Advancing Kidney Health
Through Optimal Medication Management

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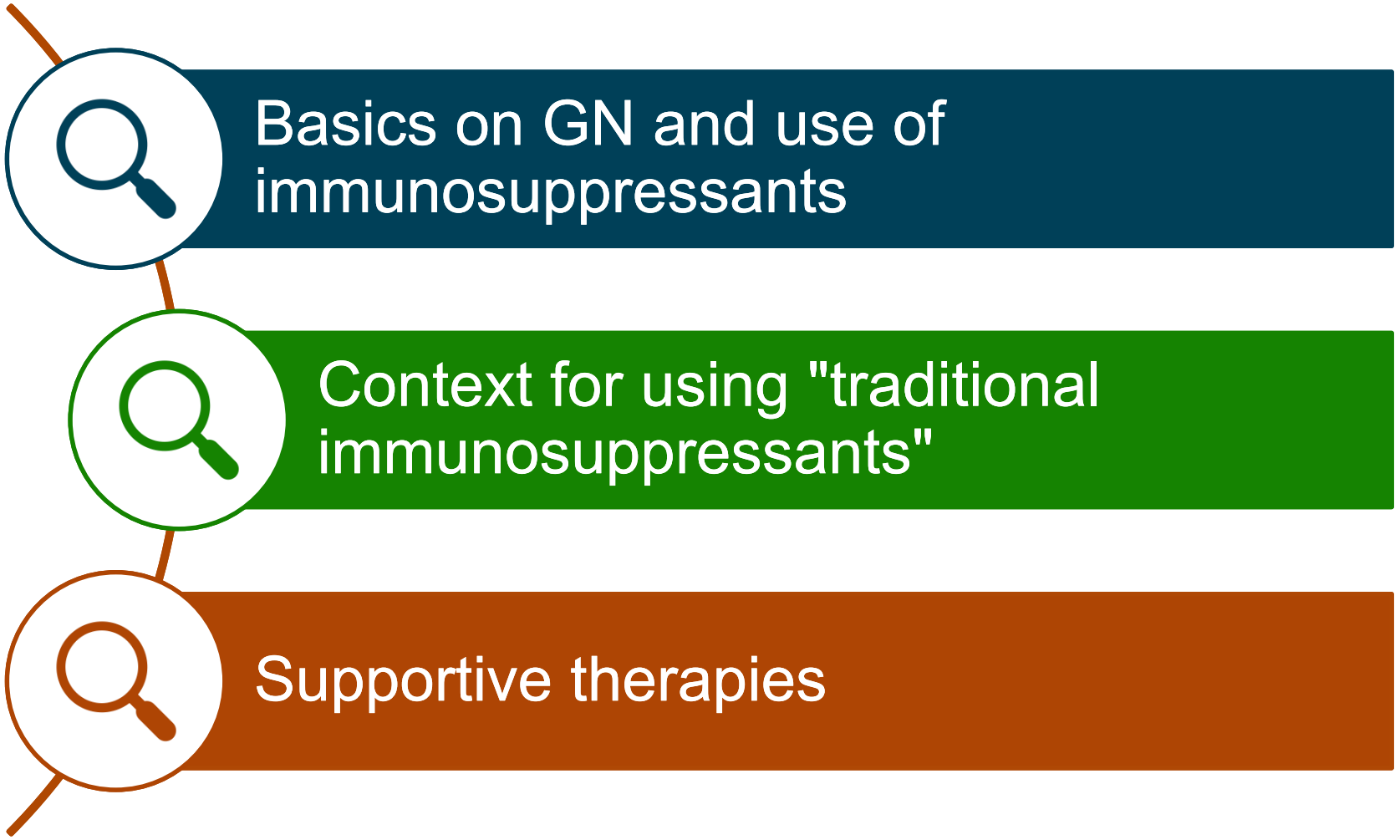
Primer on Immunosuppressants used in Glomerular Disease

Part 1: Basics and Traditional Immunosuppressants

What We're Going to Cover



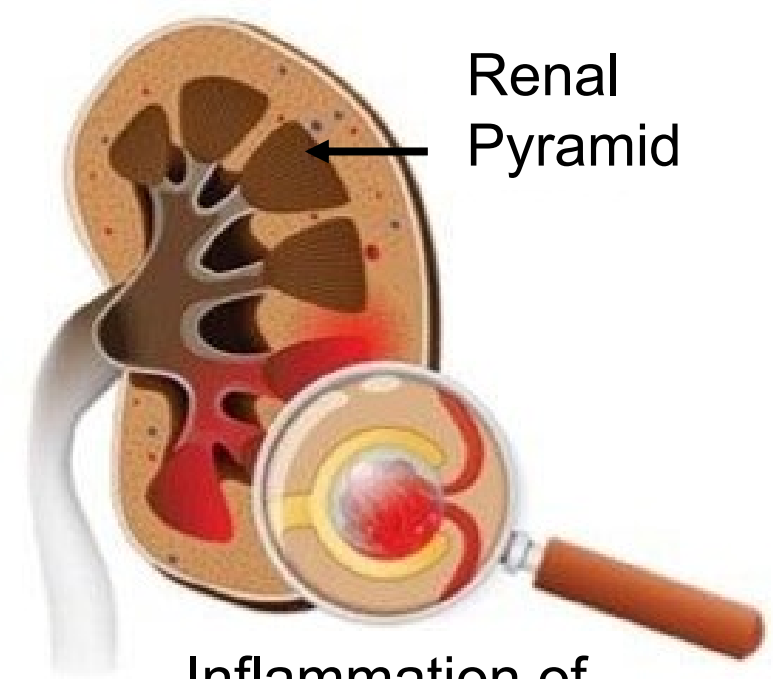
Glossary of Terms

- **ACR** = American College of Rheumatology
- **ADRs**= Adverse drug reactions
- **ANCA** = Anti-neutrophil cytoplasmic antibody
- **AZA** = Azathioprine
- **BG** = Blood glucose
- **BID** = Twice daily
- **BMT** = Bone marrow transplant
- **BP** = Blood pressure
- **C3** = Complement 3
- **C4** = Complement 4
- **CKD** = Chronic kidney disease
- **CNIs** = Calcineurin inhibitors
- **DNA** = Deoxyribonucleic acid
- **ESRD** = End-stage renal disease
- **ER** = Extended release
- **EULAR** = European Alliance of Associations for Rheumatology
- **FACS** = Fluorescence-activated cell sorting
- **FSGS** = Focal segmental glomerulosclerosis
- **FN** = Fibrillary Necrosis
- **GBM** = Glomerular basement membrane
- **GFR** = glomerular filtration rate, either estimated (e) or measured (m)
- **GN** = Glomerulonephritis

Glossary of Terms Pt 2

- **KDIGO** = Kidney Disease Improving Global Outcomes
- **LN** = lupus nephritis
- **MOA** = mechanism of action
- **MCD** = Minimal change disease
- **MMF** = Mycophenolate mofetil
- **MPA** = Mycophenolic acid
- **PCP** = Primary care provider
- **PJP** = Pneumocystis Jirovecii Pneumonia
- **PLA2R ab** = phospholipase A2 receptor antibody
- **PO** = Per os (orally)
- **PPI** = Proton Pump Inhibitors
- **RASi** = Renin Angiotensin System
- **RNA** = Ribonucleic acid
- **sAlbumin** = serum albumin
- **sCr** = serum creatinine
- **SGLT-2i** = Sodium Glucose Cotransporter 2 inhibitors
- **SLE** = Systemic lupus erythematosus
- **TAC** = Tacrolimus
- **UACR** = Urine albumin to creatinine ratio
- **Ig =** Immunoglobulin
- **IgAN**= IgA nephropathy
- **IL** = Interleukin
- **IMN** = idiopathic membranous nephropathy
- **IV** = intravenous

What is glomerulonephritis (GN)?



