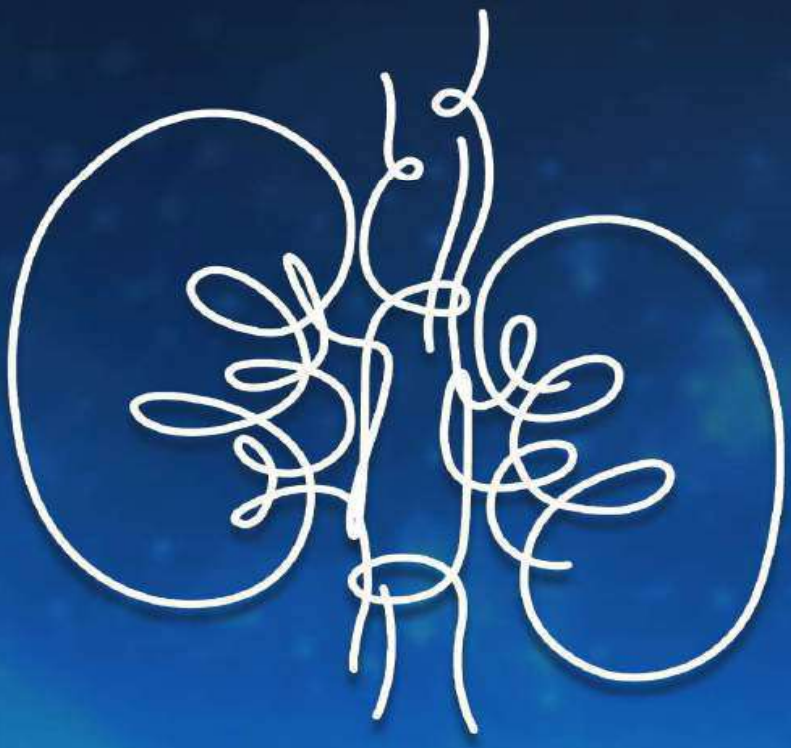
CLINICAL PEARLS



EXTRACORPOREAL

NEPHROLOGY GROUP

Compilation of 2025

ECNG

EXTRACORPOREAL NEPHROLOGY GROUP (ECNG)

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In Association with Cochin Kidney Foundation

An education initiative by

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Makers of

Foreword

This Digital folder, a compilation of Clinical Scenarios/ Pearls in Nephrology 2025 is conceived as a ready reckoner for the practicing clinician, trainee and teacher alike. Rather than lengthy theoretical discourse, it focuses on real-world situations that Nephrologists encounter.

The strength of this work lies in it's clarity and relevance. By anchoring learning in clinical contexts, it bridges the gap between knowledge and practice. The pearls presented here are concise yet impactful.

This Digital folder on Nephrology clinical Scenerio/ pearls will serve as a quick reference, a teaching aid, and a companion for day-to-day nephrology practice.

I congratulate Dr. Vilesh Valsalan, ECNG Accademic Co-ordinator for the effort and time spend and Ms. Amee Kuriachen, Secretary for compiling.

Thanks to Renauxe Foundation for designing and making this digital folder.

I wish every reader an enriching and learning Experience!.

With Best wishes
Dr. Georgy K. Nainan

From the Author

In an era of rapidly expanding knowledge and increasingly complex patient care, the ability to revise concepts quickly and apply them meaningfully at the bedside has become more important than ever. Clinical Pearls in Nephrology is a thoughtful compilation of insights drawn from online Nephrology discussions and academic meetings conducted on ECNG platform in the year 2025. This E-book captures the essence of that journey.

The Extracorporeal Nephrology Group (ECNG) is a dedicated platform for online Nephrology education. ECNG has consistently helped clinicians save time while gaining access to high-quality, practice-oriented learning. By seamlessly blending real-world clinical experience with established guidelines and expert opinions, ECNG has made learning both efficient and relevant—truly "easy learning while sitting at home."

I thank Dr. Georgy K. Nainan founder of ECNG for the opportunity as an academic coordinator and being the driving force behind this unique initiative. The strength of this initiative has been its structured academic rhythm: clinical meetings conducted every Monday , followed by concise, focused summaries presented every Friday. This ensured not only continuity of learning but also reinforcement of key messages. The present e-book is a curated compressive compilation of the one hour clinical session into 4 important slides, bringing together the most relevant clinical discussions and management strategies addressed during the online meetings. It will be particularly valuable for trainees, practicing nephrologists, and clinicians who wish to refresh concepts efficiently while staying grounded in clinical realities.

I extend my sincere gratitude to all the speakers and experts whose dedicated and insightful presentations have brought the true clinical pulse of nephrology into clear focus. Clinical Pearls in Nephrology stands as a testament to the power of collaborative online education and the commitment to continuous learning within the nephrology community.

With Best wishes
Dr.Vilesh Valsalan

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DESIDUSTAT

Introduction

- Desidustat is an orally bioavailable, small molecule, Hypoxia inducible factor - Prolyl Hydroxylase inhibitor (HIF-PHI) resulting in the stabilisation of HIF which stimulates Erythropoietin production and Erythropoiesis.

- Mobilises iron and may reduce IV iron needs.

- Works better in ESA hypo responsive states.

- Safety similar to ESAs.

- 2019 Nobel Prize Medicine -HIF: William Kaelin, Peter Radicliffe and Greg Semenza.

Dosage

- Dialysis-dependent (DD) patients-100 mg administered thrice weekly post Dialysis.

- Non dialysis dependent patients (NDD)

- Erythrocyte stimulating agent (ESA) naive -100mg three times weekly.

- Switching from an ESA-100, 125 or 150mg thrice weekly, depending on the previous dose of ESA (Epoetin, Darbepoetinor Methoxypolyethylene Glycol-Epoetinbeta).

- Maintenance dose -based on haemoglobinlevels assessed every 4 weeks, with a maximum dosage of 150mg three times weekly.

ESAs Compared to HIF-PHIs

	ESAs	HIF-PHIs
MOA	• Stimulate RBC production	• HIF stimulates EPO production & erythropoiesis, improves iron uptake • HIF-PHI prevents HIF degradation
Benefits	• Raise Hb, reduced need for RBC transfusion • Improved HRQoL (inconsistent)	• Raise Hb, reduced need for RBC transfusion • Improve HRQoL (?); network meta-analysis: daprodustat associated with reduced fatigue vs roxadustat[1]
Effectiveness	• Same if given in equivalent doses • epoetin and darbepoetin more effective SC	• No head-to-head clinical trials, but network meta-analysis showed no difference[1]
Safety	• HTN • Access thrombosis, thromboembolic events, MACE • Enhance some malignancies	• HTN • Access thrombosis, thromboembolic events, MACE • Enhance malignancies?

Acknowledgement - Slide contributed by :
Dr. Jaison George ,Nephrologist (MOSC Kolanchery)

KDIGO 2025 DRAFT GUIDELINES ON ANEMIA

Recommendation 3.1.1: In people with anemia and CKD in whom correctable causes of anemia have been addressed, we suggest using an ESA rather than a HIF-PHI as first-line therapy for treatment of anemia (*2D*).

3.5. HIF-PHI treatment initiation and maintenance

Practice Point 3.5.1: In people with anemia and CKD, including those with ESA hyporesponsiveness, do not use ESAs and HIF-PHIs in combination.

Practice Point 3.5.2: In people with anemia and CKD, the Hb thresholds for the initiation and maintenance of HIF-PHIs are unknown, but it is reasonable to use the same Hb thresholds as those recommended or suggested for ESA therapy (Recommendations 3.2.1, 3.2.2, 3.3.1).

Practice Point 3.1.3: In people with anemia and CKD, HIF-PHIs should be avoided in those at increased risk of adverse events (Table 6).

Table 6 | Considerations for people with anemia and CKD at risk for adverse events with hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHI) therapy

Theoretical risk or experimental evidence of risk for disease development or progression	Concern for risk based on adverse event profiles in clinical trials	Insufficient data for risk assessment; dedicated studies needed
• Active cancer or with a history of cancer not in complete remission for at least 2–5 years (based on trial exclusion criteria)[223] • Polycystic kidney disease[224] • Proliferative retinal disease[225, 226] • Pulmonary arterial hypertension[227-229] • Pregnancy*	• Prior cardiovascular events (i.e., stroke, myocardial infarction)[223] • Prior thromboembolic events (i.e., deep venous thrombosis, pulmonary embolism)[223] • Prior vascular access thrombosis[223] • Hepatic impairment† • Seizures, exfoliative dermatitis, hypothyroidism, bacterial infections/sepsis (roxadustat)[230]	• Post-kidney transplant anemia[223] • Children[231]

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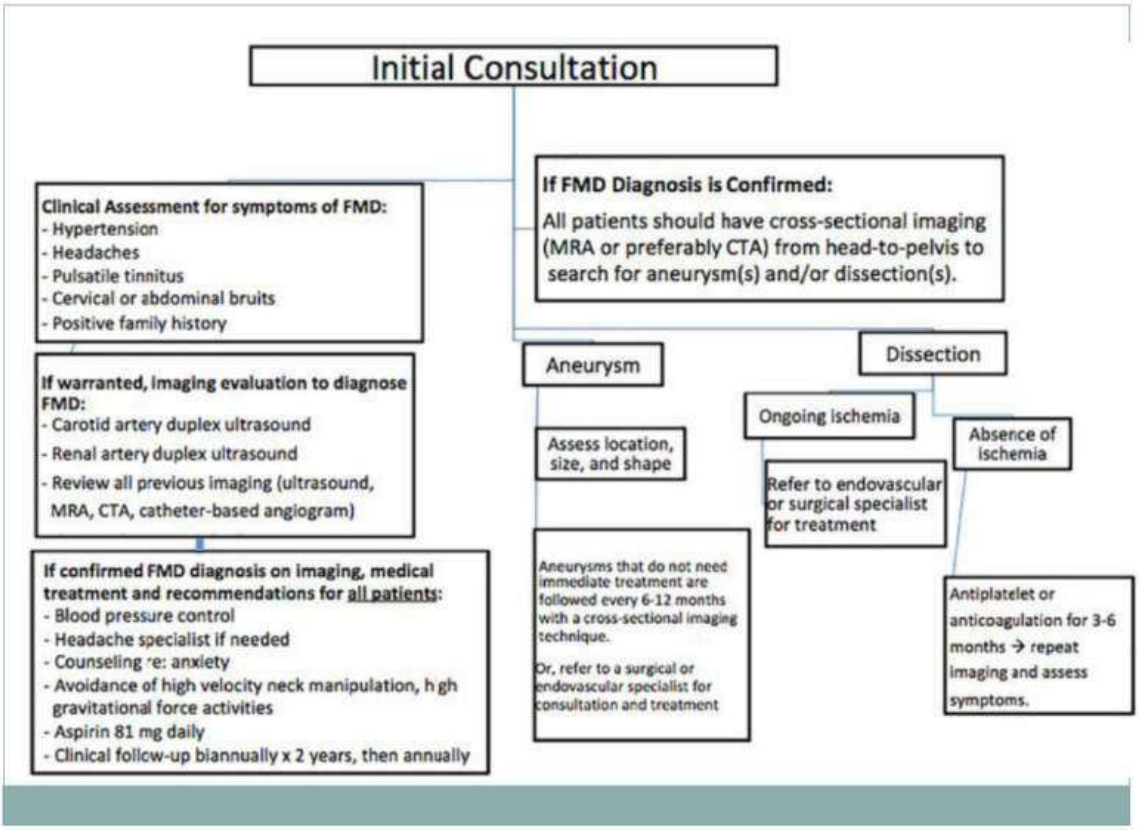
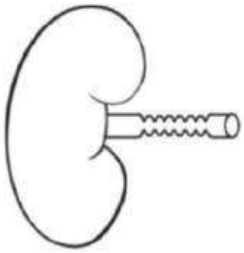
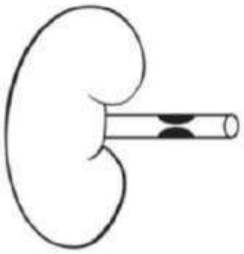
FIBROMUSCULAR DYSPLASIA

Introduction

- **Fibromuscular Dysplasia** (FMD) is an idiopathic, Nonatherosclerotic, and Noninflammatory Arterial Disease.
- Affects **small-to medium**-sized Arteries.
- Result in multifocal **aneurysms, Stenosis, Tortuosity, and Dissections.**
- Affects **young women <50 years** and accounts for **10-20% cases** of Renal Artery Stenosis. F>M-3:1.
- Etiology: Unclear. Genetic –HLA DR-w6 /environmental – smoking.



Fibromuscular dysplasia	Atherosclerotic renal artery stenosis
	
• Preserved renal blood flow.[58-60] • Preserved glomerular filtration.[9,51,55] • Intact response to renin-angiotensin system modulation.[59] • Normal renin secretion in vast majority of patients.[58,59] • Negative correlation between renin levels and blood pressure.[58] • Revascularization cures hypertension in 40-62% of the patients.[12]	• Reduced renal blood flow.[58,60] • Reduced glomerular filtration.[57,58] • Disturbed response to renin-angiotensin modulation.[62,63] • Increased renin secretion in a large subset of patients.[58,69,70] • Positive correlation between renin levels and blood pressure.[58] • Revascularization generally not superior to medical treatment.[86-89]

Treatment

- Anti-Platelet Therapy-Aspirin
- Anti-Hypertensive medications-ACEI/ARB/CCB/B blockers.
- Statin Therapy
- Migraine therapy
- Life Style: Physical activity/ stress management/ smoking cessation.
- Treatment based on vascular territory involvement.

Renal bed

Presentations: Hypertension / dissection / Renal infarcts.

Investigation: Renal angiogram / screening with CTA preferred over MRA / Duplex USG [expert].

Treatment: Revascularization for Hemo dynamically significant stenosis with Angioplasty.

☑Endovascular Therapy [stenting and coiling].
☑Anti-Platelet Therapy.
☑3-6months Anticoagulation following dissection.
☑Treat Hypertension.
☑Stop smoking.

Coronary bed

Presentation:- Spontaneous Coronary Artery Dissection [SCAD] / ACS / Arrhythmias.

Investigation- CAG.

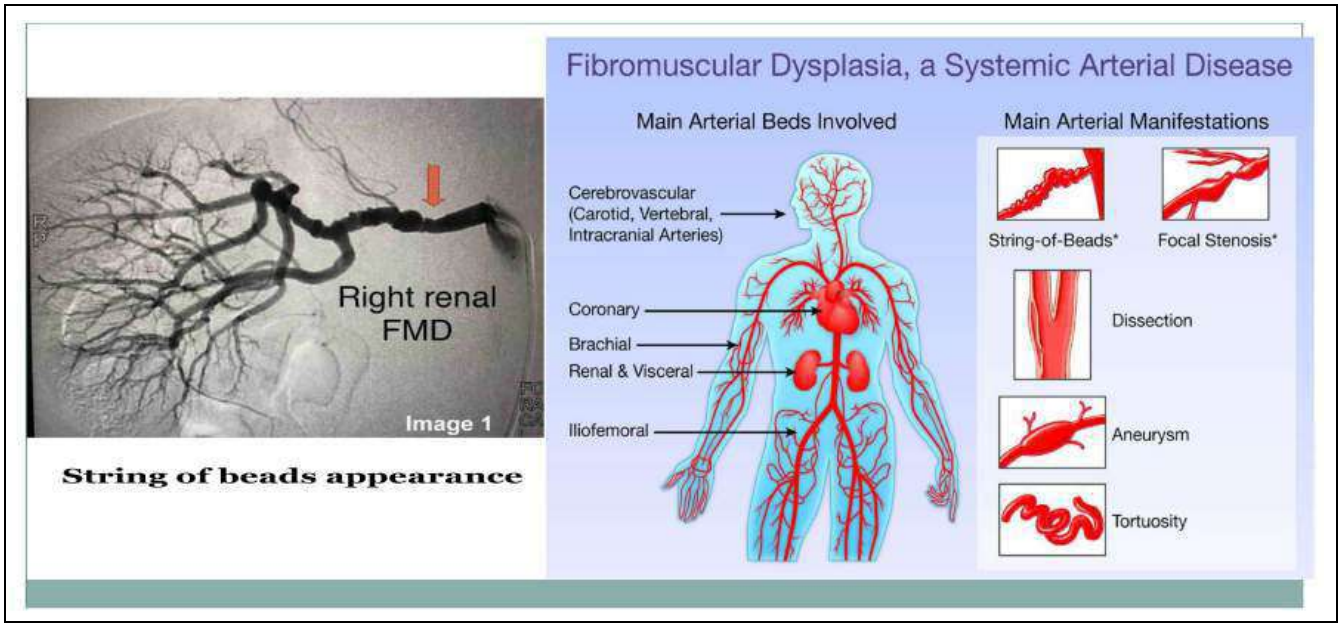
Treatment:- Conservative management in 80%
☑PCI in ongoing ischemia
☑CABG [when CAG not possible]
☑Anti-Platelet Therapy [APT]
☑DAPT [dual APT] for1year if stenting done.
☑B blockers
☑Treat Hypertension

Cerebral bed

Presentations: Pulsatile Tinnitus, Migraines, dizziness, Horner Syndrome, TIA

Investigations: Screening with CTA/MRA
☑Cerebral angiogram

Treatment: Endovascular Therapy [clipping /coiling]
☑Anti-Platelet therapy
☑Migraine treatment



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GLP1 AGONIST

Introduction

- Glucagon-like Peptide-1 (GLP-1)and Glucose-dependent Insulinotropic Polypeptide (GIP), both incretinhormones inactivated by Dipeptidyl peptidase-4 (DPP-4), stimulate insulin secretion after an oral Glucose load via the incretin effect.

- ADA 2022 approved GLP-1 A as first line therapy for treating DM in patients with Atherosclerotic Cardiovascular Disease and Obesity.

- 1980s, Jean-Pierre Raufmanof the National Institute of Health investigated the Gila monster and later John Enggisolated Exendin-4 from it.

Pharmacokinetics

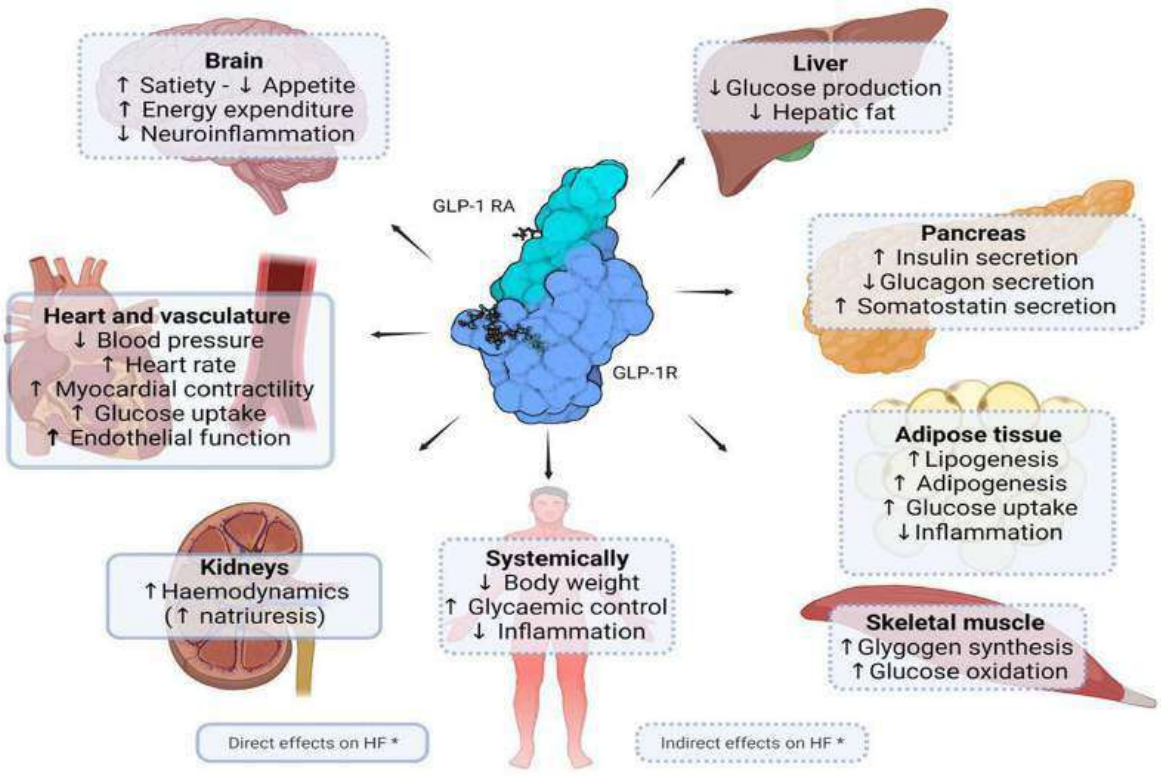
- **Absorption**: GLP-1 Receptor Agonists (RAs) like Exenatide, Liraglutide, and Semaglutide are administered subcutaneously, ensuring rapid absorption and achieving peak concentrations within hours.

- **Distribution**: Post-absorption, GLP-1 RAs (eg, Exenatide, Liraglutide, and Semaglutide) exhibit a low volume of distribution, predominantly remaining in the bloodstream.

- **Metabolism**: Exenatide undergoes primary metabolism in the kidneys and liver through hydrolysis, yielding smaller, inactive peptides. Liraglutide follows a similar pathway involving proteolytic cleavage.

- **Excretion**: Renal elimination primarily governs the clearance of GLP-1 RAs, including Exenatide, Liraglutide, and Semaglutide.

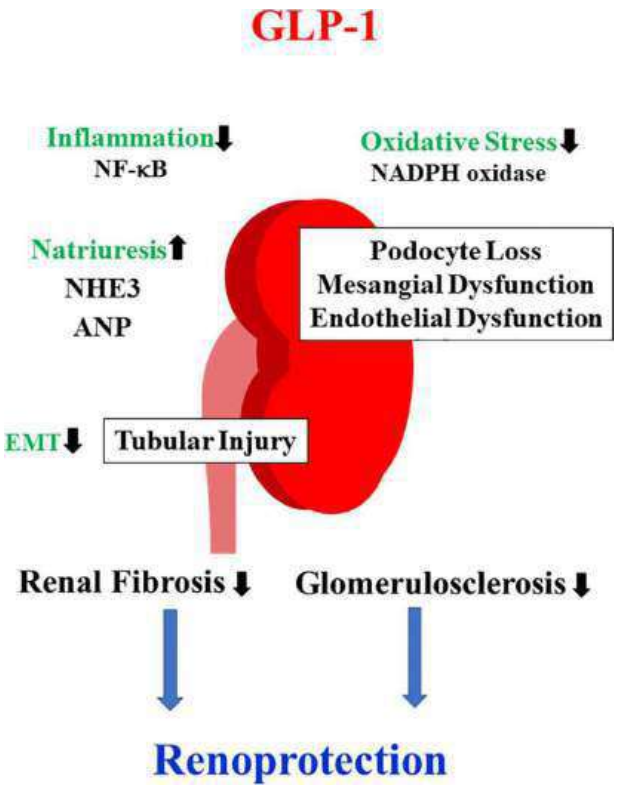
Effects of GLP1A



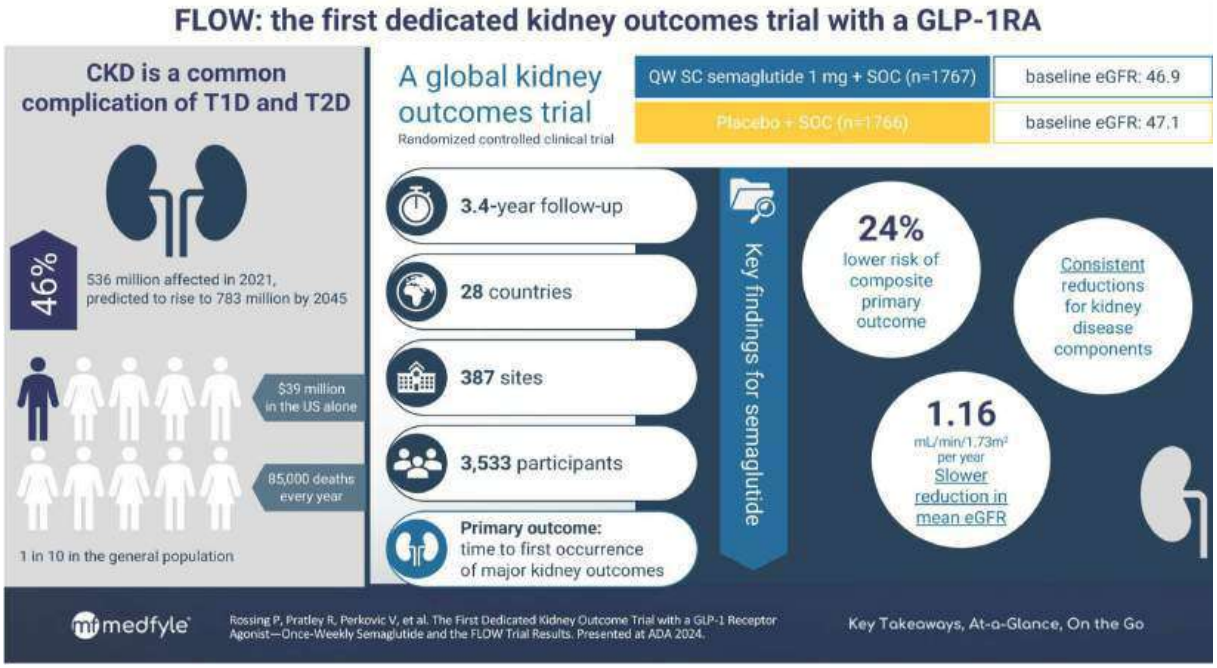
Dose and side effects

GLP-1 & GIP Receptor Agonists

Class/Main Action	Name	Dose Range	Considerations
GLP-1 RA - Glucagon Like Peptide Receptor Agonist **"Incretin Mimetic"** • Increases insulin release with food • Slows gastric emptying • Promotes satiety • Suppresses glucagon	exenatide (Byetta)	5 and 10 mcg BID	**Side effects for all:** Nausea, vomiting, weight loss, injection site reaction. Report signs of acute pancreatitis (severe abdominal pain, vomiting), stop med. Increase dose monthly to acheive targets. **Black box warning:** Thyroid C-cell tumor warning (avoid if family history of medullary thyroid tumor). *Significantly reduces risk of CV death, heart attack, and stroke. †Approved for pediatrics 10-17 yrs Lowers A1c 0.5 – 1.6% Weight loss of 1.6 to 6.0 kgs
	exenatide XR† (Bydureon)	2 mg 1x a week Pen injector - Bydureon BCise	
	liraglutide (Victoza)*†	0.6, 1.2 and 1.8 mg daily	
	dulaglutide* (Trulicity)	0.75, 1.5, 3.0 and 4.5 mg 1x a week pen injector	
	lixisenatide (Adlyxin)	10 mcg 1x a day for 14 days 20 mcg 1x day starting day 15	
	semaglutide* (Ozempic)	0.25, 0.5, 1.0 and 2.0 mg 1x a week pen injector	
	(Rybelsus) Oral tablet	3, 7, and 14 mg daily in a.m. Take on empty stomach w/H2O sip	
GLP-1 & GIP Receptor Agonist Activates receptors for GLP-1 (see above) & Glucose-dependent Insulinotropic Polypeptide (GIP).	Tirzepatide (Mounjaro)	2.5, 5.0, 7.5, 10, 12.5 and 15 mg 1x a week prefilled single dose pen Increase dose by 2.5 mg once monthly to reach targets.	**Side effects include:** Nausea, diarrhea, injection site reactions. Avoid if family history medullary thyroid tumor. Report pancreatitis or acute gallbladder problems. Lowers A1C ~ 1.8 - 2.4% Weight loss of ~ 5.4 – 10 kgs



- GLP-1RAs have been shown to activate PKA and increase the production of cyclic Adenosine MonoPhosphate (cAMP).
- NADPH oxidase and NF-κB activity are inhibited, resulting in the attenuation of oxidative stress and inflammation.
- Prevent Podocyte loss as well as mesangial and Endothelial dysfunction.
- GLP-1RAs inactivate NHE3 and promote Atrial Natriuretic Peptide (ANP) secretion, thereby inducing natriuresis.
- GLP-1RAs inhibit Tubular injury and subsequent Tubulointerstitial Fibrosis.



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PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Introduction

- The term paroxysmal nocturnal Hemoglobinuria was introduced by Enneking in 1925.
- PNH can be categorized into three types. 1. Classic PNH. 2. PNH with another Bone Marrow (BM) disorder 3. Subclinical PNH.
- Triadof hemolytic anemia, Bone Marrow failure and Thromboembolism.

Etiology

- Mutation of the X-linked gene Phosphatidylinositol Glycan class A(PIGA) deficiency in the Glycosylphosphatidylinositol (GPI) Protein, [which is responsible for anchoring other Protein Moieties to the surface of Erythrocytes].

- CD 55 and CD 59 complement regulators are prevented from attaching to the PNH affected cell.

- Chronic complement mediated Hemolysis.

Investigation

- Diagnostic flow Cytometry is considered the gold standard test for PNH diagnosis.
- Increased LDH, low Haptoglobin, and unconjugated Bilirubinemia due to intravascular hemolysis.
- High reticulocyte count.
- Peripheral smear.
- Anemia, leukopenia, and thrombocytopenia will be seen.
- Evaluation of renal dysfunction-CKD.
- Other tests:-D-dimer, brain natriuretic peptide, liver function panel, iron panel, bone marrow aspirate or biopsyand cytogenetics.
- Imaging–2 D ECHO-pulmonary HTN/ CTA –rule out thrombosis/USG abdomen.

Symptoms

- Characterized by recurrent episodes of intravascular Hemolysis, venous Thrombosis, and Cytopenias associated with bone marrow failure. General symptoms:- fatigue, generalized Malaise, Dyspnea.
- Dark urine due to marked Hemoglobinuria, Renal insufficiency from Hemosiderin deposition leading to Tubulointerstitial inflammation.

- Dysphagia or esophageal spasms, abdominal pain, back pain and erectile dysfunction which all occur due to smooth muscle Dystonia.

- The most common BM disorders that occur with PNH include Aplastic Anemia (AA), Myelodysplastic Syndrome (MDS), and primary Myelofibrosis.

