FONDAZIONE MONDINO
Istituto Neurologico Nazionale a Carattere Scientifico | IRCCS

UNIVERSITÀ DEGLI STUDI DI PAVIA
DIPARTIMENTO DI SCIENZE DEL SISTEMA NERVOSO E DEL COMPORTAMENTO

Aferesi terapeutica ed Encefaliti Autoimmuni (AE): Introduzione

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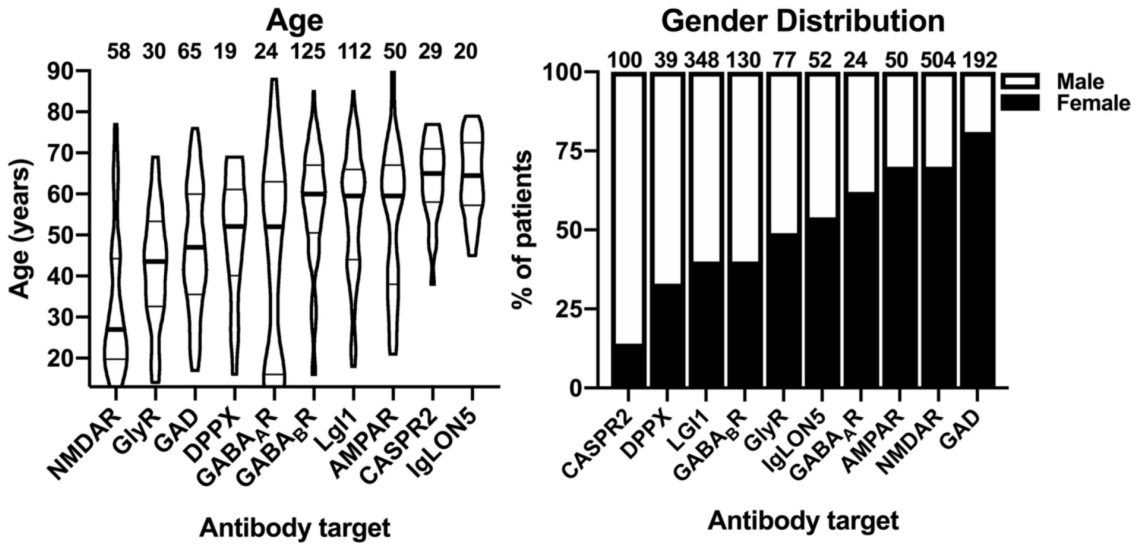
29.01.2025

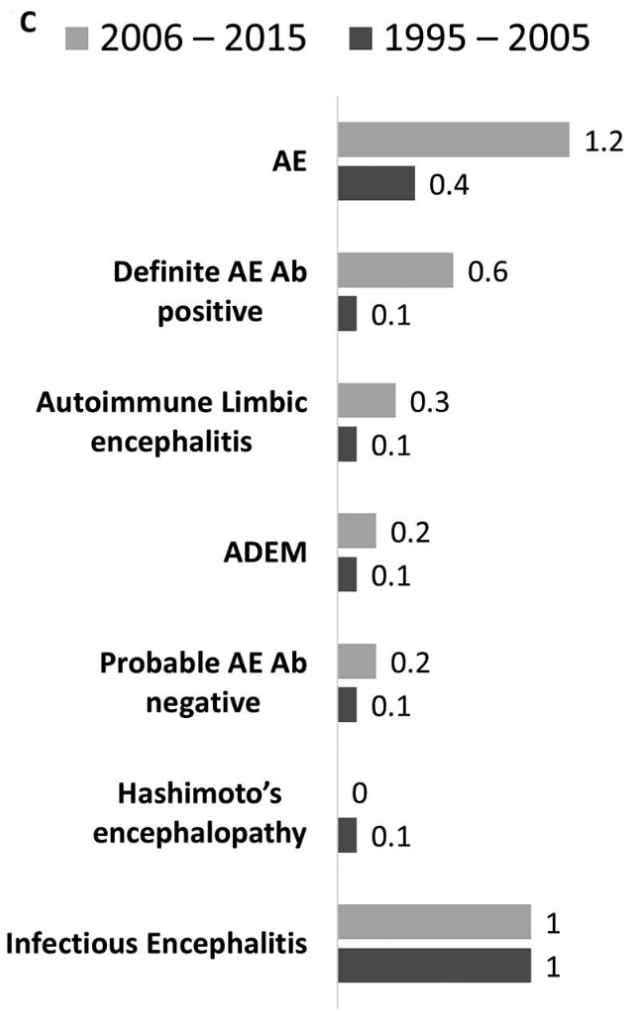
AE: Epidemiology

AE: non-infectious immune-mediated inflammatory disorders of the brain parenchyma

Increased incidence and prevalence due to better recognition; now similar to infectious AE

Different type of antibodies in different type of patients (age and sex)





