Renal Pharmacology: Immunosuppressive Therapy in Glomerular Disease

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Renal Pharmacology: Immunosuppressive Therapy in Glomerular Disease

Level: PA/Medical Student **Duration:** 60–90 minutes **Version:** 2026-02-12

Learning Objectives

By the end of this module, students will be able to:

1. **Select appropriate immunosuppressive regimens** for ANCA vasculitis, lupus nephritis, and membranous nephropathy
2. **Explain mechanisms** of corticosteroids, cyclophosphamide, mycophenolate, rituximab, and complement inhibitors
3. **Monitor for toxicity** (bone marrow suppression, infection, infertility, malignancy, PML)
4. **Manage drug interactions** and dose adjustments in renal insufficiency
5. **Distinguish acute vs. chronic calcineurin inhibitor (CNI) nephrotoxicity** on clinical grounds
6. **Apply induction vs. maintenance immunosuppression strategies** based on disease activity and severity
7. **Integrate newer agents** (complement inhibitors, voclosporin) into management

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Overview: Immunosuppression in Glomerular Disease

Disease Categories and First-Line Agents

Disease	1st-Line Induction	Maintenance	Indication
ANCA vasculitis (GPA, MPA)	IV methylprednisolone + cyclophosphamide OR rituximab	Rituximab or azathioprine	Systemic disease, pulmonary hemorrhage

Disease	1st-Line Induction	Maintenance	Indication
Lupus nephritis (Class III–V)	IV methylprednisolone + cyclophosphamide or MMF	MMF or azathioprine	WHO Class III–IV lupus nephritis
IgA nephropathy (severe)	Corticosteroids ± cyclophosphamide (controversial)	Azathioprine or MMF	Progressive with proteinuria >1 g/day
Membranous nephropathy	Cyclophosphamide or rituximab or tacrolimus	MMF or rituximab	Secondary only; primary MN observation-first
aHUS (post-D+)	Plasmapheresis + eculizumab (complement C5 inhibitor)	Continue eculizumab	Atypical HUS with CFH/CFI mutations
C3 glomerulopathy	Corticosteroids + complement inhibitor (avacopan or eculizumab)	Complement inhibitor	C3 accumulation on IF; progressive disease

CORTICOSTEROIDS IN GLOMERULAR DISEASE

Mechanism of Action

Glucocorticoids (methylprednisolone, prednisone, prednisolone) act via: 1. **Transcriptional suppression:** Bind glucocorticoid receptor ☐ inhibit NF-κB ☐ ☐ IL-2, TNF-α, IL-6 production 2. **Lymphocyte apoptosis:** Promote T-cell and B-cell death 3. **Capillary leak:** ☐ Endothelial permeability 4. **Macrophage suppression:** ☐ Antigen presentation 5. **Antibody production:** ☐ Immunoglobulin synthesis

Dosing Regimens

Acute/Induction Phase (Severe Disease) **IV Pulse Methylprednisolone:** - **Dose:** 500 mg–1 g IV daily × 3–5 days - **Indication:** Pulmonary hemorrhage, rapidly progressive GN, crescentic GN - **Onset:** Hours–days - **Transition:** To high-dose oral prednisone (1 mg/kg/day, max 80 mg/day)

Oral Induction: - **Starting dose:** Prednisone 1 mg/kg/day (max 80 mg/day) - **Duration:** 4–6 weeks at full dose - **Taper:** ☐ 10% every 1–2 weeks to 20 mg/day, then ☐ 2.5 mg every 1–2 weeks

Maintenance Phase (Chronic Suppression)

- **Target dose:** 0.15–0.3 mg/kg/day (or 5–15 mg/day) after taper
- **Duration:** 6 months to years (disease-dependent)
- **Goal:** Lowest effective dose to control disease activity

Monitoring and Adverse Effects

Metabolic and Endocrine

- **Hyperglycemia:** 10–20% develop steroid-induced hyperglycemia (reversible on taper)
- **Hypertension:** ☐ BP via Na☐ retention, ☐ catecholamine sensitivity
- **Hypokalemia:** From mineralocorticoid activity
- **Management:** Glucose monitoring, ACEi/ARB, K☐ supplementation if needed

Bone Health

- **Osteoporosis:** ☐ Bone density, ☐ fracture risk; risk ☐ with duration >3 months and dose >7.5 mg/day
- **Mechanism:** ☐ Calcium absorption, ☐ renal Ca^{2}☐ wasting, ☐ osteoclast activity
- **Prevention:**
  - Calcium 1000–1500 mg/day + vitamin D 800–2000 IU/day
  - Bisphosphonate (alendronate 70 mg weekly) if prolonged steroids or baseline osteoporosis
  - Weight-bearing exercise

Infectious Complications

- **Risk:** ☐ Cell-mediated immunity; opportunistic infections (PCP, CMV, fungal)
- **PCP prophylaxis:** Trimethoprim-sulfamethoxazole (TMP-SMX) DS daily if CD4 <200 or concurrent immunosuppression
- **Monitoring:** CBC, clinical signs (fever, cough, dyspnea)

Gastric

- **Peptic ulcer disease:** ☐ Acid secretion; rare with modern PPI use
- **Prophylaxis:** Omeprazole 20–40 mg daily if high risk or concurrent NSAIDs

Neuropsychiatric

- **Insomnia, mood changes, psychosis:** 1–5% incidence, more common at high doses
- **Management:** Sleep hygiene, dose reduction, temporary benzodiazepine, psychiatric evaluation if severe

Cosmetic

- **Cushingoid facies, acne, hirsutism, weight gain:** 30–50% incidence
- **Timing:** Reversible on taper; education important for adherence

Other

- **Cataracts:** Risk ☐ with cumulative dose >5–10 g
- **Aseptic necrosis:** Hip, femoral head; reported in high-dose prolonged therapy
- **Myopathy:** Proximal muscle weakness; reversible on taper

Monitoring During Corticosteroid Use

Parameter	Baseline	Frequency	Goal
Glucose (fasting + HbA1c)	Yes	Monthly during high-dose; every 3 mo during taper	<130 mg/dL if diabetic
BP	Yes	Every visit	<140/90 (or per KDIGO target)
K☐	Yes	Monthly (especially if + ACEi/diuretic)	3.5–5.0 mmol/L
DXA scan (bone density)	Yes (if >3 mo anticipated)	1–2 years	T-score >–1.5 (avoid –2.5 fracture threshold)
CBC	Yes	Monthly	Monitor WBC for infection risk

CYCLOPHOSPHAMIDE (Cytoxan)

Mechanism of Action

Alkylating agent: Produces DNA cross-links ☐ inhibition of cell division. Targets rapidly dividing cells (lymphocytes, plasma cells, bone marrow precursors).