Treatment

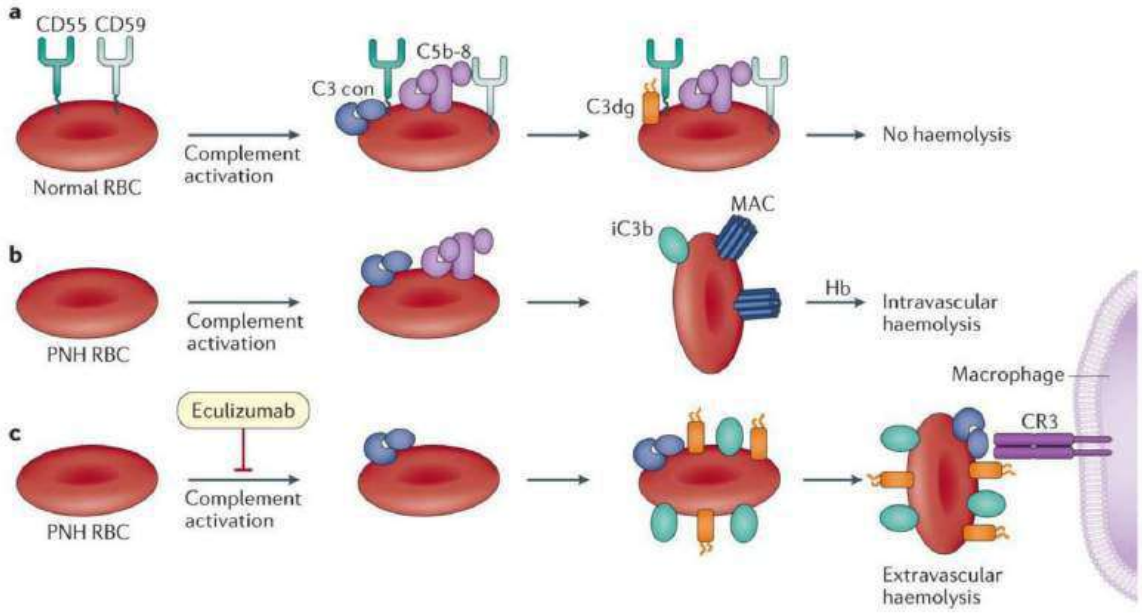
- Eculizumab [factor 5A inhibitor] is a lifesaving therapy – 50% reduction in transfusion requirements and 70% reduction in risk of thrombotic events.

- Ravulizumabhas 3 to 4 times longer half-life and requires dosing every eight weeks. [more cost-effective compared to Eculizumab].

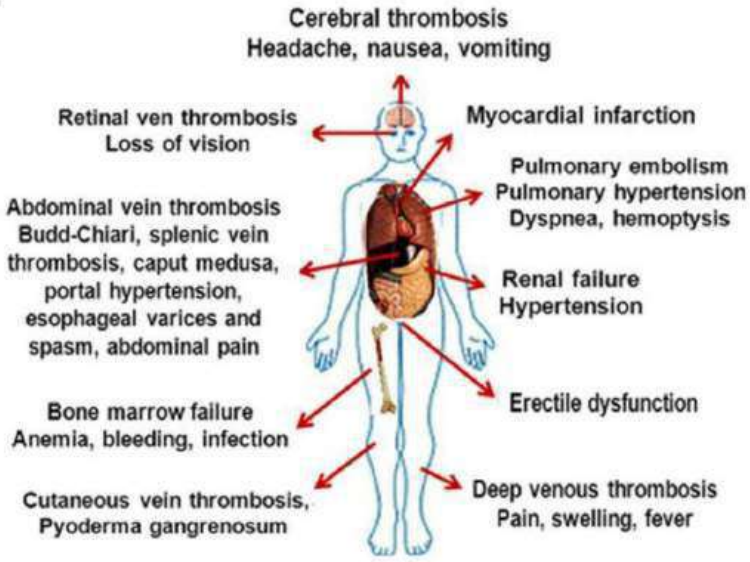
- Curativetherapy- Allogeneic Hematopoietic stem cell transplantation.

- Blood transfusions/iron therapy/Anti Thrombosis Prophylaxis.

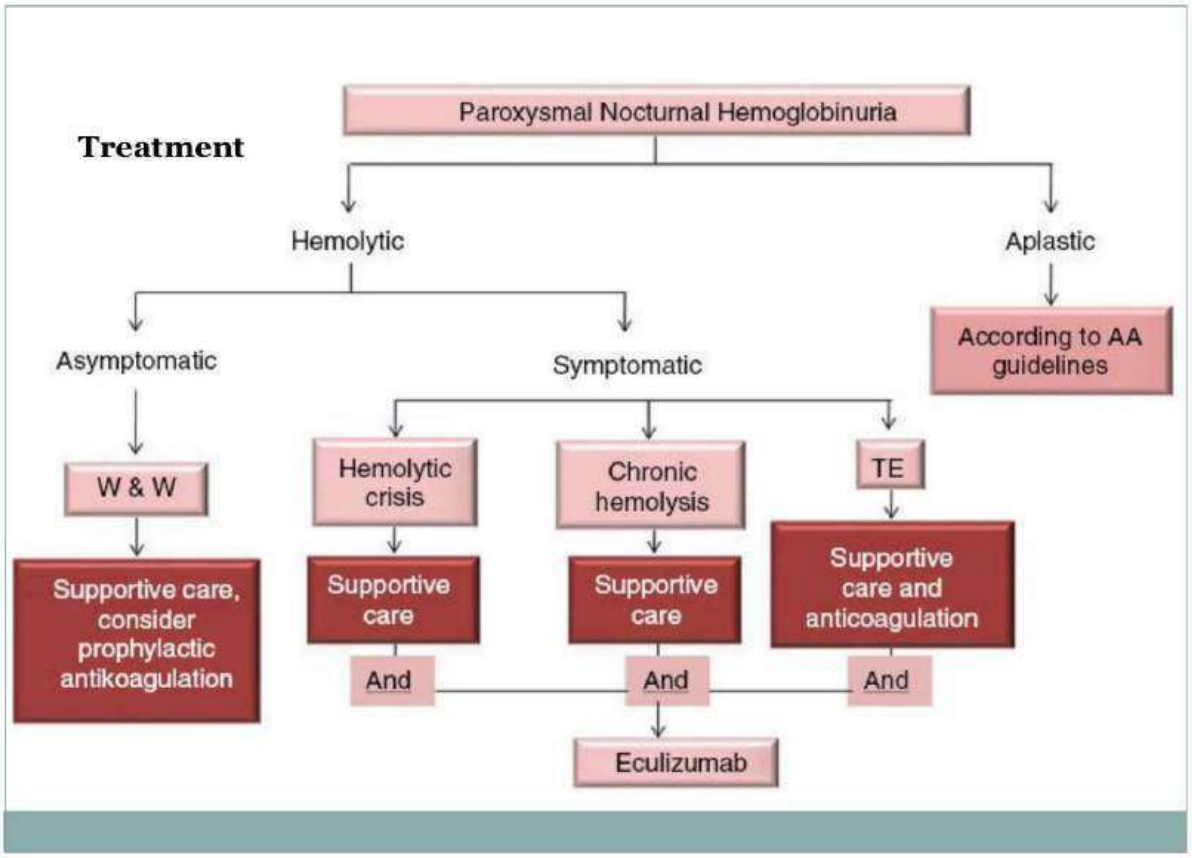
- Treatment of complications.

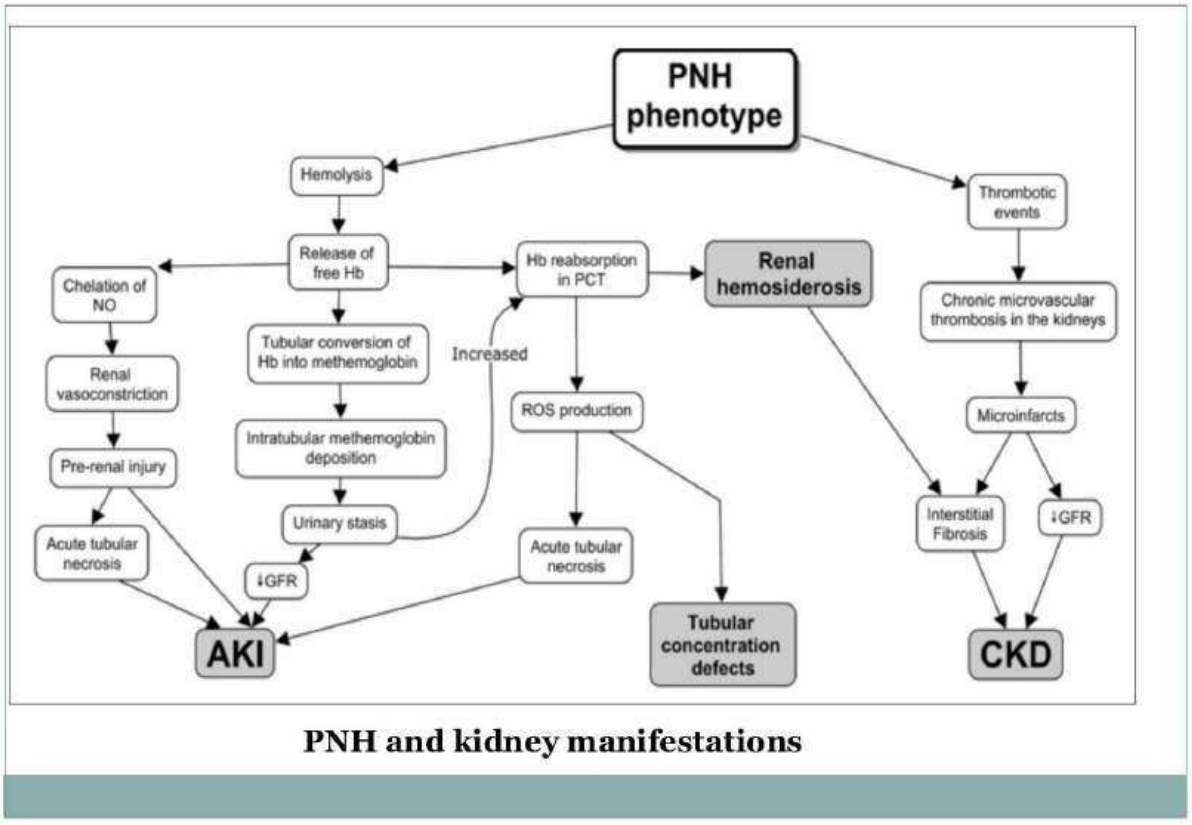


Etiology and treatment of PNH



Clinical manifestations of PNH





PNH and kidney manifestations

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CALCIFIC UREMIC ARTERIOLOPATHY [CALCIPHYLAXIS]

Investigation

- Characterized by painful skin lesions caused by Cutaneous Arteriolar calcification leading to tissue ischemia and infarction.

- Calcification of the medial layer of Arterioles and small Arteries.

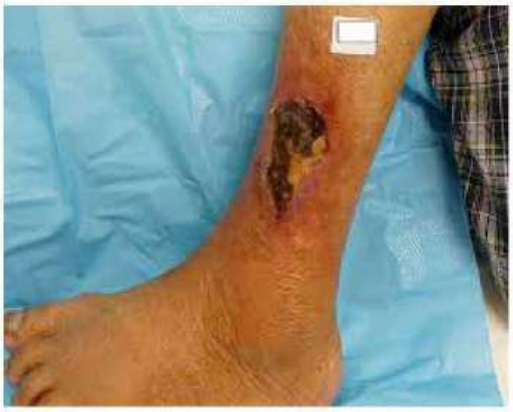
- Calciphylaxis has a poor prognosis with 1-year mortality rates between 45% and 80%.

- Response to treatment is also poor – infection the leading cause of death.

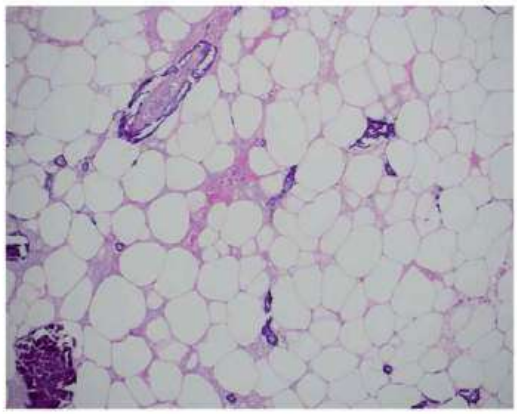
- Incidence of Calciphylaxis in Dialysis patients ranges from 0.04% to 4%.

Risk factors

Demographics	***Medications***
Caucasian ethnicity	Warfarin, Corticosteroids,
Female sex	Calcium-based phosphate binders,
Comorbidities	Activated vitamin D, Iron therapy
Kidney disease	***Abnormalities of the Chronic***
Obesity	***Kidney Disease-Bone Mineral***
Diabetes mellitus	***Disease Axis***
Hypoalbuminemia	Hyperphosphatemia
Autoimmune conditions such as lupus,	Hypercalcemia
rheumatoid arthritis, and antiphospholipid	Hyperparathyroidism
antibody syndrome	Adynamic bone disease
Liver disease	***Hypercoagulable State***
Malignancy	Tissue **trauma** resulting from
Dialysis vintage	subcutaneous injections such as insulin

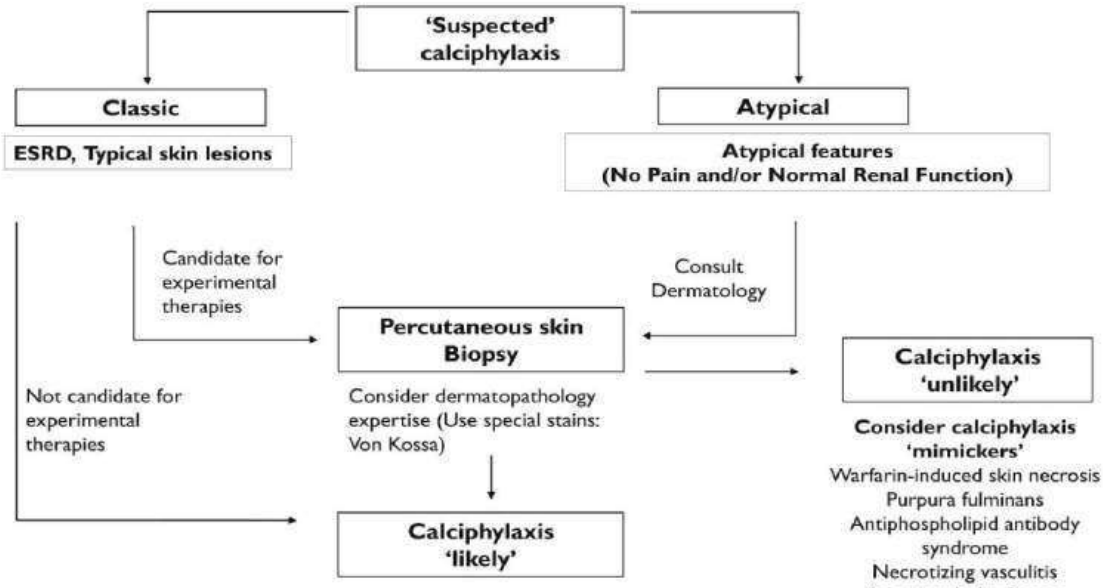


SKIN LESION

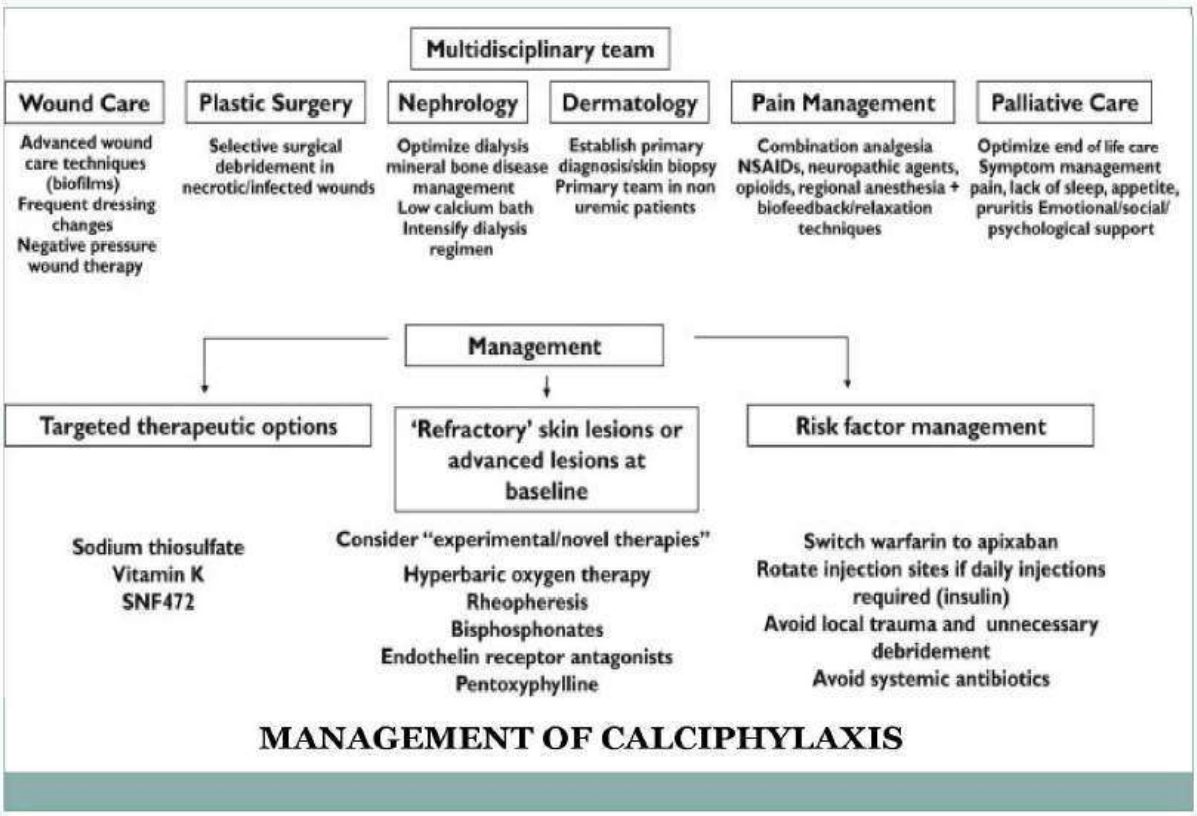


Intraluminal and extravascular calcification, intimal fibrosis of vessel walls, fat necrosis, and vascular thrombosis in subcutaneous tissue of a patient with calciphylaxis.

CALCIPHYL AXIS



APPROACH TO CALCIPHYLAXIS



Management

Sodium thiosulfate

- Route and dose - Intravenous (standard): 25gm if weight > 60 kg;12.5gm if weight< 60 kg; infusion in the last hour of Dialysis.

- Subcutaneous (nonstandard): 0.25 to 0.75gm (1 to 3 mL of 250mg/ mL); at the Periphery and centre of the lesion.

- Duration of IV infusion: minimum of 2-3 months.

- Typical total duration of 6 months or until lesions completely heal.

Hperbaric oxygen

- Delivery of 100% oxygen at 2.5 times the atmospheric pressure in a sealed chamber for 90min [20–30 sessions].

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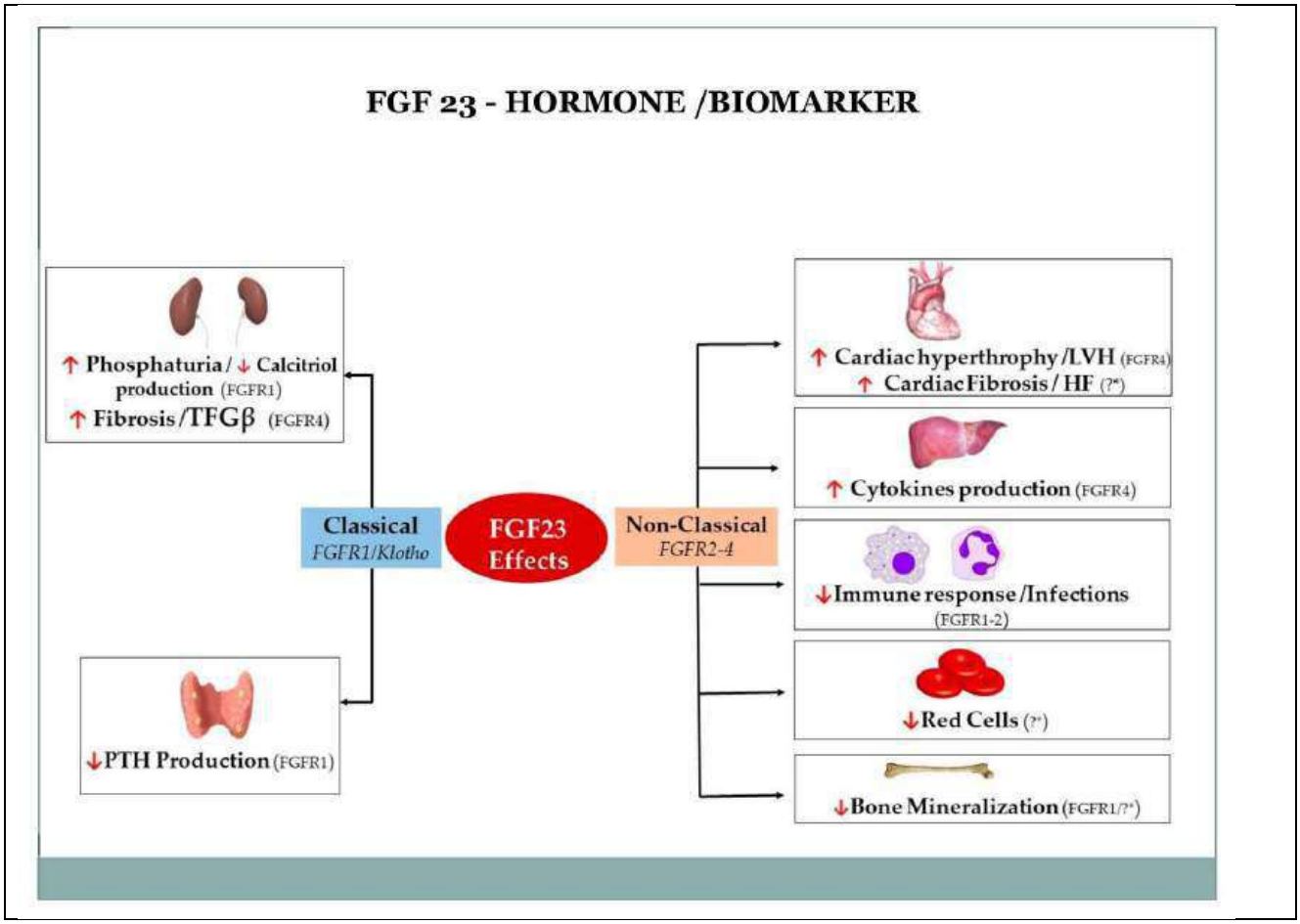
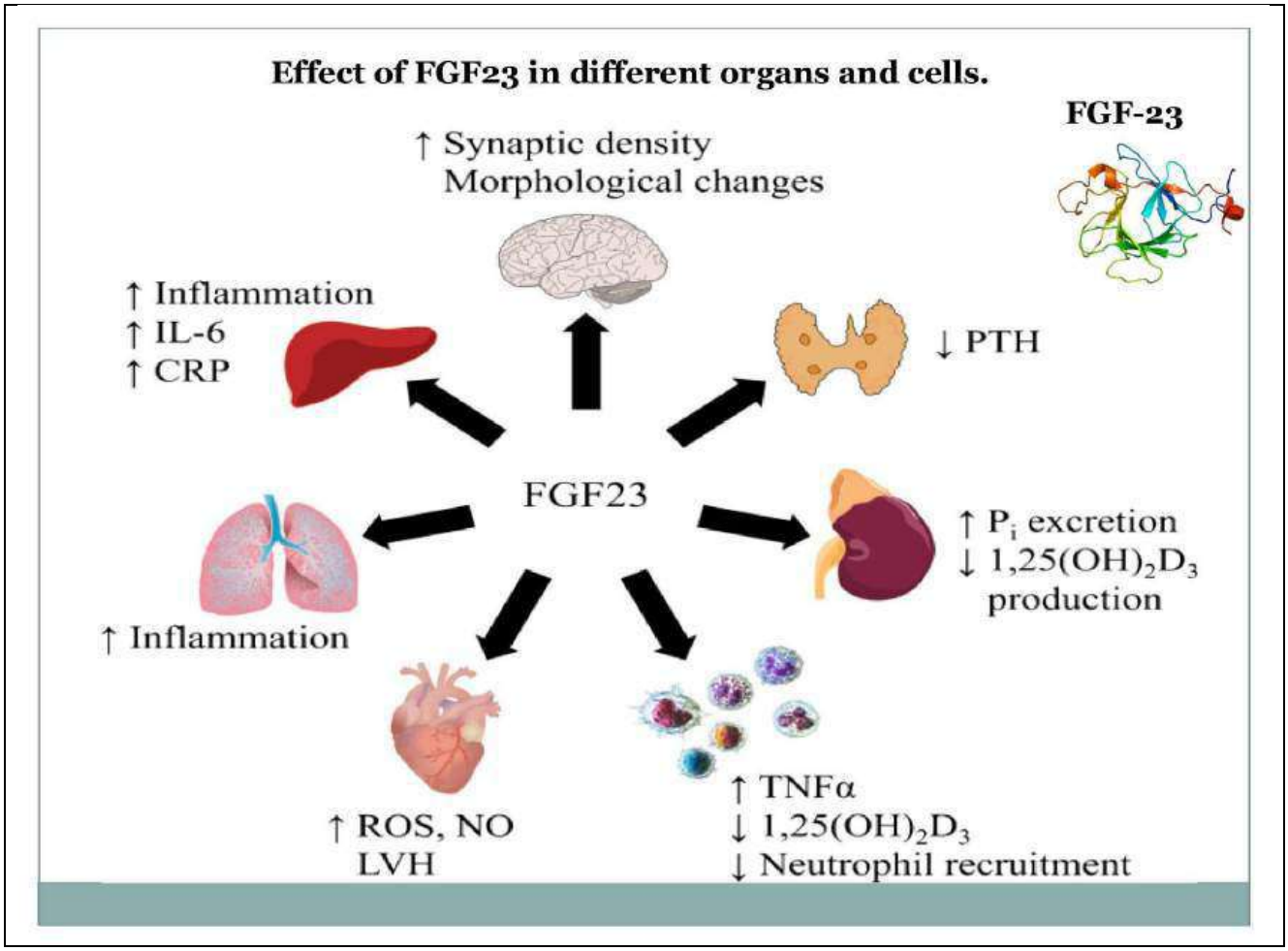
FIBROBLAST GROWTH FACTOR-23

Investigation

- Fibroblast growth factor 23 (FGF23) is a bone-derived hormone that functions as the central endocrine factor that regulates phosphate balance.
- FGF23 ismainly produced by osteocytes and osteoblasts.
- FGF23 concentrations are measured by sandwich ELISA.
- The reference range of MED FGF23 levels among healthy controls was 18.6–59.8 pg/mL when calculated as the average ±2 standard deviations (SDs).





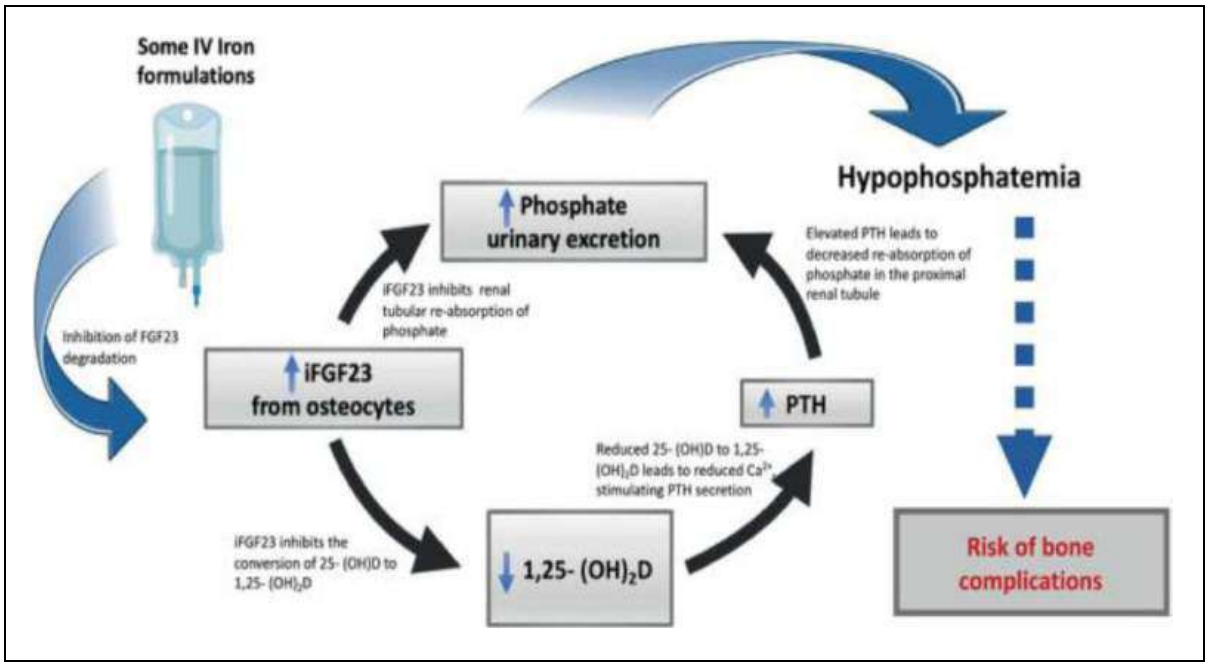
Pathological effects

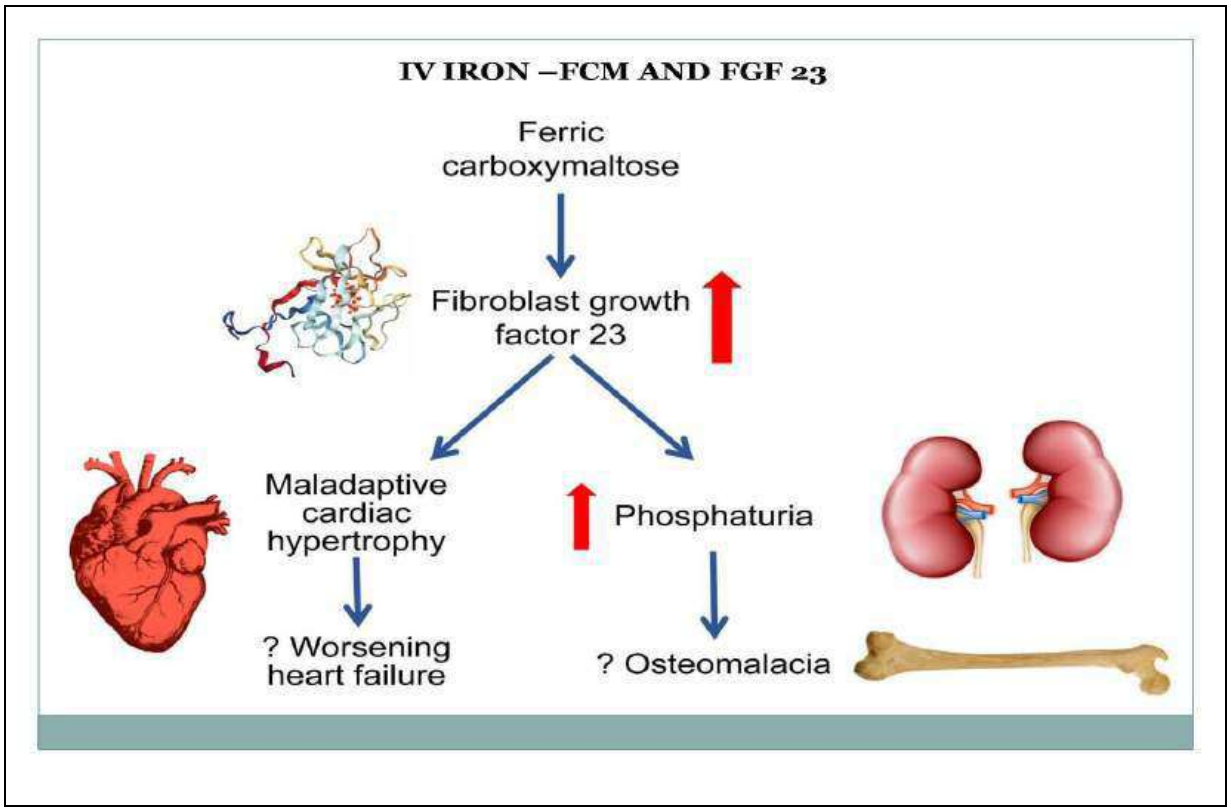
- Acute kidney injury leads to increased FGF23 levels.
- In chronic obstructive pulmonary disease, FGF23 is elevated.
- Urothelial , ovarian and Colon adenocarcinoma and are characterized by FGF23 secretion with hypophosphatemia.
- Cardiovascular: left ventricular hypertrophy, aortic calcification and atrial fibrillation in CKD.
- Brain: Hemorrhagic stroke.

