





Consensus recommendation on the use of therapeutic plasma exchange for adult neurological diseases in Southeast Asia from the Southeast Asia therapeutic plasma exchange consortium

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ABSTRACT

Therapeutic plasma exchange (TPE) is an effective and affordable treatment option in most parts of Southeast Asia (SEA). In 2018, the SEA TPE Consortium (SEATPEC) was established, consisting of regional neurologists working to improve outcome of various autoimmune neurological diseases. We proposed an immunotherapeutic guideline prioritizing TPE for this region. We reviewed disease burden, evidence-based treatment options, and major guidelines for common autoimmune neurological disorders seen in SEA. A modified treatment algorithm based on consensus agreement by key-opinion leaders was proposed. Autoimmune antibody diagnostic testing through collaboration with accredited laboratories was established. Choice of first-line immunotherapies (IVIg/corticosteroid/TPE) is based on available evidence, clinicians' experience, contraindications, local availability, and affordability. TPE could be chosen as first-line therapy for GBS, CIDP, MG (acute/short term), IgG, A paraproteinemic neuropathy, and NMDAR encephalitis. Treatment is stopped for acute monophasic conditions such as GBS and ADEM following satisfactory outcome. For chronic immune disorders, a therapy taper or long-term maintenance therapy is recommended depending on the defined clinical state. TPE as second-line treatment is indicated for IVIg or corticosteroids refractory cases of ADEM, NMOSD (acute), MG, and NMDAR/LGI1/CASPR2/Hashimoto's encephalitis. With better diagnosis, treatment initiation with TPE is a sustainable and effective immunotherapy for autoimmune neurological diseases in SEA.

KEYWORDS: therapeutic plasma exchange, plasmapheresis, Southeast Asia, autoimmune neurological disorders, central nervous system, peripheral nervous system

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Introduction

Therapeutic plasma exchange (TPE), also known as plasmapheresis, is a procedure that separates plasma from whole blood, therefore effectively removing abnormal circulating antibodies and other pathogenic factors contributing to autoimmune diseases.^{1,2} Based on this principle and mechanism of action, a

wide variety of immune-mediated diseases can be treated with TPE. In the recent years, there is growing interest among adult neurologists in using TPE for various antibody-mediated central nervous system (CNS) and peripheral nervous system (PNS) disorders.³⁻⁵ Among major contributory factors to this trend include increased cost and limited supply of intravenous



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immunoglobulin (IVIg) for acute life-threatening conditions such as Guillain-Barré syndrome (GBS), refractory myasthenia gravis (MG), and autoimmune encephalitis, as well as a significant improvement and developments in TPE technology.^{3,6,7}

From SEA perspectives, management of patients with various autoimmune neurological diseases in these under-served regions is challenging for its limited number of trained neurologists, which are also poorly equipped in terms of healthcare facilities and funding for medical supplies.⁵ In countries with low earning per capital, availability of immunotherapies such as IVIg and standard TPE is very restricted and limited to only major referral centers that come with high cost. Disease-targeted therapy with monoclonal antibodies is available in only few countries such as Brunei, Indonesia, Malaysia, Myanmar, Singapore, and Thailand, majority of them requiring special indications and approvals.^{4,5} TPE technology is considered as a more cost-effective and sustainable treatment alternative to other expensive immunotherapies in SEA.⁸

Clinicians in this region refer to published international guidelines such as the American Association of Neurologists (AAN) and the American Society for Apheresis (ASFA) in performing TPE for autoimmune neurological disorders.^{9,10} These evidence-based guidelines focus on the use of standard TPE through medical devices and other therapeutic apheresis modalities including immunoadsorption (IA) and double filtration plasmapheresis (DFPP). The suggested primary and secondary indications for TPE are based on available published evidence, taking into consideration the efficacy of other immunotherapies of a specific disorder.

However, in many parts of SEA, standard TPE devices are not available. Besides, many clinicians in less-served areas in SEA have limited experience in treating autoimmune neurological disorders, more so in performing standard TPE. For clinicians with access to TPE, but due to limited availability of alternative treatment options, strict application of TPE based on evidence-based indications is difficult to follow and, in many instances, TPE is used as primary therapy due to lack of treatment choices such as in the cases of maintenance treatment for autoimmune encephalitis, inflammatory myopathies, and MS as well as NMOSD. All above factors have resulted in significant treatment variability. Therefore, a simple and practical guide to clinicians on indications and applications of TPE in immune-medicated neurological diseases from a purely SEA perspective is relevant to provide consideration for clinicians on how best TPE is applied.

In 2018, a regional SEA TPE Consortium (SEATPEC) for neurological disorders was established to enhance regional collaboration via information and technology exchange to improve delivery of best TPE knowledge in SEA. This consortium is an independent body made up of key-opinion leaders with interest in TPE from SEA countries (except Cambodia and Timor Leste at that time), supported by international experts as advisors. It is a multi-national Southeast Asian working group moving toward increasing the awareness, accessibility, education, and research for multimodality TPE within the region. The contents of this document include:

- 1) Summary of updated indications for TPE along with other available immune therapies for optimal practice, tailored to the current provision in SEA.
- 2) Consensus algorithm on management of autoimmune neurological diseases, including diagnostic workup, immunotherapies, and monitoring of treatment response.
- 3) Technical aspects of TPE procedures.
- 4) Brief overview of provision of TPE in SEA.