Inflammation of the glomeruli

Immune Mediated Disease

Associated with inflammation affecting the glomeruli (filtration units) in the kidneys.

Can Be Primary (Idiopathic) or Secondary to:

- Systemic autoimmune diseases
- Infections
- Drugs
- Malignancies

Management of Idiopathic GN

Often involves uses of immunosuppressants to control the immune process.

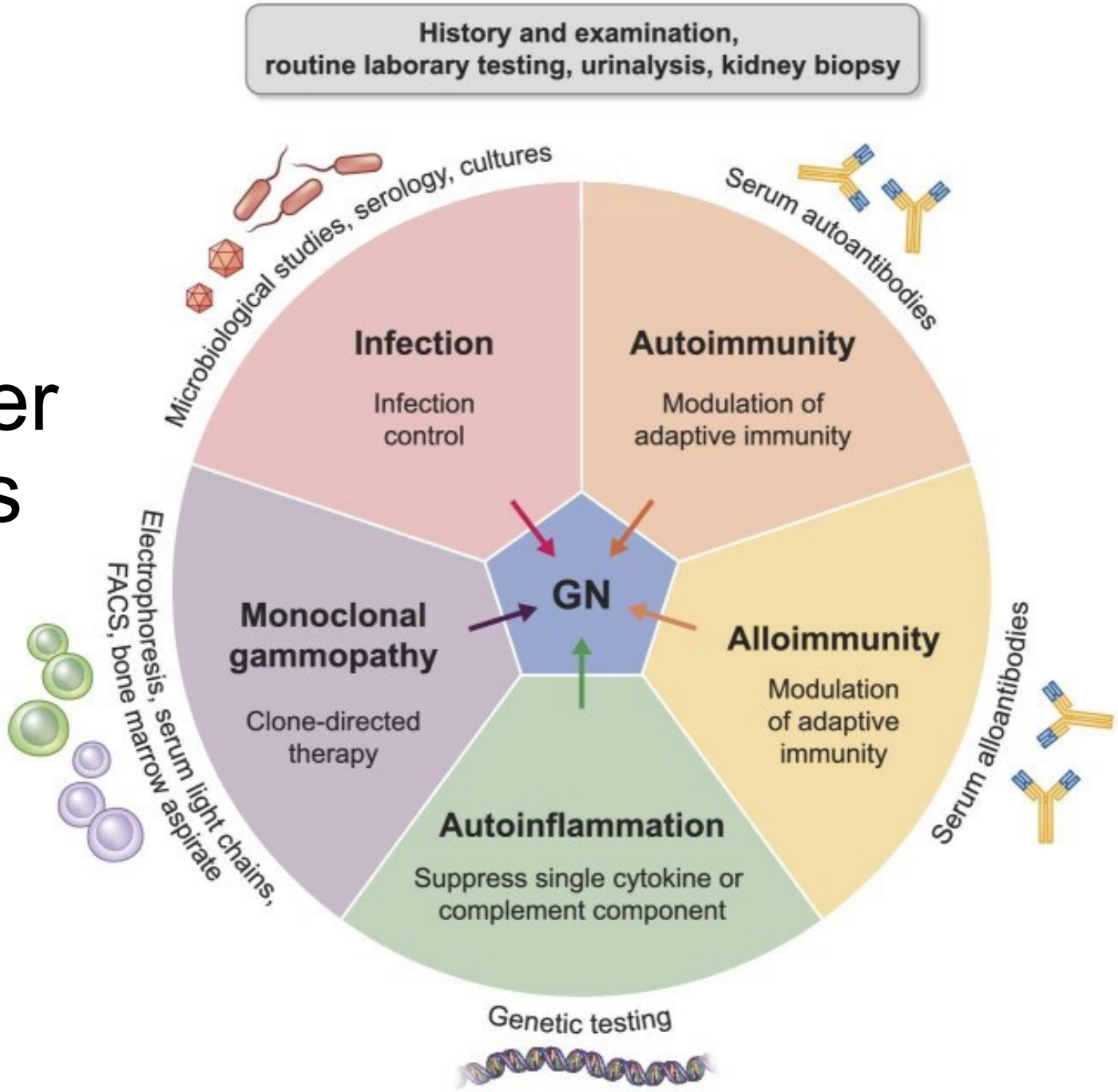
Management of Secondary GN

Focuses on addressing the underlying cause, such as:

- Treating infection or malignancy
- Removing offending drug

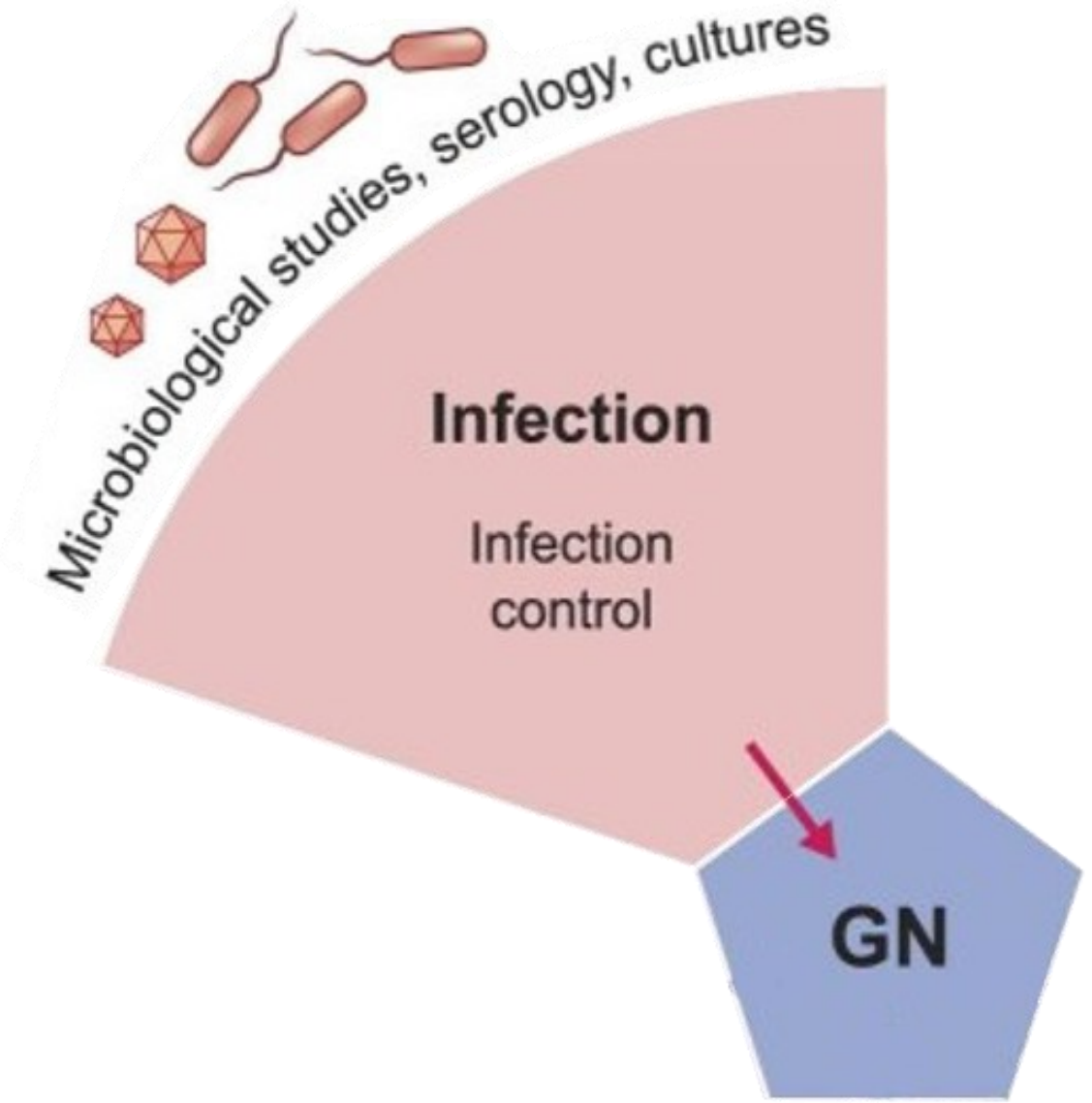
Classifying GN By Immunological Subtypes