- Associated with increased Insulin resistance.
- Hyperphosphatemic disorders due to loss of function and resistance to FGF-23.
- Hypophosphatemic disorders due to mutation leading to lack of cleavage of FGF -23.

FGF 23 and IV Iron RX

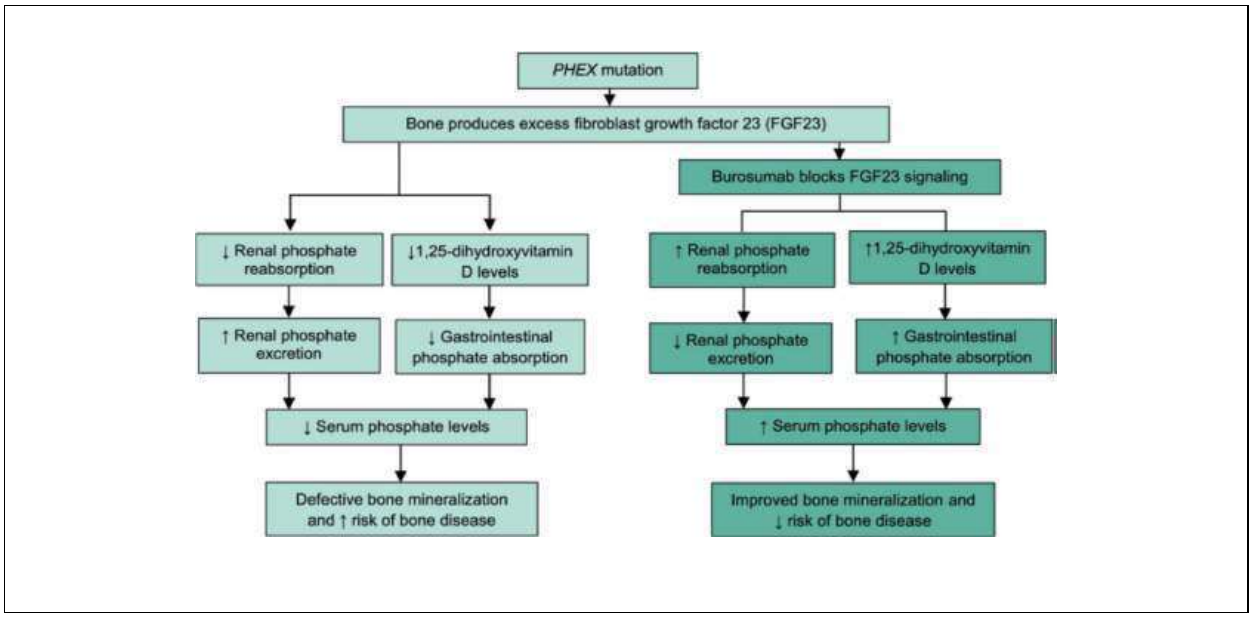
- In the absence of CKD, iron deficiency is associated with an elevation of C FGF-23.
- Treatment of iron deficiency with intravenous iron lowers cFGF23 on a transcriptional level.
- Ferric Carboxymaltose increases iFGF23 due to an inhibitory effect on its degradation and leads to Hypophosphatemia.





Newer agent

- Burosumab is an antibody against FGF23 that is approved and therapeutically used in the treatment of X-linked Hypophosphatemia.



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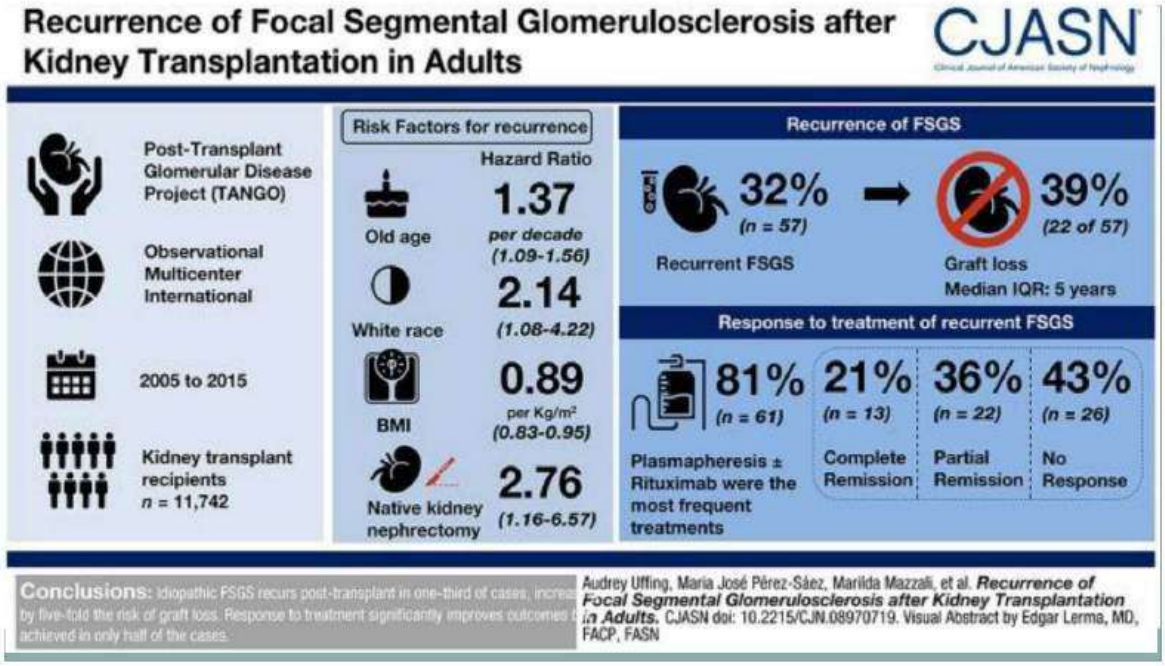
POST TRANSPLANT FSGS RECURRENCE

Introduction

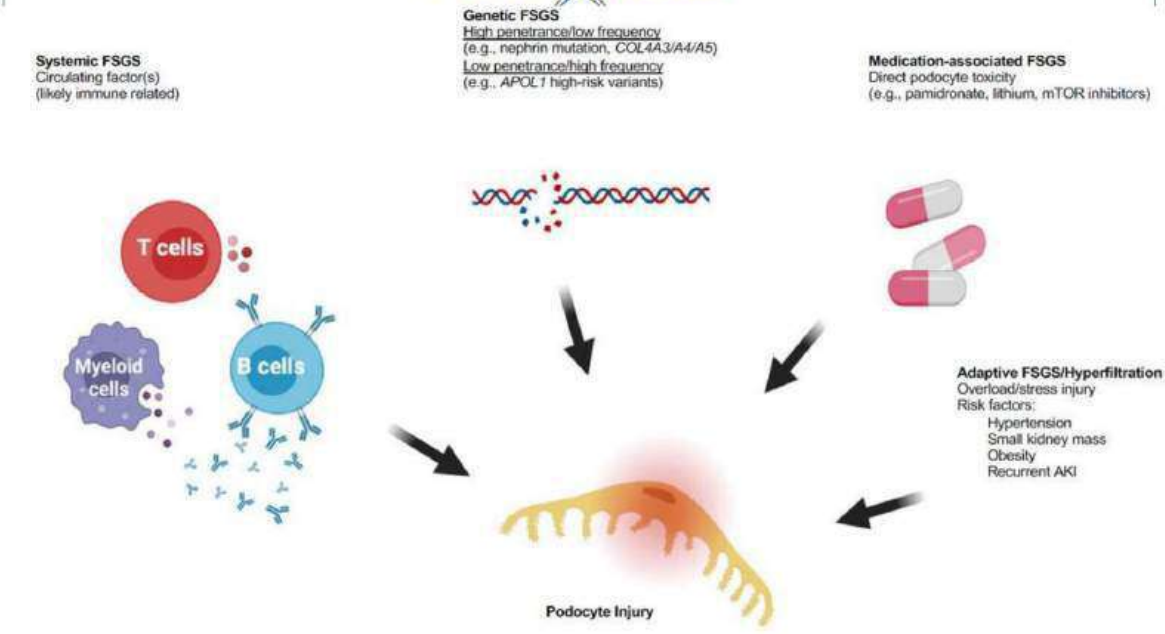
- Recurrence of FSGS in graft is 30-50% and is the cause for graft loss.
- Present with rapid nephrotic -range Proteinuria with a median time to recurrence of 1.5 months.
- Proteinuria from native Pidneys decreases significantly within 1 month of transplantation hence Proteinuria detected more than 1 month after KT is most likely derived from the allograft.
- Rare in patients with genetic FSGS and those without Nephrotic Syndrome at onset.

Risk factors

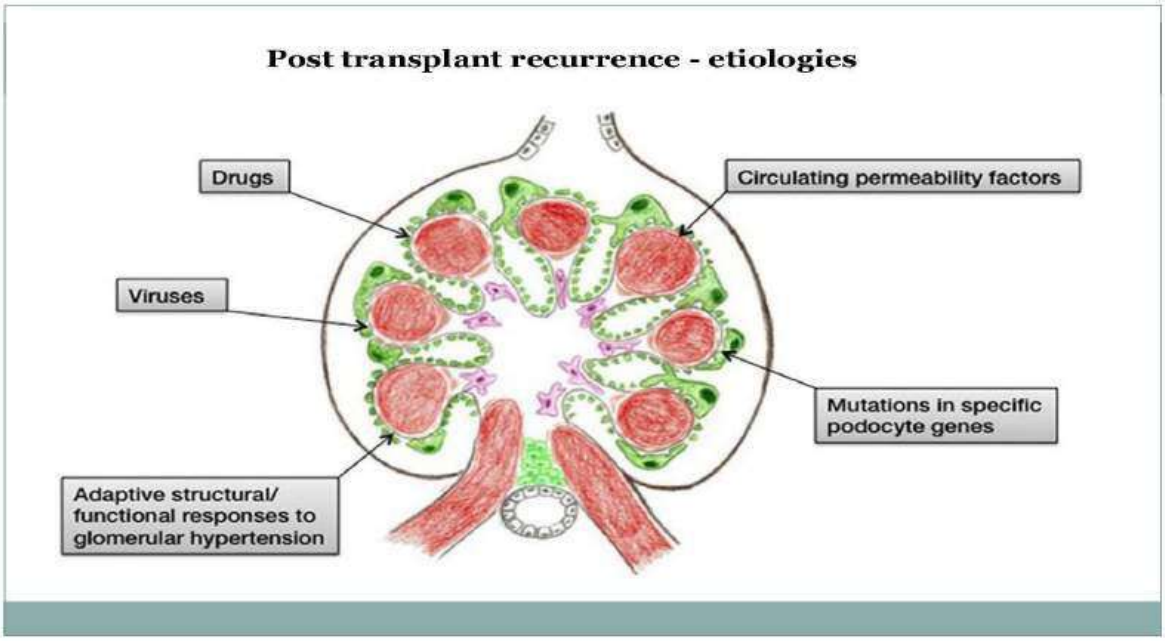
- Higher risk of recurrence: younger age of disease onset, White race, rapid progression of initial disease [< 3 years], living-related KT, history of recurrence in a previous Kidney allograft, and native Kidney Nephrectomies.
- A family history of FSGS, histologic subtype in the native Kidney, and choice of transplantation immunosuppressive therapy have not been shown to alter the risk of recurrence.



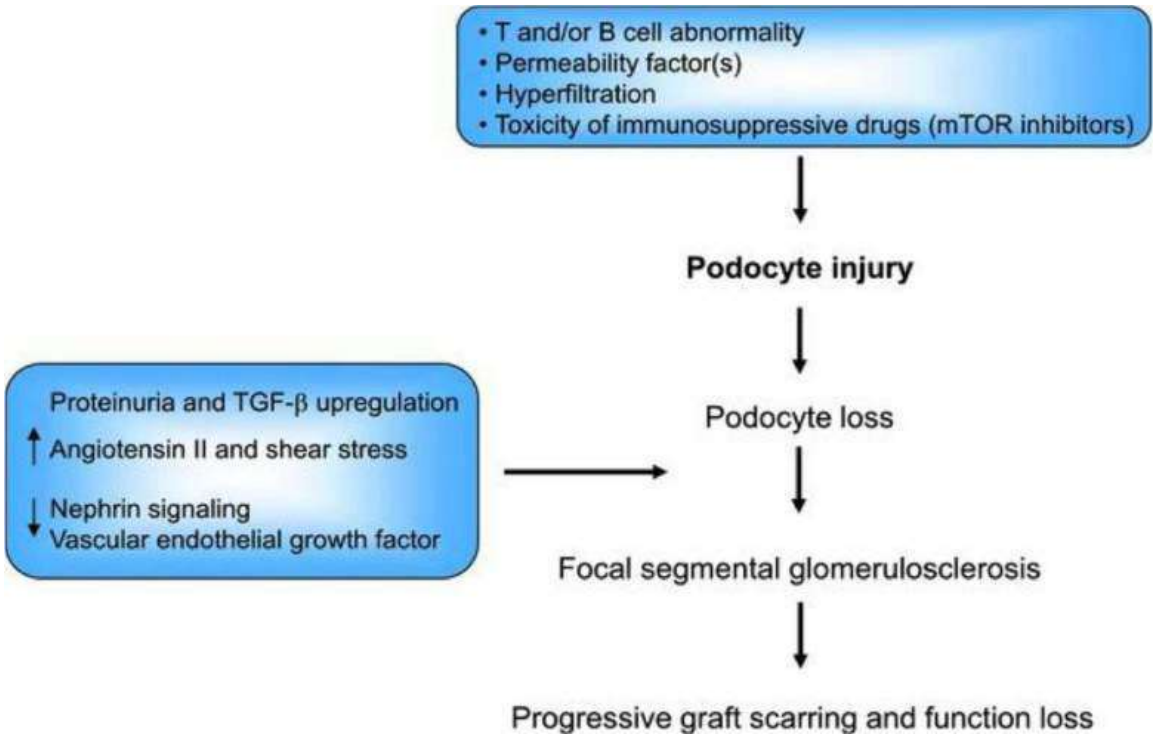
Underlying etiologies for the podocytopathy in FSGS patients

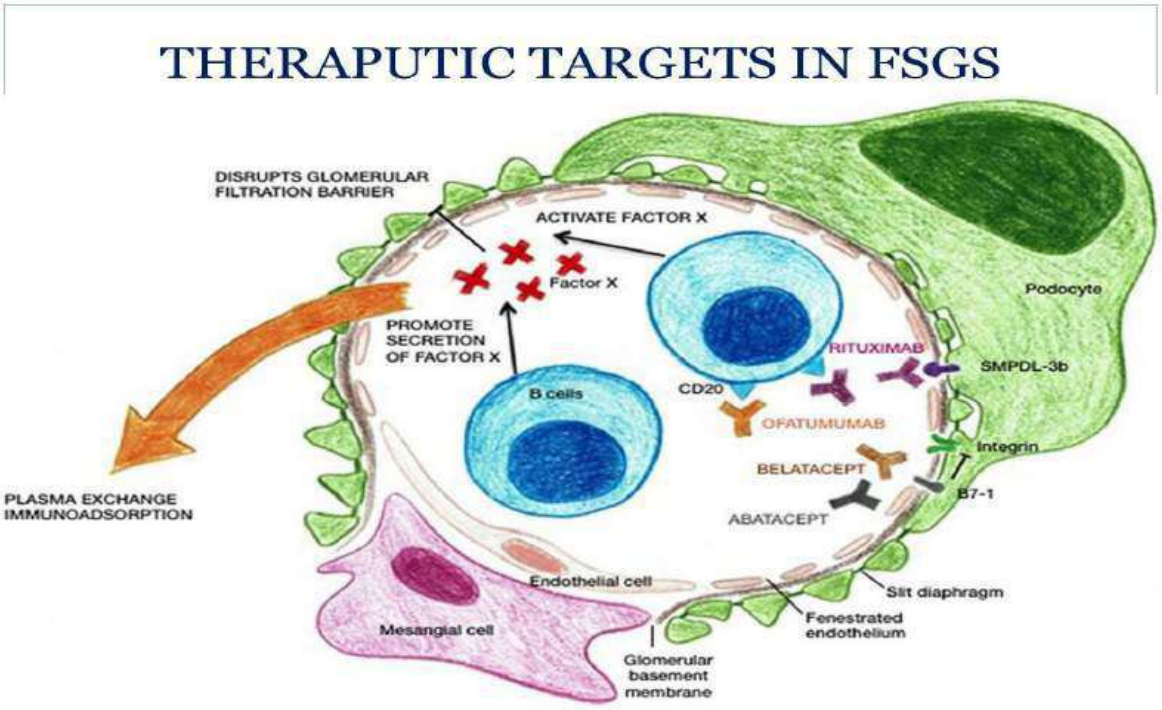


AKI, acute kidney injury; mTOR, mammalian target of rapamycin. Created with BioRender.com.



Mechanism of recurrence



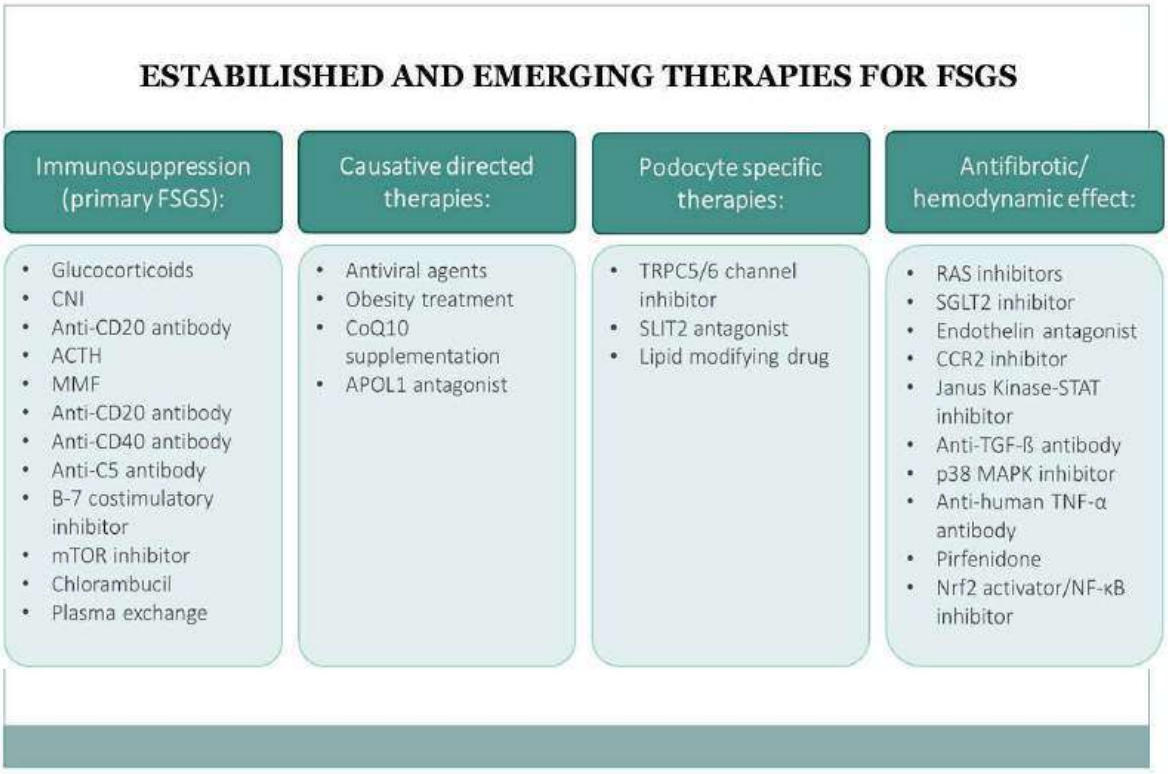


Treatment options

- PLASMAPHERESIS – most effective in removing circulating permeability factors.
- RITUXIMAB - Anti-CD 20 monoclonal antibody.
- OFATUMUMAB – fully human anti- CD 20 monoclonal antibody that depletes B – cells.
- BELATAOCEPT – co - stimulation blocker.
- ABATACEPT – selective T cell co stimualation blocker.
- LIPID APHERESIS – LDL Apheresis.

Re-transplant

- FSGS in the first KT are at very high risk (up to 75%) for recurrence in subsequent Kidney allografts.
- Second KT should be delayed for 1−2years ➡ disappearance of the circulating factors responsible for the Glomerular injury.
- A third KT in patients with two previous transplant losses due to recurrent FSGS should generally be avoided.
- Prophylactic Plasmapheresis and Rituximab do not appear to decrease the rate of recurrence after transplantation.



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PRE-IMPLANTATION BIOPSY–

DECEASED DONOR TRANSPLANTATION

Introduction

- Marginal cadaveric kidney donors can be definedas: All donors older than 60 years, donors older than 50 years with any of the following criteria:
  (1) Hypertension,
  (2) Cerebro - Vascular cause of brain death or
  (3) Pre-retrieval serum creatinine (SCr) level >1.5mg/dl, with a degree of Glomerulosclerosis >15% and prolonged cold ischemia.

- Pre implantation deceased donor Kidney Biopsy helps in utilizing organs from marginal donors and predict long term outcome.

Scoring systems

- Remuzzi protocol.

- Marryland Aggregate Pathology Index [MAPI].

- BANFF scoring system.

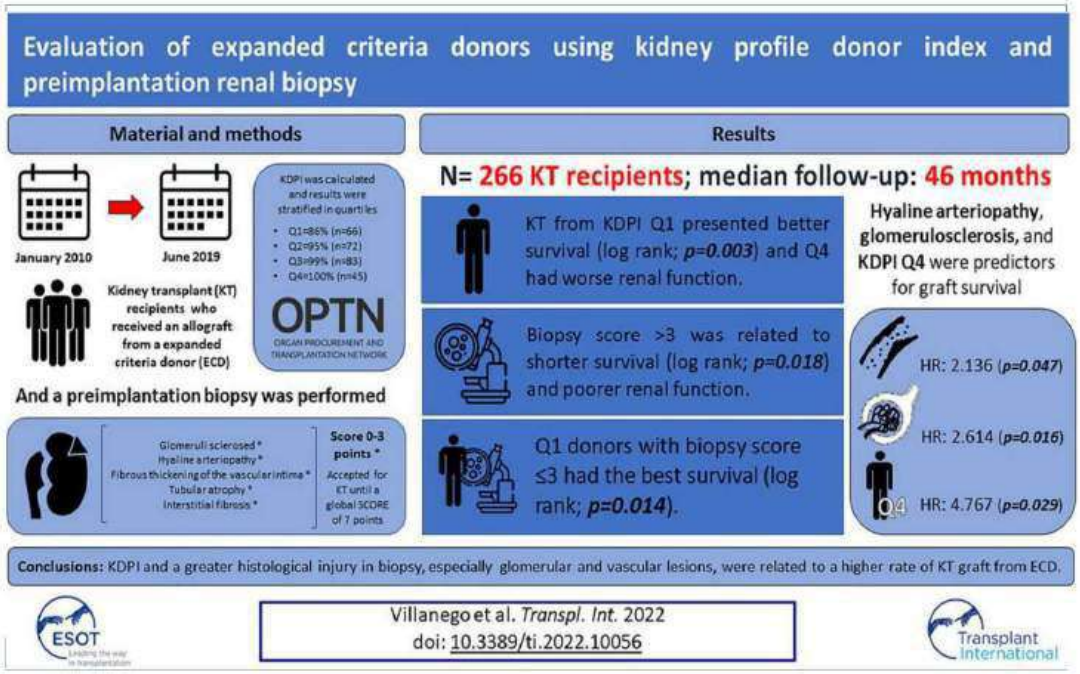
- Leuven scoring system.

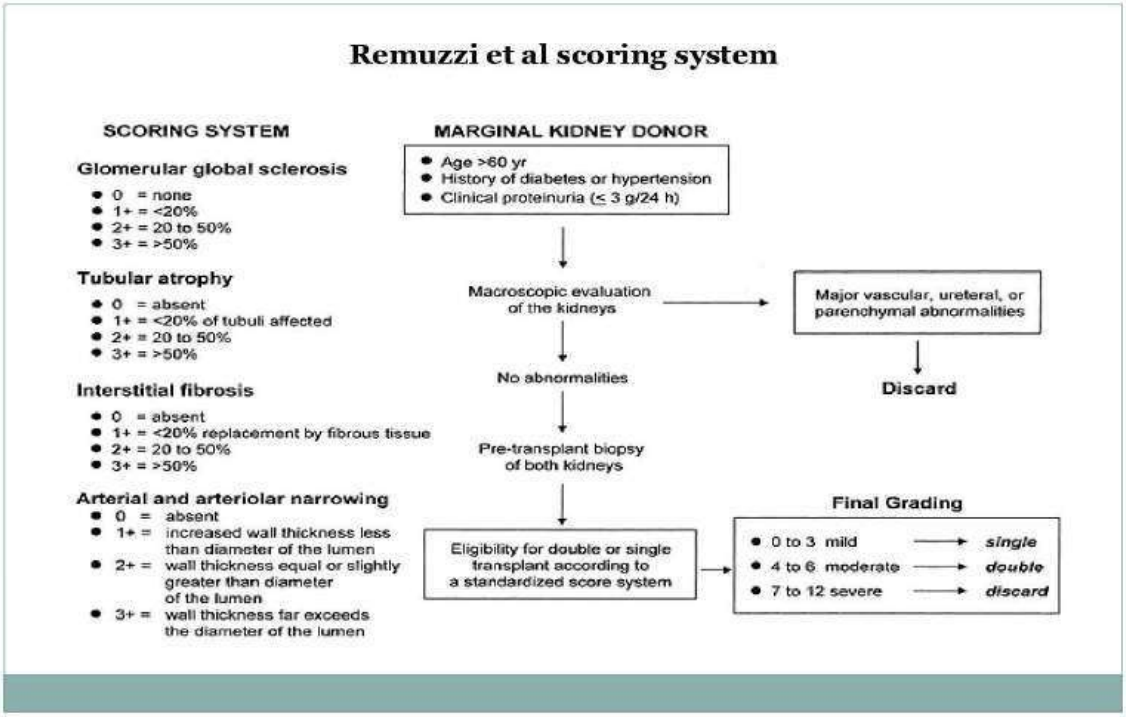
- Core Biopsy v/s Wedge biopsy –no much difference in scoring outcomes.

- Expert renal pathologist showed better interpretation of Biopsies compared to routine pathologist.

- Stains used Hematoxylinand Eosin stain.

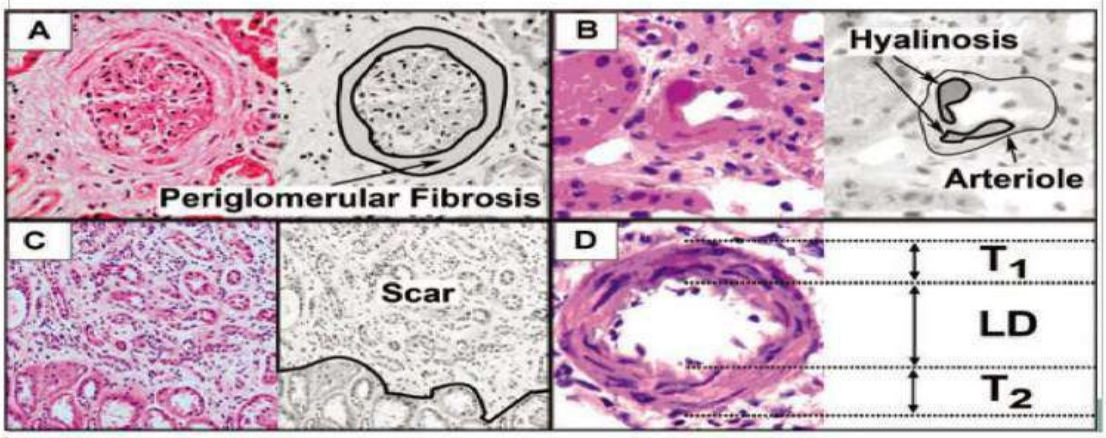
- Also periodic acid–Schiff and Masson's Trichrome- useful in evaluating parameters such as Hyaline Arteriolosclerosis, Tubular Atrophy and interstitial fibrosis.





The Maryland Aggregate Pathology Index: A Deceased Donor Kidney Biopsy Scoring System for Predicting Graft Failure

Pathologic features used in MAPI as seen on frozen section preparations. (A) **Periglomerular fibrosis**, (B) **arteriolar hyalinosis**, (C) **scar** including features of interstitial fibrosis, tubular atrophy and glomerulosclerosis, and (D) measurements for **arterial wall-to-lumen ratio** (WLR) calculation, including the thickness of two opposing walls (T_1 and T_2) and the luminal diameter (LD). WLR=$(T_1+T_2)/LD$



Our experience

- 20 preimplantation biopsies done out of 66 cadaver transplants done.
- 4 donor Kidneys rejected: 1 had extensive intra Glomerular Thrombi,1 case of Glomerular cystic disease and 2 cases of increased IFTA.
- Preimplantation Biopsy helped procuring the organ which would have otherwise been rejected and is an important tool for expanding donor pool.

Case 1

- 18 year old deceased donor with no comorbidities and death due to road traffic accident.
- His creatinine - 1.4 mg/dl and all other biochemical parameters were within normal limits.

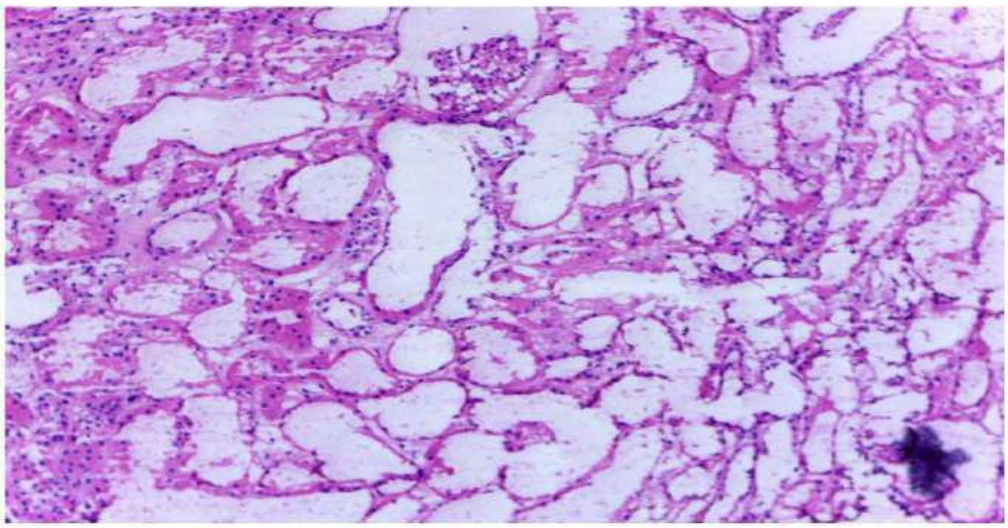
- His urine routine showed protein 1+ and no RBCs. He had no history of Hypertension or renal disease in family. He was declared brain dead after 48 hours of admission.