This document does not intend to discuss in detail the specific pathogenesis and treatments of these disorders including the mechanism of action of TPE, but rather provides a general guidance in using TPE as part of immunotherapy which is subject to individual countries' caveats and respective local situations as well as legislation.

Methods

The production of this document was done based on 3 stages of working processes involving different methodologies. In stage 1, we gather relevant data on disease spectrum, burden, and treatment challenges in the SEA region. A thorough review of available literature in TPE for neurological diseases was conducted. In stage 2, clinical consensus and treatment algorithms were proposed, based on expert opinion and the best available research evidence. The resulting statements for which consensus is achieved identified opportunities to improve patient care and clinical outcomes. In stage 3, a clinical consensus statement was presented for review and final agreement by SEATPEC members. A clinical consensus statement is considered the best model when available evidence was insufficient for a clinical practice guideline (CPG).

First stage: *Understanding disease spectrum, burden, and treatment challenges in SEA*

We first determined the most frequently encountered adult autoimmune neurological disorders encountered by neurologists in SEA and their disease burden. Due to the limited published literature from this region, we conducted an online survey to neurologists from major neurology institutions within the region to identify the current neuroimmunological disease spectrum. From the same survey, we identified available immune treatment options in various parts of SEA, taking into consideration the practice of both standard and alternative therapies. To understand disease burden, we conducted a literature search in Medline search of all published articles from SEA on both CNS and PNS disease prevalence and incidence.

Second stage: *Proposal for TPE treatment algorithm based on expert opinion and the best available research evidence*

We summarized the latest available evidence on diagnosis and immunotherapies, specifically on indications for TPE for various autoimmune neurological diseases. Major guidelines, consensus

recommendations, and updated review articles were reviewed. Particular emphasis was placed on the use of TPE as standard of care, and in disorders in which TPE works better than other immunotherapies. A proposed treatment algorithm was suggested.

Third stage: *Review of proposed treatment algorithm by key-opinion leaders from SEATPEC*

Proposed TPE treatment algorithm was then presented and discussed among SEATPEC members during the recent second SEATPEC meeting held in Yangon, Myanmar. All member countries contributed equally to the discussion with final agreement to endorse the proposed treatment algorithm.

Consensus statements

Autoimmune neurological disease in SEA. Based on a recent survey conducted in 2018 among neurologists from major neurology institutions in SEA, the spectrum of immune-mediated neurological disorders seen in SEA was, in general, very similar in most countries.⁵ NMOSD, multiple sclerosis (MS), idiopathic transverse myelitis, and autoimmune encephalitis were the most commonly encountered CNS disorders. Paraneoplastic neurological disorders, acute disseminated encephalomyelitis (ADEM), chronic relapsing inflammatory optic neuropathy (CRION), and CNS vasculitis were less commonly diagnosed. For PNS disorders, MG and Guillain-Barré syndrome (GBS) were the most commonly treated, followed by CIDP, multifocal motor neuropathy (MMN), and IgM neuropathy as well as inflammatory myositis. As the survey was conducted among adult neurologists, pediatric spectrum of autoimmune disorders was not reported.

We found very few publications on the burden of autoimmune neurological diseases across SEA countries. For CNS demyelinating diseases, the prevalence of multiple sclerosis (MS) is estimated to be between .20 and 6.6 per 100,000 population, while for NMO, it is estimated to be between .40 and 3.8 per 100,000 population based on 3 separate studies from Malaysia, Singapore, and Thailand.¹¹⁻¹³ In comparison, the prevalence of MS in some SEA region is almost 3 times higher compared to other countries from the equatorial region (1-2/100,000) and, similarly, the prevalence of NMO in some countries in SEA is more than 3 times of the western population (~1/100,000).¹⁴⁻¹⁶ We found no published epidemiological data on incidence of GBS in SEA. Due to its monophasic presentation, the estimated incidence of GBS from Southeast Asian countries ranges from .44 to 1.14 per 100,000.¹⁷ This is relatively similar to the incidence in Europe and North America (.84-1.91/100,000). Based on worldwide data, myasthenia gravis prevalence is estimated to be in between 1.5 and 17.9 per 100,000 while CIDP at .6-1.6 per 100,000.^{18,19}

Consensus recommendation for TPE in SEA

The neurological diseases treated with TPE have been categorized by the American Academy of Neurology (AAN) and

the American Society for Apheresis (ASFA).^{9,10} Neurological indications for TPE are summarized in [Table 1](#). The list below does not represent complete neurological disorders that can be treated with TPE, but only those commonly encountered adult autoimmune neurological disorders across SEA and those which have sufficient published evidence to provide recommendations.

Proposed treatment algorithm for individualized use of TPE in adult autoimmune neurological disorders

From the above recommendation, we developed a treatment algorithm for individualized use of TPE in adult immune-mediated neurological disorders ([Figure 1](#)).

