AUTOIMMUNE AND ANTIBODY-MEDIATED CAUSES OF RAPIDLY PROGRESSIVE DEMENTIA

Jeffrey M. Gelfand, MD, MAS, FAAN
University of California, San Francisco

LECTURE GOALS

1) To provide an update about Autoimmune and Antibody-Mediated Causes of Dementia – "Autoimmune Dementias" – an important, relatively common (i.e. as a cause of RPD) and often readily treatable cause of Rapidly Progressive Dementia
2) To provide a practical framework for diagnosis of Autoimmune Dementia
3) To provide an update about emerging evidence for treatment of Autoimmune Dementia
4) To provide an update about emerging understandings about pathophysiology and mechanisms of Autoimmune Dementias

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DEFINITIONS

Encephalopathy - Impairment of brain structure or function; confusion, altered consciousness, behavior change; many potential causes

Encephalitis - Brain inflammation (clinical and/or pathological); encephalopathy from brain inflammation

Meningitis - Meningeal inflammation (without abnormal brain function)
Meningoencephalitis: Meningitis & Encephalitis
Encephalomyelitis: Encephalitis & Myelitis

Autoimmune Encephalitis (AE): There are many potential ways to define AE. Most earlier "encephalitis" case definitions for were heavily weighted towards acute infectious causes of encephalitis. An international consensus position paper published in *Lancet Neurology* in 2016[1] proposed new definitions for Autoimmune Encephalitis that reflect emerging understandings about phenotype and pathogenesis:

Possible Autoimmune Encephalitis[1]

1) Subacute onset (rapid progression of less than 3 months) of working memory deficits, AMS (includes decreased level or consciousness, lethargy and personality change) or psychiatric symptoms
2) At least one of the following:
   - New focal CNS finding
   - Seizures (that are not explained by a previously known seizure disorder)
   - CSF pleocytosis
   - MRI features of encephalitis
3) Reasonable exclusion of other causes (infection, tumor, neurodegenerative, metabolic)

Definite Autoimmune Encephalitis[1]

1) Subacute onset (rapid progression of less than 3 months) of working memory deficits, AMS (includes decreased level or consciousness, lethargy and personality change) or psychiatric symptoms
2) Bilateral brain abnormalities on T2/FLAIR MRI highly restricted to the medial temporal lobes (or hypermetabolic on FDG-PET)
3) At least one of the following:
   - CSF pleocytosis
   - EEG with epileptic or slow-wave activity
4) If cannot satisfy #'s 1-3 above, the detection of an CNS autoantibody associated with AE will suffice
5) Reasonable exclusion of other causes (infection, tumor, neurodegenerative, metabolic)

(The above position paper also provides specific definitions for antibody-negative AE, Hashimoto's encephalopathy, NMDAR Encephalitis, ADEM and Bickerstaff's that will be discussed in context).

As recognized phenotypes of AE syndromes expand – and readier availability of antibody biomarkers has already allowed for such "phenotypic expansion"[2] – case definitions will necessarily need to as well.

Similarly, as the extent of CNS autoantibody disease expands to include non-neuronal antigens (i.e. autoimmune astrocytopathies (GFAP, AQP4), autoimmune oligodendrocytopathies (MOG), antibodies that target protein accumulations (A-beta antibodies), it will be important to consider these under the heading of autoimmune causes of dementia, even if some may not strictly be autoimmune "encephalitis."

Testing for autoantibodies associated with autoimmune dementia can include either a targeted or broader screening panel approach. In select circumstances (i.e. young patient highly suspected to have NMDAR encephalitis clinically) the targeted approach may be most efficient and cost-effective; however, as phenotypes for AE can overlap and some patients may have more than one associated autoantibody, panel-based screening is an increasingly efficient option. Most recognized autoantibodies are now readily available through major reference clinical laboratories, although some (typically the newest discoveries) may still only be available through research laboratories under research protocols. Testing methodology reflects the antibody, but in general traditional ELISA/western blot approaches are still widely used for intracellular antigens. For cell-surface directed antibodies – especially as the 3D conformational structure of the antigen on the cell-surface may influence antibody binding making traditional detection techniques less sensitive – a combination of cell-based assays (in which the antigen is transfected into a cell likely, such as HEK-293, and expressed on the cell surface), brain slice assays (typically rodent brains stained with serum or CSF using immunofluorescence and analyzing staining patterns, either as suggestive of a specific antibody or of neuropil binding more generally even if not associated with a known/discovered antibody) or staining of cultured hippocampal neurons (research-based). Radioimmunoassays may also be used (such as for voltage-gated potassium channel complex, although more specific antigen targets (LGI1, CASPR2) are now recognized in association with clinical phenotypes vs nonspecific laboratory findings). Confirmation of binding on multiple assays (i.e. cell-based + brain slices) improves confidence in the finding.