Dubey et Al., Ann Neurol, 2018

Segal et Al., Annals of Clinical and Translational Neurology 2024

Blinder et Al, Frontiers in Neurology, 2019

AE: Clinical manifestations

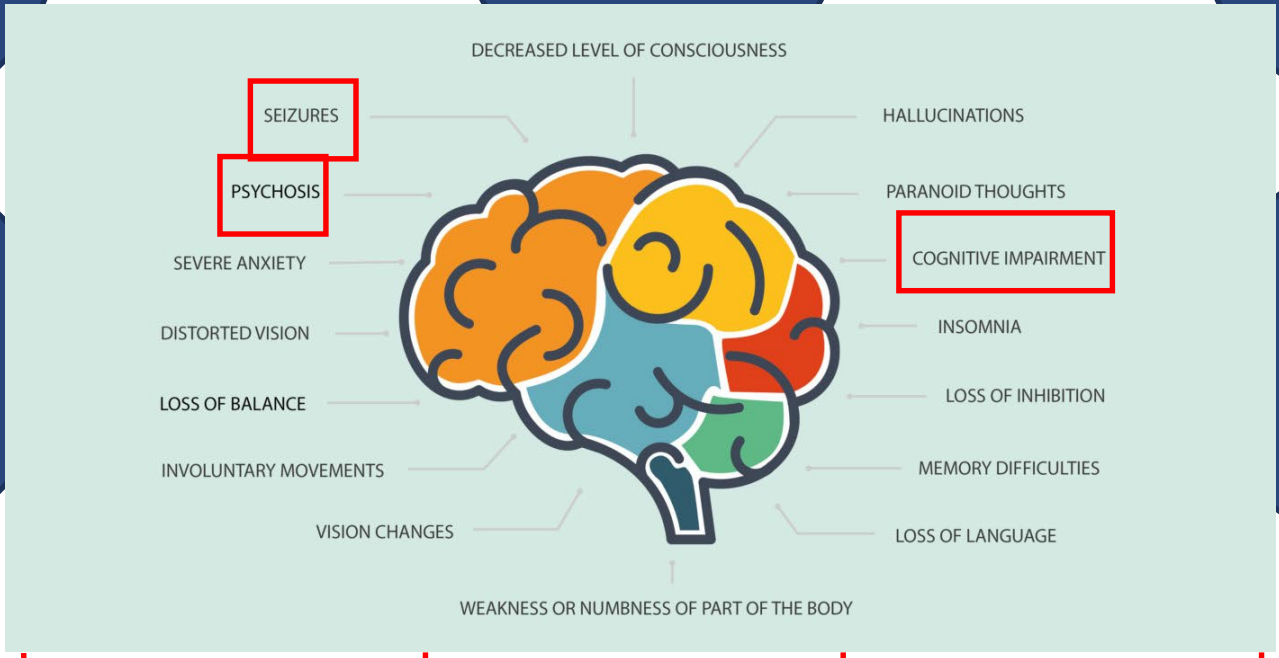
Gastrointestinal manifestations - diarrhea, gastroparesis, and constipation (DPPX)

Peripheral nerve hyperexcitability (CASPR2)

Rapidly progressive dementia (AK5)

Psychiatric symptoms – hallucinations, psychosis, orofacial dyskinesia (NMDAR)

Faciobrachial dystonic seizures, hyponatremia (LGI 1)



Viral encephalitis

Dementia

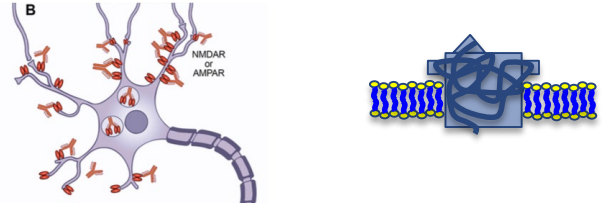
Parkinsonism

Schizophrenia

AEis in differential diagnosis with common neurological conditions

AE: Classification

AE with neuronal surface antibodies (NS-abs)



- Surface antigens (NMDAR, LGI1, CASPR2, AMPAR)
- Abs are pathogenic
- Not strictly paraneoplastic
- Neurological syndrome responds to immunosuppressive therapy
- Abs are conformational