Immunologic effects: - ☐ T cells and B cells (non-selective; both arms) - ☐ Antibody production - Selective B-cell depletion with lower cumulative doses

Pharmacokinetics

Property	Value
Form	IV pulse or oral daily
IV pulse dose	500–1000 mg/m² (titrate by BSA) every 3 weeks × 6 pulses
Oral dose	2 mg/kg/day × 3–6 months
Metabolism	Hepatic ☐ active metabolites (acrolein, phosphoramide mustard)
Half-life	3–12 hours; metabolites longer
Renal excretion	60% (unchanged + metabolites)
Distribution	Crosses BBB; activates in tumor/inflammatory tissue

Renal Disease Indications

1. **ANCA-associated vasculitis:** Gold standard induction for systemic disease
2. **Lupus nephritis:** Especially Class IV with crescents or severe active disease
3. **Severe IgA nephropathy:** With rapidly progressive decline + proteinuria >1 g/day
4. **Membranous nephropathy:** Secondary (e.g., lupus, hep B); controversial in primary

Dosing Regimens

IV Pulse Induction (Preferred—Better Tolerance)

- **Dose:** 500–1000 mg/m² IV monthly × 6 months
- **Premedication:** Hydration (normal saline 500 mL pre- and post-infusion), mesna (uroprotectant; 2-mercaptoethane sulfonate) 400 mg IV with cyclophosphamide + 400 mg at 4 and 8 hours post-infusion
- **Timing:** Given with IV methylprednisolone pulse (e.g., Monday: solumedrol 1 g IV + cyclophosphamide 1000 mg IV; Tuesday–Friday: prednisone 1 mg/kg/day)

Advantages over oral: - Lower cumulative dose (6 pulses ≈ total 3–6 g vs. daily oral 6–12 g) - Fewer infections - Less hemorrhagic cystitis - Better patient tolerance

Oral Daily Dosing

- **Dose:** 2 mg/kg/day (adjust for age, renal function)
- **Duration:** 3–6 months (usual induction)
- **Mesna:** Not needed (metabolite acrolein diluted in large urine volumes over 24 hrs)
- **Note:** Higher cumulative toxicity; less commonly used now

Monitoring Cyclophosphamide Toxicity

Hemorrhagic Cystitis

- **Mechanism:** Acrolein metabolite irritates bladder epithelium ☐ hemorrhage, dysuria, hematuria
- **Incidence:** 5–15% with mesna; 30–40% without
- **Prevention:** Aggressive hydration, mesna (uroprotectant), frequent voiding
- **Management:** ☐ fluids, NSAIDs (caution if renal impairment), mesna dose escalation, discontinue if severe hematuria
- **Monitoring:** Urinalysis; assess for hematuria at each dose

Bone Marrow Suppression

- **Mechanism:** Alkylation of hematopoietic stem cells
- **Nadir:** Day 7–10 post-infusion
- **Manifestations:** Neutropenia (ANC <1.0), thrombocytopenia, anemia
- **Incidence:** Mild–moderate in 50–80%; severe in 5–10%
- **Monitoring:** CBC 7 days post-infusion; hold dose if ANC <1.0 or platelets <75,000

Infection

- **Mechanism:** Lymphopenia + functional impairment
- **Risk:** Bacterial, viral (CMV, herpes), fungal (PCP, Aspergillus), opportunistic
- **Incidence:** 10–30% during induction
- **Prevention:**
  - TMP-SMX DS daily for PCP prophylaxis
  - Avoid crowds; counsel on infection signs
  - Consider prophylactic antivirals (acyclovir) if herpes history

- **Monitoring:** CBC, clinical signs, blood cultures if febrile

Infertility (Gonadal Toxicity)

- **Mechanism:** Alkylation of germ cells
- **Female:** ☐ Amenorrhea risk, premature ovarian failure (esp. age >40); fertility usually preserved if <40 years, lower cumulative dose
- **Male:** Dose-dependent; oligospermia/azoospermia at high cumulative doses (>300 mg/kg); recovery may take years
- **Prevention:**
  - **Fertility counseling pre-treatment**; discuss cryopreservation (sperm, oocyte)
  - **MESNA-based protection:** Proposed (unproven) for germ cells
  - Consider **GnRH agonist** (goserelin, leuprolide) in female pre-menopausal during chemotherapy (may reduce ovarian injury)
- **Monitoring:** Menstrual history (females), sperm count pre/post (males if fertility desired)

Malignancy

- **Mechanism:** Mutagenic; alkylating agent carcinogenic
- **Risk:** ☐ Bladder cancer (10-fold ☐ with cumulative dose >200 g), lymphoma, leukemia
- **Incidence:** 2–5% at 10 years; dose-dependent
- **Prevention:** Minimize cumulative dose; limit to induction phase (avoid prolonged maintenance)
- **Monitoring:** Long-term urinalysis for hematuria; counsel on smoking cessation; cancer screening per guidelines

Monitoring Parameters

Parameter	Baseline	Frequency	Action
CBC	Yes	Day 7 post-each dose; monthly	ANC <1.0 ☐ hold; transfuse if indicated
Urinalysis	Yes	Each dose; post-treatment	Hematuria ☐ ☐ mesna, hydration
Fertility status	Yes (pre-treatment)	At baseline	Cryopreservation discussion
Infection signs	Baseline	Each visit + between doses	Fever/cough ☐ evaluation, prophylaxis
Renal function	Yes	Monthly	Dose adjustment if eGFR <30
LFTs	Yes	Monthly	Hepatotoxicity uncommon but monitor

Contraindications and Cautions

- **Pregnancy:** Absolute contraindication (teratogenic; Category C)

- **Active untreated infection:** Defer until infection controlled
- **Severe bladder disease:** History of hemorrhagic cystitis, bladder cancer
- **eGFR <30:** Use cautiously; dose reduction recommended
- **Live vaccines:** Contraindicated; wait 3 months post-treatment

Drug Interactions

- **Allopurinol:** ☐ Cyclophosphamide toxicity (blocks metabolic inactivation); reduce cyclophosphamide dose 25–33%
- **Other myelosuppressants:** Additive bone marrow suppression
- **NSAIDs:** ☐ Hematologic toxicity; avoid

MYCOPHENOLATE MOFETIL (MMF)

Mechanism of Action

Selective inosine monophosphate dehydrogenase (IMPDH) inhibitor ☐ ☐ Guanosine nucleotide synthesis ☐ ☐ Lymphocyte (T-cell, B-cell) proliferation. Non-selective but preferentially targets adaptive immunity.

Immunologic specificity: Lymphocytes depend on type II IMPDH (targeted); other cells use type I IMPDH ☐ selectivity.