This consensus-based algorithm included 4 sections

- 1) Diagnosis (workup) of autoimmune neurological disorders,
- 2) Initiating first-line treatment (monotherapy or with combination),
- 3) Consideration for second-line treatment (as treatment escalation), and
- 4) Third-line treatment (disease-specific individualized therapy).

Diagnosis (workup) of autoimmune neurological disorders. This consensus does not intend to address the detailed and extensive investigations needed to confirm the wide variety of autoimmune neurological diseases. Many of these disorders have existing standard diagnostic criteria and supporting laboratory investigations. Diagnosis is possible through a logical approach in clinical reasoning, supported by standard diagnostic tests (MRI, EEG, and CSF studies). At a regional level, there are a number of local guidelines available for some disorders for reference. We summarized the diagnostic reference for common autoimmune neurological diseases in [Table 2](#).

Autoantibody testing panel

With the advent of specific antibody testing, we are now better able to diagnose various autoimmune disorders and distinguish disorders with overlapping symptomatology such as the case between MS, NMOSD, and myelin oligodendrocyte glycoprotein antibody (MOG-Ab)-associated disease.³⁰ Realizing the important role of autoimmune antibody testing in assisting the diagnostic workup, SEATPEC has, in collaboration with a center in India, mooted to offer affordable neuroimmunology panels for selected SEATPEC countries with good clinical expertise, but lack diagnostic funding or testing facilities ([Table 3](#)). The test panels offered are crucial antibody tests, carried out on serum specimens which are to be couriered over to this center, which would process all received samples and report results directly to the

Table 1. TPE for neurological indications and evidence from AAN 2011 and ASFA 2019.

DISEASE		QUALITY (AAN 2011)	CONCLUSION	ASFA 2019	CATEGORY	GRADE
Central nervous system						
Multiple sclerosis						
	Relapses	Class I	Probably effective	Acute attack/ relapse	II	1A
	Fulminant	Class II	Probably effective			
	Progressive	Class I	Established ineffective	Chronic	III	2B
NMOSD						
	Acute			Acute attack/ relapse	II	1B
	Maintenance			Maintenance	III	2C
ADEM		Class II	Probably effective	Steroid refractory	II	2C
LGI1/CASPR2 encephalitis					II	1B
NMDAR encephalitis					I	1C
Steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)					II	2C
Paraneoplastic neurological syndromes					III	2C
Peripheral nervous system						
Guillain-Barré syndrome		Class I	Established effective	Primary treatment	I	1A
CIDP		Class I	Established effective		I	1B
Myasthenia gravis						
	Crisis	Class III	Insufficient evidence	Acute, short-term treatment	I	1B
	Prethymectomy	Class III	Insufficient evidence	Long-term treatment	II	2B
Paraproteinemic polyneuropathies						
	IgA/IgG	Class I	Probably effective		I	1B
	IgM	Class I	Probably ineffective		I	1B
	Anti-MAG neuropathy				III	1C
Multifocal motor neuropathy					IV	1C

Category Definitions for Therapeutic Apheresis.

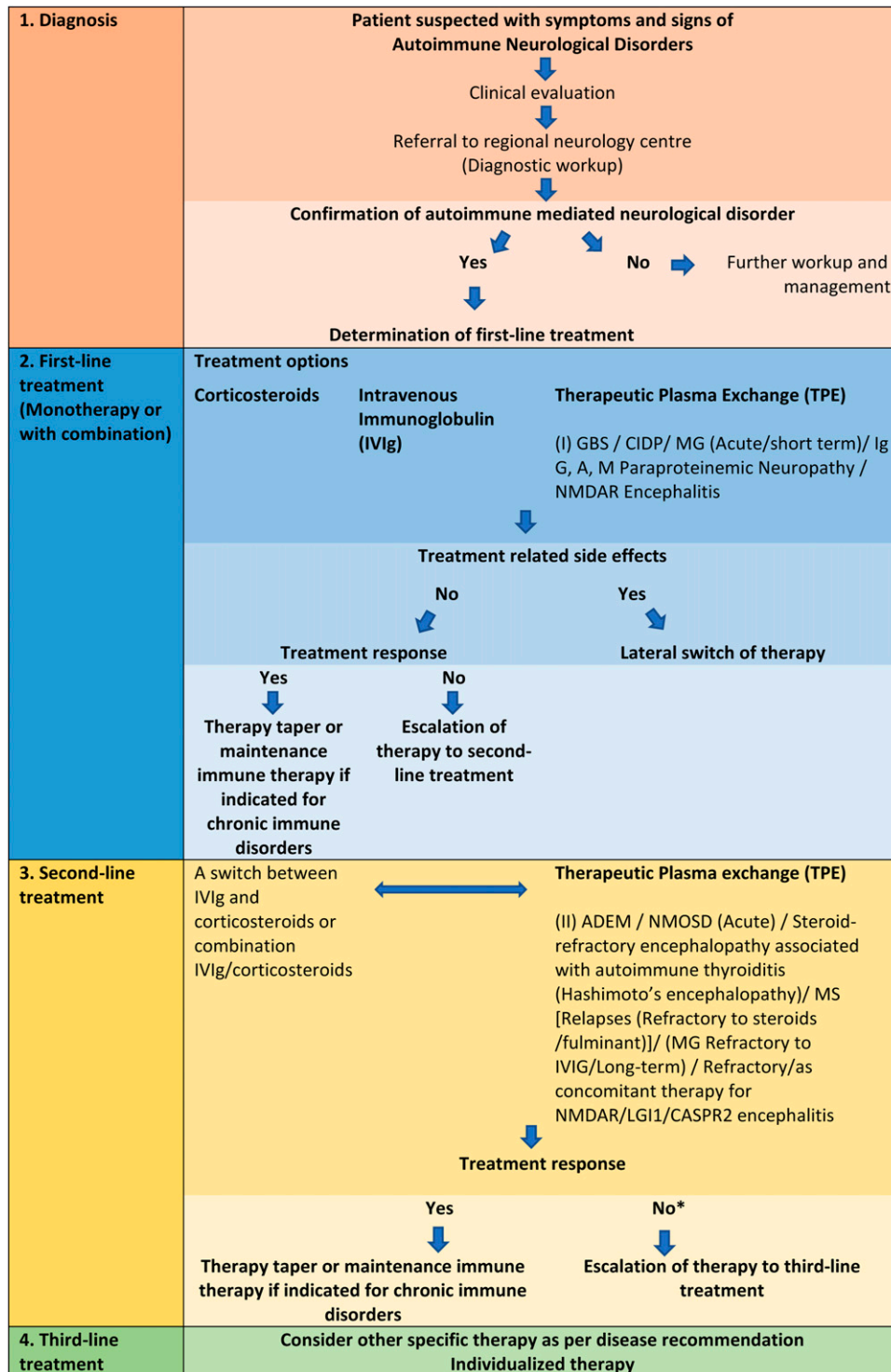
I Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.

II Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.

III Optimum role of apheresis therapy is not established. Decision making should be individualized.

IV Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

AAN: American Association of Neurologists; ADEM, Acute Disseminated Encephalomyelitis; ASFA: American Society for Apheresis; CASPR2: Contactin Associated Protein 2; CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; Ig: Immunoglobulin; LGI1: Leucine-Rich Glioma-Inactivated 1; MAG: Myelin Associated Glycoprotein; NMDAR: N-Methyl-D-Aspartate Receptor; NMOSD, Neuromyelitis Optica Spectrum Disorders; TPE, Therapeutic Plasma Exchange.



*Consider alternative diagnosis

Figure 1. Management algorithm for autoimmune neurological disorders. Consider alternative diagnosis. Abbreviations: ADEM, acute disseminated encephalomyelitis; CASPR2: contactin associated protein 2; CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré Syndrome; IVIg, intravenous immunoglobulin; LGI1: leucine-rich glioma-inactivated 1; MG, myasthenia gravis; MS: multiple sclerosis; NMDAR: N-Methyl-D-Aspartate Receptor; NMOSD, neuromyelitis optica spectrum disorders; TPE, therapeutic plasma exchange

clinician within a pre-determined time frame, commiserate to the urgency of the test.

The funding for this autoantibody testing project is by Project Woodpecker, which is a non-profit community project

supported by public donations. Clinicians intending to deliver serum samples are advised to consult local customs and health authorities for sample delivery procedures and required ethical approval. In keeping with current ethical issues and data

Table 2. Recommended regional and international guidelines for diagnosis and work-up of patients with autoimmune neurological diseases.

AUTOIMMUNE DISORDERS	GUIDELINES
Multiple sclerosis	Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria ²⁰ Clinical practice guidelines: Multiple sclerosis and neuromyelitis optica spectrum disorder Thailand 2018 ²¹ Clinical practice guideline: Management of multiple sclerosis Malaysia 2015 ²²
NMOSD	International consensus diagnostic criteria for neuromyelitis optica spectrum disorders ⁶ Clinical practice guidelines: Multiple sclerosis and neuromyelitis optica spectrum disorder Thailand ²¹ Clinical practice guideline: Management of multiple sclerosis Malaysia ²²
GBS	Diagnostic criteria for Guillain-Barré syndrome (GBS) ²³
CIDP	EFNS diagnostic criteria for CIDP 2010 ²⁴
MMN	EFNS diagnostic criteria for MMN 2010 ²⁵
Paraproteinemic polyneuropathies	EFNS diagnostic criteria for paraproteinemic neuropathy 2010 ²⁶
Myasthenia gravis	Myasthenia gravis: Association of British neurologists' management guidelines ²⁷ International consensus guidance for management of myasthenia gravis 2016 american academy of neurology ²⁸
Autoimmune encephalitis Anti-NMDA receptor encephalitis Autoimmune limbic encephalitis Acute disseminated encephalomyelitis (ADEM) Hashimoto's encephalopathy	A clinical approach to diagnosis of autoimmune encephalitis 2016 ⁷
Paraneoplastic neurological syndromes	Recommended diagnostic criteria for paraneoplastic neurological syndromes 2004 ²⁹

ADEM, acute disseminated encephalomyelitis; CIDP, chronic inflammatory demyelinating polyneuropathy; EFNS: european federation of neurological societies; GBS, guillain-barré syndrome; MMN: multifocal motor neuropathy; NMDAR: N-Methyl-D-Aspartate Receptor; NMOSD, neuromyelitis optica spectrum disorders.

protection acts, as well as the methodology of counseling patients for sending these samples, the potential results whether positive or negative, possibility of samples getting lost, and clinical and ethical implications would be very much at the discretion of individual participating neurologists from individual SEATPEC countries and comply with local regulations. But this project provides much needed accessibility and availability of testing to member countries from resource-limited settings. It bodes for future consideration at a global and more international level for other regions.