AUTOIMMUNE DEMENTIAS AS A CAUSE OF RPD

The emerging recognition that autoantibody-associated and autoimmune causes of dementia are an important cause of RPD, may mimic other RPD syndromes such as prion disease, and are often readily treatable and sometimes even reversible, has transformed the field.

The classical teaching has been that Autoimmune Encephalopathies associated with neuronal cell-surface antibodies (i.e. NMDAR, LGI1/CASPR2, AMPA, etc) typically respond favorably to immunosuppression. Neuronal cell surface directed autoantibodies can also directly affect neuronal function by binding to cell-surface receptors and activating signaling pathways.[2-4]

On the other hand, classical paraneoplastic encephalitis and paraneoplastic CNS syndromes associated with antibodies that target intracellular antigens (i.e. Hu (ANNA-1), CRMP5 (CV2)) are increasingly thought of as more general humoral markers of anti-tumoral immunity with a prominent T cell response on neuropathology, probably do not affect neuronal function as opposed to being associated with an immune process that causes neuronal destruction, and are often frustratingly refractory to immunosuppression; tumor removal and/or cure of the malignancy, when possible, is a priority.[5]

In this lecture, we will review archetypical syndromes of autoimmune dementia in detail.

Key cell-surface syndromes include:

NMDAR Encephalitis – a disease of the young (95% of cases occur in people <age 40 and 30% in children <age 18); Flu-like or vague prodrome followed by early psychiatric features especially psychosis; amnesia, language dysfunction; movement disorders; autonomic dysfunction; decreased level of consciousness (sometimes including a prolonged coma); associated with an ovarian teratoma (over 50% of adult cases), as teratomas can include neuronal-type tissue with NMDAR antigens). More favorable outcomes with aggressive immunosuppression in severe cases (case series level of evidence).[6] In the UK, 3% of new onset psychosis cases have +NMDAR serum autoantibodies.[7]

VGKC-complex Encephalitis – A collection of syndromes. The radioimmunoassay brings down the whole channel complex with associated proteins and phenotypes are associated with more specific antibodies to LGI1 or CASPR2. While some VGKC-complex positive patients with negative LGI1 and CASRP2 antibodies may have compelling autoimmune phenotypes, many do not and the VGKC-complex antibody probably not causative or clinically relevant.[8,9]

LGI1:[10-13]

Median age of onset in early 60s. Triad of rapidly progressive amnesia, seizures, hyponatremia (often called SIADH before the link is realized); may have a prodrome of faciobrachial dystonic seizures or ictal bradycardia. <20% of cases are tumor associated. Can have a normal MRI and CSF exam, so a high index of clinical suspicion and serological testing (typically serum) may be required to secure a diagnosis. Rarely may also mimic CJD including with cortical ribboning findings (probably seizure related).[14]

CASPR2[15,16]

Median age of onset in 60s. Can be classic limbic encephalitis but can also have neuromyotonia, autonomic dysfunction, peripheral nerve hyperexcitability, seizures; weight loss; higher associations with thymoma, also SCLC).

AMPA-R[17,18]

Median age of onset in the early 60s. Limbic Encephalitis. Seizures. Malignancy associated in up to 50-60%.

GABA-B[19]

Median age of onset in early 60s. Limbic Encephalitis. Seizures. SCLC 50%.

GABA-A[20]

Median age in 40s. Seizures. Encephalopathy/Behavioral Changes. Movement Disorders. Prominent white matter lesions on T2/FLAIR.

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Hu[21]

Median age in 60s, 75% men. Limbic Encephalitis. Can also have sensory neuronopathy. Tumor in ~75%, overwhelmingly SCLC but can be others.

CRMP5[22]

Variety of neurological syndromes including encephalopathy, retinitis, optic neuritis, myelopathy. Neuronally destructive. Often prominent MRI changes.

And others.

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Hashimoto Encephalopathy / Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis [123]

Associations of encephalopathy with thyroid autoantibodies, but unclear causation. Challenge is that up to 13% of otherwise healthy individuals can have thyroid antibodies (especially as no disease specific cutoff of titer) and perhaps up to that many of RPD patients could have such antibodies, leading to a high risk of misdiagnosis or overdiagnosis of this putative syndrome as a cause of RPD and leading to exposure to immunosuppression or failure to do additional diagnostics. Strictly defined, the syndrome of HE consists of

1. Encephalopathy with seizures, myoclonus, hallucinations or stroke-like episodes
2. Presence of thyroid antibodies (and not clinically uncorrected hypo or hyperthyroidism)
3. Exclusion of other causes including no other neuronal autoantibodies, no other diagnosis evident on brain MRI and rigorous exclusion of other causes for the clinical syndrome.