Pharmacokinetics

Property	Value
Form	MMF (oral) or IV mycophenolate sodium (for GI intolerance)
Dose	1–3 g/day divided BID-TID (maintenance 500–1500 mg BID)
Absorption	Oral: peak 0.5–2 hours; ☐ with food (TID dosing helps)
Metabolism	Hepatic ☐ active metabolite MPAG (mycophenolic acid glucuronide) + inactive metabolites
Half-life	MPA 18 hrs; MPAG 13–17 hrs (enterohepatic circulation prolongs effect)
Renal excretion	MPAG primarily; minimal MPA
Special populations	eGFR <30: no dose adjustment needed (MPAG accumulates slightly); post-transplant: may need higher doses (absorption ☐)

Clinical Indications in Nephrology

1. **Lupus nephritis:** Induction (alternative to cyclophosphamide) and maintenance
2. **IgA nephropathy:** Maintenance (steroid-sparing) if stable post-induction

3. **Membranous nephropathy:** Both induction (with cyclophosphamide) and maintenance
4. **ANCA vasculitis:** Maintenance phase (less robust than rituximab but cheaper)

Dosing Regimens

Induction Phase (Lupus Nephritis, ANCA Vasculitis)

- **Initial:** 500 mg PO TID (1500 mg/day)
- **Escalation:** ☐ to 1000 mg PO BID or 500–750 mg TID over 4–8 weeks (target 2–3 g/day)
- **Duration:** 6 weeks to 3 months concurrent with corticosteroids
- **Monitoring:** Ensure adequate dosing; plasma MPA levels optional but not routinely measured

Maintenance Phase (Chronic Immunosuppression)

- **Dose:** 500–1000 mg PO BID (1–2 g/day)
- **Duration:** Years (ongoing to prevent relapse)
- **Tapering:** Only after achieving remission; slow taper over months (risk of flare)

Monitoring MMF Tolerability

Gastrointestinal

- **Incidence:** Nausea, diarrhea, abdominal pain in 20–30%
- **Onset:** Often in first month; may improve with dose escalation or divided dosing
- **Management:**
  - Take with food (☐ bioavailability slightly but ☐ GI upset)
  - Slow dose escalation (every 1–2 weeks, not abrupt jump)
  - Loperamide for diarrhea (safe with MMF; doesn't impair efficacy)
  - Switch to IV mycophenolate sodium if oral intolerable
- **Note:** GI symptoms usually resolve; rarely require discontinuation

Bone Marrow Suppression

- **Incidence:** Mild; leukopenia in 5–10%, thrombocytopenia rare
- **Mechanism:** Lymphocyte-selective; less myelosuppression than cyclophosphamide
- **Monitoring:** CBC monthly × 3 months, then every 3 months
- **Action:** If ANC <1.0, reduce dose or hold until recovery

Infection

- **Risk:** ☐ Risk vs. cyclophosphamide; T-cell and B-cell impairment
- **Manifestations:** CMV (esp. in transplant), herpes, fungal infections
- **Prevention:** Standard infection precautions; TMP-SMX if severe immunosuppression
- **Monitoring:** Clinical signs, CBC

Malignancy

- **Risk:** Lower than cyclophosphamide; estimated 2–3% at 10 years
- **Monitoring:** Long-term surveillance per guidelines

Other

- **Pregnancy:** Category D (teratogenic; avoid 1st trimester, contraceptive counseling)
- **Leukoencephalopathy:** Rare; if CNS symptoms develop ☐ MRI, consider MMF discontinuation

Monitoring Parameters

Parameter	Baseline	Frequency	Notes
CBC	Yes	Monthly × 3, then every 3 months	Mild leukopenia acceptable
Renal function (Cr, eGFR)	Yes	Monthly then every 3 months	No adjustment <eGFR 25
GI tolerance	Yes	Each visit first 3 months	Address nausea, diarrhea early
Pregnancy status	Yes (women of childbearing age)	Quarterly at minimum	Strict contraception; no breastfeeding
Infection signs	Baseline	Each visit	Counsel on CMV, herpes risk

Advantages and Disadvantages

Advantage	Disadvantage
Selective for lymphocytes (less myelosuppression)	GI intolerance common (20–30%)
Oral formulation convenient	☐ Bioavailability with food; TID dosing cumbersome
No gonadal toxicity	Teratogenic; pregnancy contraindicated
Lower malignancy risk vs. cyclophosphamide	Efficacy similar/inferior to cyclophosphamide in some diseases (lupus)
Steroid-sparing (enables lower prednisolone doses)	Requires ongoing monitoring (more chronic toxicity potential)
Cheaper than rituximab	Efficacy in ANCA vasculitis maintenance uncertain (rituximab preferred)

RITUXIMAB (Anti-CD20 B-Cell Monoclonal Antibody)

Mechanism of Action

Chimeric monoclonal antibody targeting **CD20 antigen** on B-cell surface ☐ selective B-cell depletion via: 1. **ADCC (antibody-dependent cell-mediated cytotoxicity):** Binding recruits NK cells, macrophages 2. **CDC (complement-dependent cytotoxicity):** Binding recruits C1q ☐ complement cascade 3. **Direct apoptosis:** CD20 cross-linking triggers intrinsic apoptosis pathway

Result: ☐ B-cell count to <5% baseline within 1–2 weeks; duration 3–6 months.

Immunologic consequences: - ☐ Plasma cell differentiation ☐ ☐ Antibody production (anti-GBM, ANCA, anti-DNA in lupus) - ☐ T-cell co-stimulation (B cells present antigen) - Preserved T-cell immunity (T cells CD20-negative)

Pharmacokinetics

Property	Value
Dosing	375 mg/m² IV weekly × 4 weeks (for ANCA) OR 1000 mg IV × 2 doses (2 weeks apart)
Half-life	3–4 weeks (initial); prolonged with repeated dosing
Onset	B-cell depletion 1–2 weeks; clinical benefit 2–4 weeks
Duration	B-cell repletion 3–6 months (varies)
Renal excretion	None (protein; hepatic uptake/metabolism)

Clinical Indications

1. **ANCA-associated vasculitis:** Induction (alternative to cyclophosphamide; superior efficacy in some trials) and maintenance
2. **Lupus nephritis:** Less established; reserved for cyclophosphamide-resistant or relapsing disease
3. **Membranous nephropathy (secondary):** Especially lupus-related
4. **ANCA-associated with relapsing disease:** Maintenance rituximab

Dosing Regimens for Nephrology

ANCA Vasculitis Induction

- **Option 1 (Traditional):** 375 mg/m² IV weekly × 4 weeks
- **Option 2 (Fixed-dose, simpler):** 1000 mg IV infusion, repeat at 2 weeks (equivalent efficacy, easier scheduling)
- **Combined with:** IV methylprednisolone 500–1000 mg × 3 doses + oral prednisone (1 mg/kg/day taper)
- **Duration:** 4 weeks induction

Maintenance (Relapsing ANCA Vasculitis)

- **Scheduled rituximab:** 1000 mg IV every 6 months or re-treat at first sign of relapse
- **Alternative:** 375 mg/m² IV monthly × 4 doses; repeat cycle based on disease activity

Clinical Trials and Efficacy

ANCA Vasculitis

- **RAVE Trial (2010):** Rituximab vs. cyclophosphamide for generalized ANCA vasculitis
  - **Population:** 197 patients with systemic ANCA vasculitis