Initiating first-line treatment (monotherapy or with combination). The treatment algorithm is summarized in [Figure 1](#). This is a stepwise escalation algorithm for immunotherapy in autoimmune neurological disorders.

Using existing two-tier grading systems based on both a category for an indication for apheresis, I through IV, and a grading recommendation, 1A thru 2C, we developed a treatment algorithm by identifying conditions for first-line treatment categorized as category 1 indication for TPE. These are conditions for which apheresis is accepted as first-line therapy, either as a primary stand-alone treatment or in conjunction with other modes of treatments. Disorders for which apheresis was accepted as second-line therapy, either as a stand-alone treatment or in conjunction with other modes of treatment, are those in category 2 indication for TPE.

Once a diagnosis of autoimmune disorders is confirmed, patients are treated with one of the first-line immune therapies (IVIg/corticosteroids/TPE). When immunotherapy is deemed necessary, a choice between IVIg, corticosteroids, and TPE is made based on available evidence, local clinician experience, contraindications, and availability and affordability. For clinicians choosing TPE as first-line treatment, latest evidence recommends the following indications:

(I) GBS/CIDP/MG (acute/short term)/IgG, A, M paraproteinemic neuropathy/NMDAR encephalitis.

In the event of patients experiencing intolerable adverse effects of therapy, lateral switch of therapy between first-line agents is recommended.

Treatment response is assessed after an appropriate period (NB, the interval of which has not been well researched but wise to be kept as short as possible immediately to 1 to 2 weeks) depending on the nature of the disorder, choice to therapy, and expected clinical response after a pre-determined treatment period or regime. The use of validated short- and long-term outcome measures for treatment response is recommended whenever possible. For patients who have responded to first-line therapy, treatment is stopped for acute monophasic conditions such as GBS and ADEM. For chronic immune disorders, a therapy taper may be considered in stable patients suspected of being in a state of remission. Patients not relapsing are monitored every 6–12 months either clinically, serologically,

Table 3. List of autoimmune antibodies offered for selected neurology centers in under-resourced counties in SEA.

TESTS	COMPONENTS	TYPE OF ANTIBODY	NATURE OF SPECIMEN	TEST METHOD	MANUFACTURER
ANTI-AQUAPORIN-4 IIFT	Aquaporin-4	IgG	Serum, EDTA, heparin or citrate plasma and CSF	Cell based IFA	Euroimmun, Germany
ANTI-NEURONAL/ ONCONEURAL ANTIBODY PROFILE	Amphiphysin, CV2, PNMA2 (Ma2/Ta), Hu, Yo, ri, recoverin, Sox1, titin, GAD65 and Tr (DNER)	IgG	Serum, EDTA, heparin or citrate plasma and CSF	Line immunoassay (LIA)	Euroimmun, Germany
ANTIBODY TO AMPA 1 and AMPA 2	AMPA 1 and AMPA 2	IgG	Serum, EDTA, heparin or citrate plasma and CSF	Cell based IFA	Euroimmun, Germany
ANTIBODY TO GABA B RECEPTOR	GABA B RECEPTOR (GABARB1/B2)	IgG	Serum, EDTA, heparin or citrate plasma and CSF	Cell based IFA	Euroimmun, Germany
ANTIBODY TO NMDA RECEPTOR	NMDA receptor	IgG	Serum, EDTA, heparin or citrate plasma and CSF	Cell based IFA	Euroimmun, Germany
ANTIBODY TO VGKC ASSOCIATED PROTEINS	VGKC (CASPR2 and LGI1)	IgG	Serum, EDTA, heparin or citrate plasma and CSF	Cell based IFA	Euroimmun, Germany
AUTOIMMUNE ENCEPHALITIS PANEL	NMDA receptor, VGKC (CASPR2 and LGI1), GABA B RECEPTOR (GABARB1/B2), AMPA 1 and AMPA 2	IgG	Serum, EDTA, heparin or citrate plasma and CSF	Cell based IFA	Euroimmun, Germany
NMOSD SCREEN	Aquaporin-4 and MOG (myelin-oligodendrocyte glycoprotein)	IgG	Serum, EDTA, heparin or citrate plasma and CSF	Cell based IFA	Euroimmun, Germany
MYOSITIS PROFILE TEST (IMMUNOBLOT)	M1-2 β , Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, P1-12, EJ, OJ, and Ro-52	IgG	Serum, EDTA, heparin or citrate plasma and CSF	Line immunoassay (LIA)	Euroimmun, Germany
ANTI-ACETYLCHOLINE RECEPTOR ANTIBODY	Acetylcholine receptor	IgG	Serum, EDTA, heparin or citrate plasma and CSF	ELISA	Euroimmun, Germany
ANTI-GANGLIOSIDE IgM AND IgG ANTIBODY	GM1, GD1b and GQ1b	IgG and IgM	Serum	ELISA	Buhlmann, Switzerland
MUSK ANTIBODY ELISA	Muscle-specific receptor tyrosine kinase (MuSK)	IgG	Serum	ELISA	IBL, Germany

AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CASPR2: Contactin Associated Protein 2; CSF: Cerebrospinal Fluid; EDTA: Ethylenediaminetetraacetic acid; ELISA: Enzyme-linked Immunosorbent Assay; GABA: Gamma-aminobutyric Acid; IFA: Immunofluorescence Assay; Ig: Immunoglobulin; LGI1: Leucine-Rich Glioma-Inactivated 1; LIA: Line Immunoassay; MOG: Myelin-Oligodendrocyte Glycoprotein; MuSK: Muscle-Specific Receptor Tyrosine Kinase; NMDAR: N-Methyl-D-Aspartate Receptor; VGKC: Voltage Gated Potassium Channel-Complex.

electrophysiologically, or with neuroimaging according to specific disease entity and whichever available. For those known chronic relapsing immune disorders, or in patients who deteriorate/relapsed during treatment taper, clinician should consider starting long-term maintenance therapy.

Consideration for second-line treatment (as treatment escalation). Patients experiencing treatment ineffectiveness, due to no or suboptimal response with first-line treatment, or confirmed relapse of disease, should be considered for escalation of treatment to second-line treatments. Patients not achieving expected treatment goals with

IVIg or corticosteroids are considered to be therapy-refractory and are to be treated as such, with a switch between IVIg and corticosteroids, with a combination of IVIg/corticosteroids or a course of TPE.

TPE indications as second-line therapy (either as a stand-alone treatment or in conjunction with other modes of treatment) are as follows:

(II) (ADEM/NMOSD (acute)/steroid-responsive encephalopathy associated with autoimmune thyroiditis (Hashimoto's encephalopathy)/(MG refractory to IVIG/MG long term)/refractory/as concomitant therapy for NMDAR/LGI1/CASPR2 encephalitis.

Third-line treatment (disease-specific individualized therapy). In rare occasions, where treatment with first- and second-line therapies have failed to provide optimal outcomes or patients are experiencing intolerable adverse effects, special consideration for third-line treatments using disease-specific targeted therapy is recommended. The choice of third-line treatment alternatives should be individualized and guided by the latest evidence-based recommendations. Treatment recommendations for each type of autoimmune neurological disorder as well as the use of newer generation therapies are outside the scope of this document. Alternative diagnosis should also be considered in treatment of refractory cases.

Special considerations

Effectiveness of immunotherapy and other medications. Mechanism of TPE involves non-selective removal of plasma and therefore removing both normal and pathologic plasma components. In patients recently receiving IVIg therapy, TPE is not recommended as it removes circulating IVIg. Similarly, certain circulating drugs may be removed by TPE. Clinician should confirm with local pharmacists with regard to the effect of TPE on the pharmacokinetics of these medications. Additional dose of medication may be indicated after TPE procedures.

Guillain-Barré syndrome

In patients with GBS, corticosteroids have not been proven in randomized controlled trials to improve outcomes. Oral corticosteroids and IV methylprednisolone were not beneficial in patients with GBS.^{31,32} Combination of IVIg and methylprednisolone is no more effective than IVIg alone. Therefore, corticosteroid use as first- or second-line therapy is not recommended. IVIg or TPE is recommended as first-line therapy for GBS with similar efficacy. There is no evidence to suggest 1 is superior to another. TPE is most beneficial when started before 4 weeks (and ideally prior to 2 weeks) after onset of symptoms. TPE is contraindicated for haemodynamically unstable patients because of changes in the total blood volume during TPE treatment which may result in exaggerated fluctuations in blood pressure. In patients with predicted poor outcomes showing poor recovery despite adequate doses of IVIg, there is currently no conclusive evidence to suggest the use of repeated doses of IVIg. Similarly, TPE followed by IVIg does not appear to improve patient outcomes.¹⁰

Chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy is a chronic relapsing immune-mediated inflammatory polyneuropathy. Due to its nature of disease, the majority of the patients require long-term maintenance treatment with repeated courses of either IVIG or corticosteroids. Although TPE is considered one of the first-line therapies in CIDP, it is less frequently used as

maintenance therapy due to its related inconveniences. Long-term TPE via peripheral vascular access is an option for those patients who do not respond to corticosteroids or IVIg treatment or are unable to tolerate adverse effects. Furthermore, it is a more easily available and cost-efficient alternative to IVIg. In a subset of CIDP patients with IgG4 NF 155 paranodal antibody with poor response to IVIg and corticosteroids, the use of TPE has shown beneficial effects in some patients.^{33,34}

Multifocal motor neuropathy

The mainstay of therapy for MMN is IVIG. The use of corticosteroids and plasma exchange has not been shown to be beneficial in MMN and in some cases even resulting in paradoxical clinical worsening.^{10,25,35}