TREATMENT OF AUTOIMMUNE DEMENTIA

Ideally, treatments should be targeted based on the specific disease and emerging understanding of pathogenesis, but current treatment approaches are still very much empiric. As yet there are no published

randomized randomized controlled clinical trials for autoimmune or paraneoplastic encephalitis. Evidence to guide treatment selection comes from observational studies, expert opinion and insights from other neuroimmunological conditions (the biology of which may or may not be analogous). Current treatments are focused on immunosuppression and symptom management. Future treatments will likely be directed at downstream targets to restore physiology, similar to the paradigm of treating myasthenia gravis in which there is immunosuppression as well as acetylcholinesterase inhibitors to restore physiology (even if only partial).

Acute immunosuppressive therapy: A therapy that rapidly suppresses harmful inflammation and/or the consequences of CNS inflammation.

Induction immunosuppressive therapy: Aggressive and relatively rapid suppression of inflammation to allow for disease suppression/remission. *Many induction therapies are not truly "acute" in terms of the temporal clinical effect against the disease (even if the pharmacological effect may be rapid).*

Maintenance immunosuppressive therapy: Maintain remission or acceptable levels of disease activity, thereby preventing worsening. This approach is most useful for chronic processes as opposed to shorter monophasic illnesses. Such agents can take considerable time to achieve maximal clinical efficacy, particularly with dosing regimens that favor gradual titrations to improve tolerability and reduce toxicity.

Current strategies typically include a combination of glucocorticoids, IVIG, plasma exchange, B-cell depletion and/or cytotoxic therapy.

SYLLABUS APPENDIX

STRATEGIES FOR IMMUNOSUPPRESSION FOR AUTOIMUNE ENCEPHALITIS

ACUTE IMMUNOSUPPRESSIVE THERAPIES

GLUCOCORTICOIDS

Glucocorticoids (aka steroids) are the mainstay of treatment for autoimmune encephalopathies and a first-line acute therapy. At lower to moderate chronic doses, steroids also serve as maintenance therapy. The goal should be to control the disease and then work to reduce the dose as low as possible with acceptable efficacy.

Glucocorticoids affect immune function at many different levels and through a variety of biological mechanisms.[24,25]

- Agent binds to intracellular glucocorticoid receptor, travels to the nucleus, interacts with DNA (including at glucocorticoid-responsive elements) and affects gene transcription. They also reduce stability of mRNA, including those needed to make key cytokines involved in the immune response.
- Impair exit of lymphocytes from the circulation to target organs (by reducing endothelial adhesion). Monocyte and macrophage migration to target organs is reduced, as well as neutrophil migration and eosinophil function. Circulating T cells are reduced, as well as B cells.
- Reduce the effect of pro-inflammatory pathways

***Pulse dose* steroids** refers to very high dose glucocorticoid treatment, which may or may not be followed by a taper. Pulse steroids in bioequivalent doses may be administered intravenously or orally. In the context of rapidly progressive encephalopathies, IV is typically favored but oral dosing may be considered in some circumstances, particularly in the outpatient setting when access to care and cost considerations for IV infusions threaten to delay therapy initiation.

- *Some classic studies of the immunological effects of pulse steroids in humans provide insight about mechanism. After infusion of pulse dose 1000 mg IV methylprednisolone for 3 days in people with rheumatoid arthritis, T cell predominant depletion of circulating lymphocytes occurred within 2 hours after each infusion, reached maximal depletion at 6 hours and returned to baseline by 24 hours.[26] Another study examined the effects of 96 mg methylprednisolone daily for 3-5 days*

(given in doses of 16 mg orally Q4H) and noted a drop in serum immunoglobulin levels after several days, with a nadir at 2 weeks after 3 day dosing and 3-4 weeks after 5 days of treatment.[27]

- *Pulse dosing can be given intravenously or orally. In a pharmacokinetic study in people with multiple sclerosis, the area under the curve of drug concentration at 24 hours was similar between 1250 mg oral prednisone and the bioequivalent dose of 1000 mg IV methylprednisolone, although the peak concentration was higher and occurred earlier with IV dosing.*[28] *A Phase IV multicenter randomized controlled trial in MS recently demonstrated non-inferiority of bioequivalent oral and IV doses of methylprednisolone for clinical and radiological endpoints in MS.*[29]

Alternate day maintenance oral steroid regimens have been proposed as an alternative to daily dosing for many disease states, citing less longer-term steroid related complications.[24] However, efficacy appears to be very dependent on the disease state in question; this has not been well studied one way or another in autoimmune encephalitis.