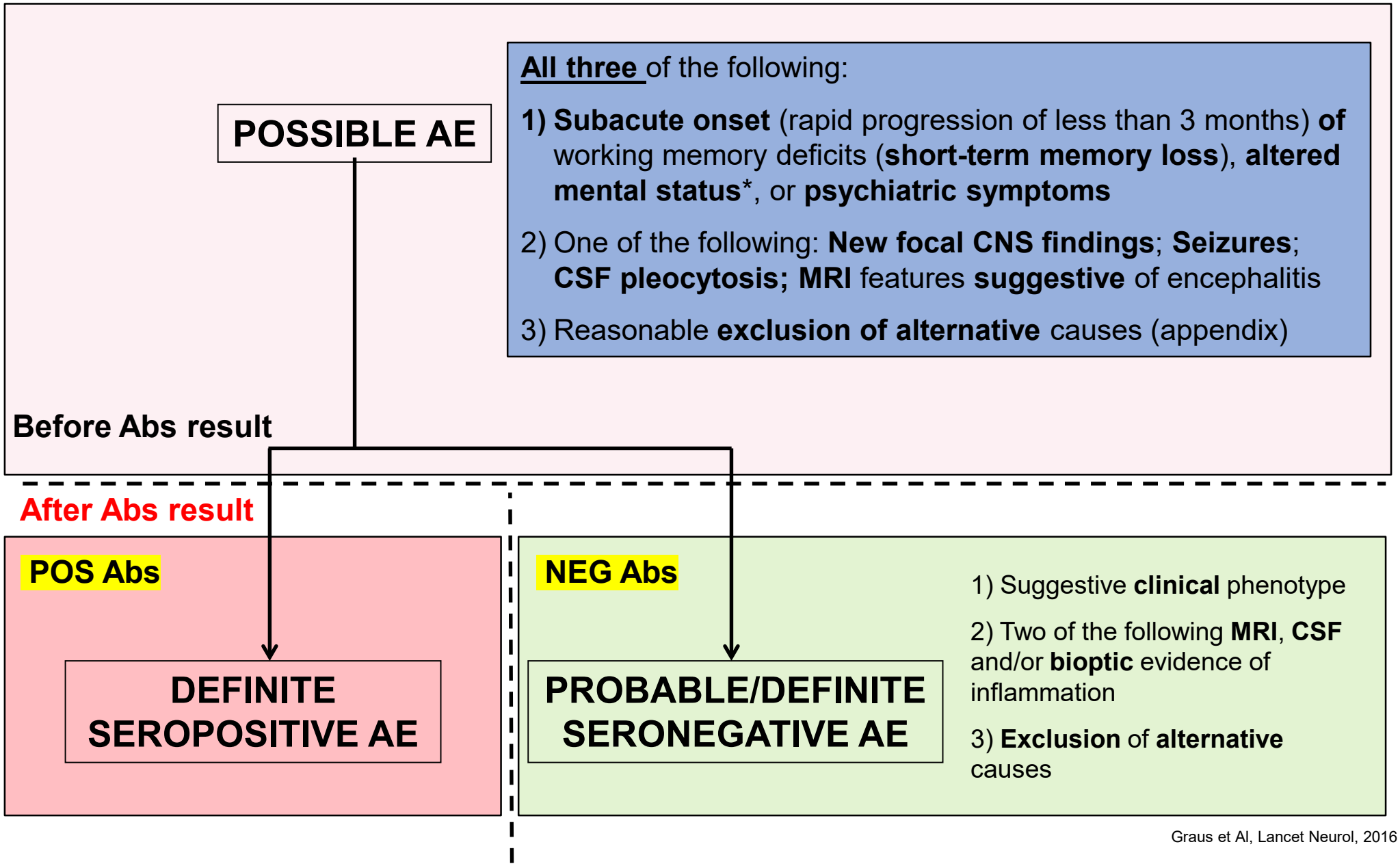
Antibodies are pathogenic

AE with onco-neural antibodies (IC-abs)

- Target Intracellular antigens (Hu, Yo, Ri, Ma2)
- Abs are not pathogenic (T-cell toxicity)
- Almost invariably associated with tumor
- Neurological syndrome not responding to immunosuppressive therapies
- Abs are not conformational

Antibodies are not pathogenic

AE: diagnostic criteria



Graus et Al, Lancet Neurol, 2016

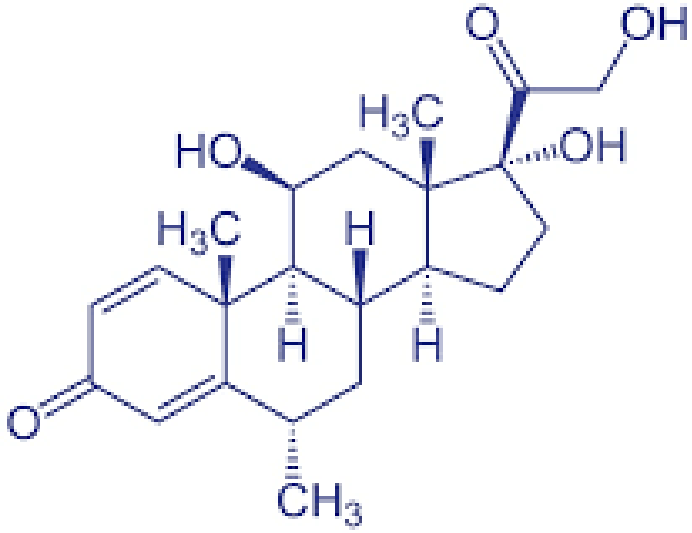
NS-ABS: 1° line treatment

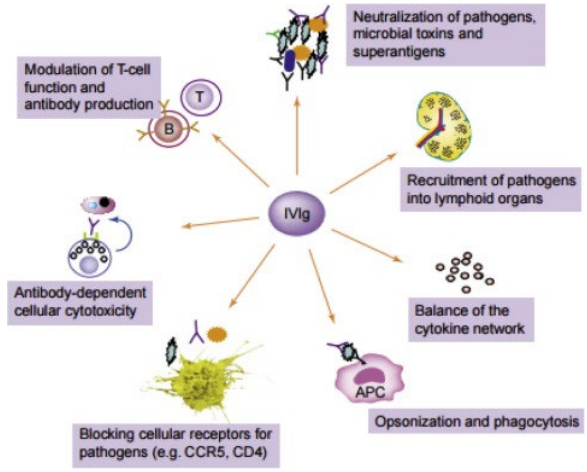
INTRAVENOUS STEROIDS	INTRAVENOUS Ig	Plasma Exchange
6-mehtylprednisolone 1g/day for 5-7 days	0,4 mg/Kg/day for 5 days	5-7 session on alternate day

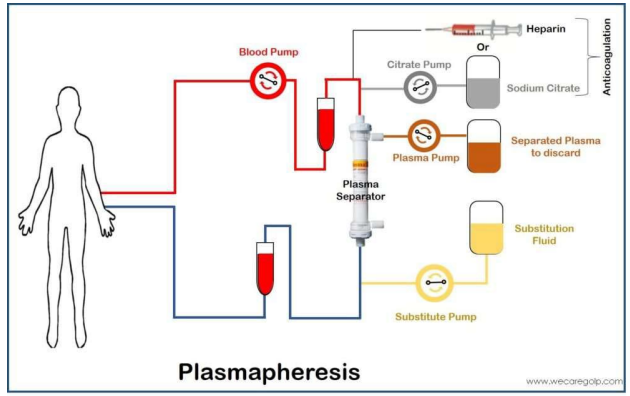
- Might worsen psychiatric symptoms

- High cost
- Low availability

- Caution in dysautonomic patients
- Hard to perform on agitated patients







Combining first line treatments might increase and accelerate clinical improvement

