COVID-19 vaccine is considered safe for use in patients on disease modifying treatments (DMTs). There is currently no data to suggest that COVID-19 vaccines will interact directly with DMTs commonly used for CNSIDD.

• With regards to specific DMTs used by patients with CNSIDD:
  ▪ Interferon-β, glatiramer acetate, dimethyl fumarate, teriflunomide, and natalizumab are not associated with marked immunosuppression. Thus, they are unlikely to interfere with COVID-19 vaccine responses.
  ▪ Fingolimod and anti-CD20 therapies (i.e. rituximab and ocrelizumab) result in attenuated vaccination responses. An immune response can still be elicited and is likely to confer some protective benefit.
  ▪ Immune reconstitution therapies (i.e. alemtuzumab and cladribine) are likely to attenuate vaccination response. An immune response can still be elicited and is likely to confer some protective benefit.
  ▪ Corticosteroids used in greater than physiological doses can reduce the immune response to vaccines. It is reasonable to infer that an immune response will still be elicited with some protective benefit, particularly at a low to moderate steroid dose (i.e. <20mg of prednisolone or equivalent).
  ▪ There is little data on the effects of azathioprine and mycophenolate mofetil on vaccination response. It is reasonable to infer that an immune response can still be elicited with some protective benefit, particularly when azathioprine at <3.0 mg/kg/day is considered as a ‘low grade’ immunosuppression.

Recommendations:
1. Patients with CNSIDD would derive an overall benefit and are recommended to receive COVID-19 vaccination. This recommendation covers patients with multiple sclerosis and neuromyelitis optica spectrum disorders, regardless of whether they are on DMTs.
2. We do not recommend stopping or changing dosing regimen of DMTs in preparation for COVID-19 vaccination.
3. Patients on Interferon-β, glatiramer acetate, dimethyl fumarate, teriflunomide and natalizumab are recommended to proceed with COVID-19 vaccination.
4. Where feasible, patients on Fingolimod and a related sphingosine-2-phosphate receptor modulator Siponimod, anti-CD20 therapies (i.e. rituximab and ocrelizumab) and immune reconstitution therapies (i.e. alemtuzumab and cladribine) are recommended to coordinate the timing of their vaccination with DMT dosing (refer to APPENDIX).
5. Patients on steroids, azathioprine and mycophenolate mofetil are recommended to proceed with COVID-19 vaccination.

NEUROMUSCULAR DISEASE
• In patients with neuromuscular disease, including those on immunosuppressant agents, the risk of COVID-19 infections likely outweighs the potential risks of COVID-19 vaccines.
• There are currently no data regarding the safety and efficacy of COVID-19 vaccines in patients with neuromuscular disease who are taking immunosuppressant agents.
vaccine benefits of reducing COVID-19 infection likely outweigh the potential risks of COVID-19 vaccines.

- There are currently no data on the safety and efficacy of COVID-19 vaccines in patients with history of Guillain-Barre syndrome and autoimmune neuromuscular disease. In clinical trial participants who received COVID-19 vaccine, there was no significant increased risk of developing autoimmune or inflammatory disorders compared with placebo. However there are no specific data on the risk of exacerbation of autoimmune neuromuscular diseases by the COVID-19 vaccine. The vaccine benefits of reducing COVID-19 infection likely outweigh the potential risks of COVID-19 vaccines.

- In patients receiving intravenous immunoglobulin (IVIG), the response to COVID-19 vaccine may be attenuated.

**Recommendations:**

1. Patients with neuromuscular disease are likely to derive an overall benefit and are recommended to receive COVID-19 vaccination. Those who are on immunosuppressants should be counselled on the lack of available safety and efficacy data of COVID-19 vaccines in this population.

2. Patients with autoimmune conditions, including history of Guillain-Barre syndrome, are likely to derive an overall benefit and are recommended to receive COVID-19 vaccination. The patients may be counselled on the lack of data regarding the risk of exacerbation of autoimmune neuromuscular disease.

3. We recommend for patients on IVIG to receive IVIG 14 days before the first dose of COVID-19 vaccination and to resume IVIG 14 days after the second dose, if feasible.