Steroid dose conversion
The glucocorticoid effect of different steroid formulations can be calculated based on standard reference tables. There are also many online calculators to help with such conversions at the bedside.

Formulation	**Approximate dose equivalent respective to prednisone 1 mg (1x)**	**Approximate dose equivalent to "Pulse" dose methylprednisolone 1000 mg**
Prednisone / Prednisolone	**Reference (1 mg)**	1250 mg
Methylprednisolone	0.8 mg	**Reference (1000 mg)**
Dexamethasone	0.15 mg	~160-200 mg *depending on source*
Hydrocortisone *(shorter acting, usually given in divided doses)*	4 mg	5000 mg

Steroids have predictable side effects and there are some helpful risk mitigation strategies:[30]

Key Risks / Adverse Effects	Risk mitigation strategy
Weight Gain / Fat Redistribution / Cardiovascular risk	Counseling about lifestyle modification
Osteoporosis / Fracture	- Calcium 1200-1500 mg/day and vitamin D3 800-1000 IU/day in divided doses. If on PPI (see below), consider calcium citrate. - Dexa scan at baseline and to follow over time. - Smoking cessation - Minimize alcohol intake - Bisphosphonates based on risk stratification (there are ACR and endocrine guidelines for this)[31,32] - Fall risk assessment/counseling
Osteonecrosis	Total dose related; consider this if new joint pain, not just hip but knee, shoulder, spine, ankle, etc.
Hyperglycemia / Diabetes	Diabetes screening
Infection	-If need live vaccines, must get prior to initiating; live vaccines are contraindicated if on more than prednisone 20 mg/day; if treated

	with high dose steroids for more than 2 weeks, wait 3 months after stopping steroids before vaccinating. -TB screening controversial but probably a good idea – response to testing is lessened after 2-4 weeks of greater than ~15 mg prednisone (but is preserved in the first few days of acute pulse dosing) - Consider PCP prophylaxis if co-treating with another immunosuppressant + steroids
Cataract	Eye exam
Glaucoma	Eye exam
Myopathy (can have normal CK, EMG, path with Type 2 fiber loss)	Monitor for superimposed myopathy, lower dose
?Peptic Ulcer Disease/GI bleeding (controversial with steroids alone, risk increased with NSAID use)	Avoid concomitant NSAID use. Little data now to support PPI or H2 blockers though still very frequently prescribed
Adrenal Suppression	Cautious tapers monitoring for steroid withdrawal and adrenal insufficiency

Principles of tapering off steroids:
Risk of steroid withdrawal as well as adrenal insufficiency. Can test for adrenal function, either with cort stim testing or can do an AM cortisol level 48 hours after stopping steroids as a screen. There may also be value in switching to hydrocortisone at lower doses to allow for more flexibility and precision in AM vs. PM dosing while tapering. Must also monitor for disease worsening/relapse.

INTRAVENOUS IMMUNOGLOBULIN (IVIG)

IVIg consists of highly purified polyvalent IgG derived from pooled immunoglobulin preparations from thousands of donors, purified and treated with a variety of strategies to reduce the risk of blood borne pathogens.[33] There are many different preparations and manufacturers.

Dosing depends on indication:
- For immunodeficiency (i.e. replacement therapy for hypogammaglobulinemia, which may be congenital or acquired), typical doses are ~300-500 mg every 3-4 weeks.
- For autoimmune disease, typical doses are 2 grams/kg in 3-5 divided doses, though this is disease specific.
- For autoimmune or paraneoplastic encephalitis, 2 gram/kg in divided doses is usually favored.[3]

Mechanism of action[34]
Unclear and may vary in different indications but may include:
- "Flooding" the system to accelerate clearance of IgG (?reduce production)
- Interacting with Fc receptors[35] on phagocytic cells and/or circulating antibodies, may neutralize culprit antibodies in some cases
- Promote clearance of immune complexes
- Effects on other immune cells such as regulatory T cells, monocytes, etc.

IVIg Risk	Mitigating Strategy
Infusion reactions	Slower rate, smaller divided dosing for first time infusions (as these reactions are more common with initial exposure rather than with repeated infusions); attentive nursing and formal protocols for stopping the infusion and medication; treat existing bacterial infections prior to IVIg (can get a flu-like reaction if not) - Premedication with acetaminophen and diphenhydramine
Thombotic/Hyperviscosity related (including stroke, MI, DVT, PE)	-Screen for cardiac/thrombotic risk factors for risk stratification -Prehydrate (avoid dehydration) -Slower infusion rates - Avoid doses >500 mg/kg per day in older patients (so if total dose = 2 g/kg this means should probably not shorten to less than 4 days in high risk patients) -DVT prophylaxis (inpatient) or preventive strategies (outpatient) -?role for antiplatelets
Headache (risk factors are history f migraine and higher dose; a small subset will have true aseptic meningitis which is usually self-limited)	Premedicate with acetaminophen, NSAIDS (if not also on steroids); steroids can be helpful in severe cases
Acute kidney injury (AKI)	Hydration, risk stratification, follow labs, avoid sucrose containing forms (now rare)
Hemolytic anemia	Monitor CBC, Coombs test pre and post