Rimozione acritica di ogni componente plasmatica

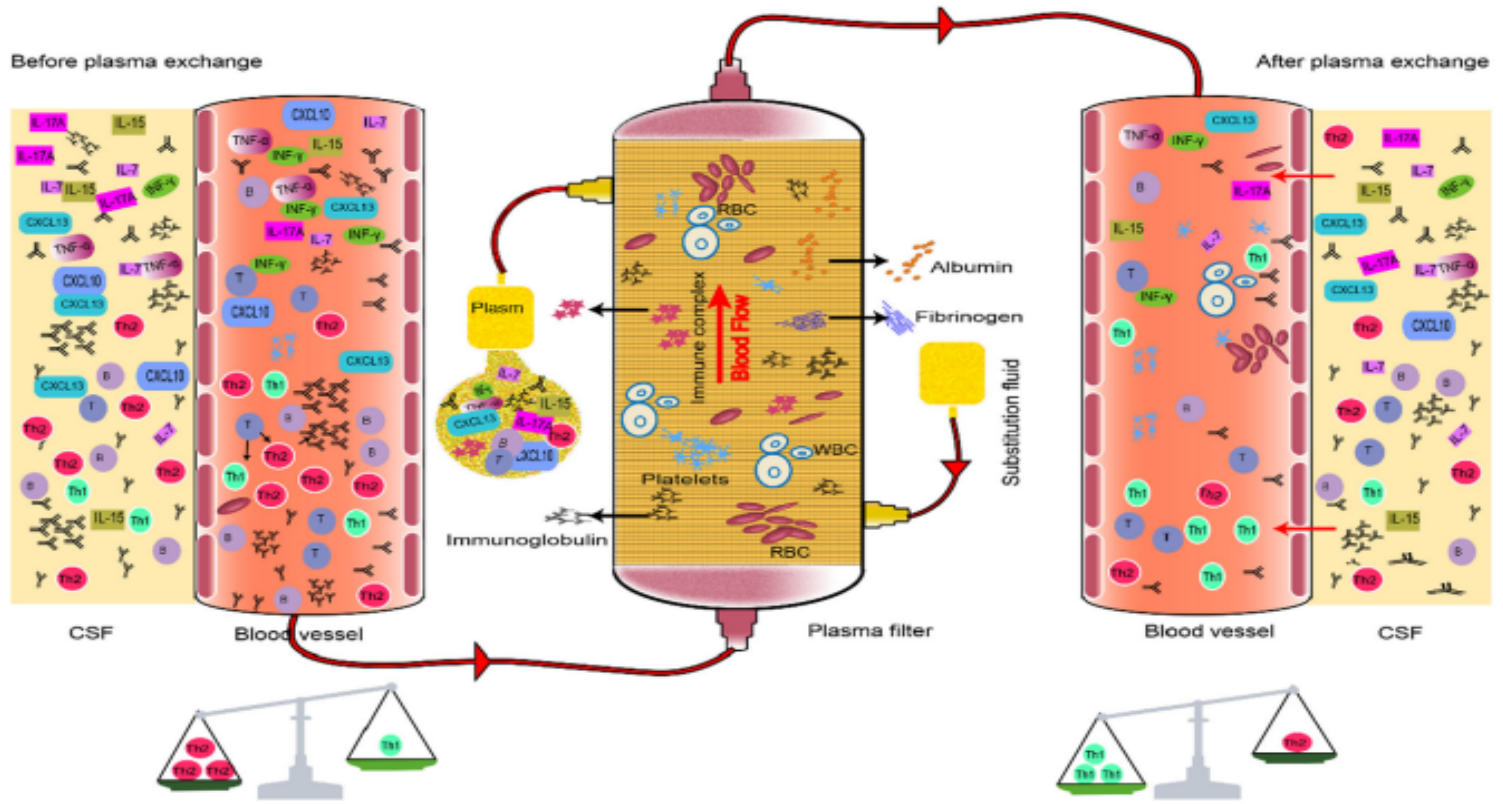


FIGURE 1 Schematic diagram of the mechanism of TPE. This illustration describes three different mechanisms for TPE: The removal of antibodies: Removal of cytokines and adhesion molecules; the regulation of immune system. It decreases antibodies and immune complexes in circulation, then promotes the redistribution of these substances in the CSF and blood, thereby reduces the concentration of pathologic substances in the CSF. TPE also can reduce the antibodies production by regulating the immune system (including shift Th1/Th2 ratio and reduce the traffic of lymphocytes to CNS) the figure below shows the balance of Th1/Th2 ratio in blood before and after TPE. B, B cells; CSF, cerebrospinal fluid; CNS, central nervous system; RBC, red blood cell; T, T cells; TPE, therapeutic plasma exchange; WBC, white blood cell.

PEX: Meccanismi d'azione

Fig. 1 Proposed mechanism of action of plasma exchange (PLEX)

PLEX

PLEX

- PEX è protrombotico
- PEX aumenta rischio infettivo
- PEX comporta extracorporea
- PEX comporta accessi venosi idonei (CVC)
- PEX attenta valutazione condizione cardiovascolare (FE) con bilancio dei liquidi di sostituzione e velocità di estrazione del plasma

Trattamento personalizzato!!!