Helps to identify proper treatment for patients



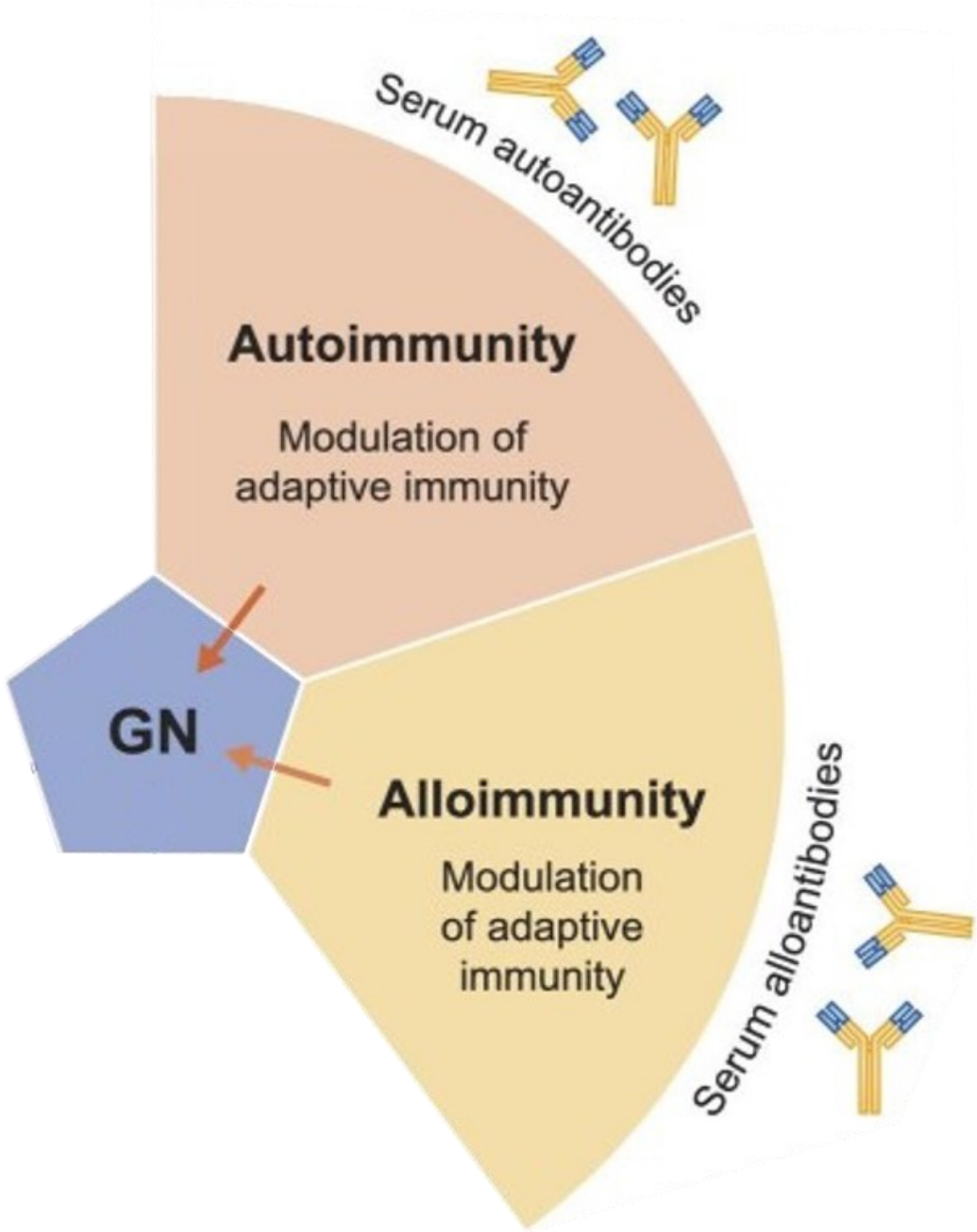
GN immunological subtypes: Infection

1. Infection:
   a. Complement activation
   b. Immune complex deposition or podocytopathy



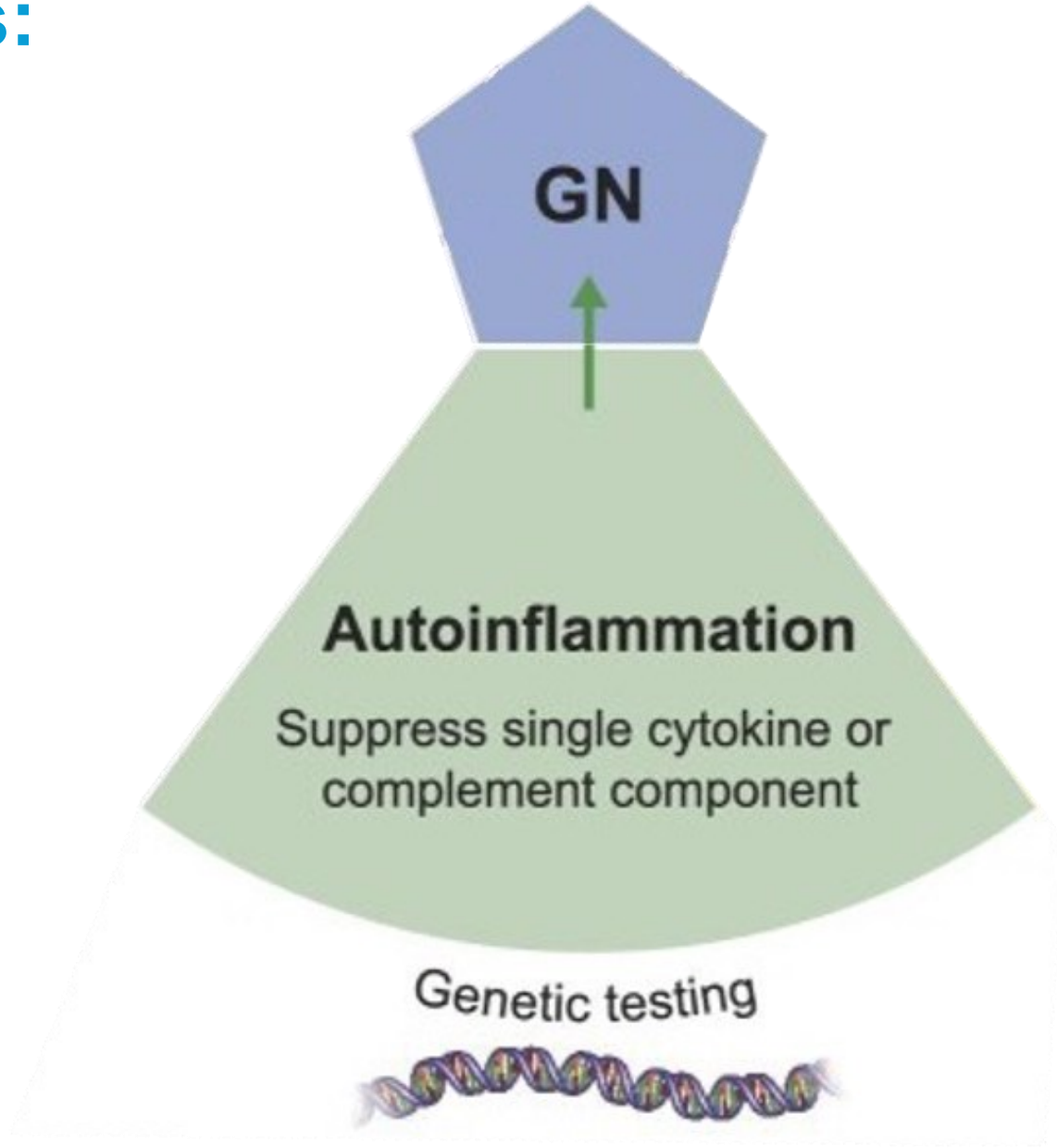
GN immunological subtypes: Autoimmunity and Alloimmunity

2. Autoimmunity:
   a. Lost of immune tolerance to self-antigens
3. Alloimmunity
   a. Solid organs or BMT



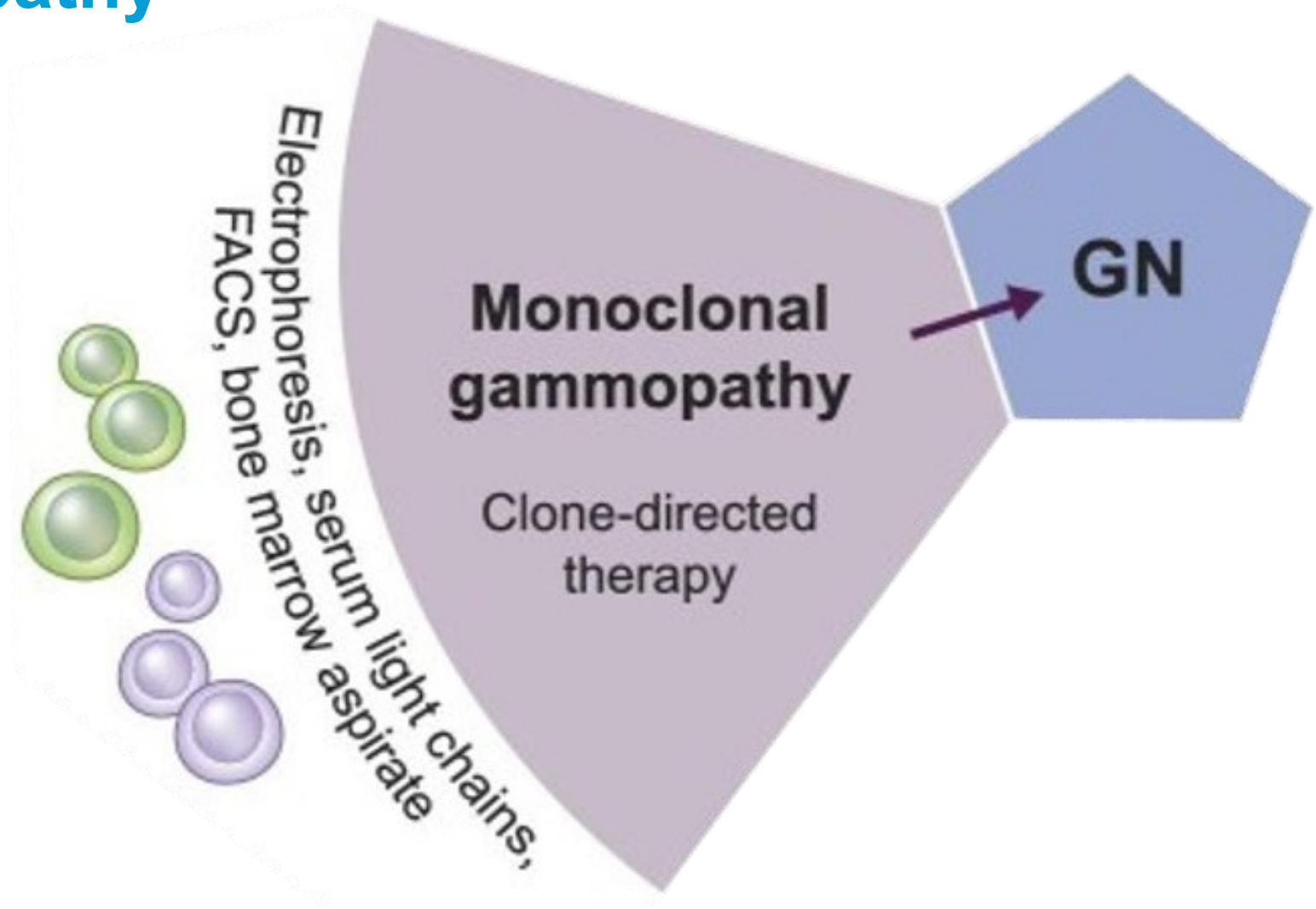
GN immunological subtypes: Autoinflammation