- On initial outlook he seemed to be a fair donor who is young with no comorbidities and well managed by ICU team.

- Since he had a baseline high creatinine for his age [Egfr -66 ml per min per 1.73 m2] we decided to do preimplantation biopsy.

- His Biopsy showed Glomerulocystic changes in all visualised Glomeruli and therefore the kidney was discarded.

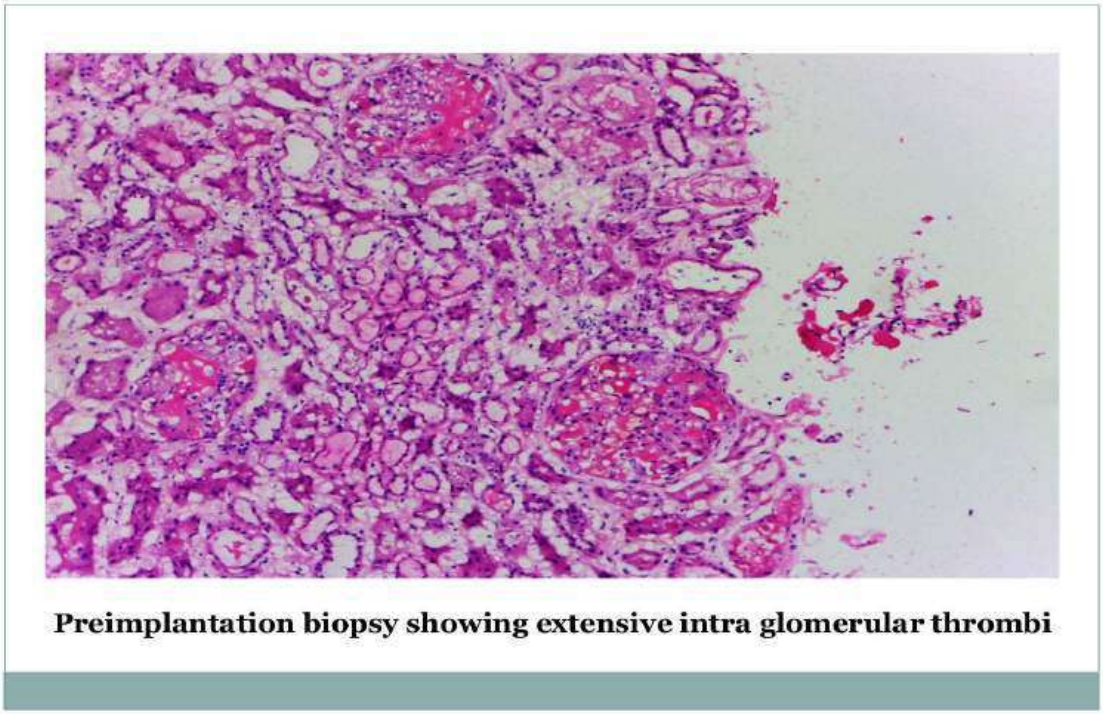
- Biopsy helped us from not transplanting a suboptimal Kidney.



Case 1 -Glomerular cystic changes on preimplantation biopsy

Case 2

- 46/year old female deceased donor with history of Hypertension and death due to road traffic accident.
- Her terminal Creatinine was 1.2mg /dl. Her Urine report showed protein 2+ And few RBCs.
- Her Preimplantation Biopsy showed extensive intra Glomerular thrombi.



Preimplantation biopsy showing extensive intra glomerular thrombi

- Intra glomerular thrombus is commonly seen in Preimplantation Biopsies.
- If present in majority of Glomeruli, Kidney is discarded because it causes delayed graft function and raises the possibility of Glomerular disease of unknown Etiology in the donor.

- Recently many papers were published on implanted Kidneys with Intraglomerular Thrombi and follow up protocol biopsies showing resolution of thrombi early in Post-Transplant period and minimal residual changes in some, at the end of one year with good graft function.

Case 3

- A male deceased donor aged 49 years, was a known case of diabetes mellitus for 10years with terminal creatinine 1.1mg/dl and urine showing 1+ protein.

- His Pre-implantation Biopsy showed interstitial fibrosis and tubular atrophy involving less than 10% with Remuzzi histological score of 2.

- In view of the above findings, the donor kidney was taken up for transplant and had good graft outcome with post-transplant creatinine of 1.2 mg/dl.

- Comorbidities like Diabetes and Hypertension with Urinary abnormalities usually put the transplant team in dilemma whether to take or discard the marginal Kidney.

- Long standing history of Diabetes Mellitus in deceased donor with Proteinuria is out rightly rejected on clinical criteria.
- Case 3 patient had long standing diabetes mellitus but it did not translate to histological injury and hence donor Kidney was selected.

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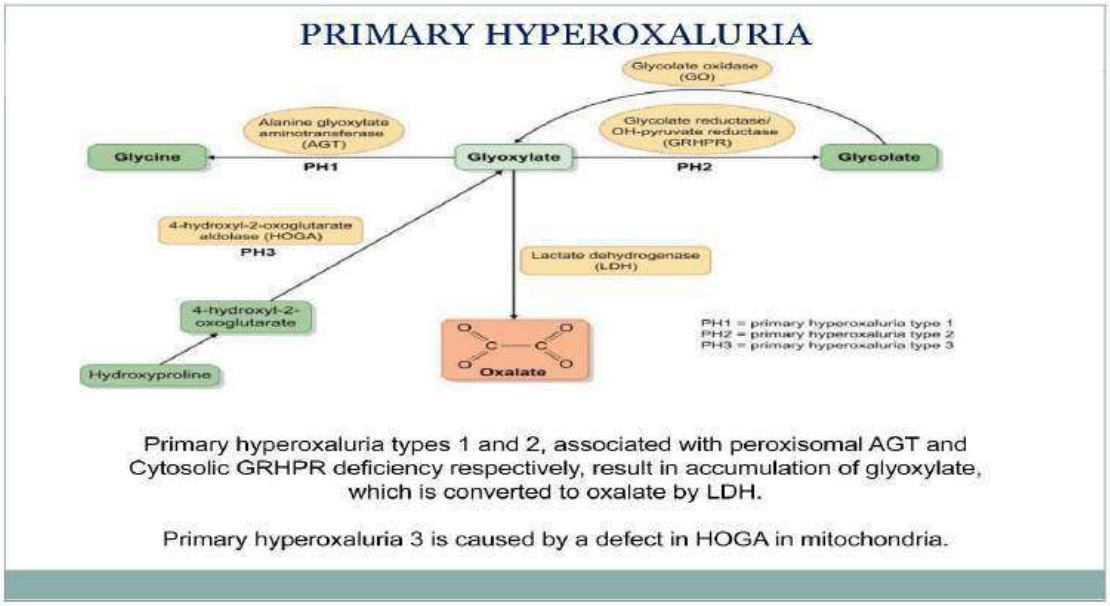
OXALATE NEPHROPATHY

Introduction

Definition of Oxalate Nephropathy:-

- Progressive kidney disease.
- Deposition of calcium oxalate crystals (Birefringent on polarized light) within Tubular Epithelial cells, Tubular lumens, and less frequently in the Interstitium, associated with Tubular injury and Interstitial Nephritis.
- Exclusion of other causes of Kidney disease (apart from non specific Microvascular lesions and/or diabetes-associated Glomerular lesions).
- Ideally, a Hyperoxaluria enabling-condition should be identified.
- Hyperoxaluria- defined as 24-h urine oxalate of >40–45mg/day.
- The urinary oxalate excretion tends to be higher in Primary Hyperoxaluria >88mg/day as opposed to 44–70mg/day in Enteric Hyperoxaluria.
- The average age that symptoms appear is 5 years old.
- About 50%of children will experiencekidney failureby age 15. About 80% will experience kidney failure by age 30.



Causes of Secondary Hyperoxaluria and Oxalate Nephropathy

Increased intestinal oxalate absorption:-

- Chronic pancreatitis**,** Pancreatectomy.
- Use of orlistat (lipase inhibitor).
- Roux-en-Y gastric bypass**,** Small bowel resection.
- Crohn's disease**,** Celiac disease.
- Cystic fibrosis.
- Use of somatostatin analogue.

Increased dietary oxalate or precursor intake

- Rhubarb,*Averrhoa Carambola*(star fruit), *Averrhoa Blimbi*, Tea, Nuts, "juicing"
- Vitamin C, Ethylene Glycol, Methoxyflurane, Naftidrofuryl oxalate.

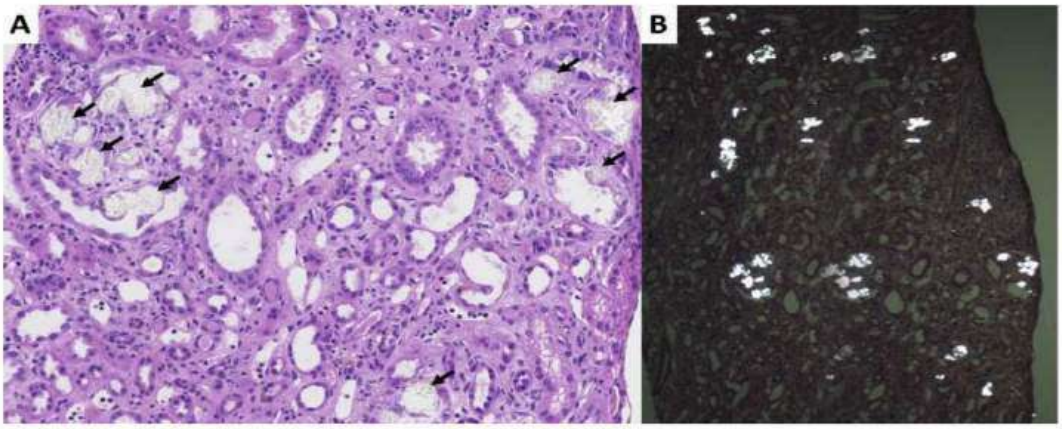
Decreased intestinal bacterial oxalate degradation

- Antibiotic use.

Others

- Obesity, genetic variations in oxalate transporters?[a]

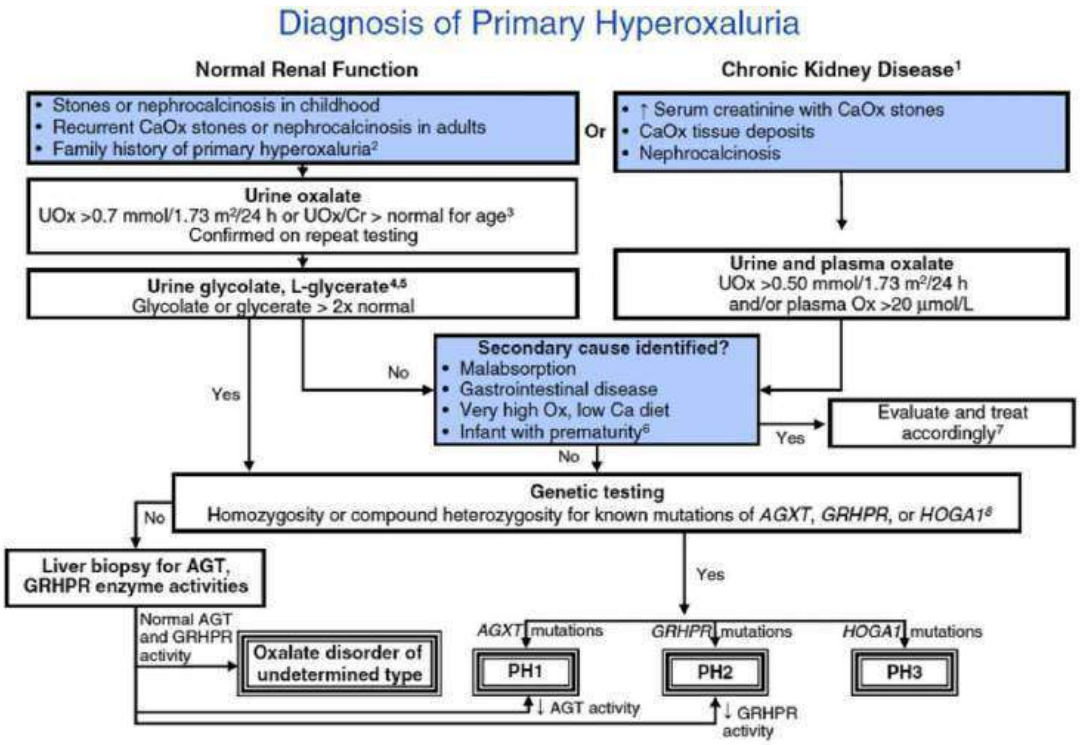
OXALATE NEPHROPATHY



(A) Intratubular translucent polyhedral or rhomboid crystals (black arrows) on light microscopy (hematoxylin and eosin stain, original magnification, x20).

(B) Crystals shown as birefringent under polarized light (original magnification, x5). Biopsy also shows acute tubular injury and mild interstitial inflammation.

Diagnostic algorithm



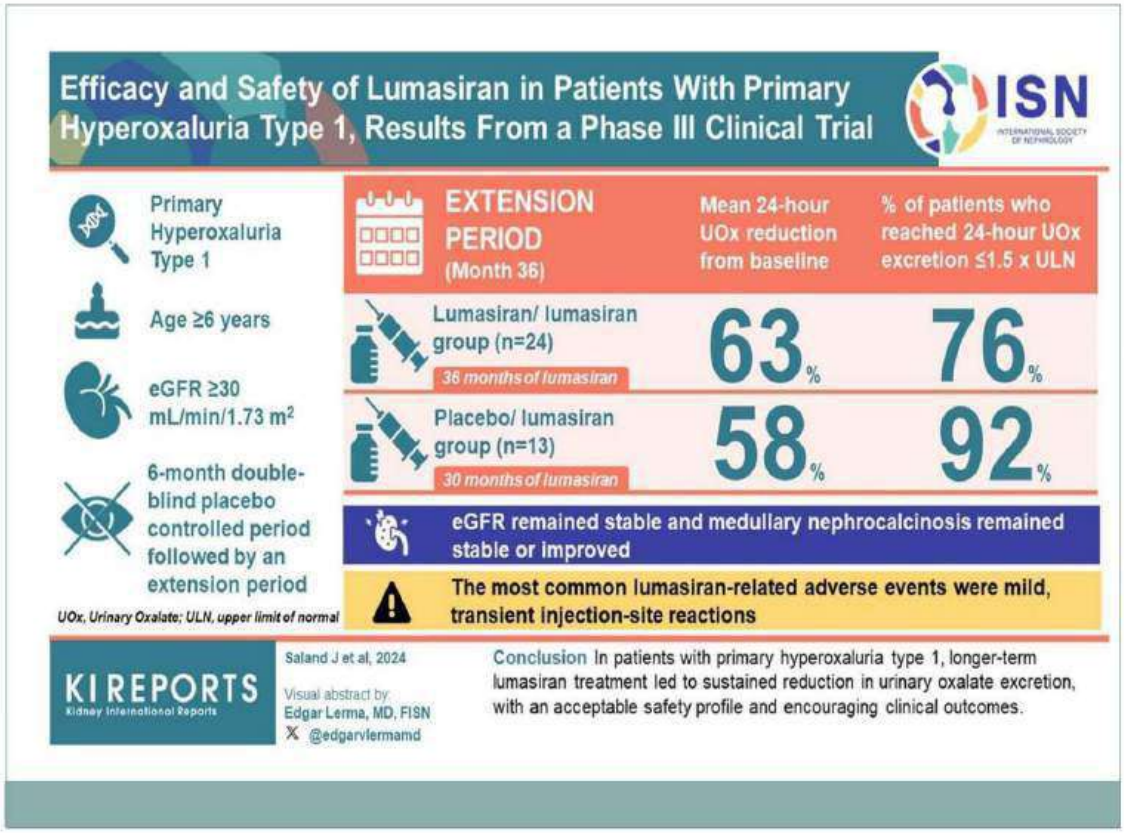
TREATMENT OF OXALATE NEPHROPATHY		
Treatment	Rationale	Supporting evidence
High fluid intake (urine output >2-3 L/d)	Reduces urine calcium oxalate supersaturation.	Reduces stone formation.
Low-oxalate diet	Reduces bioavailability of intestinal oxalate.	Reduces urinary oxalate excretion in small-sized studies; caveat: comparisons were based on a low-oxalate diet compared to a very-high-oxalate diet.
Low-fat diet	Reduces intestinal oxalate absorption (by increasing bioavailability of intestinal calcium).	Reduces urinary oxalate excretion in small studies.
Normal-calcium diet	Avoid low-calcium diets, which lead to more free intestinal oxalate.	Reduces urinary oxalate excretion in small-sized studies.
Calcium supplements	Reduce bioavailability of intestinal oxalate and its absorption.	Reduces urinary oxalate excretion but may lead to hypercalciuria. Calcium citrate may be more bioavailable than calcium carbonate.
Cholestyramine	Binds intestinal bile acids, reduces diarrhea, and binds oxalate in vitro.	Studies show contradicting results.
Oxalobacter formigenes administration	Increases intestinal oxalate degradation.	Reduces urinary oxalate excretion in rat model and plasma oxalate levels in dialysis patients with primary hyperoxaluria (phase 2 study).
Oxalate decarboxylase	Degrades intestinal oxalate.	Reduces urinary oxalate excretion in rat model and in phase 3 pilot study in humans.
NLRP3-specific inflammasome inhibitor	Reduces crystal-induced kidney damage.	Reduces calcium-oxalate crystal-induced kidney fibrosis in mouse model.

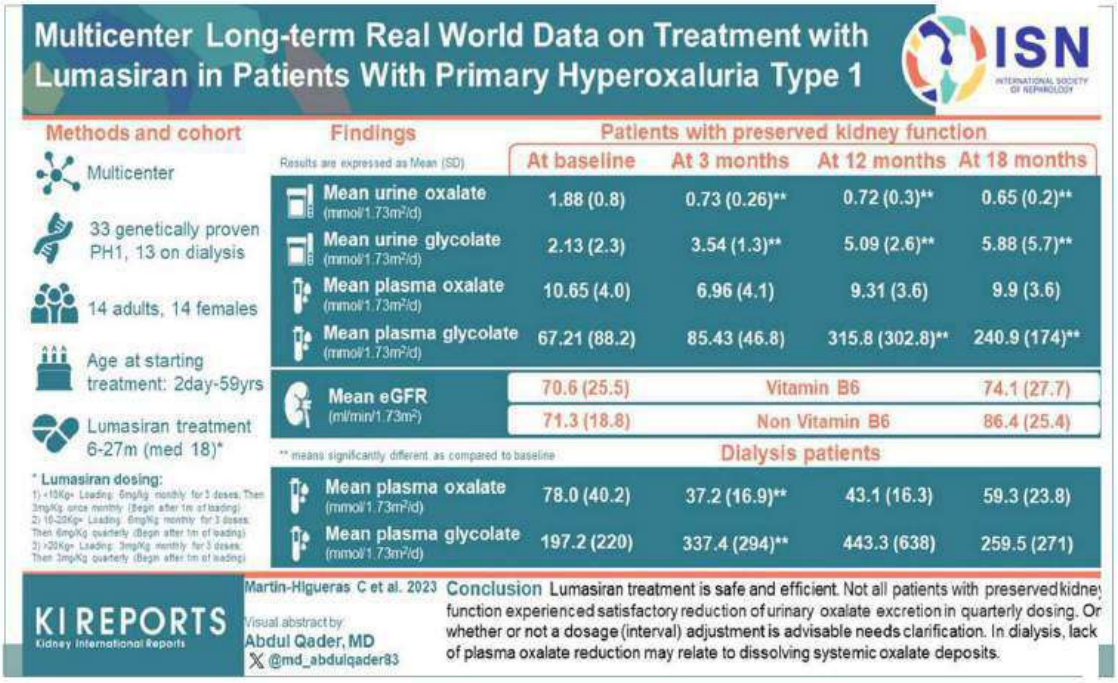
Transplant

- Combined liver and kidney transplant is the mainstay of treatment in primary Hyperoxaluria.

- Sequential liver followed by kidney transplant in patients with less severe renal disease.

- Recurrence of oxalate deposition in the graft due to secondary hyperoxaluria needs continuous monitoring and medical management with early loss of graft.





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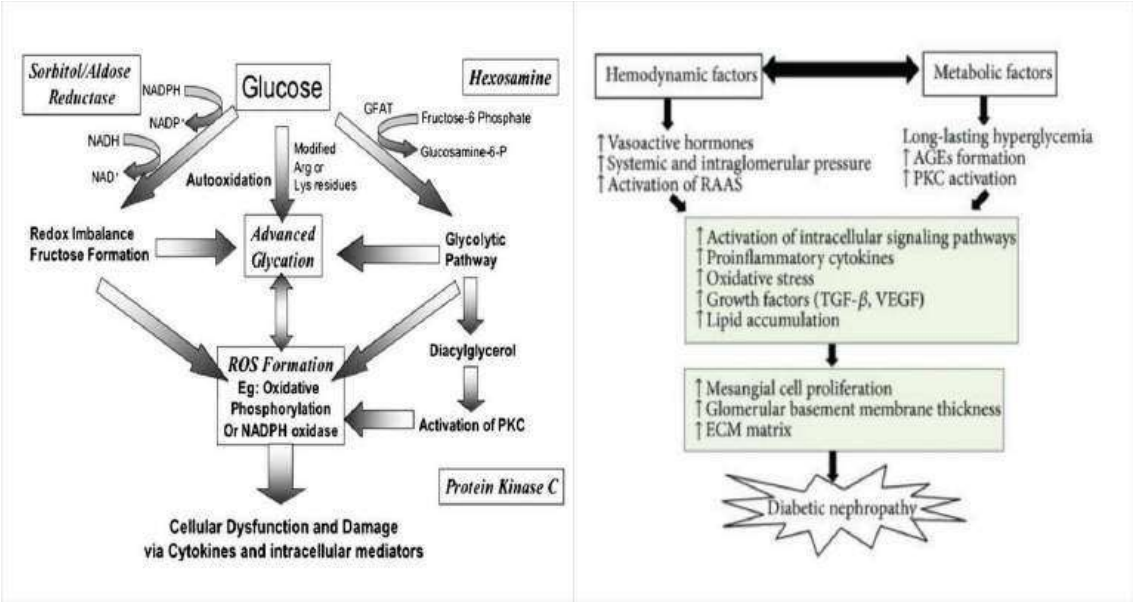
“FOUR PILLARS” IN THE TREATMENT OF DIABETIC NEPHROPATHY [DN]

Introduction

The "four pillars" of treatment for diabetic nephropathy are:

- Renin-Angiotensin System (RAS) inhibitors,
- Sodium-Glucose cotransporter-2 (SGLT2) inhibitors,
- Glucagon-like peptide-1 (GLP-1) receptor agonists,
- Non-steroidal Mineralocorticoid Receptor Antagonists (nsMRA).
- In combinations they retard progression of Diabetic Nephropathy.
- Medications are individualizedas per patient needs.

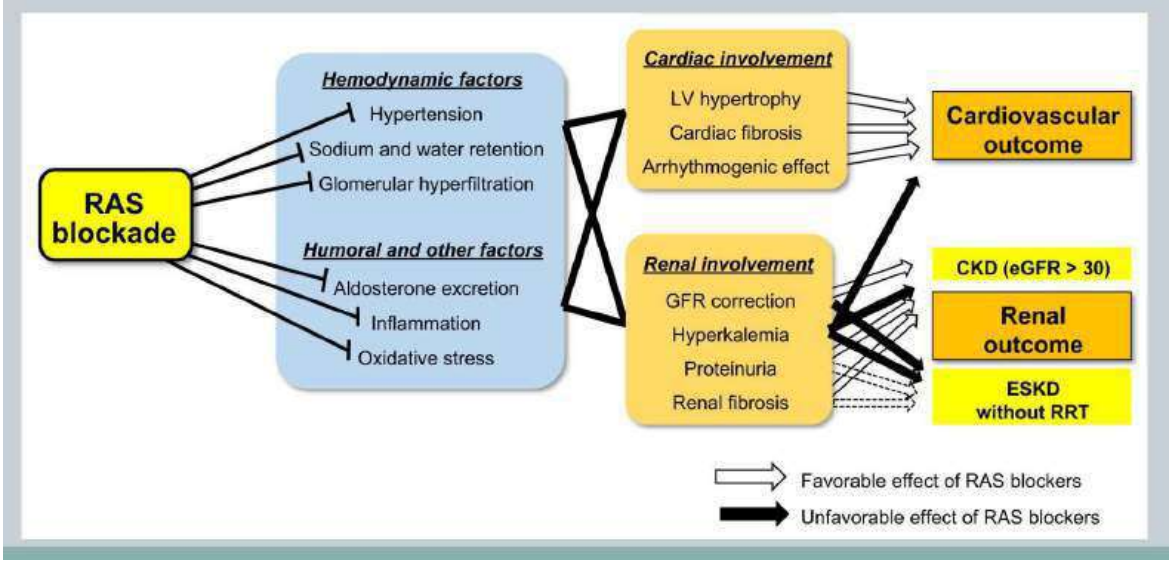
Mechanism of DN



RAAS INHIBHITORS

- Angiotensin II and other components of the renin-angiotensin-aldosterone system (RAAS) have a central role in pathogenesis.
- ACE inhibitors decrease the production of Ang II, which is a potent Vasoconstrictor, leading to lower Intraglomerular pressure and reduced Glomerular Hypertension.
- They also decrease the Glomerular permeability to urinary albumin leading to decreased proteinuria.
- ARBs act by blocking Ang II type 1 receptors (AT1receptors).
- This AT1blockade may lead to further increase in synthesis of Ang II which binds to intrarenal AT2receptors, resulting in decreased blood pressure and reduced Renal Interstitial Fibrosis.

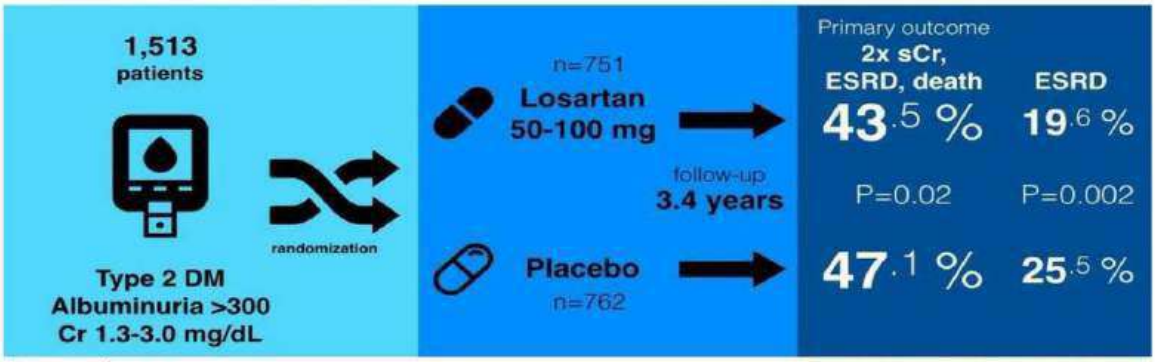
RAAS BLOCKERS



RAAS Inhibitors

LOSARTAN LED TO DECREMENT OF PROTEINURIA BY 35% AND REDUCTION OF DOUBLING OF CR AND ESKD BY 25%

Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy (RENAAL)



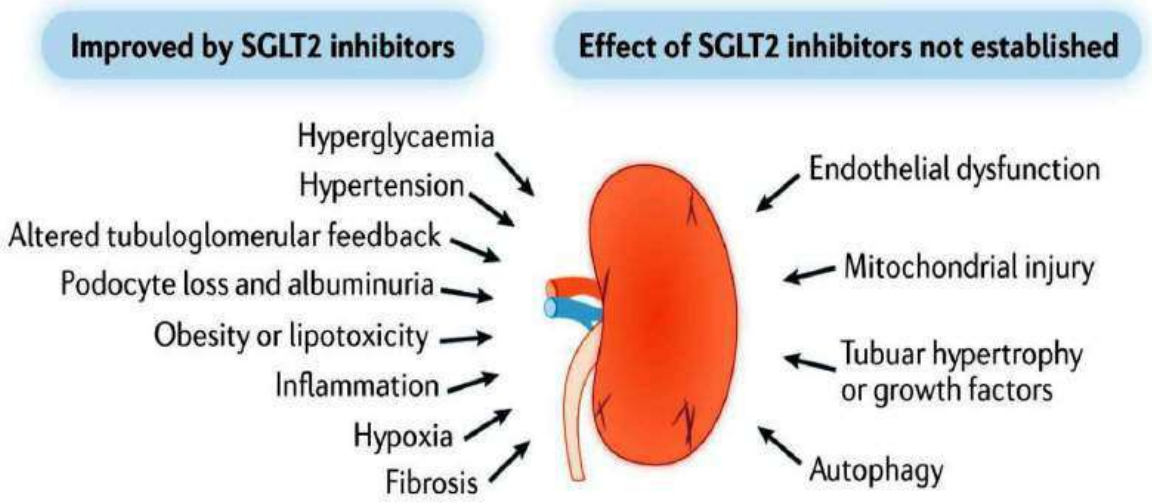
N Engl J Med, Vol. 345, No. 12 · September 20, 2001 The NEW ENGLAND JOURNAL of MEDICINE