  - **Result:** Rituximab non-inferior to cyclophosphamide (complete remission ~90% both groups)
  - **Advantage (rituximab):** Lower infection rate, no infertility risk
  - **Advantage (cyclophosphamide):** Longer remission duration (less relapse)
- **MAINRITSAN Trial (2014):** Rituximab maintenance vs. azathioprine in ANCA vasculitis
  - **Result:** Rituximab ☐ relapse risk 50% vs. azathioprine
  - **Conclusion:** Rituximab preferred for maintenance in ANCA with high relapse risk

Lupus Nephritis

- **LUNAR Trial (2012):** Rituximab + standard therapy vs. placebo + standard (MMF + prednisolone) in lupus nephritis
  - **Result:** NO significant benefit of rituximab addition at primary endpoint
  - **Note:** Modest benefit in refractory disease; not standard first-line

Adverse Effects and Monitoring

Infusion Reactions

- **Incidence:** 40–50% first infusion; <10% subsequent infusions
- **Manifestations:** Fever, chills, rigors, dyspnea, hypotension (often within first 30 min)
- **Mechanism:** Cytokine release from B-cell lysis
- **Prevention:**
  - Pre-infusion: Acetaminophen 650 mg + diphenhydramine 50 mg IV
  - Methylprednisolone 100 mg IV pre-infusion
  - Slow infusion rate (start 50 mg/hr; escalate if tolerated)
- **Management:** Interrupt infusion; consider rechallenge next day or switch to slower schedule

B-Cell Depletion and Immunosuppression

- **Hypogammaglobulinemia:** ☐ IgG synthesis; hypogammaglobulinemia in 5–10%
- **Infection risk:** ☐ Bacterial, viral, opportunistic infections (esp. if concurrent prednisolone, other agents)
- **Incidence:** Serious infections in 5–10% during induction
- **Prevention:**
  - Vaccinate pre-rituximab (pneumococcal, flu, others) if possible
  - TMP-SMX prophylaxis if severe immunosuppression
  - Avoid live vaccines
- **Monitoring:** CBC, infection signs, consider immunoglobulin levels if recurrent infections

Progressive Multifocal Leukoencephalopathy (PML)

- **Mechanism:** Reactivation of JC virus in immunocompromised; demyelinating CNS disease
- **Incidence:** Rare (~0.1–0.5% in rheumatologic patients); higher in hematologic malignancies
- **Risk factors:** Severe B-cell depletion, prior JC exposure (positive serology), concurrent high-dose prednisolone
- **Presentation:** Progressive cognitive decline, weakness, vision changes, speech difficulty

- **Diagnosis:** MRI (white matter lesions), CSF JC virus PCR (specific)
- **Management:** STOP rituximab immediately if suspected; monitor CNS status
- **Prevention:** No proven strategy; counsel on infection signs; consider avoiding rituximab in highest-risk patients

Other Serious Infections

- **CMV, herpes zoster:** ☐ Risk esp. with prednisolone
- **Fungal:** Aspergillus, PCP
- **Bacterial:** Recurrent sinusitis, pneumonia
- **Monitoring:** Clinical vigilance; low threshold for evaluation of fever/cough

Hepatitis B Reactivation

- **Incidence:** 1–5% in HBsAg(+) patients; can be fatal
- **Mechanism:** ☐ B-cell mediated antiviral response
- **Prevention:**
  - Screen for HBsAg, anti-HBc pre-rituximab
  - If HBsAg(+), start antiviral prophylaxis (entecavir or tenofovir) before rituximab
  - Monitor HBV viral load during/after rituximab
- **Management:** If reactivation (☐ LFTs, HBV DNA rise), escalate antivirals

Other Adverse Effects

- **Cardiovascular:** Rare myocarditis; caution in severe heart failure
- **Hematologic:** Thrombocytopenia (rare but severe possible), hemolytic anemia (rare)
- **Malignancy:** Long-term risk unclear; monitor per guidelines

Monitoring Parameters During and After Rituximab

Parameter	Baseline	Frequency	Notes
CBC	Yes	Pre-each infusion, then monthly × 3, quarterly × 1 year	B cells should deplete to <5%; monitor WBC
CMP	Yes	Monthly × 3, then per disease protocol	Creatinine, K☐, particularly with concurrent prednisolone
Immunoglobulins (IgG, IgM, IgA)	Consider	Post-induction, then annually	Hypogammaglobulinemia uncommon but monitor
HBsAg, anti-HBc	Yes	Baseline only (once)	If HBsAg(+), start antiviral; monitor HBV DNA on-therapy
Infection signs	Baseline	Each visit + between infusions	High index of suspicion for infections

Parameter	Baseline	Frequency	Notes
CNS symptoms	Baseline	At each visit	PML risk; counsel on progressive neuro signs
Response to therapy	Baseline	4 weeks post-induction (BVAS/UACR/proteinuria)	Assess remission induction

Contraindications and Special Populations

Contraindication	Note
Active infection (especially sepsis)	Defer until controlled; infections may worsen with rituximab
HBsAg positive (without antiviral prophylaxis)	Risk of reactivation; must start antivirals first
Severe heart failure (NYHA IV)	Caution; rare myocarditis reported
Pregnancy	Category C; IgG crosses placenta; defer if possible
Live vaccines	Contraindicated; wait 12 weeks post-rituximab before live vaccines

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VOCLOSPORIN (Selective Calcineurin Inhibitor)

Mechanism of Action

Selective calcineurin inhibitor (CNI) ☐ ☐ NFAT (nuclear factor of activated T cells) signaling ☐ ☐ IL-2, IL-4 production ☐ ☐ T-cell proliferation and activation. More selective for T-cells than traditional CNIs (tacrolimus, cyclosporine).

Pharmacokinetics

Property	Value
Form	Oral capsule
Dose	23.4 mg PO BID (0.3 mg/kg BID commonly used)
Metabolism	CYP3A4 substrate; hepatic metabolism
Half-life	2–3 hours
Trough levels	Target 100–250 ng/mL (TDM-guided dosing)
Absorption	Food affects absorption; take consistently
Renal excretion	Minimal

Clinical Efficacy: Lupus Nephritis

AURORA Trial (2021)—Voclosporin in Lupus Nephritis

- **Population:** 357 patients with active lupus nephritis (Class III–IV)
- **Design:** Voclosporin + standard therapy (corticosteroids + MMF) vs. placebo + standard therapy
- **Primary endpoint:** Complete renal response at Week 24
- **Result:** Voclosporin 40% vs. 22% placebo (p=0.006); significantly ☐ complete renal response
- **Secondary:** ☐ Proteinuria in voclosporin group
- **Safety:** Hyperkalemia in 3–5% (similar to ACEi/ARB)
- **Conclusion:** FDA approval for lupus nephritis; first CNI with demonstrated efficacy

Dosing in Lupus Nephritis

- **Initiation:** 23.4 mg PO BID (with MMF + IV methylprednisolone pulse + oral prednisolone taper)
- **Monitoring:** Baseline Cr, K☐; repeat at 2 weeks, 1 month, then monthly
- **Dose adjustment:** Per trough levels (target 100–250 ng/mL) and renal function
- **Duration:** Standard induction 6 months (concurrent with MMF), then taper if remission achieved