PEX: Liquidi di sostituzione

1)PFC

2) Soluzione fisiologica

3) Soluzione albumina 5%

4) PFC + albumina

PEX: Accertamenti ematochimici

1) All'arruolamento: emocromo, elettroliti, coagulazione completa di ATIII, PCR e PCT

2) Dopo ogni procedura (dopo 6-12 ore almeno): emocromo, elettroliti, coagulazione completa di ATIII

La valutazione dei pazienti deve essere puntuale e giornaliera

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Aferesi terapeutica e psicosi di nuova insorgenza: Caso clinico

Dr. Pietro Businaro
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29.01.2025

Clinical presentation

Healthy female, 22 years old; PMS: negative — 05/2019

New onset of insomnia and anxiety — Begin 06/2019

Progressive worsening on anxiety and difficult in IADL — End 06/2019

Dysorientation, visual hallucination, hyperactivity, weight loss (10kg). Psychiatric evaluation: «Brief Psychotic Disorder» — Begin 07/2019

Psychiatric department - 1

Admission to the Psychiatric department

End
07/2019

Decision 1: **Administer antipsychotic drug (Haloperidol)**

Goal: **control the psychosis**

Result: **Better control of psychosis but very early and severe drug-induced parkinsonism**

Psychiatric department - 2

Admission to the Psychiatric department

End
07/2019

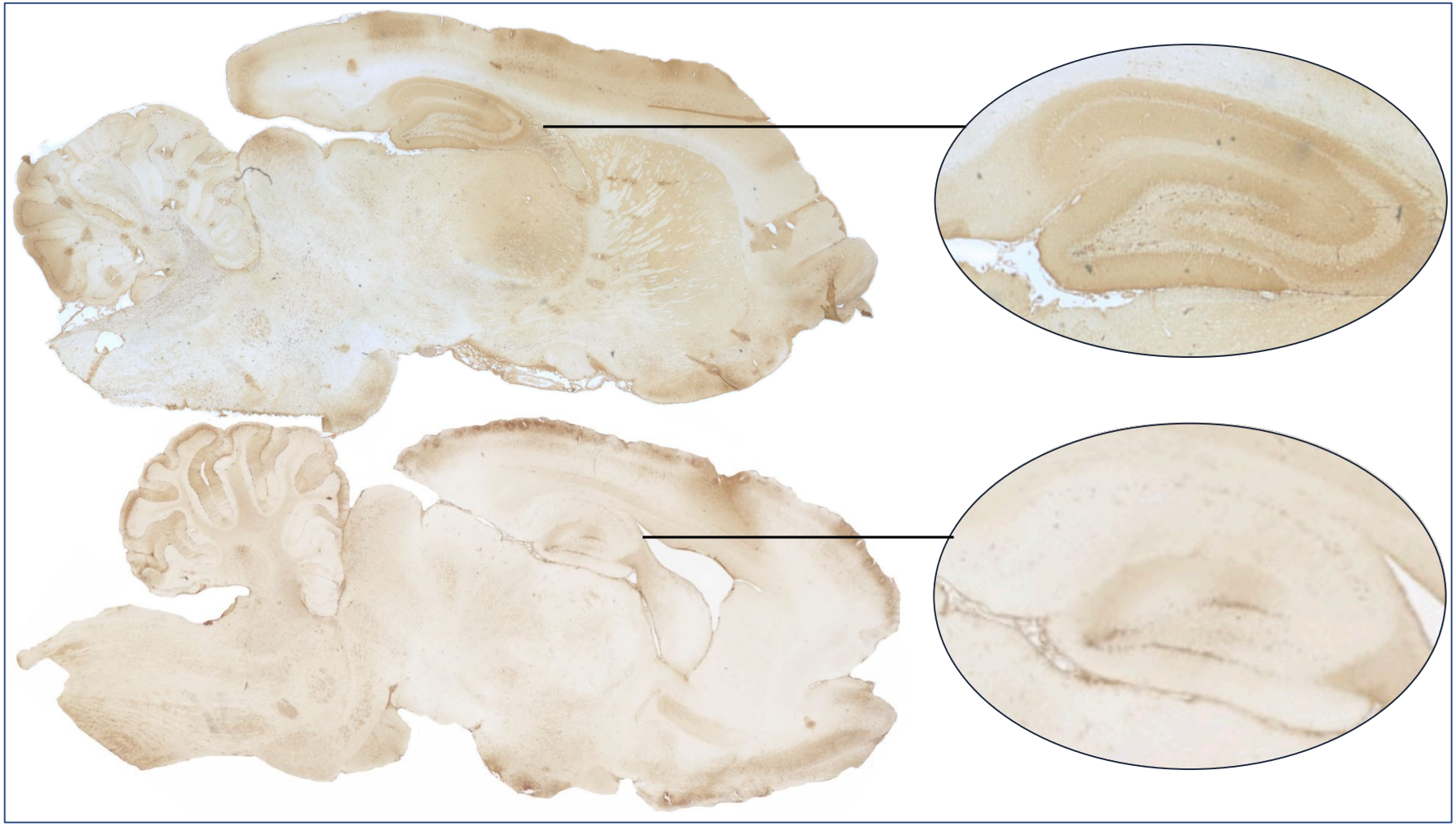
Decision 2: **Change antipsychotic drug (Aripiprazole and Olanzapine) and ask for neurological evaluation**

Goal: **control the psychosis, improve the control of neurological side effects**