Practical Considerations:
- Note that plasma exchange (see below) gets rid of IVIg (as it's a replacement immunoglobulin), a consideration when deciding on timing and PLEX vs. IVIg for autoimmune encephalitis
- IVIg is most typically given as an adjunct to steroids, although there may be a role for monotherapy in select conditions/cases.

PLASMA EXCHANGE (PLEX)

Plasmapheresis refers to removal of plasma (i.e. for blood banking).

Plasma exchange (PLEX) refers to removal of plasma to filter out pathologic components of blood and the replacement of that volume with another substance. That other substance is most typically albumin or albumin and saline, but can consist of other blood products, such as FFP or cryoprecipitate (i.e. for TTP).

PLEX removes pathologic antibodies and other immunological substances, such as immune complexes. The mechanism of action of PLEX does NOT typically involve suppression of antibody production or suppression of whatever is driving the underlying pathological inflammatory process. For this reason, for treatment of neuroinflammatory diseases like autoimmune or paraneoplastic encephalitis, PLEX is best considered as an acute adjunctive or rescue therapy and not as a monotherapy alternative to steroids. Furthermore, there can be a "rebound" production of IgG after stopping PLEX without another form of immunosuppression on board.

Key principles of PLEX for neuroinflammatory disease:[36]
-About 45% of IgG is intravascular, the compartment PLEX filters. Five exchanges are needed to remove 90% of the initial "body" IgG? burden assuming an equilibration factor and no new antibody production. Whether this

exchange factor truly reflects the CNS immunoglobulin burden (CSF, parenchymal) is less clear. The half-life of IgG is about 21 days.
-About 75% of IgM is intravascular. It is easier to reduce circulating IgM levels with PLEX compared to IgG.
- Most treatment plans for neurological disease replace 1 to 1.5 “plasma volumes” per treatment every other day. This usually takes about 1-2 hours per exchange. Whether more frequent exchanges (i.e. daily) can achieve acceptable efficacy, shorten length of stay and provide acceptable safety remain to be determined.
- PLEX can be performed as an inpatient or outpatient depending on the health care system.
- PLEX can be performed with central or peripheral venous access depending on the health care system and local protocols.

PLEX risks	PLEX risk mitigation
Complications of venous access	- Expert central line placement and handling
Sepsis	-Line safety protocols
Electrolyte abnormalities (hypocalcemia or metabolic alkalosis from citrate, an anticoagulant used in the machinery)	-Symptomatic monitoring; ECG and check ionized Ca if symptomatic -Prophylactic CaCl
Bleeding (as PLEX filters out and dilutes clotting factors)	-Check coags and fibrinogen (the latter is sensitive given the kinetics) -FFP if bleeding or high risk -Caution with DVT prophylaxis (many protocols hold during PLEX)
Bradykinin induded flushing, hypotension, GI disturbances	Hold ACE inhibitors
Hypotension	Monitor BP
Anaphylaxis	Monitor for transfusion related reactions, particularly if FFP or other blood products in replacement fluid
Removal of wanted antibodies or medications (i.e. IVIg, Rituximab or other therapeutic monoclonal antibodies, can also remove small molecules like methotrexate or azathioprine)	Medication review. Thoughtful timing of such medications (i.e. after and not right before the PLEX procedure)

There are now several reports discussing favorable responses with PLEX for treatment of NMDA encephalitis.[6,37,38] The potential benefit of PLEX, beyond steroids, for VGKCc/LGI1 encephalitis is less clear.[2,39]

There is randomized controlled trial evidence for PLEX in CNS inflammatory-demyelinating neurological disease. In 1999 Weinshenker *et. al.*, published a randomized controlled trial of PLEX in 22 patients with acute inflammatory-demyelinating attacks (12 had MS, 12 had other demyelinating diseases). The study was blinded and involved sham PLEX as a control. All participants received at least 5 days of IV pulse steroids with minimal to no improvement. Meaningful improvement in disability was observed in 42% of treated patients and 5.9% of controls.