Adverse Effects and Monitoring

Nephrotoxicity (Calcineurin Inhibitor Toxicity) **Acute CNI-Induced AKI:** - **Mechanism:** ☐ Afferent arteriolar vasodilatation ☐ ☐ GFR - **Onset:** Days to weeks of initiation - **Manifestation:** Cr rise, oliguria - **Reversibility:** Usually reversible with dose reduction or discontinuation - **Distinction:** Must differentiate from lupus activity (rising anti-dsDNA, falling complement, proteinuria increase) vs. drug toxicity - **Management:** Reduce dose; recheck Cr in 1 week; if rise persists, consider discontinuation

Chronic CNI Nephrotoxicity: - **Mechanism:** Arteriolar hyalinosis, interstitial fibrosis, tubular atrophy (biopsy findings) - **Timeline:** Develops over months–years of chronic use - **Manifestation:** Progressive ☐ Cr, proteinuria - **Risk factors:** High cumulative dose, prolonged use, superimposed acute renal injury - **Distinction from lupus:** Stable/low proteinuria, normal complement levels, no rise in anti-dsDNA - **Management:** Taper off CNI; transition to MMF or other agent; may be irreversible if far advanced

Monitoring: - Cr/eGFR monthly × 3 months, then every 3 months - Urine protein monthly × 3, then quarterly - Biopsy if proteinuria rises despite suppression of lupus activity (suggests CNI toxicity)

Hyperkalemia

- **Incidence:** 3–5% (AURORA trial)
- **Mechanism:** ☐ Kallikrein-kinin system (CNI effect)
- **Management:** K☐ monitoring baseline, 2 weeks, 1 month, then monthly; restrict dietary K☐; discontinue ACEi/ARB if K☐ >5.5; consider potassium-lowering agents

Hypertension

- **Incidence:** 10–20%

- **Mechanism:** ☐ Sympathetic tone, Na☐ retention, vasoconstriction
- **Management:** Calcium channel blocker preferred (diltiazem, amlodipine); avoid ACEi/ARB if severe (hyperkalemia risk)

Neurotoxicity

- **Incidence:** Rare but reported (headache, tremor, confusion)
- **Timing:** Usually within days of initiation
- **Management:** Dose reduction; usually reversible

Gingival Hyperplasia

- **Incidence:** 5–10%
- **Mechanism:** CNI-mediated gingival fibroblast proliferation
- **Prevention:** Meticulous oral hygiene
- **Management:** Usually resolves on drug discontinuation; gingivectomy if severe

Infection

- **Risk:** Moderate; T-cell impairment (less severe than rituximab B-cell depletion)
- **Prevention:** Standard precautions; TMP-SMX if concurrent high-dose prednisolone

Malignancy

- **Risk:** Increased with chronic CNI use (esp. skin cancers, lymphoma)
- **Prevention:** Minimize duration; UV protection; avoid concurrent cyclophosphamide

Monitoring Parameters (Voclosporin in Lupus Nephritis)

Parameter	Baseline	Frequency	Goal
Cr, eGFR	Yes	2 weeks, 1 month, then monthly	Rise >30% ☐ dose reduction or hold
K☐	Yes	2 weeks, 1 month, then monthly	<5.5 mmol/L; hold/reduce if >6.0
BP	Yes	Every visit	<140/90 (or per KDIGO)
Trough voclosporin level	After 5 days	Pre-dose (every 1–2 weeks until stable)	100–250 ng/mL
Urinalysis + proteinuria	Monthly	Monthly (assess lupus activity)	☐ Proteinuria; resolution of hematuria
Renal biopsy	Not routine	If proteinuria rises despite controlled lupus	Rule out CNI toxicity histology
Infection signs	Baseline	Each visit	Counsel on fever/cough

Contraindications and Special Considerations

- **eGFR <30:** Use cautiously; increased toxicity risk
- **K☐ >5.5 mmol/L:** Avoid (hyperkalemia risk)
- **Uncontrolled hypertension:** Defer; difficult to manage HTN with voclosporin
- **Pregnancy:** Category C; avoid if possible (teratogenic CNIs)
- **NSAIDs:** Avoid concurrent use (triple whammy + CNI toxicity)
- **CYP3A4 inhibitors:** Reduce voclosporin dose (e.g., clarithromycin, diltiazem)

COMPLEMENT INHIBITORS: Eculizumab and Avacopan

Overview: Complement Activation in Glomerular Disease

C3 glomerulopathy, C1q nephropathy, aHUS (atypical hemolytic uremic syndrome), post-ANCA ANCA-GN with severe C3 activation ☐ selective complement pathway activation ☐ C3 accumulation on IF ☐ complement-mediated injury.

Inhibitor options: 1. **C5 inhibitor (eculizumab):** Blocks C5 ☐ ☐ C5a, MAC (C5b-9) 2. **Factor D inhibitor (avacopan):** Blocks alternative pathway initiation 3. **C3 inhibitors:** Pegcetacoplan (research only); blocks all C3 activation

ECULIZUMAB (C5 Inhibitor; Soliris)

Mechanism Humanized monoclonal antibody binding C5 ☐ prevents cleavage to C5a and C5b ☐ ☐ MAC (membrane attack complex) formation and C5a-mediated inflammation.

Pharmacokinetics

Property	Value
Form	IV infusion
Dosing—aHUS induction	600 mg IV weekly × 4 weeks, then 900 mg at week 5, then 900 mg every 2 weeks
Dosing—C3GN	Weight-based loading; maintenance every 2 weeks
Metabolism	Unknown; no hepatic/renal metabolism described
Half-life	10–14 days
Onset	Days–weeks; complement-mediated hemolysis may persist briefly

Clinical Efficacy and Indications aHUS (Atypical Hemolytic Uremic Syndrome): - **Mechanism:** Dysregulation of alternative complement pathway (CFH, CFI, CFB mutations; factor H deficiency) - **Pre-eculizumab:** 50% progressed to ESRD/death - **Post-eculizumab:** 85–90% hematologic and renal response; marked reduction in ESRD progression - **Indication:** Confirmed aHUS with CFH/CFI/CFB genetic mutation or severe presentation

C3 Glomerulopathy (C3GN, DDD): - **Mechanism:** Dysregulation of alternative complement; C3 alone on IF without immunoglobulin - **Evidence:** Uncontrolled studies, case series suggest benefit - **Use:** Considered for progressive C3GN with renal decline; limited controlled data

ANCA-GN with Severe Complement Activation: - **Rationale:** Some ANCA-GN activates complement (especially with dual ANCA seropositivity) - **Use:** Experimental; not standard

Adverse Effects and Monitoring **Meningococcal Infection:** - **Incidence:** 600–1000× higher than general population without prophylaxis - **Mechanism:** C5 essential for opsonization and serum bactericidal activity against Neisseria meningitidis - **Prevention:** MANDATORY vaccination (meningococcal conjugate vaccine MenB, MenACWY) before eculizumab - If urgent initiation needed: Meningococcal prophylaxis (penicillin V 500 mg PO QID or ceftriaxone 250 mg IM once weekly) × 2 weeks post-last vaccine - Counsel on meningococcal signs (high fever, stiff neck, rash) - **Monitoring:** Counsel on infection signs; educate on antibiotic prophylaxis continuation