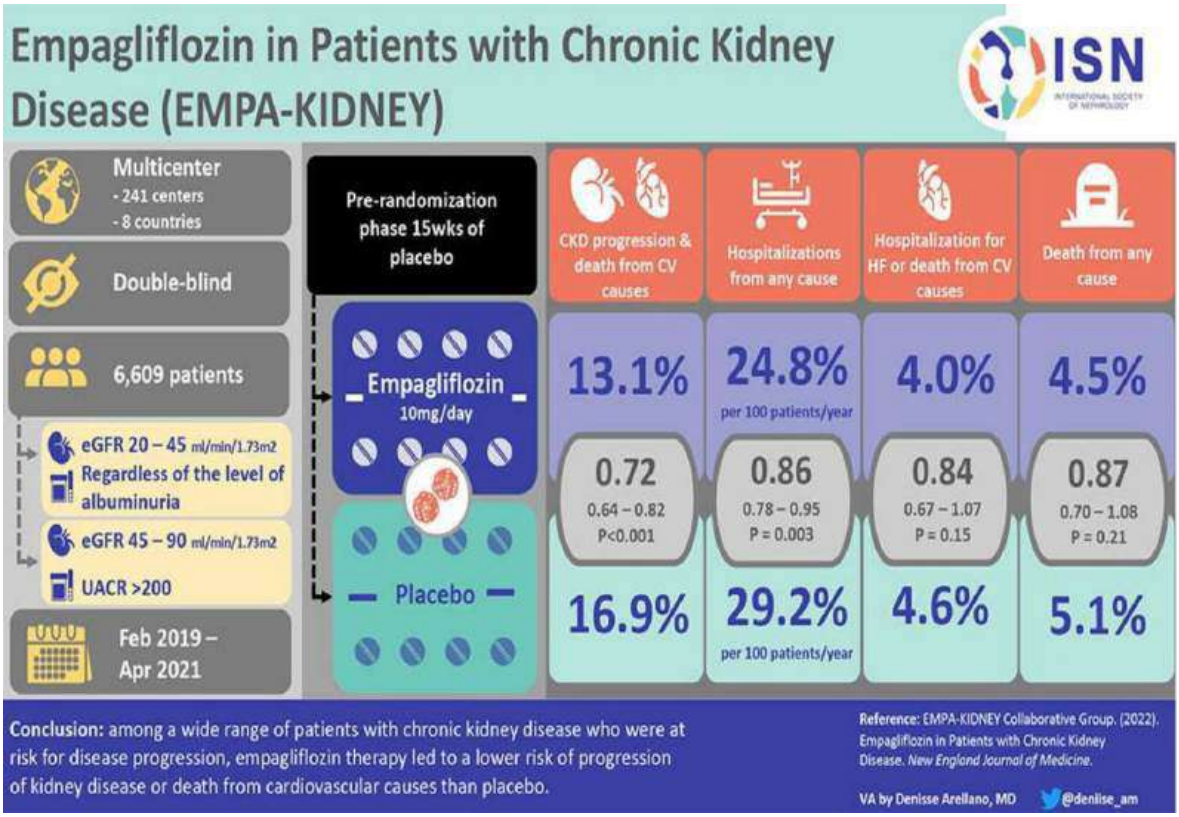
@Joel Topf @Kidney_Boy

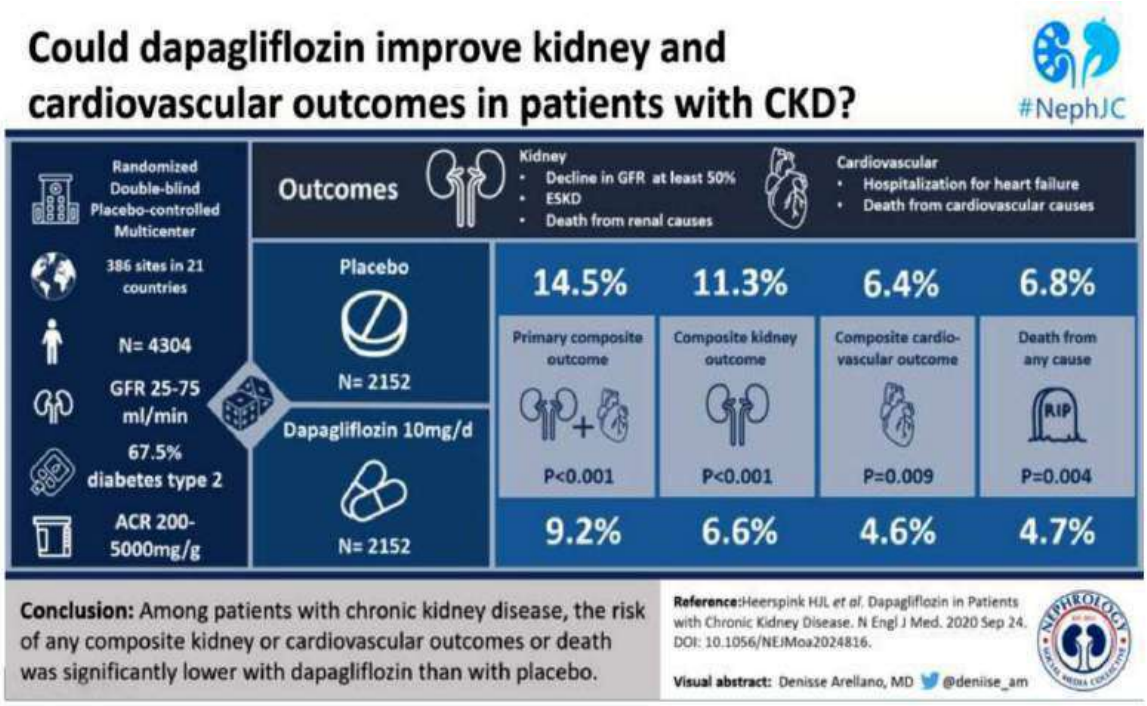
Trial	n	Design	FU	Renal outcome
DCCT [5]	1441 T1DM	Intensive versus standard glycemic control	6.5 years	Intensive glycemic control versus standard control (HbA_{1c} 7.3 versus 9.1%) reduced incident micro- and macro-albuminuria by 39 and 54%.
EDIC/DCCT [6]	1441 T1DM	Intensive versus standard glycemic control	18 years	Renoprotective efficacy of intensive glycemic control persisted and resulted in 45% risk reduction of micro-albuminuria at 18 years
UKPDS 33 [7]	3867 T2DM	Intensive versus standard glycemic control	10 years	Intensive glycemic control versus standard control (HbA_{1c} 7.0 versus 7.9%) led to 33% risk reduction for micro-albuminuria.
ADVANCE [8]	11 140 T2DM	Intensive versus standard glycemic control	5 years	Intensive glycemic control versus standard control (HbA_{1c} 6.5 versus 7.3%) reduced risk of micro-, macro-albuminuria and ESRD by 9, 30 and 65%. For those with macro-albuminuria, number needed to treat to prevent one ESRD = 41.
ACCORD [9]	10 251 T2DM	Intensive versus standard glycemic control	Terminated at 3.5 years	Targeting HbA_{1c} 6.0 versus 7.0–7.9% resulted in excess mortality (HR 1.22; 95% CI 1.01–1.46; P = 0.04).
RENAAL [10, 11]	1513 T2DM	Losartan versus placebo	3.4 years	Multivariate analysis: every 10 mmHg SBP rise increased risk of ESRD or death by 6.7%. Losartan led to decrement of proteinuria (35%; P < 0.001), risk reduction of serum creatinine doubling (25%; P = 0.006) and ESRD (28%; P = 0.002).
MARVAL [12]	332 T2DM	Valsartan versus amlodipine	24 weeks	Reduction of micro-albuminuria with valsartan (44%) greater than amlodipine (8%).
IRMA-2 [13]	590 T2DM	Irbesartan versus placebo	2 years	Irbesartan demonstrated renoprotective efficacy with reduction in disease progression compared with placebo (HR 0.3; 95% CI 0.14–0.61; P < 0.001 for 300 mg irbesartan).
IDNT [14]	1715 T2DM	Irbesartan versus amlodipine versus placebo	2.6 years	Irbesartan was renoprotective with lower risk of serum creatinine doubling (33%; P = 0.003) and ESRD (23%; P = 0.07) compared with placebo.
DETAIL [15]	250 T2DM	Telmisartan versus enalapril	5 years	Telmisartan and enalapril fared equally. No significant differences in level of albuminuria, rate of GFR decline and ESRD.
ROADMAP [16]	4447 T2DM	Olmesartan versus placebo	3.2 years	Olmesartan resulted in a reduction in time to micro-albuminuria onset by 23% (HR 0.77; 95% CI 0.63–0.94; P = 0.01). Blood pressure was similarly controlled in both study arms.
CALM [17]	199 T2DM	Candesartan/lisinopril combo versus candesartan versus lisinopril	12 weeks	Combination therapy more effective with greater reduction in urinary albumin: creatinine ratio (50%) compared with candesartan (24%) or lisinopril (39%) alone.
ONTARGET [18]	25 620 T1&2DM	Telmisartan/ramipril combo versus telmisartan versus ramipril	55 months	Combination therapy was associated with increased composite outcome of dialysis, serum creatinine doubling and death (HR 1.09; 95% CI 1.01–1.18; P ≤ 0.037).
VA NEPHRON-D [19]	1448 T2DM	Losartan/lisinopril combo versus losartan	Terminated at 2.2 years	Combination therapy offered no renal benefit but resulted in excessive risk of hyperkalemia (6.3 versus 2.6 events per 100 person years; P < 0.001) and acute kidney injury (12.2 versus 6.7 events per 100 person years; P < 0.001).
AVOID [20]	599 T2DM	Losartan versus aliskiren/ losartan combo	6 months	Aliskiren (direct renin inhibitor)/losartan combo led to reduction of urinary albumin: creatinine ratio by 20% (95% CI 9–30; P < 0.001) independent of blood pressure control.
ALTITUDE [21]	8561 T2DM	RAS blockade plus aliskiren versus placebo	Terminated at 2.7 years	Addition of aliskiren to maximal ARB offered no additional benefit. Hyperkalemia and hypotension were significantly increased in the aliskiren arm.
BEAM [22]	227 T2DM	Bardoxolone methyl versus placebo	52 weeks	Bardoxolone methyl at 25, 75 and 150 mg resulted in a higher GFR (5.8 ± 1.8, 10.5 ± 1.8 and 9.3 ± 1.9 mL/min/1.73 m^2) compared with placebo at 52 weeks.
BEACON [23]	2185 T2DM	Bardoxolone methyl versus placebo	Terminated at 9 months	Bardoxolone methyl led to a significant increase in cardiovascular morbidity (HR 1.83; 95% CI 1.32–2.55; P < 0.001).
DLN.A.S. [24]	223 T1&2DM	Sulodexide versus placebo	8 months	4 months of sulodexide (200 mg/day) significantly reduced albuminuria. Effect persisted after 8 months with 62% reduction compared with placebo (P = 0.0001).
Sun-MACRO [25]	1248 T2DM	Maximum ARB plus sulodexide versus placebo	Terminated	No significant benefit observed in end points of serum creatinine doubling and ESRD.
VITAL [26]	281 T2DM	RAS inhibition plus paricalcitol versus placebo	24 weeks	Paricalcitol at 2 μg/day reduced albuminuria (20% compared with placebo). However, 2 μg/day was poorly tolerated and patients often reduced the dosage.
CANTATA-SU [27]	1450 T2DM	Canagliflozin versus glimepiride	52 weeks	Canagliflozin caused initial decrease in GFR but subsequently stabilized while individuals in the glimepiride arm had progressive GFR decline (−1.7 versus −5.1 mL/min/1.73 m^2 after 52 weeks).
ASCEND [28]	1392 T2DM	Avosentan versus placebo	Terminated at 4 months	Avosentan reduced proteinuria compared with placebo, but, had excess adverse cardiovascular events; especially fluid overload (4.6%; P = 0.225), congestive heart failure (3.6%; P = 0.194) and death (2.6%).

ARB, angiotensin receptor blocker; RAS, renin–angiotensin system; T1DM, type 1 diabetes mellitus.

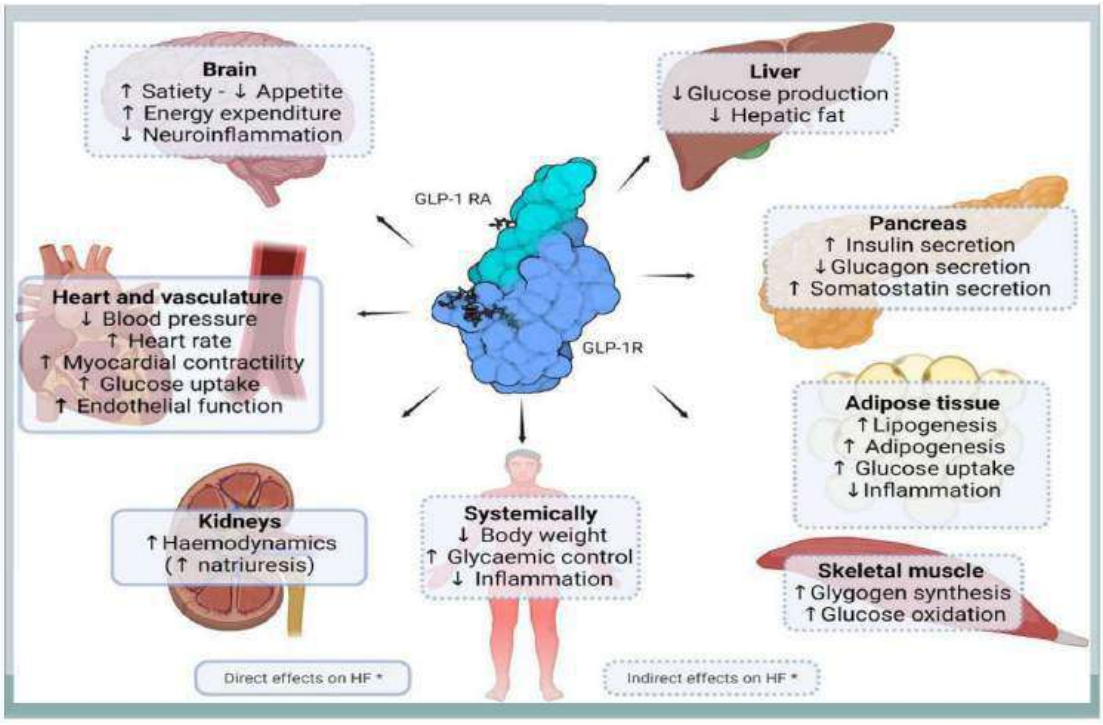
SGLT2 Inhibhitors

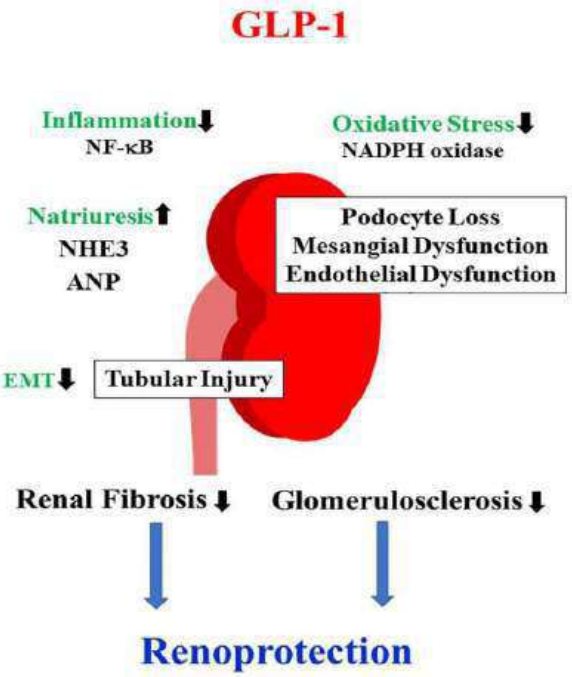






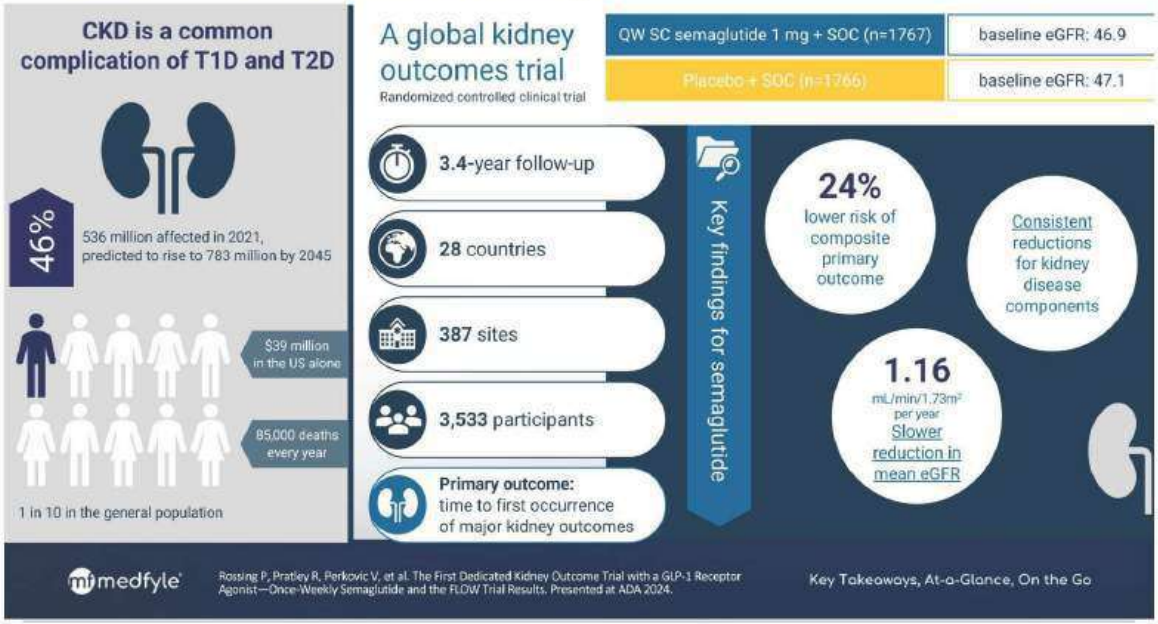
Effects of GLP1A



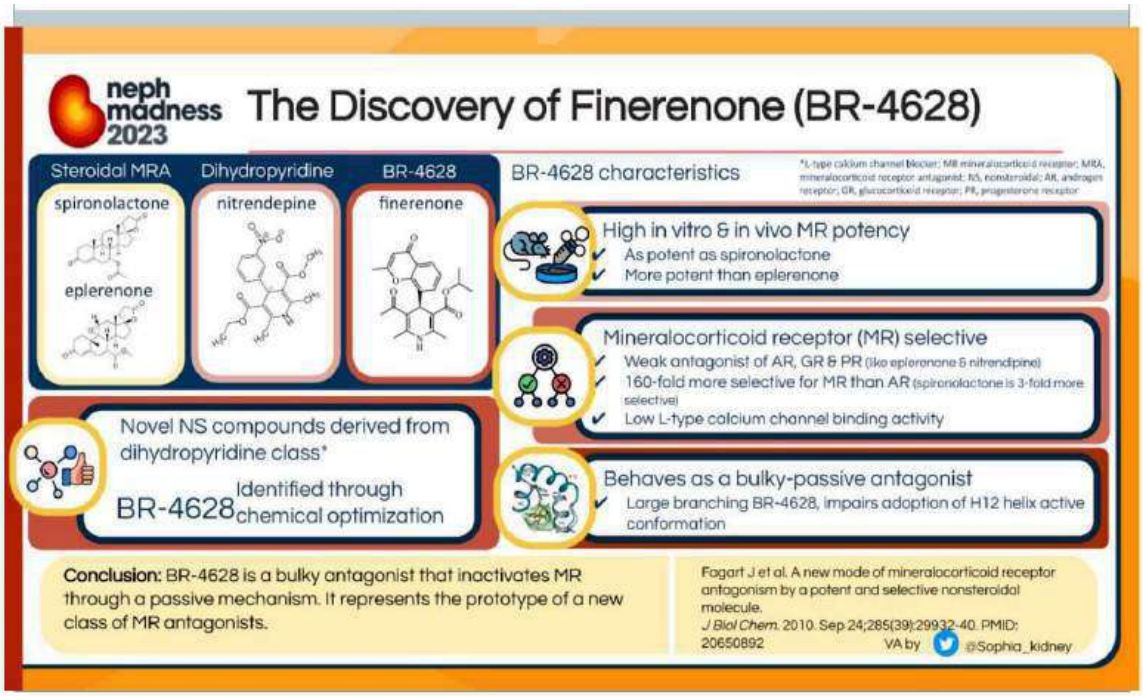


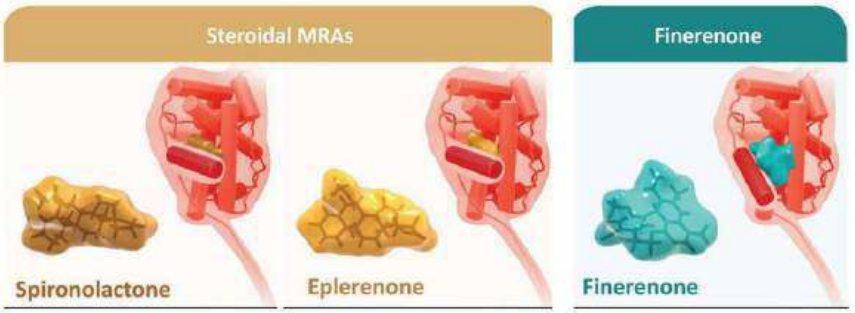
- GLP-1RAs have been shown to activate PKA and increase the production of cyclic adenosine monophosphate (cAMP).
- NADPH oxidase and NF-κB activity are inhibited, resulting in the attenuation of oxidative stress and inflammation.
- Prevent podocyte loss as well as mesangial and endothelial dysfunction.
- GLP-1RAs inactivate NHE3 and promote atrial natriuretic peptide (ANP) secretion, thereby inducing natriuresis.
- GLP-1RAs inhibit tubular injury and subsequent tubulointerstitial fibrosis.

FLOW: the first dedicated kidney outcomes trial with a GLP-1RA



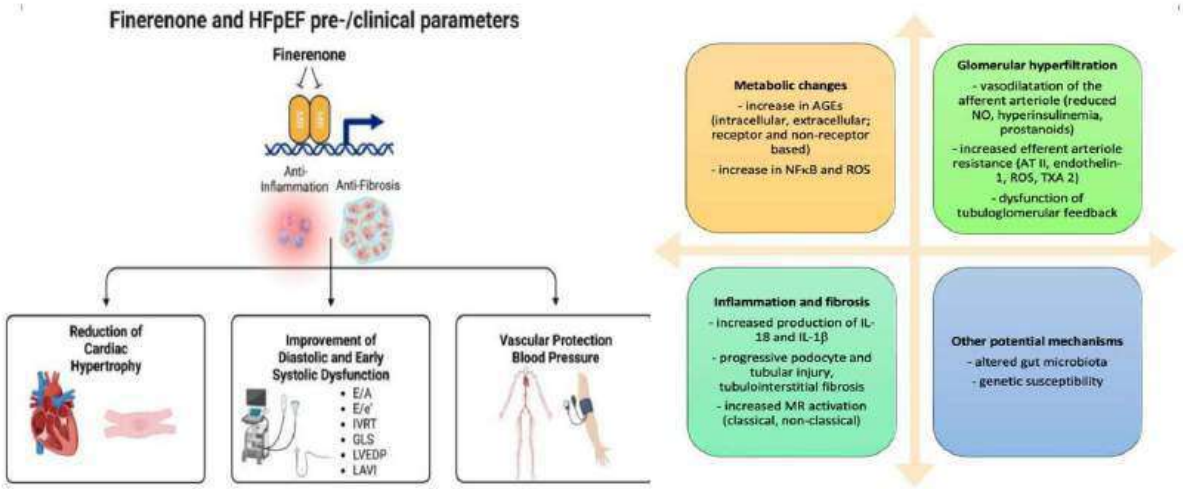
Non-steroidal Mineralocorticoid Receptor Antagonists (nsMRA)

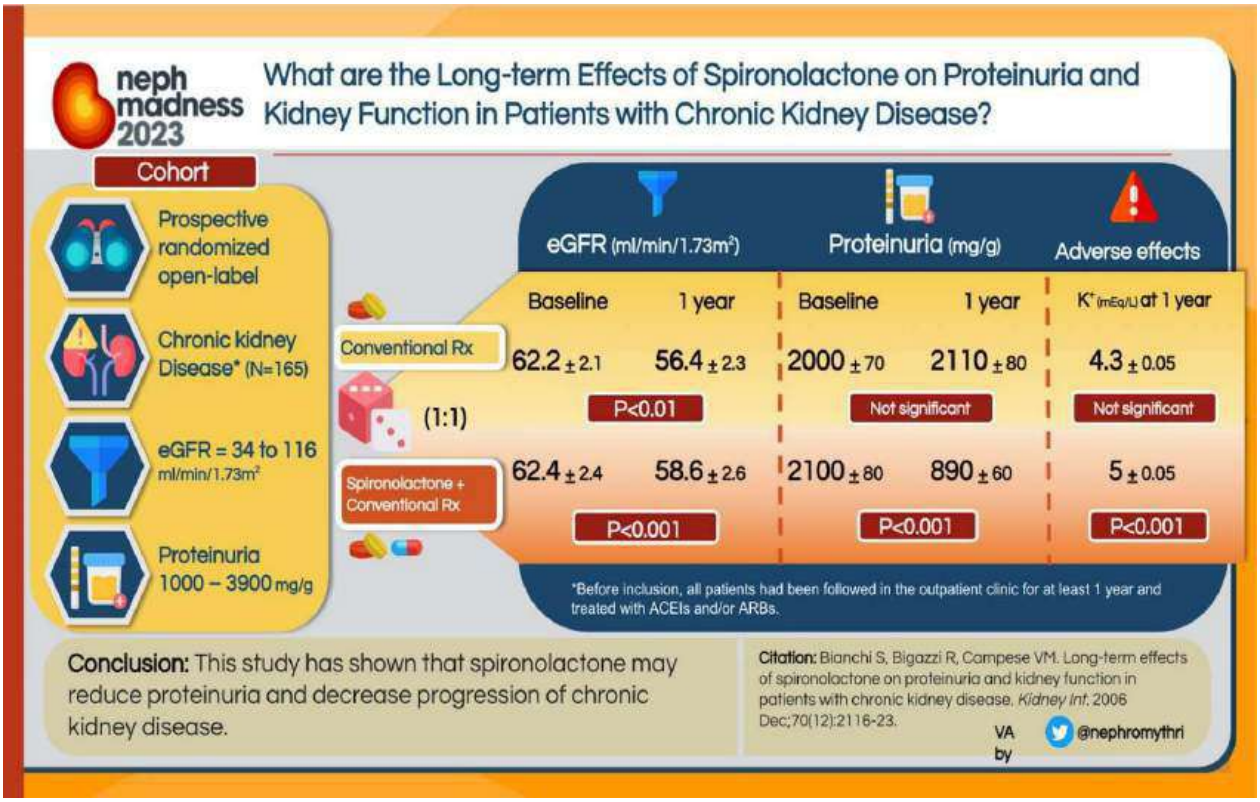


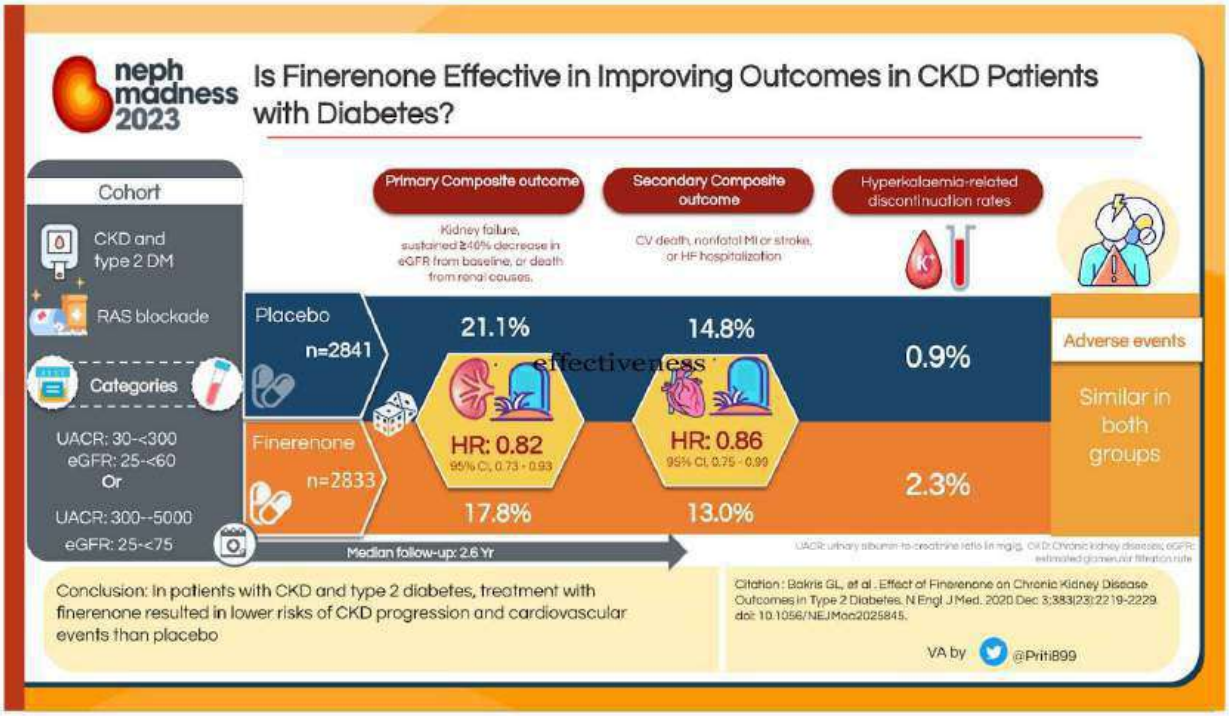


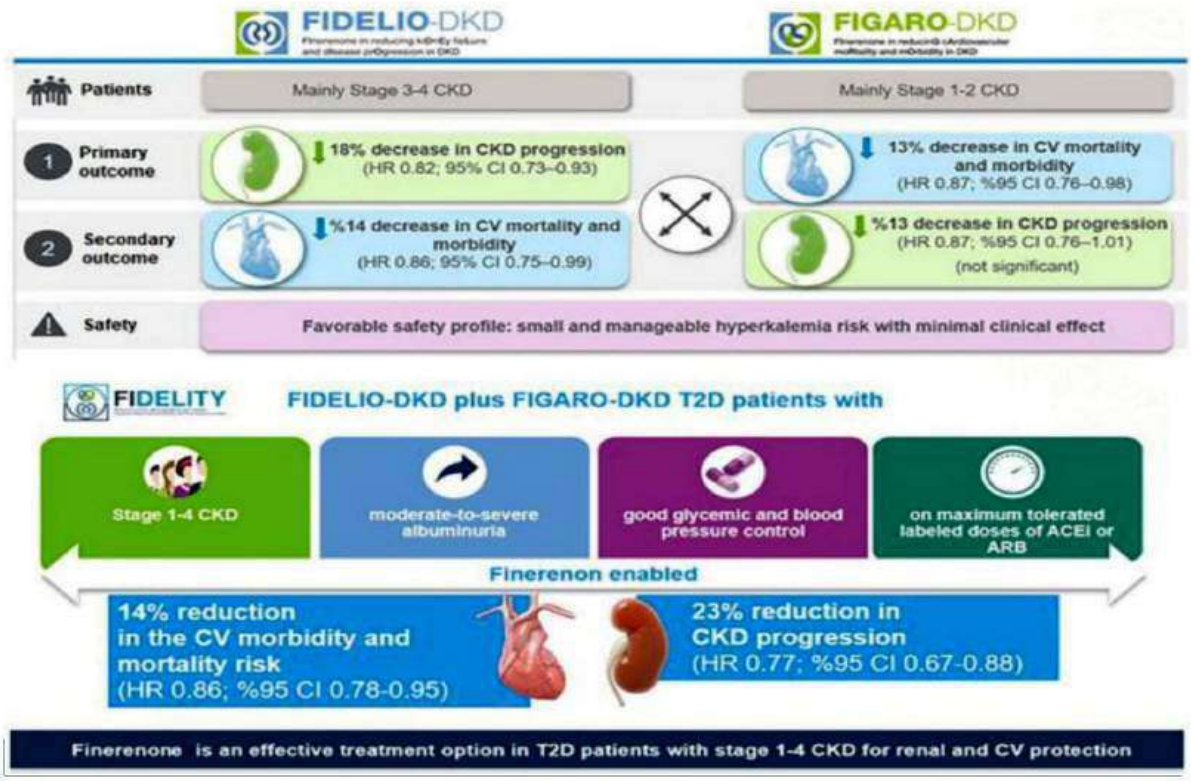
	Spironolactone	Eplerenone	Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (non-steroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	–
Sexual side effects	++	(+)	–
Half-life	>20 h**	4–6 h**	2–3 h*
Active metabolites	++	–	–
Effect on BP	+++	++	+