INDUCTION AND MAINTENANCE IMMUNOSUPPRESSIVE THERAPIES

CYCLOPHOSPHAMIDE

Cyclophosphamide is an alkylating agent that interferes with DNA causing death of rapidly dividing cells. For this reason, it is a potent chemotherapeutic agent and a potent immunosuppressant. Potency, however, does not necessarily imply a truly acute neuroimmunological effect and usual dosing regimens take some time for full clinical effect. In the current treatment era, the goal of cyclophosphamide is to induce remission and then hopefully be able to transition to other immunosuppressants as needed to maintain remission.

Cyclophosphamide dosing

Oral – as oral dosing is typically administered *daily*, oral cyclophosphamide regimens are considered to be MORE toxic than intermittent IV pulse dosing (good evidence for this in lupus nephritis for example) – oral regimens are often harder on the patient and bladder complications are greater, but efficacy can be superior and for this reason is preferred for some indications (i.e. induction in life-threatening severe vasculitis). The role of oral cyclophosphamide relative to IV for severe autoimmune encephalitis is unclear and largely unexplored.

Intermittent pulse IV – the more typical regimen in neuroinflammatory disease. Usually 500-800 mg/m^2 (and up to 1000 mg/m^2) body surface area every 3-4 weeks (*it is important to note whether dosing is in mg/m^2 or total mg when discussing or prescribing this drug*). Cumulative doses are ~50% less with intermittent rather than oral daily regimens.[40]

Myeloablative "induction" dosing of cyclophosphamide, sometimes called "high dose cyclophosphamide in the literature (i.e. 50 mg/kg/day x 4 days) has shown benefit in select patients with severe myasthenia gravis[41,42] and in exceptional cases of fulminant MS.[43,44] The potential role of such high dose regimens for severe autoimmune encephalitis remains largely unexplored.

Cyclophosphamide Risks	Mitigation Strategies[40]
Leukopenia / Infection	-Regular monitoring of CBC/diff, dose reductions if total leukocyte count (i.e. WBC) drops below 3500/mm^3 or if the absolute neutrophil count drops below 1500/mm^3. Isolated lymphopenia is expected. The nadir occurs 8-14 days after the infusion, so lab monitoring must be timed appropriately to sample and catch the nadir -PJP (PCP) prophylaxis -Avoid live vaccines
Teratogenicity	Pregnancy testing, contraception
Bladder cancer	-Monthly UAs. If blood, look for cystitis. -Prophylactic MESNA -Hydration (should be a formal part of the protocol)
Liver toxicity	Lab monitoring, dose reduction
Infertility	-Consider leuprolide in women (2 weeks) prior to each infusion
Renal injury	Lab monitoring
Longer term risk of hematological or other malignancy	Limit use to <6-12 months

Combination Cyclophosphamide and Rituximab: These two agents are commonly used together in hematology-oncology in "CHOP-R" regimens for lymphoma.[45] Some experts advocate combination therapy for severe autoimmune encephalitis, and there is ample observational experience with this combined approach for severe NMDA encephalitis.[6] The relative benefit of combination versus monotherapy in this context remains to be determined.

AZATHIOPRINE

Azathioprine is an antimetabolite that begins as a prodrug and is broken down into purine analogs that interfere with ribonucleotide production. This in turn leads to decreased circulating B and T lymphocytes and reduced antibody production. Azathioprine is widely used for treatment of systemic inflammatory disease with a robust evidence base and has an emerging evidence base for many neurological indications, including myasthenia

gravis[46] and neuromyelitis optica.[47] Azathioprine is sometimes used for treatment of autoimmune encephalitis, particularly as a maintenance therapy.

Dosing varies by indication. For autoimmune encephalitis, dosing typically is initiated low and increased gradually while monitoring for safety. By contrast, for treatment of ANCA vasculitis azathioprine is typically started at the maximum and tapered back, but toxicity can be greater.[48]

One important consideration with starting azathioprine is **thiopurine S-methyltransferase (TPMT) deficiency**, a genetic variant, that can lead to life-threatening myelosuppression after exposure to the drug and related compounds. Enzymatic and confirmatory genetic testing for TMPT is available, but expensive. Many clinicians across disciplines favor a strategy of starting with low doses, monitoring safety labs very carefully and stopping right away if there is evidence of myelosuppression (and can get TPMT testing in such cases if wish to rechallenge). For example, we and others typically start with a dose of 50 mg/day, check labs in 2 weeks, increase by 0.5 mg/kg/day (i.e. to 100 mg/day), check labs again and continue increasing every 1-2 weeks to a target dose of 1.5-2 mg/kg per day. Doses up to 3 mg/kg/day are used for some indications.