4. Autoinflammation:
   a. Inborn errors of innate immunity
   b. Genetic component



GN immunological subtypes: Monoclonal Gammopathy

5. Monoclonal gammopathy
   a. B cells or clone plasma cells producing a nephrotoxic Ig



Traditional Immunosuppressants: Options in GN

Suppress the immune system in a nonspecific manner to reduce inflammation and prevent damages to the kidneys

Steroids

- prednisone
- IV methyl-prednisolone

CNIs

- tacrolimus
- cyclosporin
- voclosporin

Antimetabolites

- mycophenolate mofetil (MMF)
- azathioprine

Alkylating agent

- cyclophosphamide

Case Study: Patient 1 Introduction

Patient
63 y/o male presents with nephrotic syndrome. He has noted swelling of his legs and fingers which has worsened over the last week, and orthopnea and nocturnal dyspnea over last 2 days. **Allergies**: NKDA , ACEi (cough).

PMH
Hypertension x 15 yrs

Medications
Candesartan, 16 mg PO BID
Nifedipine XL, 30 mg PO BID

Vital	Today	6 mo ago
Height (in)	72	
Weight (lbs)	213	180
Lab	**Today**	**6 mo ago**
sCr	1.2	0.8
sAlbumin	2.7	4.1
UACR	11,613	200

Steroids: Indications and MOA

Indications

Monotherapy:

- IgAN, steroid sensitive MCD or FSGS
- **Combination therapy:**
  - ANCA vasculitis
  - Lupus nephritis
  - Anti-GBM disease
  - Steroid dependent MCD/FSGS
  - High risk IMN (Ponticelli regimen)

MOA

At high dose (not physiological dose), it decreases inflammation by suppressing migrations of leukocytes and fibroblasts, reversing capillary permeability and stabilizing lysosomes (effects on B cells and T cells).

Steroids: Interactions and Common ADRs

Common ADRs (dose and duration dependent)

- **CYP 3A4 inducer** (carbamazepine, rifampin, etc.):
  - ↓ prednisone level
- **CYP 3A4 inhibitor** (clarithromycin, erythromycin, ketoconazole, darunavir, etc.):
  - ↑ prednisone level
- Monitor CsA and TAC dosage with tapering steroid dosage
- May increase hypokalemia with diuretics

Steroids: Interactions and Common ADRs - continued

Common ADRs (dose and duration dependent)

- Heartburn, nausea, stomach ulcers ***(prophylaxis with H2-blocker or PPI)***
- Osteoporosis ***(prophylaxis with Calcium/vitamin D +/- bisphosphonate)***
- Infections ***(PJP prophylaxis for prednisone daily dose > 15-20 mg/d)***
- ↑ BP and edema
- ↑ weight, ↑ appetite, ↑ BG
- Moon shape face, stretch marks, acne, fat deposit around waist and back of the neck
- Muscle weakness
- Trouble sleeping, nervousness, anxiety
- Change in vision, cataract, glaucoma
- Bruising, slower wound healing

Case Study: Patient 1 Follow-up

Patient
63 y/o male presents with nephrotic syndrome. He has been tapering his prednisone, decreased from 40 to 35 mg daily about 10 days ago. Since then, he has noticed his urine more bubbly, weight gain ~ 20lbs, and increase nocturnal dyspnea. **Allergies**: NKDA , ACEi (cough).

PMH
Primary FSGS, diagnosed 3 months ago
Hypertension x 15 yrs

Medications
Candesartan, 16 mg PO BID
Nifedipine XL, 30 mg PO BID
Furosemide 40 mg PO BID
Prednisone 35 mg PO daily
Calcium carbonate, 500 mg PO BID
Vitamin D, 1000 units PO daily
Pantoprazole, 40 mg PO daily
Sulfamethoxazole-trimethoprim, 800/160mg PO 3 times/week

Vital	Today	2 weeks ago
Height (in)	72	
Weight (lbs)	213	190
Lab	**Today**	**2 weeks**
sCr	1.6	0.97
sAlbumin	2.2	3.9
UACR	8,970	350

Calcineurins inhibitors (CNIs): Indications and MOA

Indications

Monotherapy:

- Steroid resistant/relapsing MCD or FSGS, IMN

Combination therapy:

- Lupus nephritis
- Steroid resistant/relapsing MCD or FSGS

MOA

- Inhibit calcineurin phosphatase, which inhibits calcium-dependent events, such as IL-2 gene transcription and other cytokines essentials for T cells activation and proliferation (T1 T helper cell preferentially suppressed).
- Stabilize the podocyte by stabilizing the actin cytoskeleton, which will reduce proteinuria.

Calcineurins inhibitors (CNIs): Dosage

CsA dosage

- 3-5 mg/kg/day, split dosage BID
- Target CsA trough level:
  - 100-175 ng/mL

TAC dosage

- 0.05-0.075 mg/kg/day, split dosage BID
- ER formulation available for once daily dosing
- Target TAC trough level:
  - 4-10 ng/mL, depending on condition

Note: Levels to be done about 3-7 days after initiation or dosage adjustment,12 hrs post dose

Voclosporin

- Only studied in LN class III, IV and V
- 23.7 mg PO BID, dose reduction to 15.8 mg po BID for patient with eGFR < 45 mL/min

Calcineurins Inhibitors (CNIs): Drug Interactions: Inhibition/Inducer CYP 3A4

Inhibition CYP 3A4	Inducer CYP 3A4
Erythromycin/clarithromycin	Rifabutin/rifampin Caspofungin (TAC)
Diltiazem/Verapamil	Carbamazepin/phenytoin/phenobarbital
Azole antifungals (e.g. fluconazole, ketoconazole, voriconazole)	
Protease inhibitors (e.g. ritonavir)	
Fluoxetine, fluvoxamine (lesser degree sertraline, paroxetine, venlafaxine, mirtazapine)	
Amiodarone	
Atorvastatin/simvastatin	

Allopurinol →↑ CsA concentration (mechanism unknown)

Digoxin →↑ digoxin level and toxicity

Calcineurins Inhibitors (CNIs): ADRs

ADR	CsA	TAC	Voclosporin
Hypertension	++	+	+
Hyperglycemia	+	++	
Dyslipidemia	+	-	
Hyperuricemia	++	+	+
Neurotoxicity	+	++	+
Alopecia	-	+	+
Gastrointestinal ADRs	+	+	++
Hirsutism	+	-	
Gum hypertrophy	+	-	
Gynecomastia	+	-	

- Nephrotoxicity:
  - Hemodynamic ↓ in sCr filtration (tolerate up to a 30% ↑ in sCr)
  - High level of CNI (toxicity usually reversible)
  - Chronic CNI toxicity:
    - usually develops with long term use of CNI at higher serum level→ non reversible
- Monitor:
  - Potassium
  - Magnesium
  - Bicarbonate
  - Uric acid levels

Case Study: Patient 2 Introduction

Patient
35 y/o female, with known SLE hx presents, presents with a history of increased joined pain, fatigue and rash. **Allergies:** NKDA.