Mechanism of Finerenone

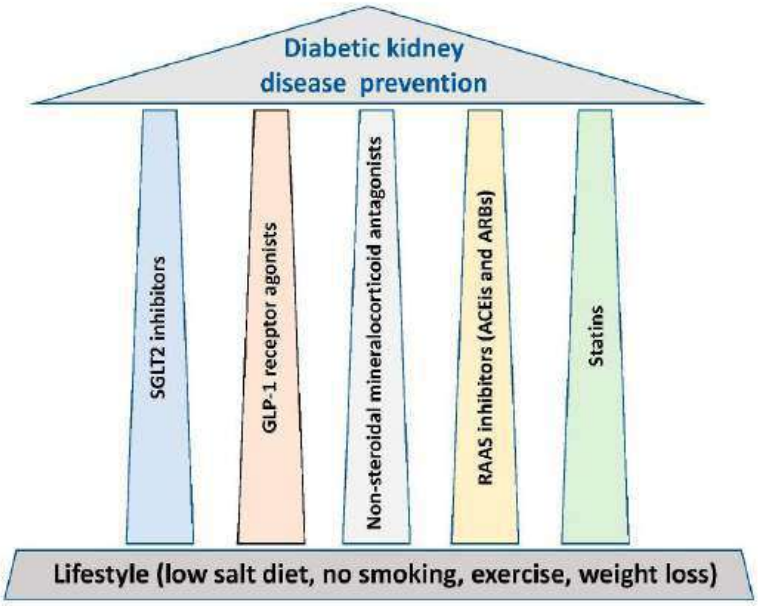





neph madness 2023
Is Finerenone Effective in Improving Outcomes in CKD Patients with Diabetes?
Cohort
CKD and type 2 DM
RAS blockade
Categories
UACR: 30-<300
eGFR: 25-<60
Or
UACR: 300--5000
eGFR: 25-<75
Primary Composite outcome
Kidney failure, sustained ≥40% decrease in eGFR from baseline, or death from renal causes.
Secondary Composite outcome
CV death, nonfatal MI or stroke, or HF hospitalization
Hyperkalaemia-related discontinuation rates
Placebo
n=2841
21.1%
14.8%
0.9%
effectiveness
HR: 0.82
95% CI, 0.73 - 0.93
HR: 0.86
95% CI, 0.75 - 0.99
Finerenone
n=2833
17.8%
13.0%
2.3%
Adverse events
Similar in both groups
Median follow-up: 2.6 Yr
UACR: urinary albumin-to-creatinine ratio in mg/g, CKD: Chronic kidney disease, eGFR: estimated glomerular filtration rate
Conclusion: In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo
Citation : Bakris GL, et al . Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes. N Engl J Med. 2020 Dec 3;383(23):2219-2229. doi: 10.1056/NEJMoa2025845.
VA by @Priti899


FIDELIO-DKD
FIGARO-DKD
Patients
Mainly Stage 3-4 CKD
Mainly Stage 1-2 CKD
1 Primary outcome
18% decrease in CKD progression (HR 0.82; 95% CI 0.73–0.93)
13% decrease in CV mortality and morbidity (HR 0.87; %95 CI 0.76–0.98)
2 Secondary outcome
%14 decrease in CV mortality and morbidity (HR 0.86; 95% CI 0.75–0.99)
%13 decrease in CKD progression (HR 0.87; %95 CI 0.76–1.01) (not significant)
Safety
Favorable safety profile: small and manageable hyperkalemia risk with minimal clinical effect
FIDELITY
FIDELIO-DKD plus FIGARO-DKD T2D patients with
Stage 1-4 CKD
moderate-to-severe albuminuria
good glycemic and blood pressure control
on maximum tolerated labeled doses of ACEi or ARB
Finerenon enabled
14% reduction in the CV morbidity and mortality risk (HR 0.86; %95 CI 0.78-0.95)
23% reduction in CKD progression (HR 0.77; %95 CI 0.67-0.88)
Finerenone is an effective treatment option in T2D patients with stage 1-4 CKD for renal and CV protection

PREVENTION OF PROGRESSION OF DN



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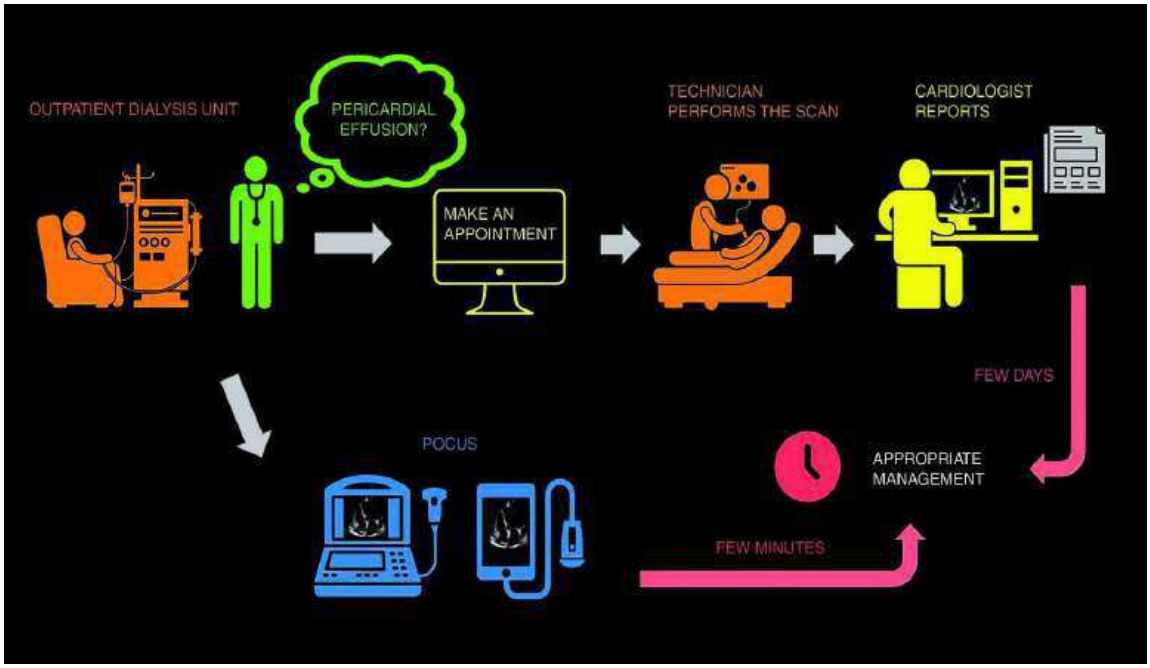
POCUS [POINT-OF-CARE ULTRASONOGRAPHY] IN NEPHROLOGY

Introduction

- Point-Of-Care Ultrasonography (POCUS) consists of limited Ultrasound examinations performed by the clinician at the patient's bedside to answer focused questions to confirm a suspected diagnosis, narrow the differential, or guide a procedure.

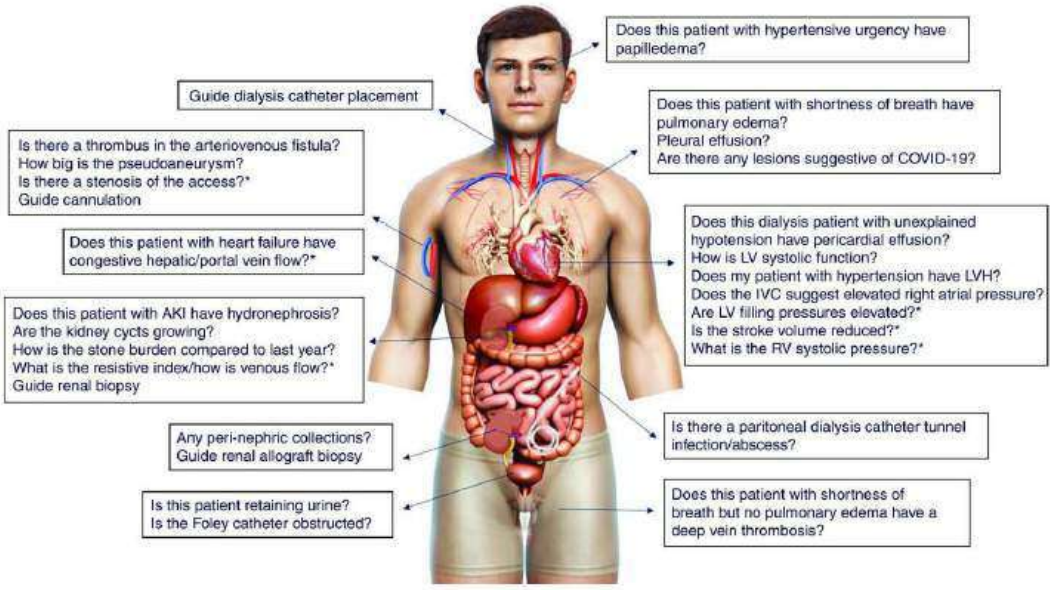
- Adjunct to physical examination, to arrive at the diagnosis early and help management.

- Physical examination is important and irreplacable.

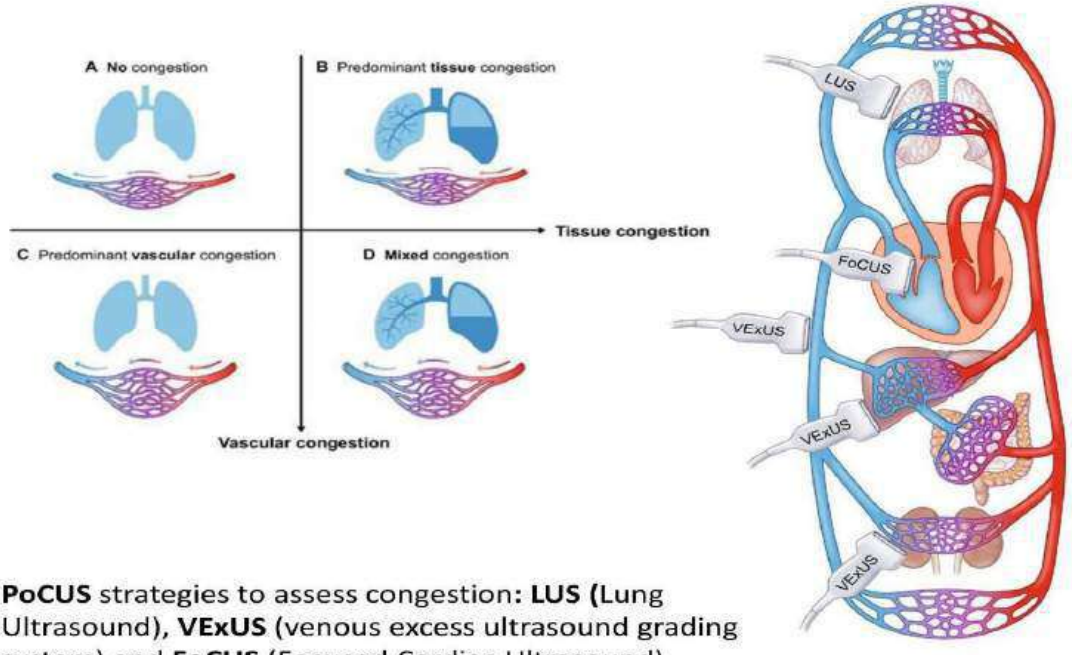


Expedited patient care with point-of-care ultrasonography (POCUS).

This infographic illustrates how POCUS can provide answers to focused clinical questions (pericardial effusion in this case) within minutes as opposed to consultative imaging.

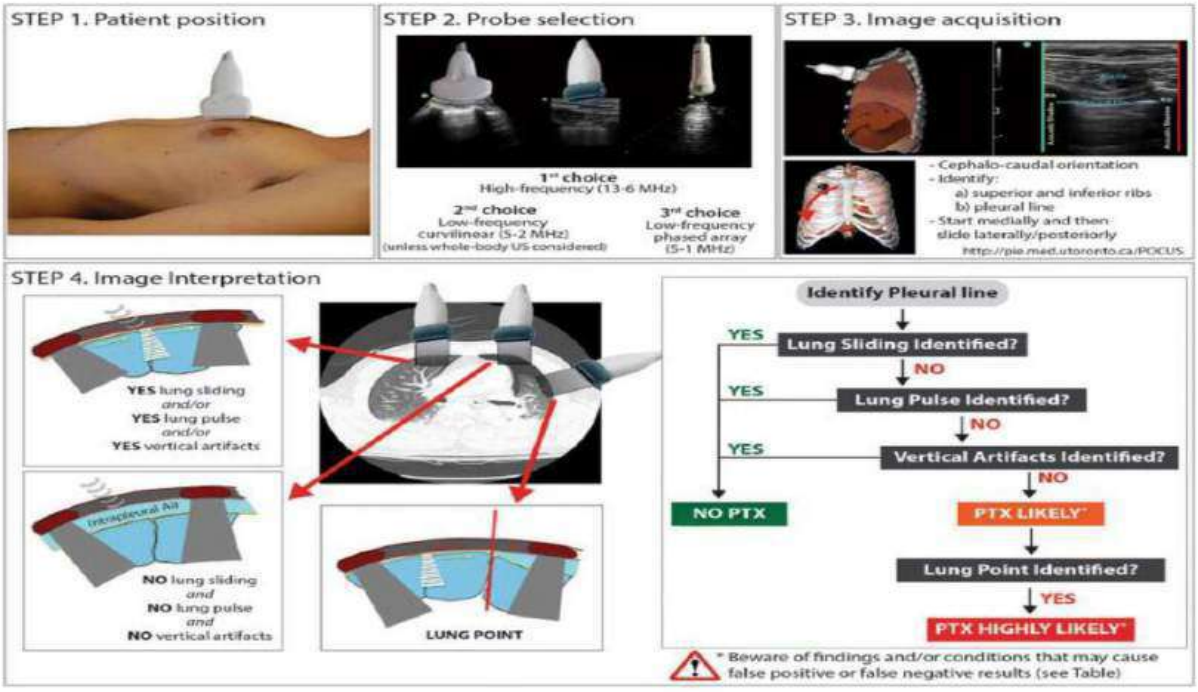


Organ-specific focused questions that can be answered by bedside ultrasonography

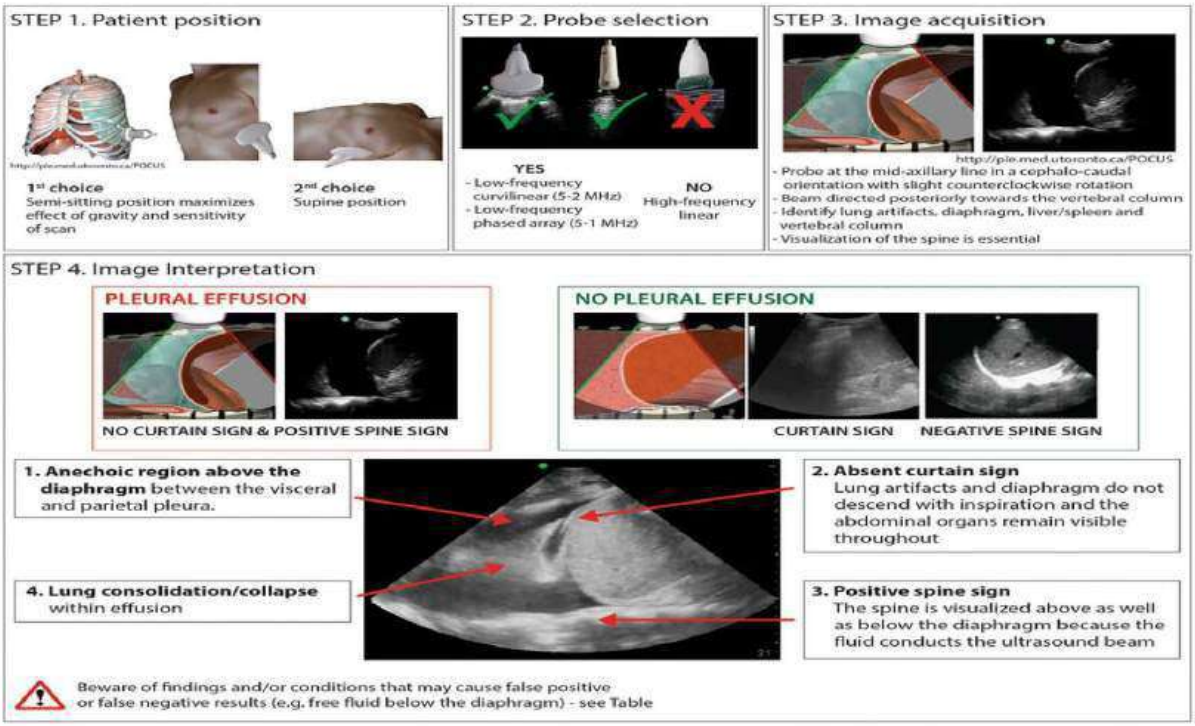


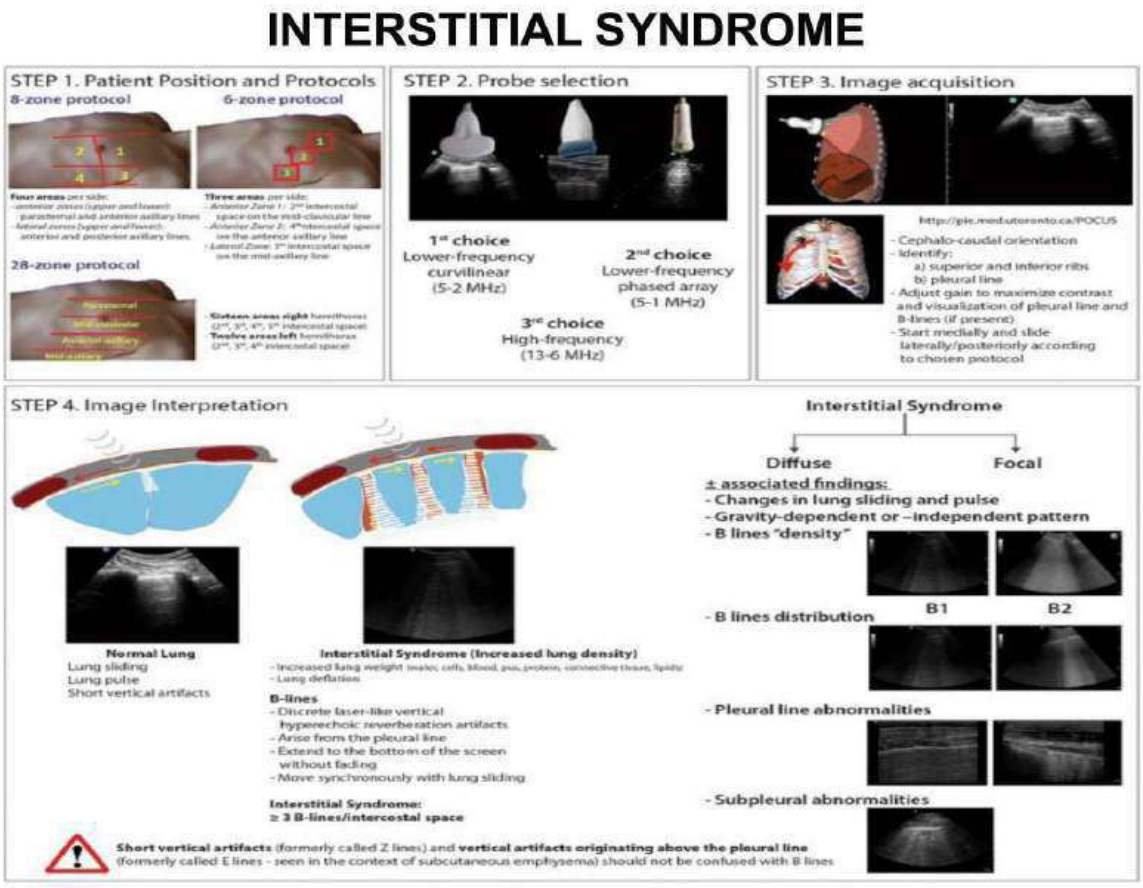
PoCUS strategies to assess congestion: **LUS** (Lung Ultrasound), **VExUS** (venous excess ultrasound grading system) and **FoCUS** (Focused Cardiac Ultrasound).

PNEUMOTHORAX



PLEURAL EFFUSION





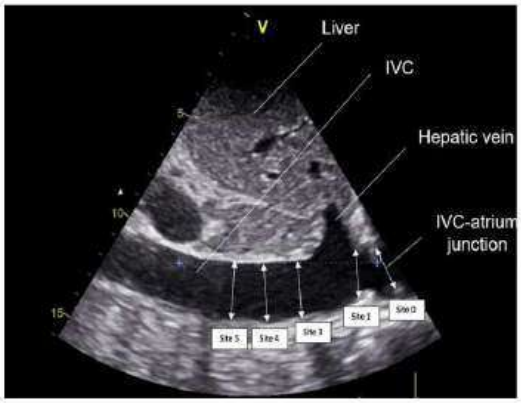
IVC Diameter

IVC assessment in the POCUS setting can assist with the following:-

- Evaluating volume status in hypovolemic shock patients.
- Guiding fluid resuscitation.
- Assessing fluid responsiveness.
- Monitoring patients with heart failure.

LIMITATIONS:-

- Body habitus and increased intra-abdominal pressure.
- Respiratory effort and mechanical ventilation.
- The right heart function can impact IVC appearance independent of volume status.



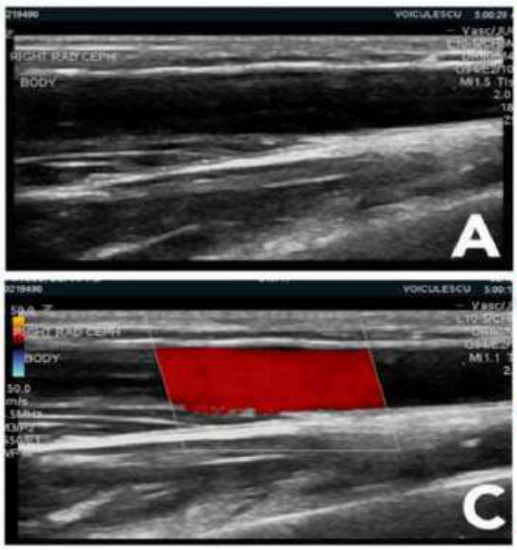
IVC Diameter	IVC Variability	Estimated RA Pressure (mm Hg)
<1.5 cm	>50%	0-5
>1.5 cm	>50%	6-10
>1.5 cm	<50%	11-15
>2 cm	None	>15

Abbreviations: IVC, inferior vena cava; POCUS, point-of-care ultrasound; RA, right atrial.

Bi-dimensional ultrasound recording of the inferior vena cava (IVC) generated using the sub-costal, long-axis view. Measurement of IVC diameters were carried out at five sites: at the IVC–right atrium junction (site 0), then at 1 (site 1), 3 (site 3), 4 (site 4) and 5cm (site 5) caudal to the IVC–atrial junction

IVC DIAMETER TO ASSESS VOLUME STATUS

AVF ASSESSMENT USING POCUS

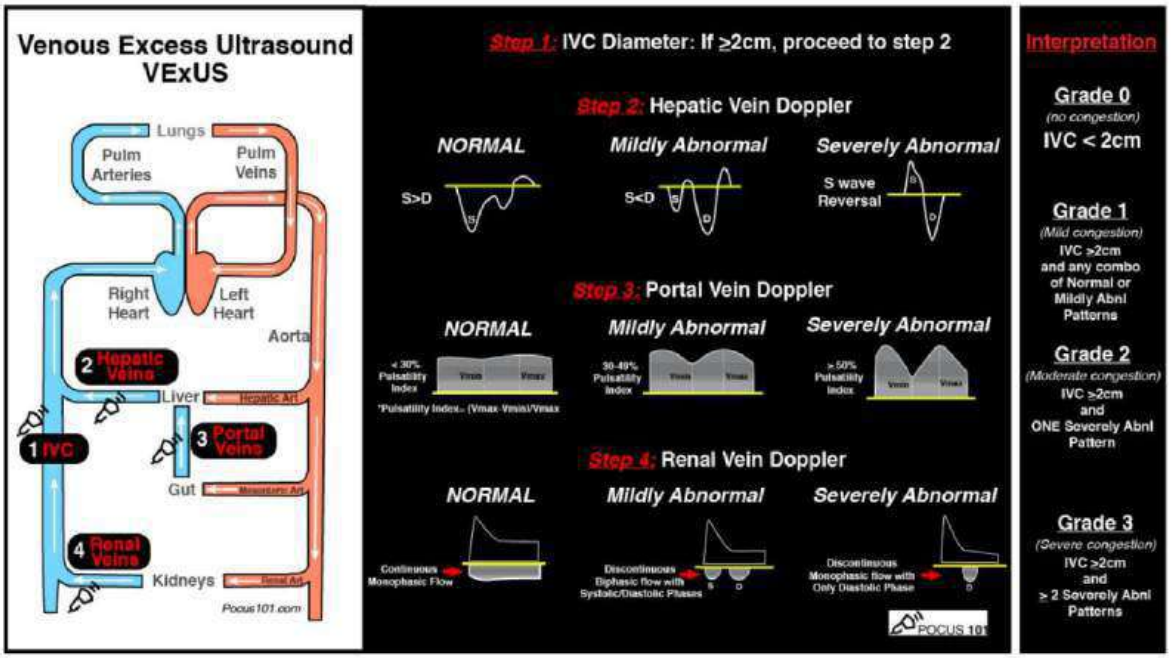


B-mode is used to identify the access and other surrounding structures such as blood vessels or fluid collections.
Color Doppler is used to assist and confirm findings on the B-mode and to monitor the patency of the access.
Doppler mode is used to measure blood flow.

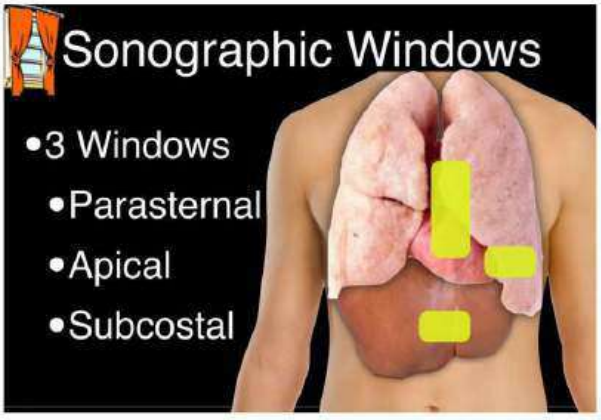
Ultrasound modes used for vascular access examination.

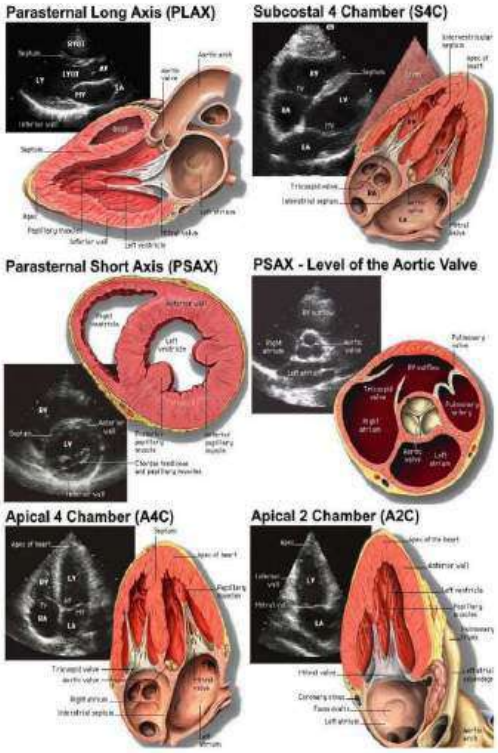
A) B-mode (brightness);
B) B) D-mode (Doppler);
C) C) C-mode (color)

VExUS Ultrasound Score – Fluid Overload and Venous Congestion Assessment



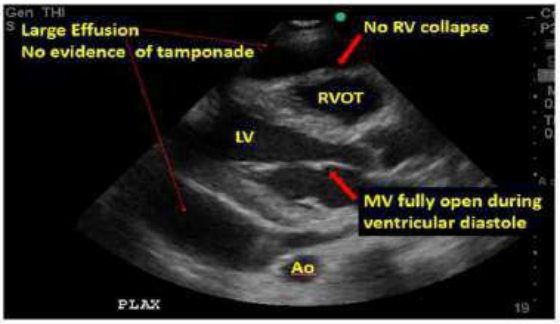
Pocus- Cardiac

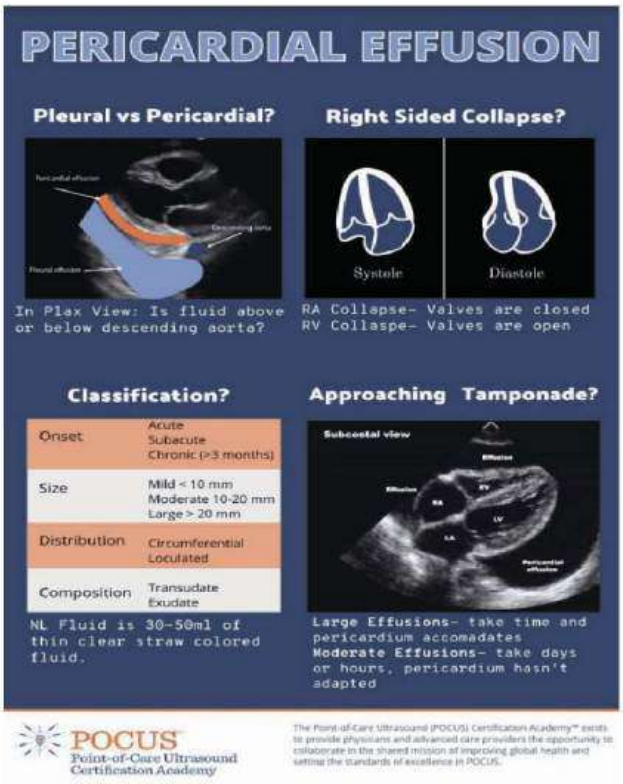




FoCUS
(Focused Cardiac Ultrasound)

PERICARDIAL EFFUSION





TAKE HOME MESSAGES

1. Improved Diagnostics and Faster Time to Treatment:

- POCUS allows clinicians to rapidly assess patients at the bedside, leading to quicker diagnoses and faster initiation of appropriate treatment.

- POCUS can identify abnormalities that augment consultation with local experts.

2. Enhanced Cost-Effectiveness:

- POCUS can reduce the need for more expensive imaging modalities and supplemental exams, leading to cost savings.

- It can also lead to shorter hospital stays and reduced healthcare expenditures.

- POCUS is a cost-effective approach that directly and indirectly saves healthcare expenses.

3. Safe and Versatile:

- POCUS uses non-ionizing radiation, making it a safe imaging modality that can be repeated without posing risks to patients.