Azathioprine leads to an increased mean corpuscular volume (MCV), and MCV correlates with level of the inflammatory marker 6-thioguanine nucleotides, a biomarker of immunosuppressive activity (r=0.76 after 6 months of therapy).[49] There is a literature, primarily in gastroenterology[50] (for inflammatory bowel disease), myasthenia gravis[51] and in NMO[47] using MCV to guide azathioprine dosing as a presumed biomarker for the immunological effect of the drug. Some experts propose adjusting azathioprine dose based on a target change in mean corpuscular volume,[3] whereas others[52] (including our center) titrate empirically to clinical efficacy based on weight based dosing as above.

Azathioprine risks	Mitigation strategies
GI discomfort (nausea, anorexia, abdominal pain, diarrhea)	Take with food, start low and increase slowly
Liver toxicity	Lab monitoring
Myelosuppression / Infection	Lower the dose if WBC <4K or platelet count <150
Teratogenicity	May be ok in pregnancy but usually counsel against this and recommend contraception
Malignancy	Black box warning, skin checks (skin cancer is common), risk of lymphoma

MYCOPHENOLATE MOFETIL

Mycophenolate Mofetil (MMF) suppresses B and T lymphocyte proliferation and antibody production by interfering with purine metabolism, primarily by inhibiting inosine monophosphate dehydrogenase, a biochemical enzyme essential for DNA synthesis in lymphocytes but not in most other cells.

Dosing typically starts at 500 mg daily or twice daily and then is titrated to a target dose of 1500-3000 mg/day in divided doses twice daily.

Mycophenolate Mofetil risks	Mitigation strategies
GI discomfort	Common but usually well tolerated though can be limiting. Start slow and titrate up
Myelosuppression / Infection	Monitor infections. Possibly increased risk of herpesvirus infections and CMV though usually do not prophylax.
Teratogenicity	Formal prescribing program now as this is a Category D drug. MMF can also interfere with hormonal contraception, an important consideration in women of childbearing age

Malignancy	Black box warning, skin checks (skin cancer is common)
Liver toxicity	Lab monitoring
Drug interactions	Rifampin (relevant if cotreating for latent TB); interactions with PPIs and antacids (can adjust dosing or use enteric coated)

METHOTREXATE

Methotrexate is an analog of folic acid that interferes with dihydrofolic acid reductase activity, thereby interfering with purine and pyramidine synthesis. This in turn leads to decreased lymphocyte and immunological function, although the precise mechanisms are still somewhat murky.

Dosing for treatment of autoimmune disease is considered "low dose" and is dosed in a **weekly** oral regimen. This is very different from the high dose methotrexate giver parenterally or even intrathecally for hematology/oncological indications.

Note that oral methotrexate is given weekly and NOT daily. This needs to be spelled out clearly to patients. The dose can be split on two consecutive days (i.e. Saturday/Sunday) for tolerability if GI side effects are prominent. Subcutaneous dosing can also be used to improve GI tolerability. The maximum dose is 25 mg/week but for most neurological indications 20 mg/week is the ceiling to minimize risk. Dosing can be started as low as 7.5 mg/week but for many patients it is ok to start at 10 or even 15 mg/week. Folic acid 1 mg/day must be given to prevent predictable dangerous and bothersome side effects.

Methotrexate can also be administered intrathecally. There is extensive experience with IT methotrexate in children and adults for treatment of CNS involvement of leukemia and lymphoma, and while generally well-tolerated, neurological toxicity is well recognized as a potential complication.[53] Whether intrathecal methotrexate can help sterilize the CNS in severe autoimmune encephalitis remains to be determined. Emerging case reports in NMDA suggest possible benefit in some but not others.[54] Of note, an open label trial in secondary progressive MS reported remarkably low toxicity (but did not clearly affect the disease course).[53]

Oral methotrexate is very inexpensive and perhaps the most accessible steroid-sparing cytotoxic oral immunosuppressant globally. It's role for treatment of autoimmune encephalitis is less studied, but on first principles remains an important treatment option for maintenance therapy.

Methotrexate risks	Mitigation strategies
Folic acid deficiency	Folic acid 1 mg/day supplementation; can also do folinic acid
GI discomfort	Divided dosing. Subcutaneous dosing if a major problem
Myelosuppression / Infection	-Check CBC/diff every month x 3 months, then every 2-3 months at minimum -PJP (PCP) prophylaxis if in combination with other immunosuppressants
Teratogenicity	Major teratogenic risk and abortifacient. Contraceptive use in men and women and stop prior to conception in men and women
Liver toxicity	Screen for liver disease including hepatitis B and C serologies, minimize/avoid alcohol while on this agent, lab monitoring
Pulmonary toxicity	Baseline CXR, monitor for symptoms
Malignancy/lymphoproliferative disorders	

B CELL DEPLETION / RITUXIMAB

Targeted B cell depletion is a form of immunosuppression beneficial in many agents. The most widely used agent to date is Rituximab, a chimeric monoclonal antibody against CD20, a B cell marker. There are many other CD20 agents in late stage clinical development.