Medications
Hydroxychloroquine, 400 mg PO 5 days/week, 200 mg PO 2 days/week
She has stopped her MMF ~2-3 months ago.

PMH
SLE x 5 years (history pleural effusion, pericarditis, Raynaud syndrome)

Vital	Today	6 mo ago
Height (in)	75	
Weight (lbs)	115	120
Lab	**Today**	**6 mo ago**
sCr	0.9	0.68
sAlbumin	3.2	4.1
U RBC	>50	1-2
ACR	2844	300
WBC	2300	4000
Pregnancy test, urine	Neg.	

Antimetabolites Indications and MOA: Mycophenolate mofetil (MMF), Mycophenolic acid (MPA), and Azathioprine (AZA)

Indications

Monotherapy:

- Stable lupus maintenance therapy (MMF/AZA)
- IgAN (MMF)
- Maintenance ANCA vasculitis (AZA)

Combination therapy:

- Lupus nephritis
- C3GN
- resistant or relapsing MCD/FSGS

MOA

Inhibits purine nucleotide synthesis and RNA metabolism

→interferes with cellular metabolism

→ inhibits T and B cells proliferation and antibody production

Antimetabolites: AZA and MMF/MPA Dosage

AZA Dosage

- 1 to 1.5 mg/kg/day given once daily

*Consider TPMT testing prior to AZA initiation.

MMF/MPA Dosage

Lupus induction: 3 g/day, given BID
Lupus maintenance: 2g/day, given BID
CNI/steroid sparing agent: 2 g/day, given BID

- Start at 500 mg po BID and increase dosage Q5-7 day up to target dose (helps with gastrointestinal tolerance)
- Empty stomach can improve GI absorption, but more difficult to tolerate
- If gastrointestinal intolerance, can consider switching to Mycophenolic acid
  - (MMF 250 mg = MPA 180 mg)

Antimetabolites: MMF/MPA Drug Interactions and ADRs

Drug Interactions

- Magnesium and aluminum containing antiacid, cholestyramine may ↓ MMF absorption
- Acyclovir, ganciclovir, valganciclovir → ↑ antiviral concentration (monitor)

Common ADRs

- Gastrointestinal ADRs:
  - Constipation
  - Diarrhea
  - Dyspepsia
  - Nausea/vomiting
  - Abdominal pain
- Myelosuppression (especially leukopenia)
- ↑ risk of infection
- Edema, pain, fever
- Insomnia
- Headaches

Risk of teratogenicity: **AVOID pregnancy AND USE IUD OR TWO methods of contraception while on therapy**

Antimetabolites: AZA Drug Interactions and Common ADRs

Drug Interactions

- Allopurinol and febuxostat → ↓ AZA metabolism
  - **AVOID** concomitant use
- Warfarin → may ↓ INR, monitor

Common ADRs

- Gastrointestinal:
  - Nausea/vomiting
  - Anorexia
  - Diarrhea
  - Ulceration or oral mucosa,
  - Steatorrhea
- Myelosuppression
- ↑ risk of infection
- Hepatotoxicity; hepato veno-occlusive disease

Case Study: Patient 2 Follow-up

Patient
35 y/o female, with known SLE hx. Unfortunately, her symptoms are not improving and renal function is deteriorating. She cannot remember taking her MMF twice daily. **Allergies:** NKDA.

Medications
Hydroxychloroquine 400 mg PO 5 days/week, 200 mg PO 2 days/week
MMF 1,500 mg PO BID, that she admits taking only AM dose
Prednisone 45 mg PO daily
Calcium 500 mg po BID
Vitamin D 1,000 units po daily
Pantoprazole 40 mg po daily
Sulfatrimethoxazole-trimethoprim 800/160mg po 3 times/week

PMH
SLE x 5 years (hx pleural effusion, pericarditis, Raynaud syndrome).
LN renal bx 1 month ago --> *LN IV with FN and crescents*

Vital	Today	1 mo ago
Height (in)	75	
Weight (lbs)	110	115
Lab	**Today**	**1 mo ago**
sCr	1.81	0.9
sAlbumin	3.2	3.2
U RBC	>50	>50
ACR	4000	2844
WBC	2000	2300

Alkylating Agent: Cyclophosphamide (CYC) Indications and MOA

Indications

- Combination therapy:
  - LN class III/IV
  - ANCA vasculitis induction therapy
  - Anti-GBM disease,
  - Frequent relapsing steroid sensitive MCD/FSGS,
  - IMN (Ponticelli regimen)

Note: Usually given with steroid

MOA

Inhibits purine nucleotide synthesis and RNA metabolism

→interferes with cellular metabolism

→ inhibits T and B cells proliferation and antibody production

Alkylating Agent: Cyclophosphamide (CYC) Dosage

Dosage

2 mg/kg/day PO, give qdaily (max. 175 mg/d) (steroid sensitive MCD/FSGS; Ponticelli (IMN))

- **Cyclophosphamide 500 mg IV** Q2weeks x 3 months (Euro-lupus protocol)
- **Cyclophosphamide 15 mg/kg IV** q2 weeks x 3 doses, then q3weeks x 3 months
  - ANCA vasculitis induction treatment
- **Cyclophosphamide 0.5 to 1 g/m^2 IV** Qmonth x 6 months (NIH protocol for lupus)

Recommended Cyclophosphamide Dosing Schedule

Dose	Schedule
eGFR less than 30 ml/min/1.73 m^2 OR age over 70 yrs	Reduce dose by 25%
eGFR less than 30 ml/min/1.73 m^2 AND age over 70 yrs	Reduce dose by 50%
WBC nadir less than 3.5 x 10^9/L	Hold until WBC recovers and reduce subsequent doses by 25%