- It can be used for monitoring disease progression or recovering injuries, as well as guiding procedures.

- POCUS is not confined to a single organ, allowing clinicians to rapidly assess multiple organ systems.

4. Improved Patient Satisfaction and Therapeutic Relationships:

- POCUS can improve patient satisfaction with their hospital providers and care overall.

- POCUS can provide reassurance to patients by interpreting images and explaining findings.

5. Enhanced Clinical Skills and Training:

- POCUS training can significantly improve diagnostic accuracy and confidence among healthcare professionals.

- It offers a unique opportunity to develop and research.

- POCUS can be used in various healthcare settings, including emergency departments, ICUs, and primary care.

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EMPHYSEMATOUS PYELONEPHRITIS

Introduction

- Emphysematous pyelonephritis (EPN) is a severe Necrotizing infection that affects the upper Urinary tract, involving the Renal Parenchyma and the Perirenal tissues of the Kidney.

- Organisms -Escherichia Coliand Klebsiella Pneumonia [most common] Proteus, Enterococcus, Clostridium, Aspergillus and rarely Candida.

- 90% of cases, patients with EPN have Diabetes Mellitus, Obstructive Uropathy, and Hypertensionas the most common risk factors.

- Gas Accumulation observed in EPN is likely a consequence of microbial fermentation of glucose and lactate, producing gases such as Carbon Dioxide, Hydrogen, and Nitrogen.

Symptoms and Labs

Symptoms:

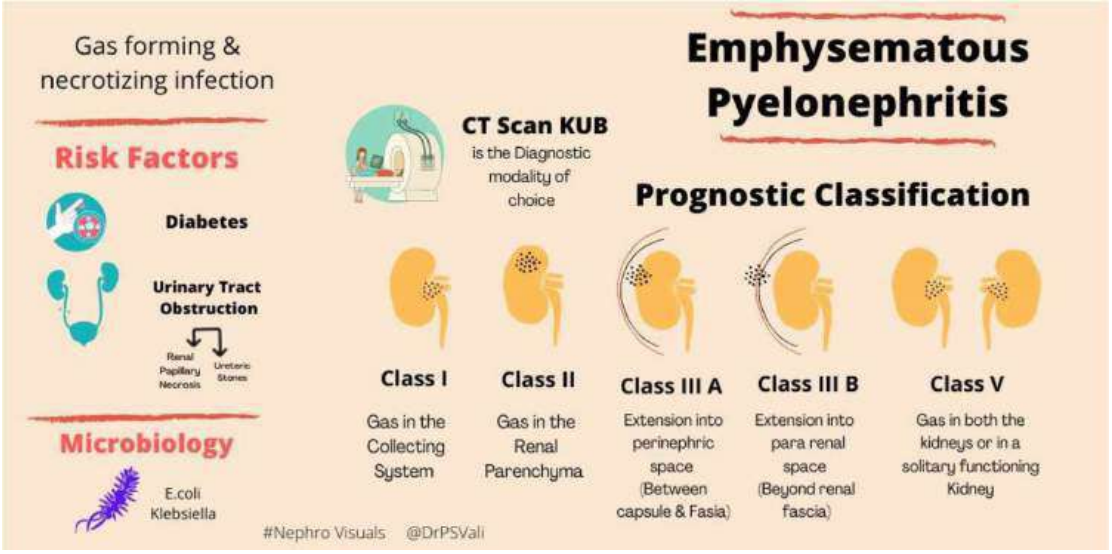
- Fevers, chills, dysuria, nausea, and vomiting are the presenting symptoms and signs of EPN.

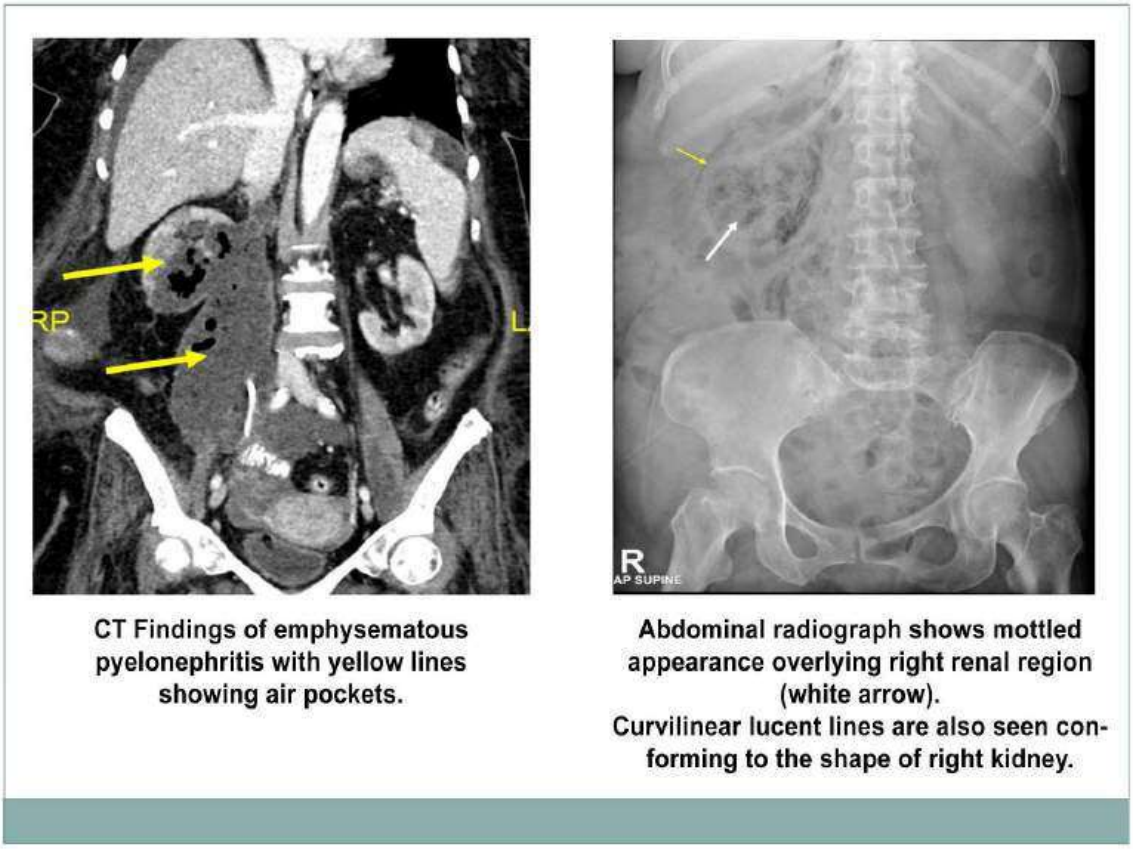
- Other physical signs include abdominal pain, Loin tenderness, and Pneumaturia or Palpable Crepitus.

Laboratory findings:

- Pyuria, Leukocytosis, Hyperglycemia, and elevated Serum Creatinine.

- Bacteremia is also relatively common. CT imaging is the most effective diagnostic tool to detect EPN.





CT Findings of emphysematous pyelonephritis with yellow lines showing air pockets.

Abdominal radiograph shows mottled appearance overlying right renal region (white arrow).
Curvilinear lucent lines are also seen conforming to the shape of right kidney.

Treatment

- Classes 1 and 2 EPN: Medical management alone or combined with Percutaneous drainage can yield favorable outcomes.

- Classes 3Aand 3B EPN:These are further divided into 2 categories:-

- 1. In patients with fewer than2 risk factors: Medical management plus Percutaneous drainage yieldsa survival rate of 85%.

- 2. Inpatients with more than2 risk factors: Medical management plus Percutaneous drainage proved unsuccessful in 92% of cases.

- Higher proportion of patients requiring nephrectomy in this group

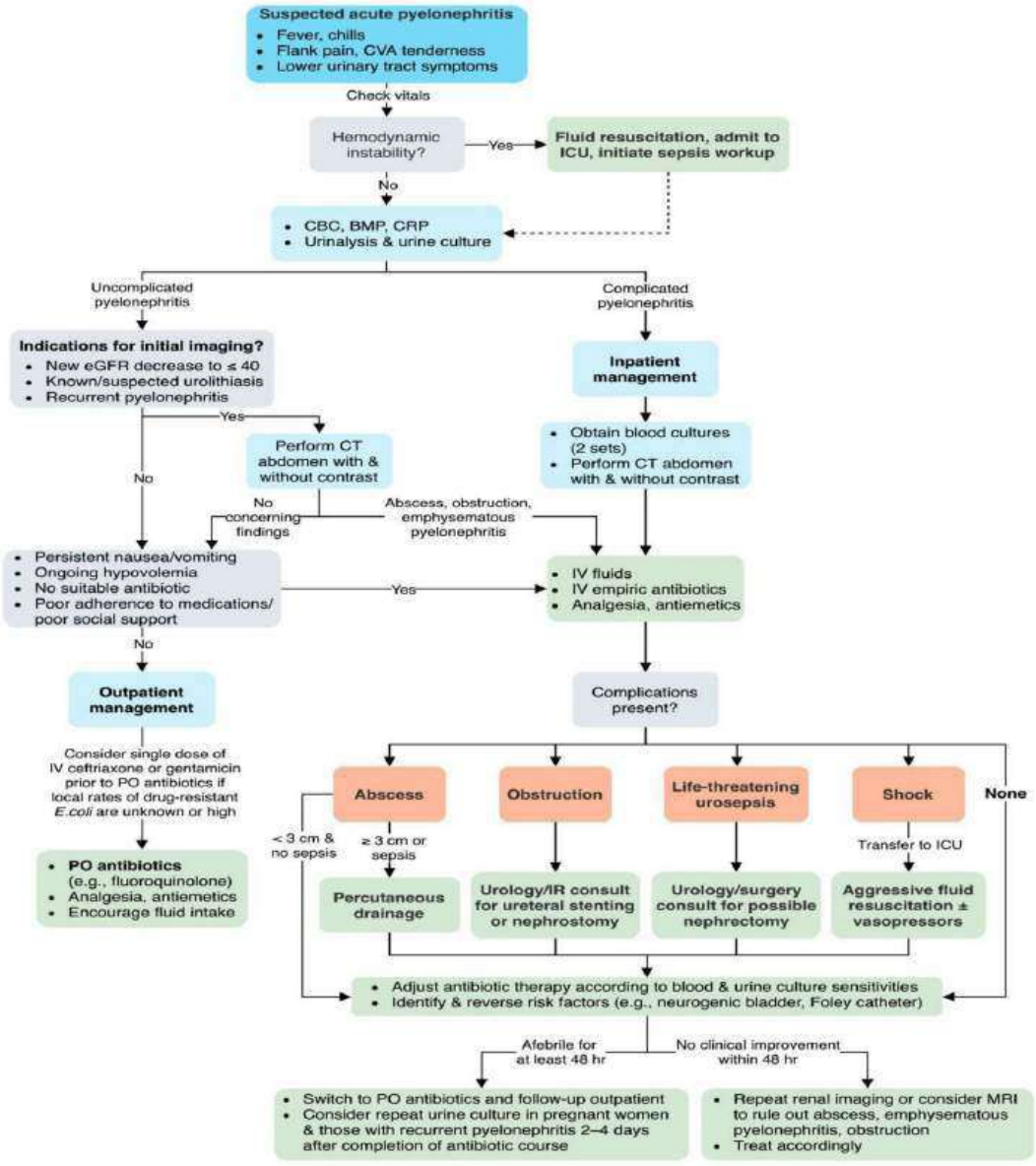
Risk factors with increased mortality:-

- 1. Diabetes mellitus, 2. Thrombocytopenia, 3. Acute Renal Failure, 4. Altered level of consciousness and 5. shock.

- Class 4 EPN:The initial step remains medical management plus percutaneous drainage.

- In any class of EPN, if Renal preservation with medical management and Percutaneous drainage proves unsuccessful, the subsequent step is Nephrectomy.

APPROACH TO PYELONEPHRITIS



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PERI-AND POST-OPERATIVE EVALUATION AND MANAGEMENT OF ATYPICAL HEMOLYTIC UREMIC SYNDROME (AHUS) IN KIDNEY TRANSPLANTATION

Introduction

- Atypical hemolytic uremic syndrome (aHUS) is a severe Thrombotic Microangiopathy characterized by over-activation of the alternative complement pathway.

- The etiology of the Dysregulated complement system is commonly a genetic variant in one or more complement proteins as identified in 60%-70%patients.

- The risk of recurrence after a kidney transplantation is high and depends on the underlying complement abnormality.

- Over the past decade, advancements in the understanding of Etiopathogenesis of aHUS and approval of the anti-complement drug, Eculizumab, have allowed for successful Kidney transplantation in these patients.

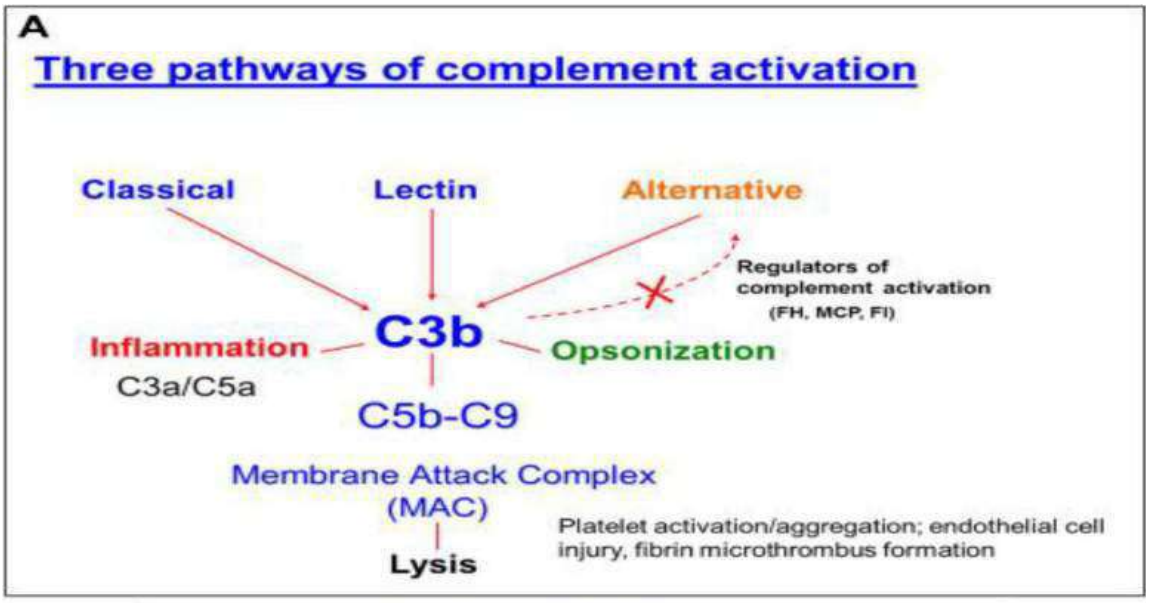
Complement Dysregulation

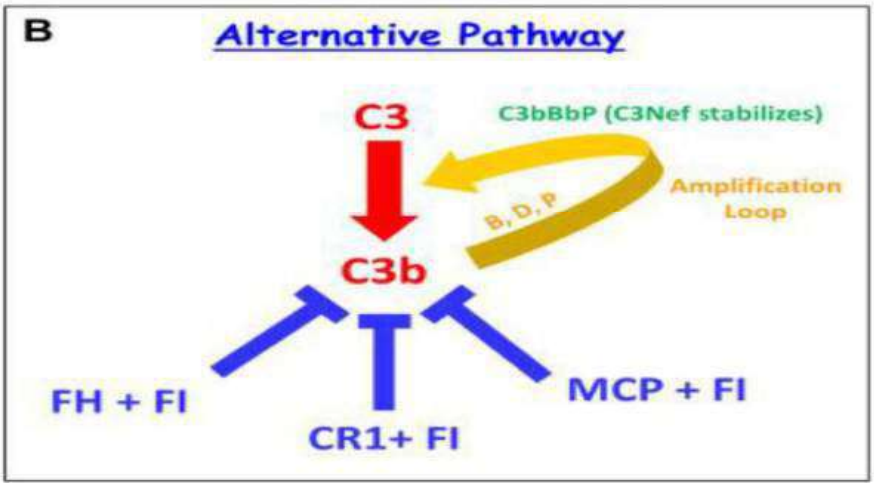
- The most common -heterozygous, loss-of-functionmutation in Factor H (FH), Factor I (FI), or Membrane cofactor protein (MCP; CD46)—all regulators of the alternative pathway (AP).

- Gain in function of Factor B and C3.

- In these cases, the protein is generally (a) not synthesized and/or not secreted or (b) secreted into the blood in normal amounts but is dysfunctional.

- Disease penetrance is 50%.





Complement Regulatory Proteins and Atypical Hemolytic Syndrome

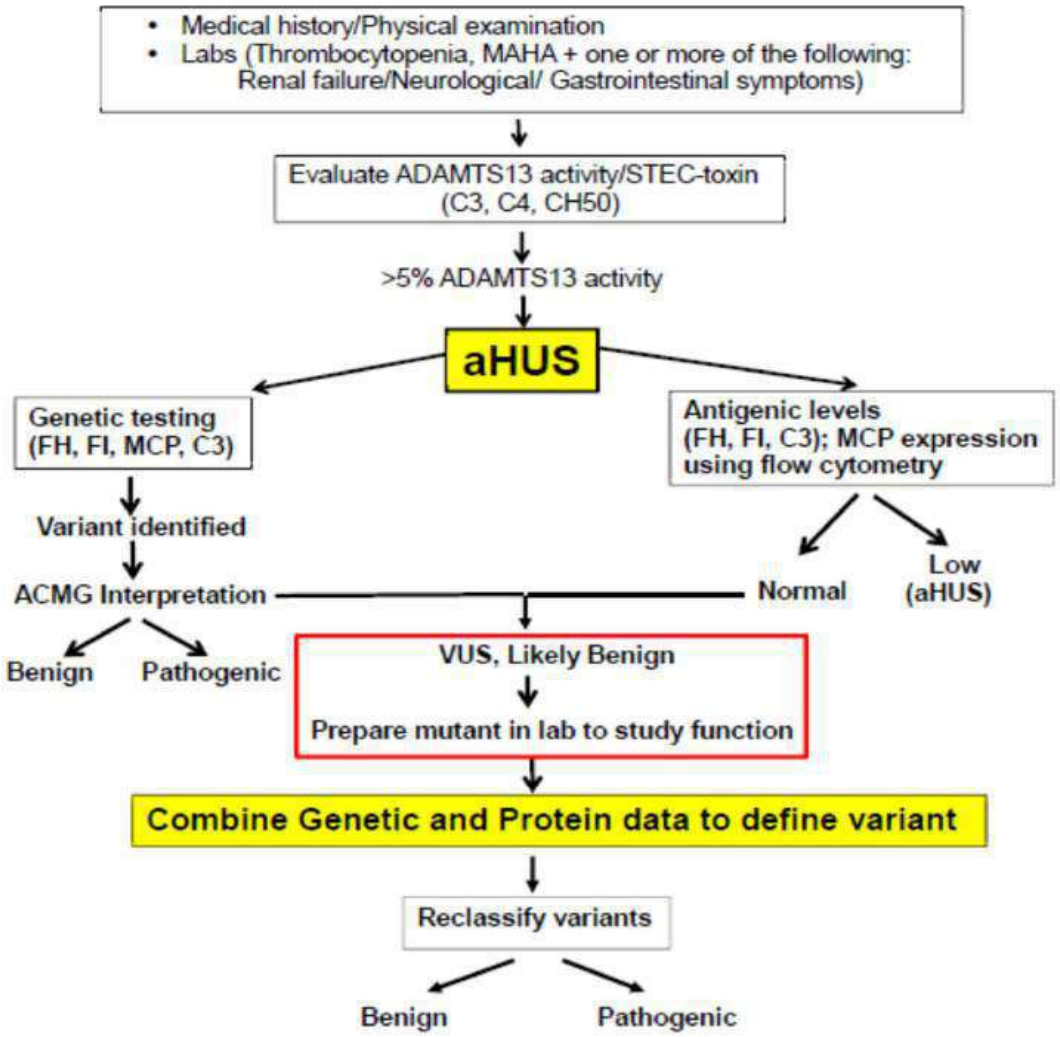
Complement Protein	Synthesis Site (Distribution)	Frequency in aHUS (%)	Risk of ESRD (%) (Pre-Eculizumab)	Risk of Recurrence After Kidney Transplantation (%) (Pre-Eculizumab)
Factor H	Liver (serum)	20-30	50-70	75-90
MCP	Cells (wide distribution)	10-20	0-6	<20
Factor I	Liver (serum)	5-15	50	45-80
C3	Liver (serum)	5-15	60	50-60
Factor B	Liver (serum)	<5	50	40-70

Recommended Testing for Pre transplantation Evaluation for aHUS

- Serum C3 C4 CH50 and ADAMTS13.
- [C4 levels high in factor H auto Ab variant.].
- Normal C3 levels do not exclude mutations in complement regulatory proteins.
- Serum FH/FI/anti factor H auto Ab levels.
- MCP expression on leukocytes by flow Cytometry [detect 75%].
- Genetic testing : –
  ADAMTS13, C3, CD46, CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR4, CFHR5, CFI, DGKE,THBD

Variants of uncertain clinical significance

- Only 50%of variants have known clinical significance.
- Genetic labs produce recombinant proteins, assess regulatory function and perform structural modeling of the variant protein.
- Reported as benign and pathogenic.
- Helps in pre transplant work up and determining need of prophylactic Eculizumab.



Live related donor

- Living-related donor Kidney transplant is relatively contraindicated for patients with aHUS. This is primarily for donor safety because Nephrectomy may trigger TMA in the genetically susceptible donor.

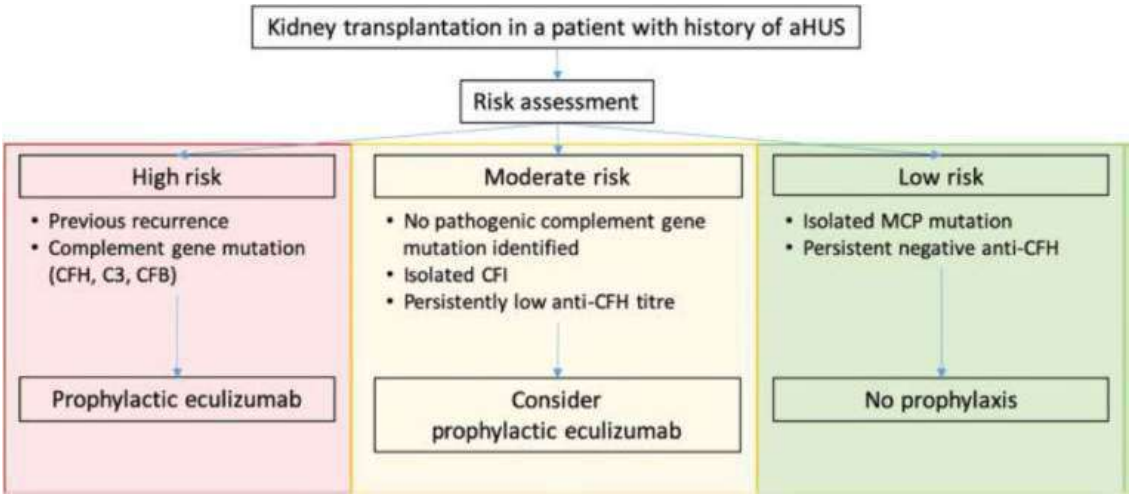
- Some patients may have more than 1 mutation.

- 1/3rd of patients with aHUS, genetic testing does not reveal a variant in the complement gene.

- Living-donor transplants could be considered with caution on a case-by-case basis.

- Donor has to test negative for the pathogenic mutation.

Risk assessment Pre-Transplant



Preparing the Child with End-Stage Renal Disease for a Renal Transplant: the Pre-transplant Assessment
Chia Wei Teoh, Moira Korus, Armando Lorenzo & Valerie Langlois
Current Paediatrics reports volume8, pages134–146 JUNE (2020)

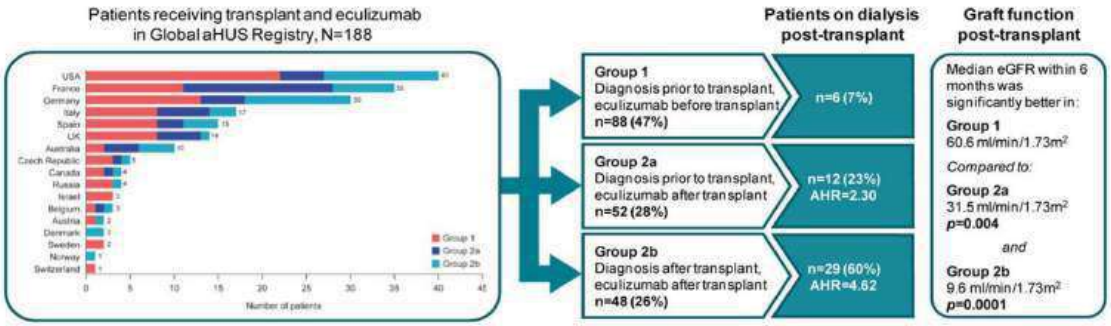
Eculizumab dosing

- In patients who are receiving a living-unrelated donor Kidney, we administer Eculizumab at 900mg intravenously 24 hours before transplantation and on days 7, 14, and 21 after transplantation, followed by 1200 mg on week 5 and then every 2 weeks thereafter.

- In patients who are receiving a deceased-donor Kidney, we administer Eculizumab at 900mg intravenously at the time of transplantation.

- Side effects:-
  HTN/ headache/ URTI/ UTI/ nausea/ vomiting/ Diarrhea/ Anemia/ Leukopenia.

Eculizumab use for kidney transplantation in patients with a diagnosis of atypical hemolytic uremic syndrome



CONCLUSION:
Delayed diagnosis of aHUS and delayed treatment with eculizumab post-transplant leads to inferior outcomes

KI REPORTS KIReports.org Siedlecki et al. *Kidney Inter Rep.* 2019

The use of highly individualized complement blockade revolutionized post-transplant outcomes and renal epidemiology of aHUS

METHODS

Study 1: transplant outcomes

Adult aHUS patients
- Complement work-up
- Kidney transplantation after 01/01/2007

↓

126 Kidney transplantations
- Risk stratification
- Tailored eculizumab prophylaxis

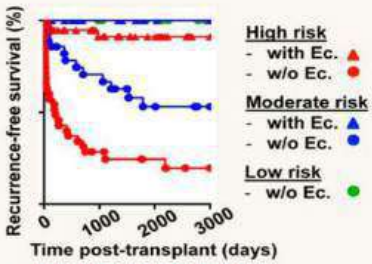
Study 2: population-based

Adult aHUS patients
- Complement work-up
- Alive between 01/01/2007 and 01/01/2016

↓

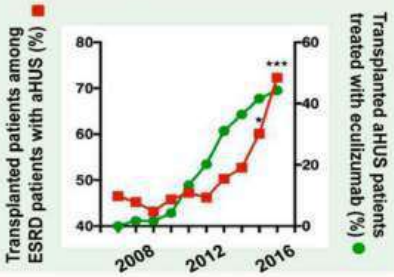
Renal status over time in 397 aHUS patients

Study 1: Post-transplant outcomes according to risk stratification and eculizumab (Ec.) prophylaxis



OUTCOME

Study 2: Changes in the aHUS epidemiology at a nationwide level



CONCLUSION:

These studies support the use of eculizumab prophylaxis in those for whom medical history and complement investigations predict a high and moderate risk of post-transplant recurrence.

doi: 10.1681/ASN.2019040331

JASN

Meningococcal Vaccine

- Life threatening Neisseria Meningitidis infection is of concern.
- Meningococcal conjugate or MenACWY vaccines and Serogroup B meningococcal or MenB vaccines to be given two weeks before transplant.
- A booster dose of MenACWY given every five years till duration of complement inhibitor.

Transplant Protocol without Eculizumab [low risk cases]

- ATG > Basiliximab induction.
- Triple immunosuppression- TAC/MMF/PRED.
- Low dose tacrolimus is preferred to keep trough level around 5-7.
- Injectable methyl Prednisolone 500mg pre transplant.
- Eculizumab only if recurrence.
- Five sessions of Plasmapheresis pre transplant and two sessions of Plasmapheresis Post Transplant.

Case series from Netherlands

- 17 pts of atypical HUS with 16 carrying genetic variants-CFH/CFI/C3/C5.

- 5 /17 patients had previous allograft loss due to Recurrent aHUS.
- Induction –BASILIXIMAB.
- NO ECULIZUMAB.
- Low dose TAC/MMF/PRED. Strict monitoring of BP.
- Patients were trained to report HTN/ Hematuria/ Proteinuria/ Deranged Renal function at home.
- At 25 months follow up- average Cr was 1.2
- One graft loss due to recurrence which could be salvaged with Eculizumab Therapy.

Post transplant Monitoring for Ahus

Immediate Posttransplant (During Hospitalization)	Daily, CH50/AH50 Before Eculizumab Administration for the 1st Four Doses
Up to 6 months	Weekly
6-12 months	Biweekly
After 12 months	Monthly

Complete Blood Count, Renal Panel, Urinalysis, Lactate Dehydrogenase, Haptoglobin.

A peripheral smear should be obtained in addition to the above if there is any concern for recurrence.

Recurrence

- Patients with recurrent aHUS usually present within 1 year and often within days to weeks.

- Triggers for recurrence after transplant:- A] ischemia-reperfusion injury.
  B] Immunosuppressive drugs (calcineurin and mTOR inhibitors),
  C] Antibody-mediated rejection.
  D] Infections (Cytomegalovirus, BK virus, upper respiratory or Gastroenteritis).

- Risk of recurrence is high in patients carrying a Pathogenic mutation in any of the complement Proteins except MCP.

- The recurrence rate is low in patients with isolated MCP mutations because the Allograft expresses normal Membrane bound MCP

- Patients at moderate risk of recurrence include those carrying a VUS in any protein and genetic variant has not been identified.

- Low risk of recurrence also include those who have been successfully treated for removal of FH Autoantibodies.