**STROKE**

- Ischaemic stroke, haemorrhagic stroke and cerebrovenous thrombosis have been reported following SARS-CoV-2 infection.\(^{18,19}\)

- Patients with a history of previous stroke have increased risk of mortality following SARS-CoV-2 infection. Among patients with previous stroke, pooled analysis of 4 studies reported a ~2.5-fold increase in odds of severe COVID-19.\(^{20,21}\)

- There are currently no data regarding the safety and efficacy of COVID-19 vaccines in patients with ischaemic stroke, haemorrhagic stroke and cerebrovenous thrombosis.

- As stroke patients harbour increased risk of adverse outcomes following SARS-CoV-2 infection, the overall benefits of COVID-19 vaccine are likely to outweigh the risk of vaccination.

- Although concurrent use of antiplatelet or anticoagulation for stroke prevention could increase the risk of bleeding, the risk of clinically significant bleeding is low and can be mitigated by direct pressure.

We endorse the recommendations by the Chapter of Haematologists (published 30 January 2021)\(^{27}\) and recommend vaccination in patients on anticoagulation treatment. However, we do not recommend interruption in anticoagulation or delaying treatment in all stroke patients on anticoagulation.
Recommendations:

1. Patients with stroke or cerebrovenous thrombosis are likely to derive an overall benefit and are recommended to receive COVID-19 vaccination.

2. The risk of clinically significant bleeding is low for patients with antiplatelet (e.g. aspirin, clopidogrel, dipyridamole or ticlodipine) and anticoagulation (warfarin, rivaroxaban, apixaban and dabigatran).

3. The vaccine should be administered intramuscularly. There is no data for subcutaneous route and it should not be done. The smallest gauge needle available (25-27 gauge) should be used, if possible. Pressure should be applied to the site for at least 5-10 minutes post-injection to reduce bleeding and swelling. Additionally, self-inspection/palpation of the injection area several minutes and 4-6 hours later is recommended to ensure that there is no delayed haematoma. Discomfort in the arm felt for 1-2 days after injection should not be alarming unless it worsens and is accompanied by swelling. Any adverse events (e.g., haematoma, allergic reaction) should be reported to the vaccination clinic or emergency department.

4. For patients on warfarin:
   - Patients with stable anticoagulation with international normalized ratio (INR) <3 on their last scheduled visit can receive intramuscular vaccination without stopping or interrupting medications.
   - Patients with higher intensity anti-thrombotic treatment (e.g. warfarin with a target INR >=3.0 or concomitant use of antiplatelet and warfarin) should be managed on an individual basis in consultation with their primary physician. Physicians may consider repeating INR at least 3 days before the scheduled vaccination and, if necessary, reduce or omit warfarin dose to ensure INR <3.0 before vaccination. Warfarin should be resumed immediately after vaccination if there are no bleeding complications.

5. For patients on direct oral anticoagulants:
   - Patients on once daily rivaroxaban and on twice daily dabigatran or apixaban can receive intramuscular vaccination without stopping or interrupting medications.

6. For patients on anti-platelet agents:
   - Patients on single agent anti-platelet therapy (e.g., aspirin or clopidogrel) can continue these medications without any adjustment.

Patients on dual antiplatelet agents should be managed on an individual basis and in consultation with their primary physician.
Excerpt from “patients with central nervous system inflammatory demyelinating diseases (including multiple sclerosis and neuromyelitis optica spectrum disorders)”.

With regards to specific DMTs used by patients with CNSIDD:

1) **Interferon-β, glatiramer acetate, dimethyl fumarate, teriflunomide, and natalizumab** are not associated with marked immunosuppression. Thus, they are unlikely to interfere with COVID-19 vaccine responses.
   - Patients on these DMTs are recommended to proceed with COVID-19 vaccination.\(^\text{22,23}\)

2) Vaccination response is known to be attenuated in **fingolimod**-treated patients.\(^8\)
   - It is recommended that patients already on fingolimod do not stop therapy in view of the risk of MS rebound disease and to proceed with COVID-19 vaccination.\(^\text{22,23}\)
   - Patients starting fingolimod for the first time should discuss with their treating clinical team to decide whether it is preferable to defer treatment until COVID-19 vaccination is complete. If vaccination is given prior to fingolimod, the second vaccination dose should be given at least 2 to 4 weeks before starting treatment.\(^\text{23}\)
   - It is reasonable to apply the same recommendation to **siponimod**, a related sphingosine-1-phosphate receptor modulator.