Alkylating Agent: Cyclophosphamide (CYC) Drug Interactions and ADRs

Drug Interactions

- Allopurinol, Hydrochlorothiazide → ↑ CYC myelosuppression effect (monitor)
- Amiodarone → ↑ risk pulmonary fibrosis
- Digoxin → ↓ digoxin serum concentration
- CYP 2B6 inducer (phenytoin, rifampin) → monitor for ↑ CYC toxicity
- Warfarin → may ↑ INR, monitor

ADRs

- Myelosuppression (leukopenia, thrombocytopenia, anemia)
- ↑ infection
  - PJP prophylaxis recommended
- Hemorrhagic cystitis/ hematuria → drink +++ water (~3L/d, unless volume restriction)
  - Mesna could be considered
- Nausea/vomiting
- Hair loss
- ↓ fertility (more prevalent if older than 30 y/o and dose > 10 g total exposure)
- Cancer (more prevalent with exposure > 20g)

↑ ***Risk of teratogenicity***: **AVOID pregnancy AND USE TWO methods of contraception while on therapy**

Case Study: Patient 3 Introduction

Patient
41 y/o woman with a new onset of edema in the last month. BP ~ 140/90, edema up to her thighs, periorbital edema, no SOB or nocturnal dyspnea. **Allergies**: NKDA.

PMH
None

Medications
None

Vital	Today	1 mo ago
Height (in)	62	
Weight (lbs)	110	97
Lab	**Today**	
sCr	0.68	
sAlbumin	2.5	
ACR	40000	

Supportive Therapy

Can be the only therapy necessary (IMN, IgAN)

Blood pressure/antiproteinuric effect

- Target BP < 120/70
- Non pharmacological measures (low sodium diet, average protein intake, exercise, weight management, obstructive sleep apnea management.
- 1st line of treatment: RAASi
- Other options: SGLT-2 inhibitors (mostly data in IgAN), spironolactone, diltiazem

Volume management

- Target euvolemic or slight volume overload (avoid acute kidney injury)
- Non-pharmacological measures (low sodium diet)
- Loop diuretic (PO/IV) +/- thiazide diuretic (metolazone)

Supportive Therapy: Dyslipidemia

Dyslipidemia

- ↑ in total cholesterol, triglyceride, apolipoprotein B, PCSK-9 level → mainly related to impaired clearance
- Proportional to serum albumin and oncotic pressure
- Risk factor for atherosclerotic cardiovascular disease, progressive kidney disease and thromboembolism
- Studies with statin:
  - Effective to reduce total cholesterol and LDL
  - No studies looking at clinical endpoint

Supportive Therapy: Anticoagulant

Anticoagulant

- Hypercoagulability due to urinary loss of antithrombotic protein (antithrombin III) and platelet hyperactivity d/t low serum albumin
- Prevalence thromboembolic event varies between 5 to 40% of pts with nephrotic syndrome
- If serum albumin < 2.0-2.5 g/dL or hx of thromboembolic event or proteinuria > 10 g/d=> consider anticoagulation
  - Low molecular weight heparin/warfarin for duration of NS
  - Limited data with NOACs (highly protein bound), antiplatelets

Supportive Therapy: Opportunistic Infection Risk Factors and Prophylaxis

Risk factors

- Current immunosuppressive therapy
- Overall immunosuppression exposure
- Age
- Comorbidities

Antimicrobial prophylaxis and vaccination

- 2021 KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases.
- KDOQI US Commentary on the 2021 KDIGO Clinical Practice Guideline for the Management for Glomerular Diseases.
- BC renal Pneumocystis jirovecii Pneumonia Prophylaxis Guidelines in Patients with Glomerulonephritis

Rituximab: Indications and MOA

Indications

- ANCA induction and maintenance therapy
- IMN treatment
- Resistant FSGS and MCD

MOA

Monoclonal antibody binding to B cells CD20 receptor → activates complement cascade causing depletion of circulating and tissue-based B cells

Rituximab: Drug interaction and ADRs

Drug Interactions

- None

ADRs

Infusion related ADRs

- 77% at first reaction, and incidence decrease to 30% by 4th infusion, also related to infusion rate
- Headaches, chills, fever, rigors, chest pain, cough/dyspnea, bronchospasms, throat swelling, nausea/vomiting, hypotension, pruritus/urticaria
- Meds prior and during infusion → Acetaminophen, diphenhydramine and methylprednisolone

Post-infusion ADRs

- Myelosuppression (leukopenia/neutropenia, hypogammaglobulinemia)
- Infections (PJP, hepatitis reactivation, shingles, PML)

Case Study: Patient 3 Follow-up

Patient

41 y/o woman continue edema despite RAASi.
BP ~ 105/70, edema up to her knee despite diuretic, no SOB or nocturnal dyspnea.
*She does have limited coverage with her extended healthcare and limited financial resources. She cannot afford expensive treatment.
Allergies: NKDA.

PMH

IMN

Medications

Ramipril 2.5 mg PO daily

Atorvastatin 10 mg po daily

Furosemide 40-80 mg po daily

Vital	Today	3 months ago
Height (in)	62	
Weight (lbs)	115	110
Lab	**Today**	**3 months ago**
sCr	0.70	0.68
sAlbumin	2.3	2.5
ACR	42900	40000
PLA2R	175	150

IMN Treatment options

Rituximab

CNIs (CsA or TAC)

Ponticelli Regimen (cyclophosphamide and steroid)