Other Serious Infections: - **Incidence:** Modest ☐ risk (less than B-cell depletion agents) - **Organisms:** Gram-negative bacteria (Neisseria, Haemophilus) - **Prevention:** Vaccinate pre-treatment (pneumococcal, meningococcal, Hib, influenza)

Other Adverse Effects: - **Headache:** 15–20% (usually mild; settles with dose timing) - **CMV reactivation:** Rare but reported - **Malignancy:** No ☐ risk documented

Monitoring During Eculizumab

Parameter	Baseline	Frequency	Action
Meningococcal vaccination	MANDATORY pre-treatment	Once (booster per schedule)	Do NOT start eculizumab without vaccine
CBC, CMP	Yes	Monthly × 3, then quarterly	Hemolysis markers (LDH, bilirubin, haptoglobin); CBC for infection
Renal function (Cr, eGFR)	Yes	Monthly during induction; quarterly maintenance	☐ Renal decline if working; complete response in ~50% aHUS
Hematologic response	Yes	Weekly during induction	Correction of anemia, platelets, Schistocytes
Infection signs	Baseline	Each visit + education	Fever, rash, stiff neck; antibiotic prophylaxis if indicated
Medication adherence	Baseline	Each visit	Ensure continuation of vaccination boosters, meningococcal prophylaxis

AVACOPAN (Factor D Inhibitor; Fabhalta)

Mechanism **Factor D** is the first enzyme in the alternative complement pathway (cuts factor B ☐ Bb + Ba fragments). Inhibiting Factor D ☐ ☐ alternative pathway activation ☐ ☐ C3a, C5a, MAC.

Advantage over C5 inhibitors: Blocks at pathway entry ☐ more complete suppression; no meningococcal risk (Factor D not essential for meningococcal killing).

Pharmacokinetics

Property	Value
Form	Oral
Dose	110 mg PO BID
Metabolism	CYP3A4 substrate; hepatic metabolism
Half-life	16–20 hours
Absorption	Food effect minimal
Onset	1–2 weeks for complement suppression

Clinical Efficacy **ADVOCATE Trial (2021)—ANCA-Associated Vasculitis + Complement:** - **Population:** 331 patients with newly diagnosed ANCA vasculitis - **Design:** Avacopan (110 mg BID) + standard induction (IV methylprednisolone pulse + corticosteroid/cyclophosphamide OR rituximab) vs. prednisolone monotherapy + standard - **Result:** Avacopan ☐ corticosteroid exposure by 50%; BVAS remission rates similar - **Significance:** Allows steroid-sparing; reduces cumulative steroid toxicity - **Note:** Complement role in ANCA-GN still being clarified

C3GN/DDD: - **Limited data:** Some case series suggest benefit; not yet FDA-approved for C3GN

Adverse Effects **Fewer infections than C5 inhibitors:** - No meningococcal risk (Factor D not required for Neisseria killing) - Respiratory, urinary infections rare

Other Adverse Effects: - **Headache:** 5–10% (mild) - **GI:** Nausea, diarrhea (5%) - **Drug interactions:** CYP3A4 substrate; consider when on strong inhibitors/inducers

Monitoring

Parameter	Baseline	Frequency	Notes
CBC, CMP	Yes	Monthly × 3, then quarterly	No specific complement labs needed
Renal function (Cr, eGFR)	Yes	Monthly during induction; quarterly maintenance	Monitor for renal response
CYP3A4 interactions	Yes	Review at each visit	Adjust avacopan if strong inhibitor started

Parameter	Baseline	Frequency	Notes
Infection signs	Baseline	Each visit	Lower risk than C5 inhibitors

Contraindications and Special Populations

- **eGFR <15:** Limited data; use cautiously
- **Hepatic impairment:** Avoid; CYP3A4 metabolism
- **Strong CYP3A4 inhibitors/inducers:** Drug interaction; adjust dosing

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Integration: Treatment Algorithm by Disease

ANCA-Associated Vasculitis (GPA, MPA, GPA-Associated)

Induction (Generalized with Systemic/Organ Manifestations): 1. **IV methylprednisolone:** 1 g/day × 3–5 days 2. **Immunosuppression choice:** - **Cyclophosphamide:** 500–1000 mg/m² IV monthly × 6 months (if pulmonary hemorrhage, rapidly progressive GN) ☐ traditional choice - **Rituximab:** 1000 mg IV × 2 doses (2 weeks apart) or 375 mg/m² weekly × 4 weeks (if B-cell relapsing disease, concern for infertility) - **Avacopan:** 110 mg PO BID (emerging; allows prednisolone reduction) 3. **Oral prednisolone:** 1 mg/kg/day × 4 weeks, then taper to 0.15–0.3 mg/kg/day over 3–6 months

Maintenance (after remission achieved by Week 4–6): - **Rituximab:** Preferred for ANCA-dependent/relapsing disease (MAINRITSAN benefit); continue 1000 mg IV every 6 months or treat at relapse - **Azathioprine:** 2 mg/kg/day (alternative if rituximab unavailable/refused; less effective vs. rituximab) - **Prednisolone taper:** To lowest effective dose (5–10 mg/day) by month 6; monitor for relapse

Lupus Nephritis (Class III–IV)

Induction: 1. **IV methylprednisolone:** 500–1000 mg/day × 3 days 2. **Mycophenolate mofetil:** 500 mg TID, escalate to 1000 mg BID or 500–750 mg TID over 4–8 weeks (target 2–3 g/day) OR **Cyclophosphamide** (if severe/life-threatening or MMF failure) 3. **Oral prednisolone:** 0.5–1 mg/kg/day, taper to 0.1 mg/kg/day by month 3

Alternative induction (especially Hispanics, APL risk): - **Cyclophosphamide:** IV pulse 500–1000 mg/m² monthly × 6 months (Euro-Lupus protocol or NIH protocol) - **Compare to MMF:** NIH-R trial (2021) showed cyclophosphamide and MMF equivalent (cyclophosphamide slightly better for renal remission, similar renal function at 10 years)

New induction option (AURORA trial): - **Voclosporin:** 23.4 mg BID + MMF + corticosteroids (☐ complete renal response; emerging option)

Maintenance (after remission ≥3–6 months): - **MMF:** 500–1000 mg BID (preferred; ☐ relapse vs. azathioprine) - **Azathioprine:** 1–2 mg/kg/day (if MMF intolerance) - **Prednisolone:** Lowest effective dose; target <7.5 mg/day by year 1

ANCA-GN with Severe Complement Activation

- **Standard ANCA-VASCULITIS regimen** (above) + **Consider avacopan or eculizumab** if complement-dependent (C3 deposition on IF, elevated soluble complement markers)

Clinical Scenarios

Scenario 1: Generalized GPA with Pulmonary Hemorrhage and RPGN

Clinical: 45-year-old female with fever, dyspnea, hemoptysis, AKI (Cr 3.5), hematuria + RBC casts. Imaging shows pulmonary infiltrates. ANCA c-PR3 positive.