3) Vaccination response is known to be attenuated in **anti-CD20 therapies** (i.e. **rituximab** and **ocrelizumab**), although an immune response can still be elicited, and is likely to confer some protective benefit.\(^\text{9-13}\)
   - It is recommended that patients with CNSIDD on anti-CD20 therapies proceed with COVID-19 vaccination as some protection is better than no protection. **However, the timing of COVID-19 vaccination may need to be coordinated with the dosing of anti-CD20 therapies.**
   - If an anti-CD20 therapy has been given recently, it is recommended to delay COVID-19 vaccination for at least 3 to 4 months from the last infusion.\(^\text{22,23}\) If possible, it may be preferable to delay COVID-vaccination such that the second vaccination dose is administered at least 2 to 4 weeks before the next treatment.\(^\text{22,23}\)
   - Patients starting anti-CD20 therapies for the first time should discuss with their treating clinical team to decide whether it is preferable to defer treatment until COVID-19 vaccination is complete. If vaccination is given prior to anti-CD20 therapies, it is recommended that vaccination is completed 2 to 4 weeks prior to starting treatment.

4) Vaccination response is likely to be attenuated in **immune reconstitution therapies** (i.e. **alemtuzumab** and **cladribine**).\(^\text{14,15}\)
   - It is recommended that patients with CNSIDD on immune reconstitution therapies proceed with COVID-19 vaccination as some protection is better than no protection. **However, the timing of COVID-19 vaccination may need to take into consideration the dosing of these therapies.**
• For patients with CNSIDD on treatment with immune reconstitution therapies, it is recommended to delay COVID-19 vaccination for at least 3 months following the last treatment, preferably when lymphocyte counts have recovered.23,24

• If the second course of alemtuzumab or cladribine is due, a delay of several months can be reasonably considered, to allow for the completion of COVID-19 vaccination.23

• Patients with CNSIDD who had completed alemtuzumab or cladribine treatment (i.e. Cycle 1 and 2 completed) more than 6 months ago and have undergone full immune reconstitution (i.e. recovery of lymphocyte count) are expected to mount an immune response to COVID-19 vaccination, thus vaccination is recommended in this group of patients.22,24,25

• Patients starting alemtuzumab or cladribine for the first time should discuss with their treating clinical team to decide whether it is preferable to defer treatment until COVID-19 vaccination is complete. If vaccination is given prior to these immune reconstitution therapies, the second vaccination dose at should be given at least 2 to 4 weeks before starting treatment.23

5) There is little evidence or guidance with regards to steroid use in patients with CNSIDD in the context of vaccination. It is known that corticosteroids used in greater than physiological doses can reduce the immune response to vaccines,16 but it is reasonable to infer that an immune response will still be elicited with some protective benefit, particularly at a low to moderate steroid dose (i.e. <20mg of prednisolone or equivalent).16

• It is advised not to delay COVID-19 vaccination for someone who is taking, has received or is soon to receive steroids in any form.26

• If additional steroids are required to control the underlying inflammatory disease, that may take priority, as a flare can also worsen the risk from COVID-19.26

6) There is little evidence or guidance with regards to azathioprine or mycophenolate use in patients with CNSIDD in the context of vaccination. It is reasonable that patients with CNSIDD on azathioprine or mycophenolate may proceed with COVID-19 vaccination, with an expectation that an immune response can still be elicited with some protective benefit, particularly when azathioprine at <3.0 mg/kg/day is considered as a ‘low grade’ immunosuppression.16

• It is recommended that patients with CNSIDD on azathioprine or mycophenolate proceed with COVID-19 vaccination, with an expectation that an immune response can still be elicited with protective benefit.
REFERENCES


## ACKNOWLEDGEMENT

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