Result: **persistance drug-induced parkinsonism, consider alternative cause**

Neurological evaluation - 2

End
07/2019



Neurology department - 1

Admission to the Neurology department

Begin 08/2019

Decision 1: **Electroencephalogram (EEG)**

Goal: **Identify epileptiform discharges and introduce specify antiseizure therapy (up to 1/3 show a specific EEG pattern called «delta brush»)**

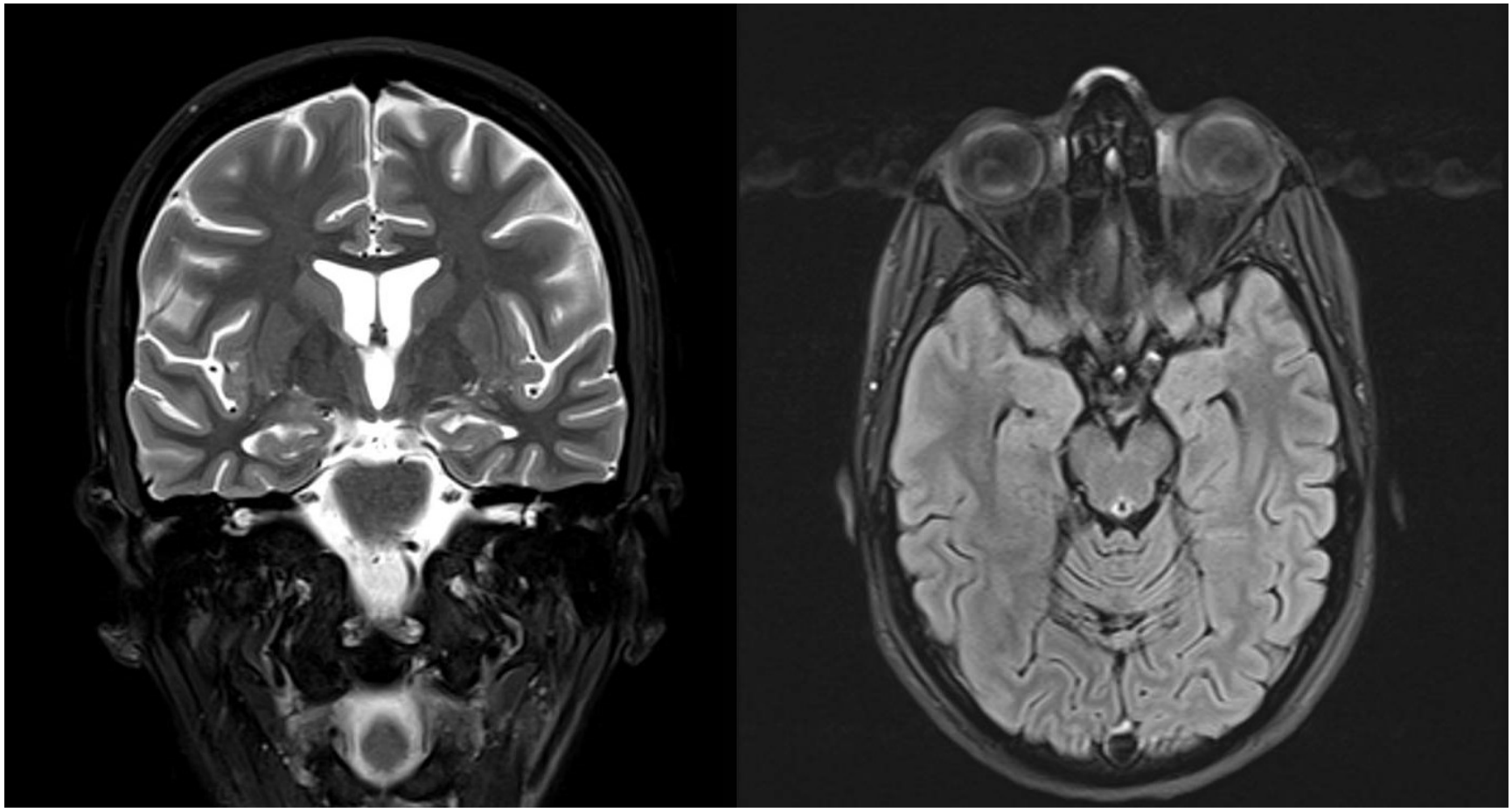
Result: **Negative for epileptiform discharges**

1. Titulaer, M. J. *et al.* Treatment and prognostic factors for long-term outcome in patients with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis. *Lancet Neurol.* **12**, 157–165 (2014).
2. 2, Schmitt SE, Pargeon K, Frechette ES, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology. (2012) 79:1094–100. doi: 10.1212/WNL.0b013e3182698cd8

Neurology department - 2

Admission to the Neurology department

Begin
08/2019



1. Dalmau, J. *et al.* Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol.* **7**, 1091–1098 (2008).
2. Titulaer, M. J. *et al.* Treatment and prognostic factors for long-term outcome in patients with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis. *Lancet Neurol.* **12**, 157–165 (2014).

Neurology department - 3

Admission to the Neurology department

Begin 08/2019

Decision 3: **Transvaginal ultrasound**

Goal: **Exclude a paraneoplastic etiology (46% of women have a paraneoplastic etiology with 94% ovarian teratoma)**

Result: **Negative for teratoma**

1. Dalmau, J. *et al.* Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol.* **7**, 1091–1098 (2008).
2. Titulaer, M. J. *et al.* Treatment and prognostic factors for long-term outcome in patients with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis. *Lancet Neurol.* **12**, 157–165 (2014).