Myasthenia gravis

In severe myasthenia gravis exacerbations or crisis, IVIG and TPE are specific immunosuppressive treatments with a rapid effect.³⁶ The efficacy of IVIG and TPE is comparable. The use of high-dose corticosteroids is not recommended due to delayed clinical response and may exacerbate clinical deterioration. A subtype of myasthenia gravis with antibodies to muscle-specific kinase (MuSK) affects 5–8% of all MG patients. MuSK Abs are predominantly IgG4, which can neither activate complement nor induce antigen internalization, but rather cause MG by direct inhibition of protein function.³⁷ Therefore, IVIg has limited effectiveness in MuSK MG and TPE is the recommended treatment in acute exacerbation or crisis. Due to the short effect of both IVIg and TPE, treatment should be combined with standard immunosuppressive drugs such as azathioprine and mycophenolate mofetil for long-term improvement. Periodic plasma exchange can be used, in addition to immunosuppressive therapy, in treating relapsing disease.

Autoimmune encephalitis

Suggested first-line immunotherapies for autoimmune encephalitis involve the use of corticosteroid monotherapy or with either IVIg or TPE which can be given together. If there is no clinical response, second-line therapy (rituximab or cyclophosphamide) is used. There is increasing evidence for the use of rituximab as first-line therapy.⁷

Neuromyelitis optica spectrum disorder

Acute NMOSD attacks are usually treated with intravenous methylprednisolone 1 g/day for 3–5 days, followed by oral steroids to avoid an early relapse.³⁸ Plasma exchange improves the short-term prognosis of NMOSD relapses if given early and has proven effectiveness, regardless of NMOSD-IgG status.³⁹ Five to 7 TPE treatments are the treatment of choice. In patients experiencing treatment relapse while on maintenance immunotherapy

drug, treatment with TPE improves outcomes. Approximately 60% of the patients experience good response to TPE.⁴⁰ In severe cases, early initiation of TPE is associated with better outcomes.⁴¹⁻⁴³

Multiple sclerosis

In acute MS attack/relapse, high-dose IV methylprednisolone (IV MP) up to 1 gm daily over a period of 3–5 days is usually the first-line treatment and has been endorsed by national and international guidelines.⁴⁴ Despite that, only 30% of the patients achieved full remission, with remaining insufficiently treated after the first course of IV MP.⁴⁵ In this context, TPE and immunoadsorption (IA) are considered as second-line therapy.⁴⁶ TPE removes circulating pathogenic humoral factors such as autoantibodies, immune complexes, and inflammatory cytokines, and involved in the modification of proinflammatory mediators and co-stimulatory signals linked to T and B cell-mediated autoimmunity.^{47,48} Treatment of MS involves either maintenance therapy or pulse therapy with one of the many disease modifying agents currently recommended by both local and international guidelines and Food and Drug Administration (FDA) approved for patients with MS subject to availability, patients and clinical preference, side effect profile, and patient's comorbidities.

Acute disseminated encephalomyelitis

ADEM is an acute inflammatory demyelinating disease of the central nervous system that is probably due to an autoimmune mechanism with a monophasic course. Initial treatment involves the use of high-dose corticosteroids, and if outcome is unsatisfactory, intravenous immunoglobulin or TPE is used.⁴⁹ IVIg has also been used either as stand-alone first-line treatment or concomitantly with corticosteroids. TPE should be considered when there is no response to treatment with corticosteroids and/or intravenous immunoglobulin.

Choice of TPE methods

Currently available standard TPE devices separate blood plasma from the whole blood by using either centrifugation or filtration technologies. Centrifugation apheresis separates blood components based on the principle of their specific gravity while the filtration device separates blood components based on their particle size across a membrane filter. Although theoretically centrifugal TPEs are more efficient in terms of plasma removal and therefore shorter treatment time, available literature supports comparable efficacy of both types of exchange devices.

We have previously published our standard TPE protocol as reference for clinicians in SEA with interest to setup TPE services.⁸ Standard TPE procedure involves a large volume of plasma being removed by a TPE device, usually 1–1.5 plasma volumes or 40 mls/kg and replaced with a replacement fluid which can be of normal donor plasma, albumin, or in

combination with colloid/crystalloid solution.^{1,50} Failing to replace the volume removed may result in depletion of patient's oncotic pressure leading to pulmonary and peripheral edema. Significant hypovolemia may result in hypotension. Replacement of plasma with human albumin 5% and crystalloids is preferred. The use of blood products such as fresh frozen plasma (FFP) as plasma replacement was not recommended due to potential infusion-related allergic reactions. Typically, 4–7 sessions of TPE performed on alternate day basis are required to therapeutic target of 150 to 200 mls of plasma per kg body weight.^{1,10,50} Along with standard TPE protocol, we also recommend the use of a pre-procedure checklist that was drawn up to ensure all necessary preparations were complete before starting TPE. Included in the checklist are details as follows: indications for TPE, pre- and post-TPE blood investigations, vital parameters during TPE, positioning of patient, preparation of catheter, observation of potential complications, and catheter care post-TPE.⁸

In addition to standard TPE, there are alternative methods of performing TPE reported in some SEA countries such as limited plasma exchange (LPE), modified plasma exchange (MPE), and small volume plasma exchange (SVPE).⁵¹⁻⁵³ The basic principle of these alternative TPE methods are similar—utilizing basic hospital medical consumables such as blood collection bags, separating plasma from whole blood in multiple small fractions using basic centrifugal machines over several days without the need of a conventional TPE device. Methods and protocols of alternative TPE varies between countries, depending on local setup. Available clinical evidence on efficacy and safety of alternative TPE is limited. SVPE has recently been proven safe and effective in small studies in patients with GBS from Bangladesh and Myanmar.^{51,52} However, due to the limited clinical data, we are unable to make recommendation for clinical application.