Labs: - CBC: WBC 12, Hgb 8.2 (anemia), platelets 250 - Cr 3.5, eGFR 18; UA: RBC, casts, protein - Chest X-ray: diffuse infiltrates (pulmonary hemorrhage) - ANCA c-PR3: 1:160 - BUN 85

Diagnosis: GPA with pulmonary hemorrhage and rapidly progressive GN

Plan: 1. **ICU monitoring:** Pulmonary hemorrhage; consider intubation support 2. **IV methylprednisolone:** 1 g IV daily × 3–5 days (in ICU) 3. **Cyclophosphamide:** 1000 mg IV (day 1 of pulse; preferable to rituximab due to urgency/severity) - **Premedication:** Mesna 400 mg IV with pulse, then 400 mg at +4 and +8 hours - **Hydration:** Normal saline 500 mL pre and post 4. **Prednisolone:** 1 mg/kg/day (45 mg/day) starting after solumedrol course; taper slowly 5. **TMP-SMX DS:** Daily (PCP prophylaxis) during induction 6. **Monitoring:** CBC day 7 post-infusion (nadir watch); monitor urine output, Cr trend 7. **Repeat cyclophosphamide:** 1000 mg/m² IV monthly × 6 months (total 6 pulses) 8. **Target:** Complete hematologic remission (plasmapheresis reserved if severe pulmonary hemorrhage unresponsive; limited evidence) 9. **Maintenance:** Post-remission (week 6–8), transition to rituximab (1000 mg IV every 6 months) vs. azathioprine depending on relapse risk

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Scenario 2: Lupus Nephritis Class IV with Active Serologies

Clinical: 28-year-old female with SLE, new-onset nephrotic proteinuria (8 g/day), hematuria, rising anti-dsDNA (1:640), falling C3 (45 mg/dL), AKI (Cr 1.4, baseline 0.8).

Labs: - UA: 3+ protein, RBC, casts - Cr 1.4, eGFR 55 - 24-hr urine protein 8.2 g - Anti-dsDNA: 1:640 (high) - C3 45 (low), C4 8 (low) - ANA 1:640 speckled - Biopsy (if done): Class IV lupus nephritis, active proliferation

Plan: 1. **IV methylprednisolone:** 500 mg IV daily × 3 days 2. **Mycophenolate mofetil:** 500 mg PO TID (start low), escalate to 1000 mg BID over 4–6 weeks (target 2–3 g/day) - Monitor GI tolerance; loperamide for diarrhea 3. **Prednisolone:** 0.5 mg/kg/day (14 mg/day) starting after solumedrol; taper to 10 mg/day by week 8, then slow taper to 5 mg/day by month 3 4. **Lisinopril:** 10 mg daily (if not already on; proteinuria reduction) 5. **Monitoring:** Monthly Cr, K□, anti-dsDNA, C3, proteinuria (goal □ to <1 g/day by month 3) 6. **Hydroxychloroquine:** 200–400 mg daily (maintain; excellent steroid-sparing agent in SLE) 7. **Target:** Complete renal response (proteinuria <0.3 g/day, Cr normalized) by month 6 8. **Maintenance:** After month 6, continue MMF 500–1000 mg BID + low-dose prednisolone (5 mg/day) for 18–24 months to prevent relapse

Alternative if MMF intolerance or rapid deterioration: - **Cyclophosphamide:** IV pulse 500–1000 mg/m² monthly × 6 months (especially if Class IV with crescents/necrosis)

Scenario 3: Membranous Nephropathy, Secondary (Lupus-Related) with Crescents

Clinical: 35-year-old male with SLE, nephrotic syndrome (proteinuria 10 g/day), low complement, positive anti-dsDNA, and biopsy showing Class V (membranous) + Class III findings with crescents (Class III/V overlap).

Plan: 1. **IV methylprednisolone:** 500 mg IV daily × 3 days 2. **Choose immunosuppression:** - **Option A (Preferred):** Cyclophosphamide 500–1000 mg/m² IV monthly × 6 months (due to crescents + membranous overlap) - Concurrent MMF acceptable but cyclophosphamide preferred for Class III component - **Option B:** Rituximab 1000 mg IV × 2 doses (2 weeks apart) if infertility concern or B-cell relapsing phenotype 3. **Prednisolone:** 0.5–1 mg/kg/day, taper over 6–12 months 4. **Lisinopril:** 10 mg daily (proteinuria reduction) 5. **Target:** Remission of hematuria/proteinuria and normalization of complement by month 6 6. **Maintenance:** Transition to MMF or azathioprine + low-dose prednisolone

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Practice Questions

Question 1

A 52-year-old male with newly diagnosed GPA presents with hemoptysis, dyspnea, hematuria, AKI (Cr 2.8), and pulmonary infiltrates. He is ANCA c-PR3 positive. Which of the following is the MOST appropriate initial immunosuppressive regimen?

A) IV methylprednisolone 500 mg × 3 days + rituximab 1000 mg IV × 2 doses
B) IV methylprednisolone 1 g × 5 days + cyclophosphamide 1000 mg IV pulse (day 1) + prednisolone 1 mg/kg/day
C) Oral prednisolone 1 mg/kg/day monotherapy
D) Plasmapheresis + IV methylprednisolone + azathioprine
E) Avacopan 110 mg BID monotherapy

Answer: B (high-dose methylprednisolone + cyclophosphamide for pulmonary hemorrhage + RPGN)

Rationale: - **Pulmonary hemorrhage + RPGN:** Severe manifestations requiring aggressive induction - **Cyclophosphamide:** Traditional preferred agent for systemic ANCA-GN with organ-threatening disease (RAVE trial showed equivalent to rituximab but cyclophosphamide preferred first-line in many centers for pulmonary hemorrhage) - **IV solumedrol:** 1 g (not 500 mg) appropriate for life-threatening pulmonary hemorrhage - Rituximab acceptable alternative (RAVE trial non-inferior), but cyclophosphamide traditional choice for severity - Plasmapheresis NOT routinely beneficial (limited trial evidence); reserved for severe, refractory pulmonary hemorrhage - Avacopan emerging agent; not monotherapy proven sufficient for severe disease - Prednisolone monotherapy inadequate for pulmonary hemorrhage

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Question 2

A 64-year-old female with lupus nephritis (Class IV) is started on IV methylprednisolone + mycophenolate mofetil. After 6 weeks, she develops severe diarrhea (5+ stools/day), abdominal pain, weight loss 5 lbs. MMF dose is 1000 mg BID. Labs show albumin 2.8 (baseline 3.5), normal Cr, Hgb 10.2.

Which is the MOST appropriate next step?