Neurology department - 4

Admission to the Neurology department

Begin
08/2019

Decision 4: **Neuropsychological evaluation**

Goal: **Evaluate the degree of cognitive impairment (>than 80% present with cognitive impairment)**

Result: **Cognitive impairment with involvement of long-term memory and executive-frontal abilities**

1. Dalmau, J. et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol. 7, 1091–1098 (2008).
2. Titulaer, M. J. et al. Treatment and prognostic factors for long-term outcome in patients with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis. Lancet Neurol. 12, 157–165 (2014).

Neurology department - 5

Admission to the Neurology department

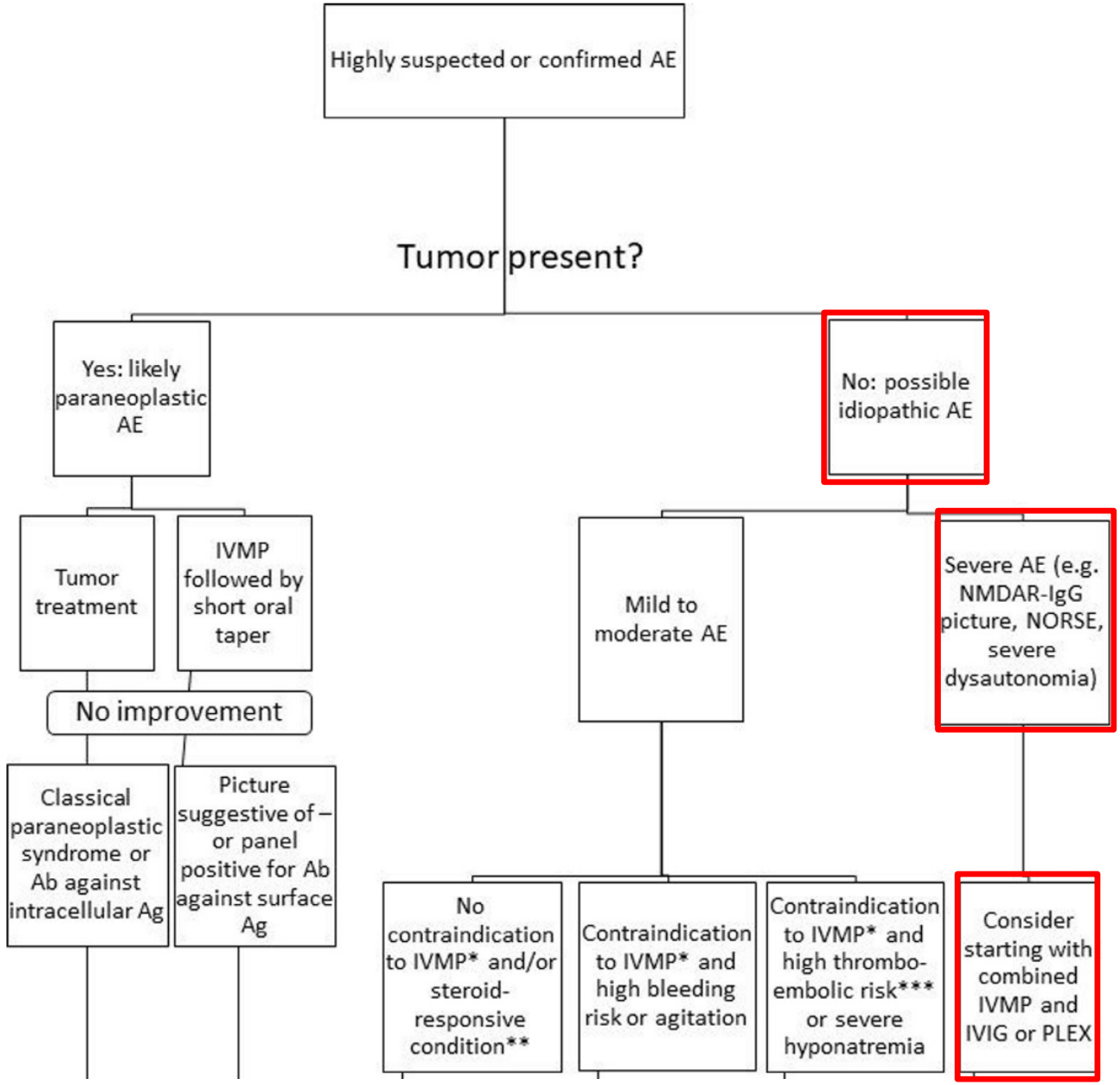
Decision 5: **Holter EKG**

Goal: **Exclude the involvement of autonomic nervous system (around 50% present an involvement of the autonomic nervous system)**

Result: **normal**

1. Dalmau, J. *et al.* Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol.* **7**, 1091–1098 (2008).
2. Titulaer, M. J. *et al.* Treatment and prognostic factors for long-term outcome in patients with anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis. *Lancet Neurol.* **12**, 157–165 (2014).

Treatment Consensus – Autoimmune encephalitis Alliance



1. Abboud, H. *et al.* Autoimmune encephalitis: Proposed best practice recommendations for diagnosis and acute management. *J. Neurol. Neurosurg. Psychiatry* **92**, 757–768 (2021).

Treatment guidelines – American Society for Apheresis

N-METHYL-D-ASPARTATE RECEPTOR ANTIBODY ENCEPHALITIS

Incidence: rare

Procedure	**Category**		**Grade**	
TPE/IA	I		1C	
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	0	3 (112)	>10 (>200)	NA

Recommendation	**Description**	**Methodological quality of supporting evidence**	**Implications**
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available

Volume treated: TPE: 1 to 1.5 TPV; IA: 2 to 2.5 liters for tryptophan-IA (manufacturer's recommendation) or up to 2.5 TPV with regenerative immune adsorbers

Frequency: 5 to 12 treatments with TPE or IA over 1 to 3 weeks with individually adjusted number of and intervals between treatments

Replacement fluid: Albumin

1. Connelly-Smith, L. *et al.* Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Ninth Special Issue. *J. Clin. Apher.* **38**, 77–278 (2023).