Establishment of local and regional TPE registry

In order to capture information on TPE indications, procedure parameters, complications, and outcome efficacy, a local TPE registry establishment is recommended. This is to maintain a systematic record and database of all TPE procedures and for future improvement of services and standard of care. All local TPE registries from individual institutions can be combined to form a more robust registry for the region. This can provide a real-world perspective of TPE practices in SEA region and to improve patient outcomes and safety.

Provision of TPE in SEA

SEA consists of 11 countries with more than 640 million population, about 8.5% of the world's population.⁵⁴ The average gross domestic product (GDP) per capita is US\$3853 according to a 2015 United Nations report. However, there is a considerably big income gap between countries, ranging from US\$1298 (Myanmar) to US\$64,041 (Singapore).⁵⁵

From a recent survey carried out among neurologists from the region, the number of tertiary centers with standard TPE facilities was very limited. Estimated ratio between number of neurology centers with TPE facilities to the country's population ranges from the lowest 1:1.1 million population (Singapore) to highest of 1:26 million (Indonesia).⁵ Although majority of the countries have existing technology to perform standard (conventional) full TPE procedures, the use was limited by the high treatment-related costs and restriction in reimbursement.

Majority of the neurology centers in major SEA cities rely on the TPE services and facilities supported by hematology, nephrology, and intensive care teams. Nephrology hemodialysis units typically utilize membrane filtration TPE via central venous catheters. In contrast, hematologists often perform TPE with centrifugation technique, either via central or peripheral venous access. Some neurology centers in SEA are equipped with in-house standard modern TPE facilities under the provision of neurologists.⁸

To improve delivery of TPE services in SEA, concrete measures are to be introduced in many aspects. First, there is a need to equip standard TPE facilities in major neurology centers, supported by trained TPE operators. Establishment of regional centers for TPE support is important to provide wider service coverage for surrounding areas. An efficient referral networks is needed in each SEA countries. However, transportation of patients to major institutions in the region can be complicated in geographical diverse countries like Indonesia. Larger neurology centers are encouraged to establish their own in-house TPE services for both in- and out-patients. Such services need not utilize much start up resources as with the Malaysian experience.⁸ Initial utilization of existing space with careful regulation, training of existing staff with in-house care bundles, TPE protocols, and limited start-up from governmental support can lead to an establishment of in-house TPE services even in regions with economic challenges.

Conclusions

TPE is an essential treatment modality in many resource-limited countries including SEA for various autoimmune neurological disorders. This article guides SEA clinicians on application of TPE and other available options of immune therapies for adult autoimmune disorders based on available evidence, patient's response, and healthcare resources.

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Authors contributions

Ideas and development of concepts for the initiation of the manuscript (study concept and design): Equal contributions by Drs Shanthi Viswanathan and Hiew Fu Liong

Initial writing up of the Manuscript/Consensus and structuring: Dr Hiew Fu Liong Initial review of the manuscript for intellectual content and structuring of methodology: Dr Shanthi Viswanathan Drafting of manuscript: Dr Hiew Fu Liong

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Appendix

AAN	American Association of neurologists
ADEM	acute disseminated encephalomyelitis
AE	autoimmune encephalitis
ASFA	American society for apheresis
CASPR2	contactin associated protein 2
CIDP	chronic inflammatory demyelinating polyneuropathy
CNS	central nervous system
CPG	clinical practice guideline
CRIO	chronic relapsing inflammatory optic neuropathy
CSF	cerebrospinal fluid
DFPP	double filtration plasmapheresis
EEG	electroencephalogram
FDA	food and drug Administration
GBS	guillain-barré syndrome
GDP	gross domestic product
IA	immunoabsorption
IG	immunoglobulin
IVIG	intravenous immunoglobulin
IV MP	intravenous methylprednisolone
LGI1	leucine-rich glioma-inactivated 1
LPE	limited plasma exchange
MG	myasthenia gravis
MMN	multifocal motor neuropathy
MOG-ab	myelin oligodendrocyte glycoprotein antibody
MPE	modified plasma exchange
MRI	magnetic resonance imaging
MS	multiple sclerosis
MuSK	muscle-specific kinase
NMDAR	N-methyl-D-Aspartate receptor
NMOSD	neuromyelitis optica spectrum disorders

PNS peripheral nervous system
SVPE small volume plasma exchange
SEA southeast Asia

SEATPEC southeast Asia therapeutic plasma exchange
consortium
TPE Therapeutic Plasma Exchange