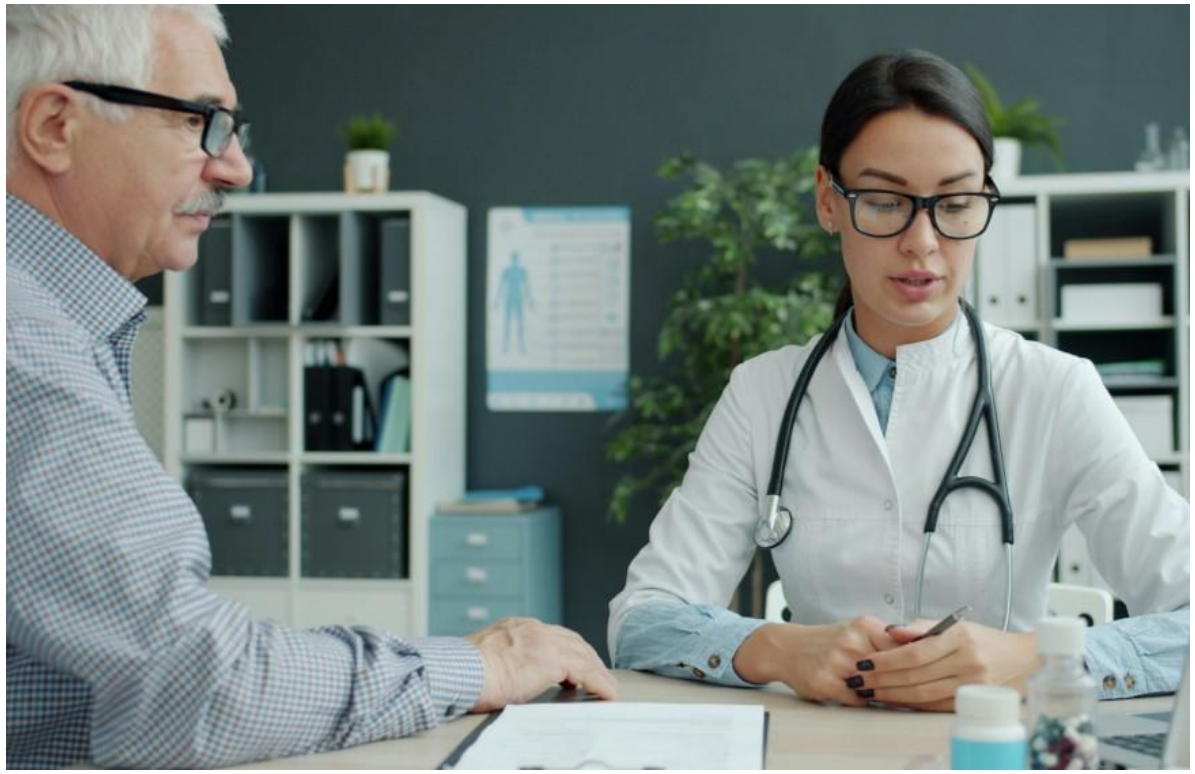
Supportive Therapy

Treatment Options for IMN

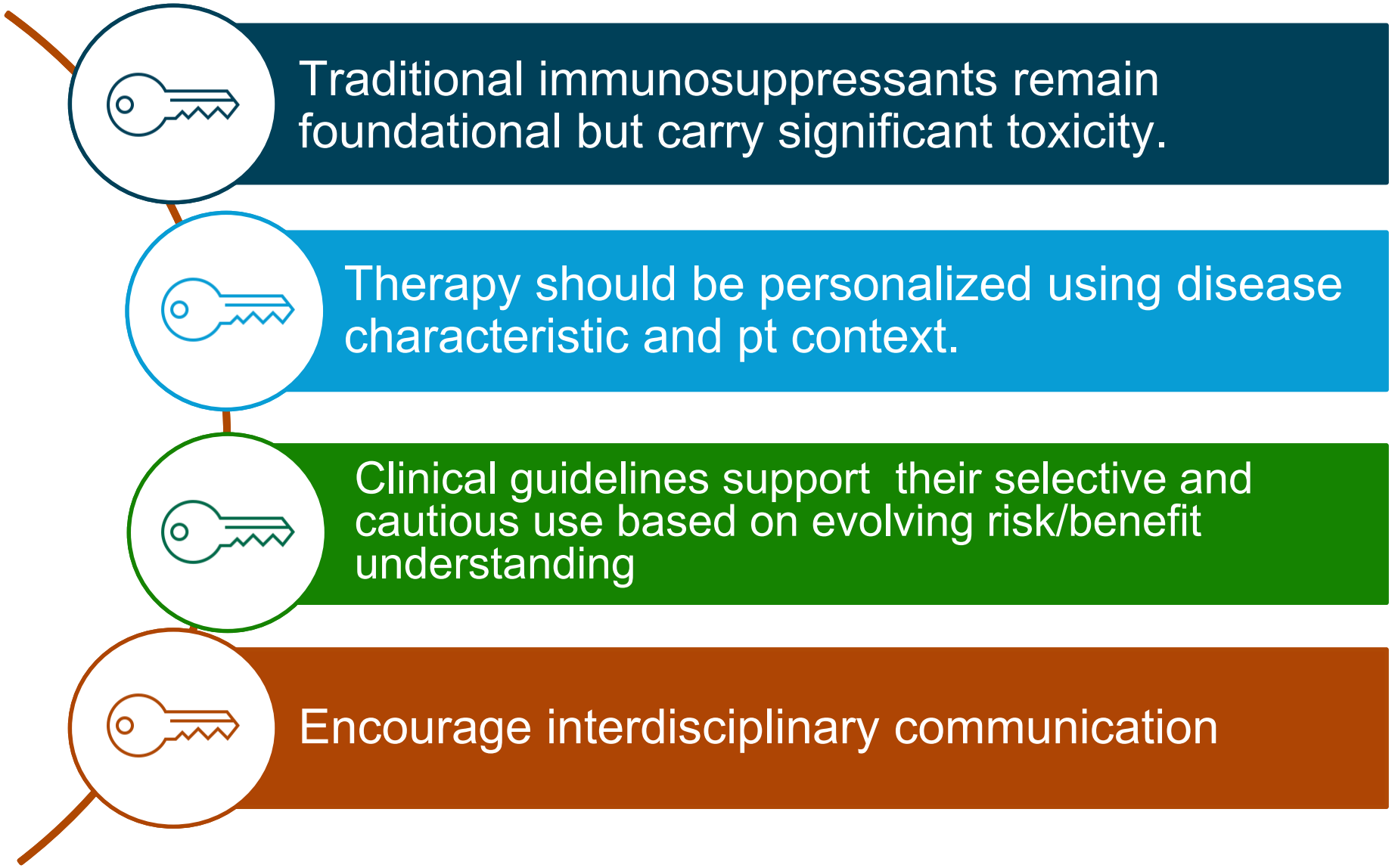
Treatments Options	PROS	CONS
Supportive therapy	• Avoid immunosuppression related toxicity	• Doesn't halt progression in patient at high risk, and significant risk of ESRD.
Rituximab	• Non-inferior to CsA to induce remission, with fewer relapse and better eGFR at 24 months (MENTOR trial) • Lower incidence ADRs • Shorter treatment (2 infusion over 2 weeks, may need to repeat treatment in 6 months)	• Limited long-term safety and efficacy data • Expensive
CNIs (TAC or CsA)	• More favorable safety and tolerability profile than Ponticelli regimen • Less expensive than Rituximab	• Require frequent monitoring (CNI trough level) • Higher risk of relapse with CNI (MENTOR study) and risk of nephrotoxicity • Less effective than cyclophosphamide • Longer duration of treatment
Ponticelli regimen (Cyclophosphamide and steroid)	• Long term efficacy data in reducing progression to ESRD and sustained remission	• Significant toxicity (infection/risk of malignancy/myelosuppression/gonadotoxicity) • Steroid induced ADRs • Affordable option (if no complications)

Modern Role of Traditional Therapies in GN

- Traditional immunosuppressants remain the foundation in the management of many GNs.
  - As well as supportive therapy.
- In GN diseases like FSGS/MCD/SLE, traditional therapies are currently still first line of treatment, supported by guidelines (KDIGO/EULAR, ACR).
- Evolution in GN treatment with the arrival of targeted therapies.
  - Individualized therapy based often on disease subtype and risk stratification
  - Evolving evidence



Key Takeaways



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Advancing Kidney Health

Through Optimal Medication Management

Thank you!