Neurology department - 6

Admission to the Neurology department

Begin
08/2019

Acute Immunotherapy

IV-6Methylprednisolone 1g x 5 days, then 500 mg for 3 days, then 250mg for 3 days
Plasma Exchange 6 times every other day

Neurology department - 7

Admission to the Neurology department

Antipsychotic treatment

Antipsychotic (aripiprazole, olanzapine)

Benzodiazepine (delorazepam).

Neurology department - 8

Discharge from the Neurology department

End
08/2019

Therapy at discharge
Antipsychotic (olanzapine)
Benzodiazepine (delorazepam)
Oral prednisone 25mg

Acknowledgments

IRCCS MONDINO
Dr. Matteo Gastaldi
Dr. Enrico Marchioni
Dr. Diego Franciotta
Dr. Luca Diamanti
Dr. Stefano Masciocchi
Dr.ssa Silvia Scaranzin
Dr. Giacomo Greco
Dr.ssa Federica Zuliani
Dr.ssa Chiara Morandi
Dr. Ruggero Barnabei
Dr. Matteo Scucchi
Dr. Antonio Malvaso

IRCCS SAN MATTEO
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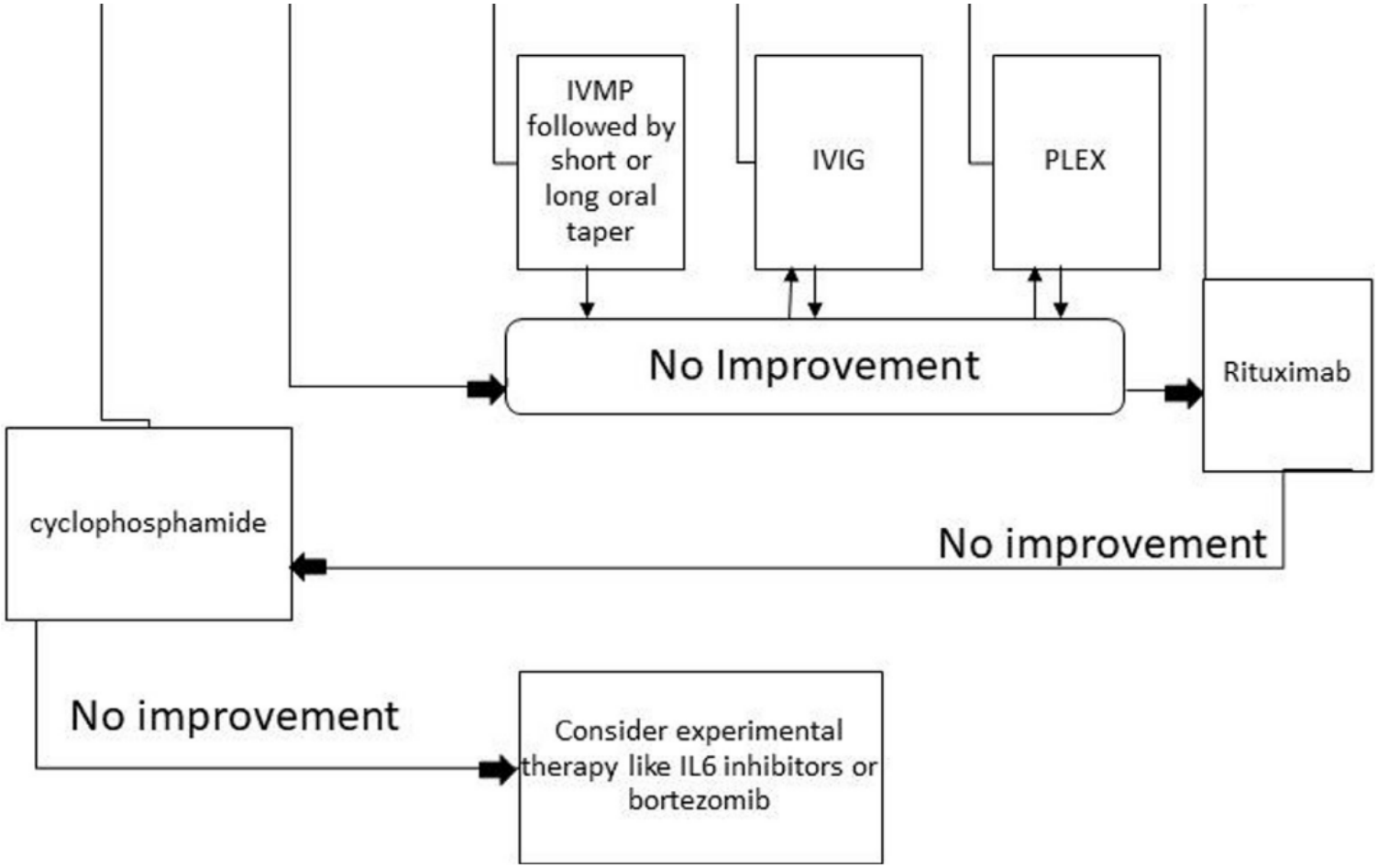
Dr.ssa Alice Mandrini

Second part of the algorithm