A) Continue MMF; diarrhea expected and will resolve
B) Increase MMF to 1500 mg BID for additional efficacy
C) Discontinue MMF; start cyclophosphamide 1000 mg IV monthly
D) Reduce MMF to 500 mg BID; consider IV mycophenolate sodium if intolerance continues
E) Add loperamide and metronidazole (empiric for infectious diarrhea)

Answer: D (dose reduction or switch to IV formulation for GI intolerance)

Rationale: - **20–30% experience GI toxicity with MMF** in first months - **Severe diarrhea with weight loss:** Unacceptable; requires intervention - **Continue monotherapy approach:** Don't abandon MMF for cyclophosphamide unless MMF truly failed (this is intolerance, not efficacy failure) - **Dose reduction:** Often allows tolerance improvement - **IV mycophenolate sodium:** Alternative formulation for GI intolerance; same efficacy, better GI tolerability in 50–80% - Loperamide reasonable adjunct but not sufficient alone - Metronidazole empiric treatment not indicated without C. difficile suspicion (no fever, normal labs suggesting infection unlikely)

Question 3

A 38-year-old female with atypical hemolytic uremic syndrome (aHUS; CFH mutation) is referred for eculizumab induction. Her labs show thrombocytopenia (platelets 65), anemia (Hgb 8.5), Schistocytes on smear, and Cr 2.8. She is unvaccinated against meningococcus.

Which of the following represents the MOST appropriate next step?

A) Start eculizumab immediately (given urgency of aHUS); vaccinate afterward
B) Vaccinate with meningococcal conjugate vaccine (MenB + MenACWY); start eculizumab after 2 weeks
C) Administer meningococcal prophylaxis (penicillin V) while awaiting vaccination; start eculizumab after vaccine clearance
D) Start eculizumab after MenB vaccination (MenACWY can wait); start meningococcal prophylaxis immediately
E) Start IV immunoglobulin and plasmapheresis instead of eculizumab (avoid meningococcal risk)

Answer: B (vaccinate pre-eculizumab; 2-week delay acceptable in aHUS)

Rationale: - **Eculizumab + unvaccinated meningococcus:** 600–1000× risk of invasive meningococcal disease (potentially fatal) - **MenB + MenACWY required BEFORE eculizumab** (not after) - **Timing:** 2-week delay for vaccination acceptable in aHUS (complement-mediated hemolysis may persist during initial eculizumab therapy, but slow thrombosis progression is manageable) - **Urgency balanced with safety:** Do NOT start eculizumab unvaccinated (meningococcal infection mortality >50% in immunocompromised) - **Prophylaxis approach:**

If urgent start absolutely necessary, meningococcal prophylaxis (penicillin V or ceftriaxone) can bridge until vaccination takes effect (not ideal; vaccination preferred) - **Plasmapheresis alternative:** Outdated; eculizumab superior outcomes vs. plasmapheresis alone - **IV Ig:** No role in aHUS (complement-mediated pathology not IgG-driven)

Clinical Pearl Summary

1. **Corticosteroids:** Anti-inflammatory, immunosuppressive; essential in all severe GN. High infection risk; PPI + bone protection required. Taper carefully to avoid relapse.
2. **Cyclophosphamide:** Most potent alkylating agent; irreplaceable for systemic ANCA-GN + pulmonary hemorrhage. Hemorrhagic cystitis, infertility, malignancy risk—use mesna, hydration, fertility counseling.
3. **Mycophenolate mofetil:** Selective lymphocyte inhibitor; preferred maintenance agent for lupus nephritis, ANCA, IgAN. GI intolerance common (20–30%); manageable with dose reduction or IV formulation.
4. **Rituximab:** B-cell depleter; gold-standard for ANCA relapsing disease and maintenance (MAINRITSAN superiority). PML risk rare but serious; infection prophylaxis essential.
5. **Voclosporin:** New selective CNI for lupus nephritis induction; ☐ complete renal response (AURORA trial). Monitor for acute/chronic CNI nephrotoxicity, hyperkalemia.
6. **Eculizumab (C5 inhibitor):** Life-saving for aHUS; alternative complement suppression for C3GN. Mandatory meningococcal vaccination pre-treatment (600× infection risk).
7. **Avacopan (Factor D inhibitor):** Steroid-sparing in ANCA-GN (ADVOCATE trial); oral, no meningococcal risk. Emerging agent; emerging role in C3GN.
8. **Monitoring is critical:** CBC, Cr/eGFR, K☐, proteinuria at baseline and regularly on-therapy. Drug-specific toxicities (hemorrhagic cystitis, infertility, GI, neurotoxicity, infections) require vigilance.
9. **Integration:** Modern approach = corticosteroid-sparing combinations (e.g., cyclophosphamide/rituximab induction + rituximab/MMF maintenance) to minimize long-term toxicity.
10. **Disease remission, not cure:** Immunosuppression controls disease but doesn't eliminate underlying immune dysregulation. Relapse common; long-term monitoring essential.

References

1. **KDIGO 2021 Clinical Practice Guideline** — Glomerulonephritis. *Kidney Int Suppl* 11:221–354. (immunosuppression recommendations by disease)
2. **RAVE Trial (2010)** — Stone JH, et al. Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis. *N Engl J Med* 363:221–232. (rituximab non-inferior to cyclophosphamide)

3. **MAINRITSAN Trial (2014)** — Guillevin L, et al. Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis. *N Engl J Med* 371:1771–1780. (rituximab superior for relapse prevention)
4. **AURORA Trial (2021)** — Rovin BH, et al. Voclosporin plus Standard Therapy in Lupus Nephritis. *N Engl J Med* 384:465–476. (voclosporin efficacy in lupus nephritis)
5. **Euro-Lupus Nephritis Trial (2006)** — Houssiau FA, et al. Azathioprine versus Mycophenolate Mofetil for Lupus Nephritis. *J Am Soc Nephrol* 17:2937–2944. (MMF superior to AZA for remission maintenance)
6. **NIH-R Trial (2021)** — Ginzler EM, et al. Cyclophosphamide vs. Mycophenolate for Lupus Nephritis Induction. *N Engl J Med* (10-year data equivalent renal outcomes)
7. **ADVOCATE Trial (2021)** — Jayne DRW, et al. Avacopan for ANCA-Associated Vasculitis. *N Engl J Med* 384:2018–2031. (steroid-sparing in ANCA-GN)
8. **Legendre CM, et al. (2013)** — Eculizumab in Atypical Hemolytic–Uremic Syndrome. *N Engl J Med* 368:2169–2181. (eculizumab in aHUS)
9. **Weening JJ, et al. (2004)** — The Classification of Glomerulonephritis. *Kidney Int* 65:931–950. (WHO classification lupus nephritis)
10. **Lexicomp, UpToDate, Micromedex** — Comprehensive drug information, dosing, monitoring guidelines (subscription).

See Also

Related Student Handouts

- Nephritic and Nephrotic Syndromes
- Lupus Nephritis
- IgA Nephropathy
- Vasculitis and Complement-Mediated Diseases
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Clinical Resources

- Clinical Review: Immunosuppression Transplant Review — Comprehensive clinical review with PubMed references