Importantly, very mature B cells that differentiate into plasmablasts and plasma cells that secrete antibodies do not express CD20. Some plasma cells and plasmablasts, do express CD19, another B cell marker. Rituximab leads to profound depletion of CD20+ lymphocytes in the periphery as well as in the CSF[55] and brain perivascular spaces.[56]

Rituximab is widely used as empiric therapy for autoimmune encephalitis, sometimes as monotherapy and sometimes in combination with cyclophosphamide (see above).
Why Rituximab is beneficial for certain inflammatory diseases but not others is an area of active investigation. It is possible that Rituximab may work by affecting antigen presentation by B cells and interactions with T cells. Rituximab may also target specific subsets of IgGs more than others.

Rituximab Dosing
There are 2 well-established dosing regimens:

- 1000 mg IV Rituximab x 2 doses given 2 weeks apart; can be redosed up to every 6 months (*a regimen approved for treatment of rheumatoid arthritis*)

- 375 mg/m^2 weekly x 4 weeks (*the regimen typically used in hematology-oncology and some neuro-oncology contexts as well*).

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In our clinical practice, we tend to favor the 1000 mg IV dosing regimen, one reason being the need for fewer infusions, but either approach is reasonable.

Rituximab risks	Mitigation strategies
Infusion reactions (up to 20%, as it is a chimeric, not humanized antibody, some have been fatal, usually during the first dose)	Pretreatment with at least 100 mg IV methylprednisolone or equivalent. Also pretreat with acetaminophen and diphenhydramine.
Mucocutaneous reactions	Monitor
Infection	-Check full hepatitis B serologies. Great caution for risk of hepatitis B reactivation. Consider suppressive antiviral treatment even if “cleared” infection (i.e. +core antibody) -Rare PML risk (JCV antibody not routinely used as unclear how it will help post-test risk stratification given the rarity of the outcome) - Annual TB testing - Check IgG, consider repletion if acquired deficiency and pulmonary infections -Avoid live vaccines
Teratogenicity	Unclear risk, standard recommendation is effective contraception during and for up to 1 year after treatment
Liver toxicity	Labs
Possible malignancy/lymphoproliferative disorders	

Rituximab is frequently used for treatment of severe NMDA encephalitis.[6,57] Rituximab may also be helpful in a subset of patients with LGI1 encephalitis.[39] There is also emerging experience using this agent with other disorders, including DPPX and GAD-65 associated disorders. There is ample experience and safety data using Rituximab in children for treatment of a variety of CNS inflammatory disorders.[58]

IMMUNOSUPPRESSION EXPERIENCE IN CLASSICAL PARANEOPLASTIC DISORDERS

Antibodies are probably not directly pathogenic in many cases. There is emerging evidence for a T cell mediated neuronally destructive process.

Acute and induction immunosuppressive strategies are frequently ineffective for paraneoplastic disorders associated with neuronal intracellular antibodies, but there is enough suggestion of possible benefit or stabilization in a small subset of patients in the literature and combined clinical experience to consider offering such therapies to patients if functional status allows, but must weigh risk vs unclear benefit in this context.[5]

Tumor removal/cure is favored if possible (which is unfortunately often not the case) and the treatment strategy best demonstrated to lead to sustained clinical improvement.[5,59]

Select examples:

Hu:

- Anti-tumor therapy trended towards benefit if started early enough and with good functional status[60]
- Plasma exchange, tumor treatment, steroids, Cytoxan in variable combinations not effective.[61]
- IVIg not effective (open label analysis)[62]
- Combination of steroids, IVIg and pulse IV cyclophosphamide: No improvement if poor functional status, stabilization in subset with better functional status[63]
- Sirolimus (open label),[64] 1/17 improved, 1/17 stabilized, 15/17 no effect. Median survival 21 months.
- Possible benefit of Rituximab in a subset of patients[65]
- Possible benefit of HCG in a subset of patients[66]

Yo:

- Ovarian tumor removal helpful when possible[67]
- IVIG not effective (open label analysis)[62]; other reports of benefit with IVIG[68]
- Steroids + Cytoxan helpful for case of cerebellar degeneration[69]
- Combination of steroids, IVIg and pulse IV cyclophosphamide: No improvement if poor functional status, stabilization in subset with better functional status[63]; Plasma exchange, tumor treatment, steroids, Cytoxan in variable combinations not effective.[61]

Ma:

- Mixed experience, with no clear benefit associated overall with immunosuppression in a large series, although some individuals stabilized or had substantial improvement; tumor removal can be helpful.[70]

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