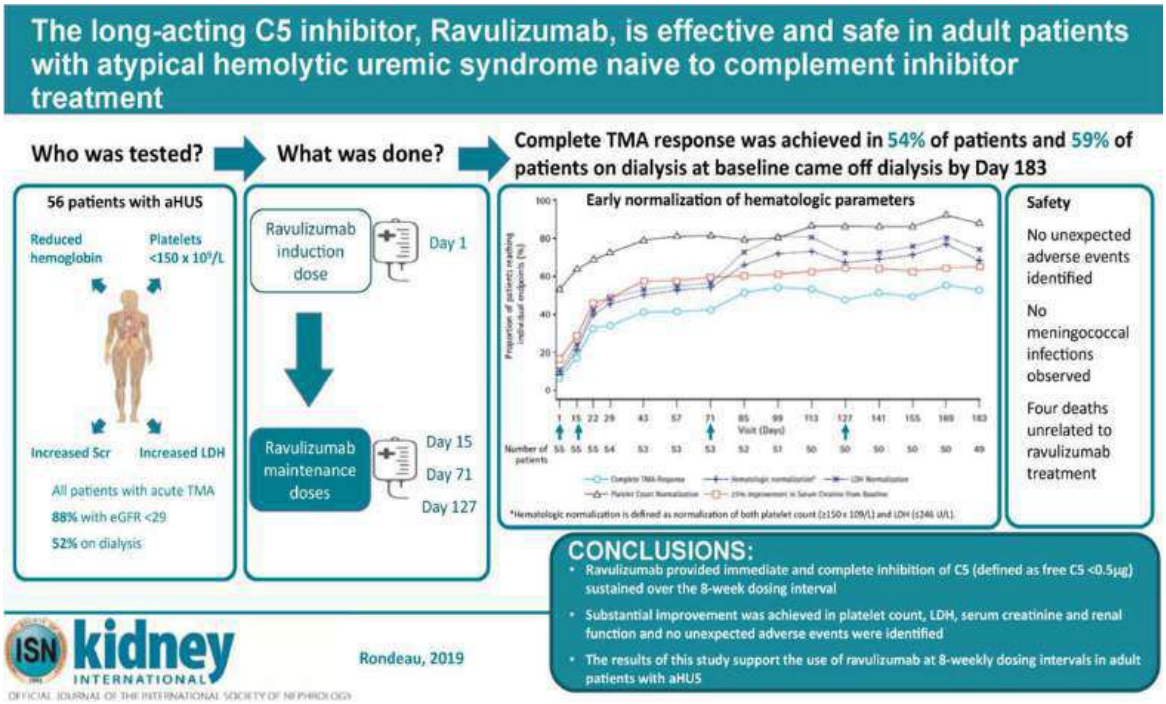
Recurrence Treatment

- Eculizumab 900 mg weekly for four weeks followed by 1200 mg at week 5 and thereafter every two weeks and Plasmapheresis.

- Few reports of replacing tacrolimus with belatocept
- In high risk cases give lifelong treatment.
- In low risk cases give for 24 months and assess and consider stopping Eculizumab.

De Nova a HUS after kidney transplant

- 1-5% cases reported.
- In one series complement variants were identified in 29% patients.
- Patients may carrying a low risk of a-HUS, risk multiplies after transplant due to multiple factors like Reperfusion injury/ ABMR/ infections.



Kidney InternationalVolume 97 Issue 6 Pages 1287-1296 (June 2020)

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ADENOVIRUS NEPHROPATHY [HAdVN]

Introduction

- HAdV in the healthy population to be associated with self-limitedrespiratory, Gastroenteritis, and conjunctivitis illness.

- In Kidney transplant recipients: ranges from Asymptomatic Viremia to Hemorrhagic Cystitis to Allograft loss and mortality

- HAdVin Kidney Transplant recipients may be secondary to reactivation of Latent disease, De Novo from environmental sources or from endogenous transmission through a donor organ.

- Clinically symptomatic patients with HAdV viremia and 2 or more organ systems involved is considered disseminated disease.

Signs and symptoms

- The most frequent signs and symptoms at presentation include Dysuria, Fever, Hematuria, Sterile (bacterial) Pyuria, Hemorrhagic Cystitis, obstructive Uropathy and acute kidney injury.

- Common extrarenal manifestations among Kidney transplant recipients with disseminated disease include Orchitis, Lymphopenia, Gastroenteritis, and Pneumonitis.

- A 10-year review of 170 kidney transplant recipients reported an incidence of 4.7% for Hemorrhagic cystitis with median time to onset of 1 year.

Investigation

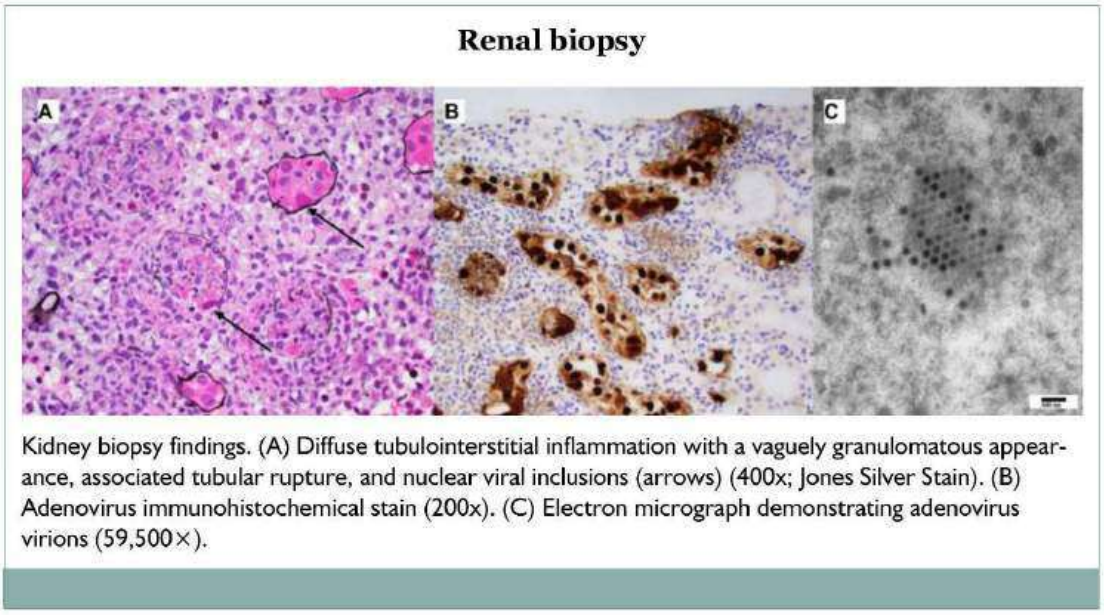
- HAdV PCR quantification.
- Allograft biopsy.

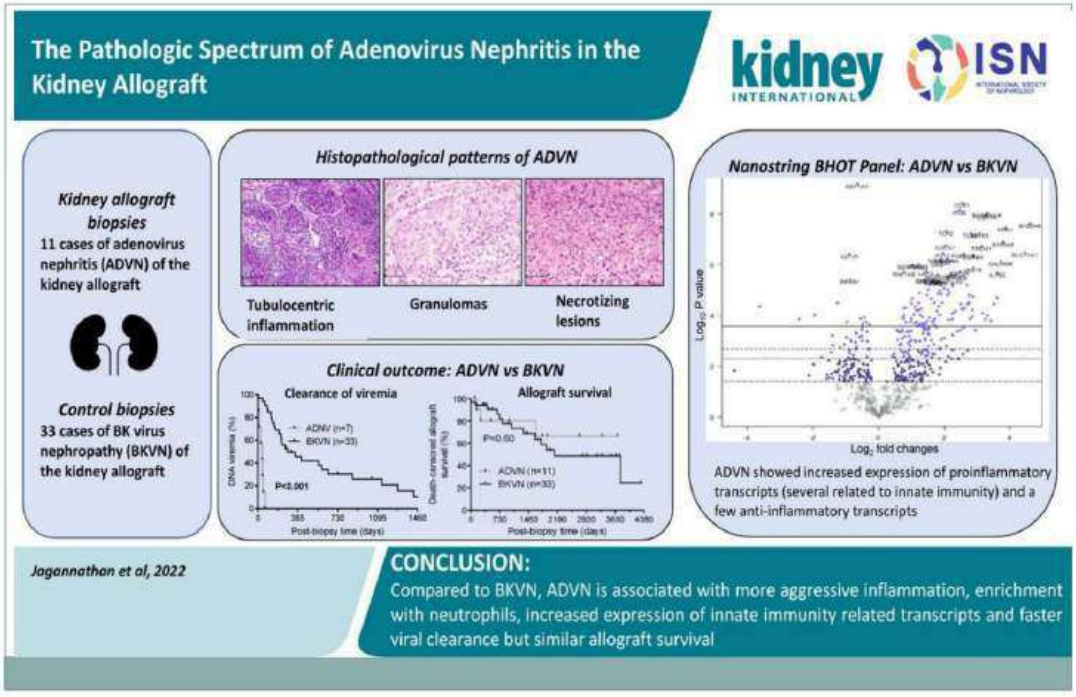
- The most common histologic manifestations included Granulomas (82%), Tubulocentric inflammation (73%), and Tubular degenerative changes consistent with Acute Tubular Necrosis (73%).

- Viral inclusions -smudgy Basophilic Intranuclear inclusions with enlarged nuclei of infected cells. Distal tubules are more commonly involved than proximal tubules

- Viral culture [In some cases]

- PCR is sensitive to all known serotypes of HAdV, and has the benefit of serial monitoring for response to treatment.





TREATMENT

- First step :- Reduction of the Immunosuppressive regimen.

- A PCR quantification of 1 log reduction within 2 to 3 weeks is considered a Therapeutic response.

Antiviral therapies in kidney transplant recipients include:

- Cidofovir [s/e-Hematological and nephrotoxicity],
- Ganciclovir
- Ribavirin
- Brincidofovir and
- i.v. Ig.

- Intravenous Ig is proposed to promote antiviral activity and to provide passive Immunotherapy.

- Intravenous Ig has been used in combination with Cidofovir.

- Brincidofovir (formally CMX101) is a new lipid derivative of Cidofovir [AdVise Study].

- The lipid formulation allows increased Intracellular penetration that minimizes Proximal Tubular Accumulation, and reduce the risk of Nephrotoxicity.

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DONOR SPECIFIC ANTIBODIES [DSA]

Introduction

- Donor-specific antibodies [DSA] - biomarker predicting antibody-mediated rejection [ABMR].

- Preformed DSA in sensitized patients can trigger hyperacute rejection, accelerated acute rejection and early acute ABMR.

- De novo DSA are associated with late acute ABMR, chronic ABMR and transplant glomerulopathy.

- “Benign” DSAs that may not be clinically relevant, because they are not associated with ABMR or graft failure.

Sensitization

- Presence of DSA in recipient's serum to HLA antigens from the donor pool.

- Panel Reactive Antibody test [PRA] test is a marker of sensitization.

- PRA <20 % low risk and >80% is high risk for ABMR.

- Pregnancy, blood transfusion and previous transplant triggers sensitization.

Pathogenesis

- Donor Antigen-presenting cells include Macrophages, Dendritic cells, and B cells.

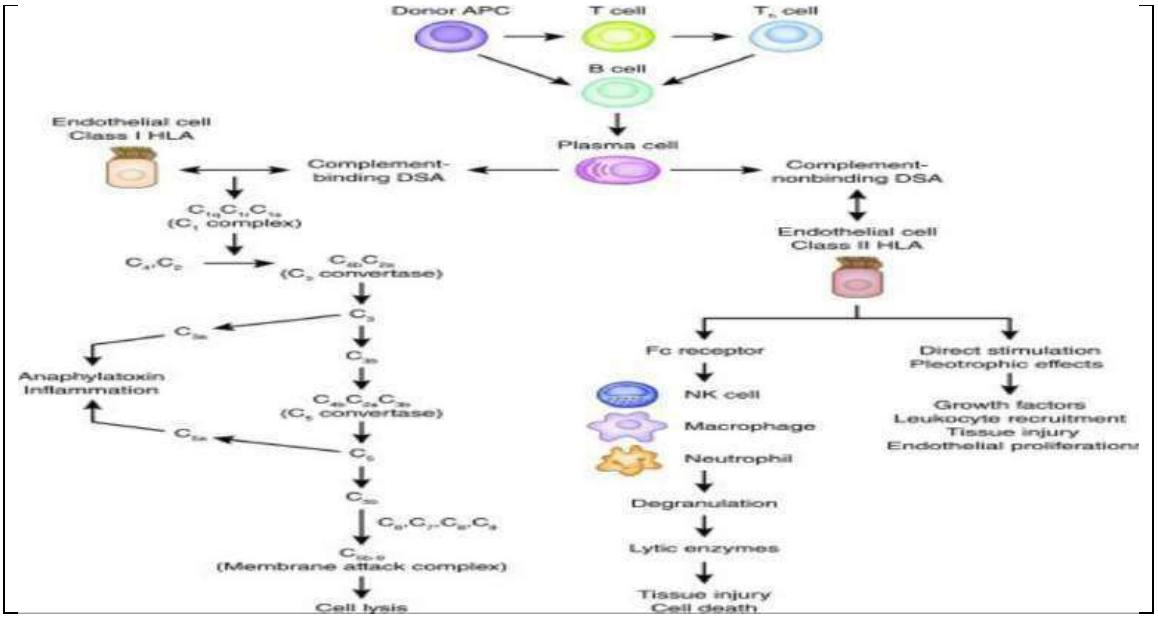
- Complement binding DSAs target the class 1 HLA on endothelial cells, activate the classic complement cascade, and deliver complement-dependent Cytotoxicity in ABMR.

- Complement nonbinding DSAs recruit innate immune cells (NK cells, Macrophages, and neutrophils) through Fc Receptors and lead to Antibody-dependent cellular Toxicity.

- In addition, complement nonbinding DSAs have direct stimulation and Pleotropic effects that cause tissue injury, Cellular Recruitment, and endothelial proliferation.

- The latter two mechanisms play an important role in ABMR with negative C4d deposit in peritubular capillaries as well as Chronic ABMR, Transplant Glomerulopathy, and Vasculopathy.

The three proposed pathogenesis of donor specific antibodies (DSAs) in antibody-mediated rejection.



Comparison of the dominant characteristics of classes 1 and 2 DSA s

	Class 1 Donor-Specific Antibodies	Class 2 Donor-Specific Antibodies
HLA		
Antigens	A, B, and C	DR, DQ, and DP
Epitopes location	α-chain	α- and β-chains
Expression	All nucleated cells	Antigen-presenting cells
Preformed donor-specific antibodies		
Important	Very	Less
Positive crossmatch	T cells	B cells
Transplant decision	No transplant	Permissible
***De novo* donor-specific antibodies**		
Detection	Sooner	Later
IgG subclasses	IgG1, IgG3	IgG2, IgG4
Complement binding	Strong	Weak/no
Frequency	Fewer	Common, especially DQ
Antibody-mediated rejection		
Phenotypes	Acute	Chronic, subclinical
Presentation	Early	Later
Graft dysfunction	Rapidly	Slowly
C4d deposit	Positive	Negative
Treatment	More responsive	Less responsive
Graft loss	Early	Later

DSA Class and Specificity

- Preformed DSAs in sensitized patients can be class 1, class 2, or both.

- Positive T cell crossmatch secondary to Cytotoxic IgG Antibody, which is usually complement binding IgG1 or IgG3 subclass – not to proceed with transplant.

- The majority of de novo DSAs are class 2 antibodies, especially DQ.

- Class 1 de novo DSAs are usually detected sooner after transplant and more likely IgG1 and IgG3 subclasses. They are associated with acute ABMR and early Graft loss.

- Class 2 de novo DSAs appear later – non complement binding IgG2 or IgG4 subclass , associated with chronic ABMR and transplant Glomerulopathy.

- Eliminate class 2 DSA, especially the DQ, may not be successful and it can put patients at great risk of excessive immunosuppression without much benefit.

- C1q binding DSAs are associated with significantly higher risk of

- Antibody-mediated rejection, severe tissue injury and Graft loss.

C4d

- C4d is a degradation product of the classic complement pathway.

- C4d binds covalently to the endothelial basement membrane, thereby avoiding removal during tissue processing.

- Positive C4d deposit in peritubular capillaries serves as an Immunologic footprint of ABMR.

- It is in a linear pattern and best shown by immunofluorescence in frozen tissue section.

- Positive DSA but negative C4d staining:- 1.Technique error (false negative)
  2. Non complement-activating DSA.

- Positive C4d deposit without DSA against HLA:- ABMR caused by non-HLA Antibodies.

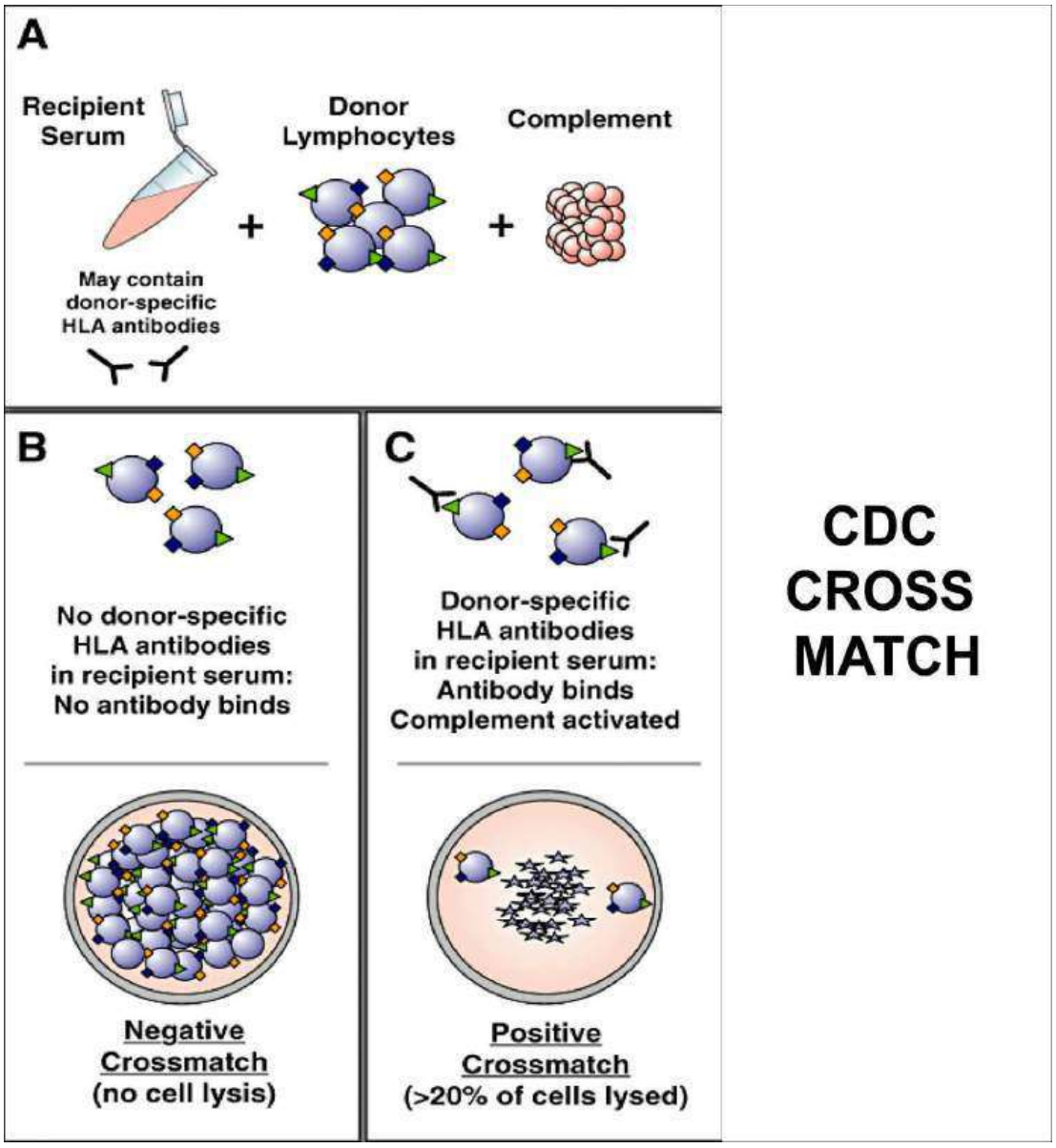
De Novo DSA

- Risk factors that develop de Novo DSA :-

1. Female sex of the recipient.
2. Young age of the recipient.
3. Viral infection (especially Cytomegalovirus and Epstein-Barr Virus)
4. Class II HLA mismatching,
5. Prior cellular rejection.
6. Sensitizing events (blood transfusion, Retransplantation, Pregnancy, etc.) and
7. Non-adherence to Immunosuppressant medication.

8. Nephrectomy is considered as a factor that facilitates production of DSA.

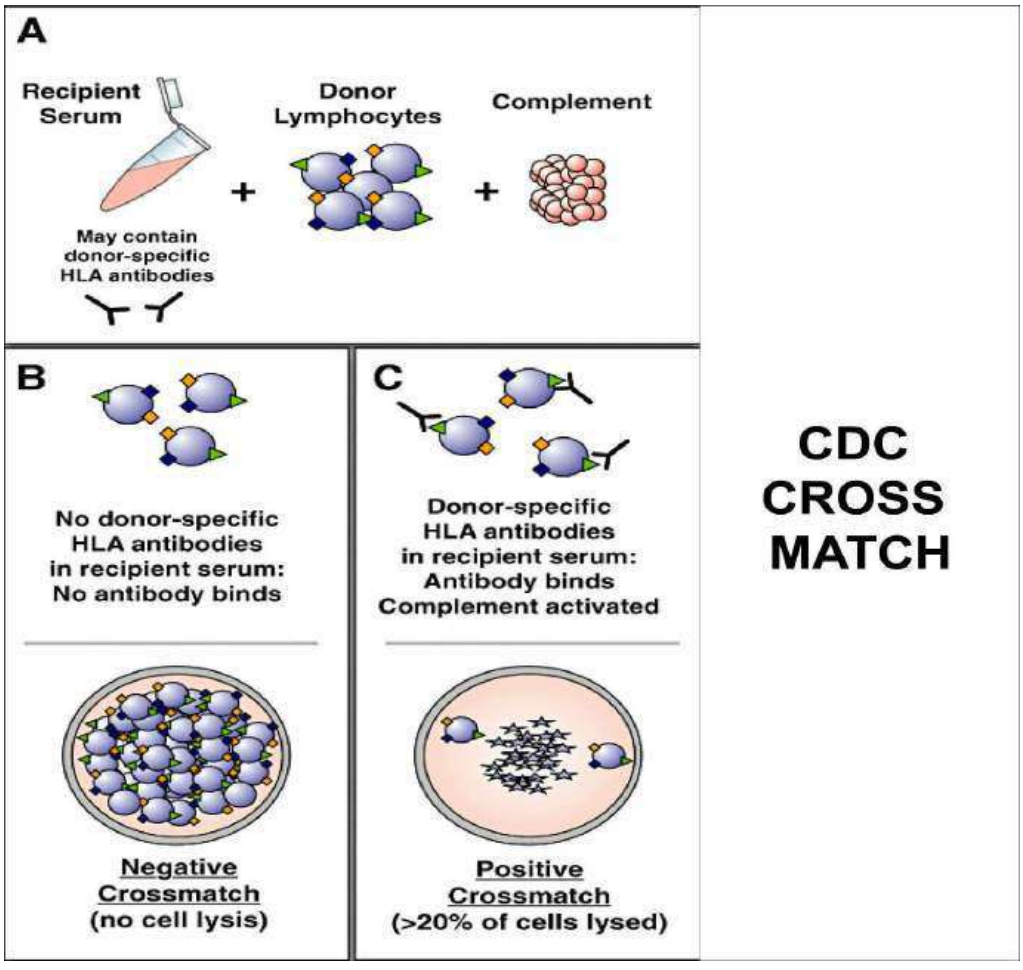
- De novo DSA Post-Transplant has been reported to be associated with AMR, increased risk of Graft loss and poor Transplant outcomes.

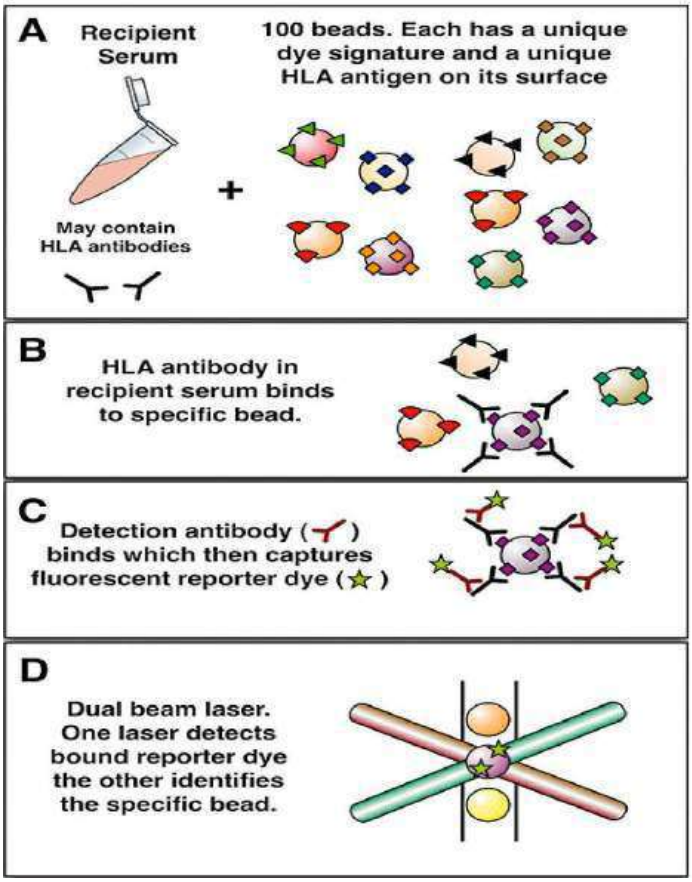


Interpretation of Crossmatch result

[+ve, positive; −ve, negative, DSAb: donor-specific anti-HLA antibody; HLA, human leucocyte antigen, XM: crossmatch.]

T-Cell XM	B-Cell XM	Interpretation
−ve	−ve	No DSAb to HLA class I or II OR DSAb titre too low to cause positive reaction OR (DSAb that is not complement-fixing – relevance unclear).
+ve	+ve	DSAb/s to HLA class I OR Multiple DSAbs to HLA class I +/− II.
−ve	+ve	DSAb/s to HLA class II OR Low level DSAb/s to HLA class I.
+ve	−ve	Technical error (possibly related to B-cell viability). The test should be repeated.





VIRTUAL CROSSMATCH

MFI –MEAN FLUORESCENCE INTENSITY

1. MFI is a measure of the fluorescence emitted by a bead, indicating the amount of antibody bound to it.
2. Don't necessarily represent antibody strength or predict clinical outcomes.

MFI Range	Interpretation
< 1,000	Negative or very low; usually considered insignificant
1,000 – 3,000	Low-level antibodies; may warrant monitoring
3,000 – 5,000	Moderate antibodies; potential clinical impact
5,000 – 10,000	High-level antibodies; increased risk of rejection
> 10,000	Very strong antibodies; often contraindication for transplant or requires desensitization

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NOSTONE
TRIAL

Introduction

- Full Title: Hydrochlorothiazide for the Prevention of Kidney Stone Recurrence.
- Published In: The New England Journal of Medicine (NEJM), 2023.
- Location: Conducted in Switzerland.
- Duration: Median follow-up ~3 years.
- Objective: To assess whether low- or moderate-dose hydrochlorothiazide reduces the risk of recurrent calcium kidney stones compared with placebo.

Study Design

- Design: Multicenter, double-blind, randomized, placebo-controlled trial.
- Population: - Patients: 416 adults.
- Inclusion criteria:
    - History of recurrent calcium-containing kidney stones (≥2 episodes in the last 10 years).
    - Age: 18–75 years.
- Exclusion criteria:
    - Non-calcium stones

    - Secondary causes of stones (e.g., hyperparathyroidism).

Study Groups

Intervention Groups:

- Participants were randomized into four groups:
    1. Placebo
    2. HCTZ 12.5 mg/day
    3. HCTZ 25 mg/day
    4. HCTZ 50 mg/day
- All participants received standard dietary counselling for stone prevention.
- Primary Outcome:
- Composite of symptomatic or radiologic recurrence of kidney stones.

Results

- No significant difference in stone recurrence among the placebo and HCTZ groups.
- Recurrence rates over ~3 years:
    1. Placebo: ~59%
    2. HCTZ 12.5 mg: ~59%
    3. HCTZ 25 mg: ~60%
    4. HCTZ 50 mg: ~49%
- Trend toward benefit with the highest dose, but not statistically significant.

- Adverse Events:- More common with higher doses of HCTZ:
    - Hypokalemia, Hyperuricemia, Gout, New-onset diabetes.

Conclusion

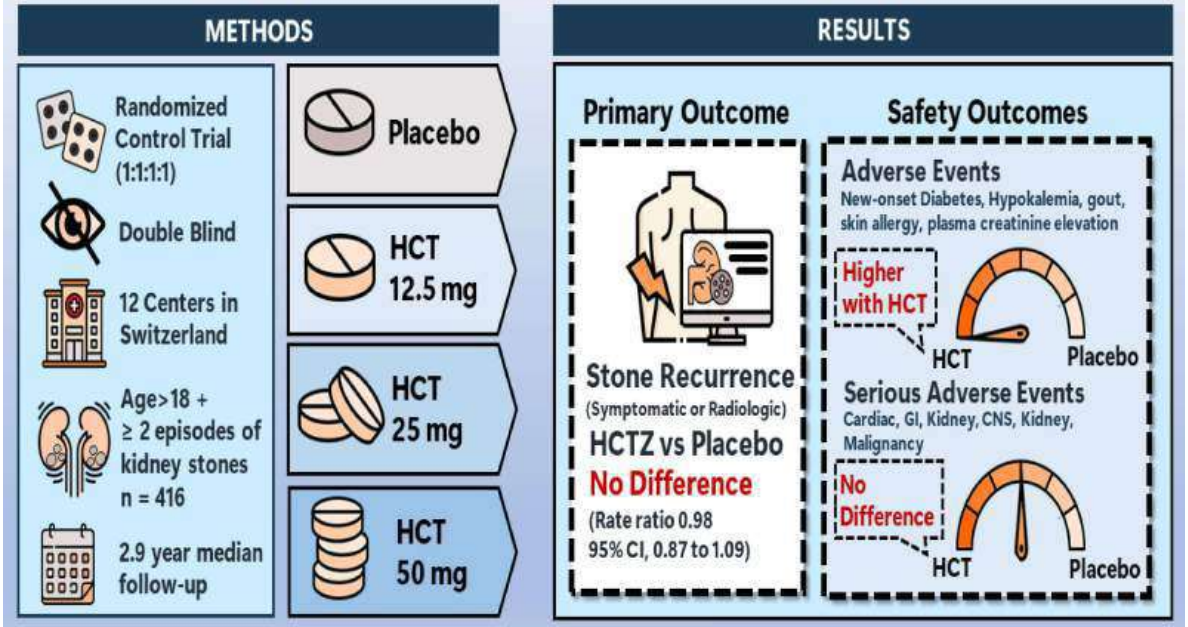
Hydrochlorothiazide did not significantly reduce the risk of recurrent calcium kidney stones compared to placebo, even at higher doses.

NOSTONE Trial: Limitations and Implications

Limitation	Description	Clinical Implication
Short Follow-up	Median ~3 years	May miss long-term benefits of HCTZ in stone prevention
Composite Outcome	Includes asymptomatic radiologic recurrence	Could overestimate clinical recurrence; less meaningful for patients
Unconfirmed Stone Composition	Not all patients had recent confirmed calcium stones	Potential misclassification; thiazides may not work on non-Ca stones
Medication Adherence	Dropouts, dose changes, and side effects affected drug exposure	Could dilute true effect of HCTZ
Low Baseline Risk	General dietary counseling provided; patients not selected for hypercalciuria	Reduced ability to detect incremental benefit of HCTZ
Generalizability	Swiss cohort, mostly White	May not apply to diverse populations or settings
Adverse Effects at Higher Doses	Increased risk of hypokalemia, gout, hyperglycemia	Challenges the risk-benefit ratio of HCTZ for primary prevention

NOSTONE: Is Hydrochlorothiazide (HCT) Beneficial in Recurrent Kidney Stone Prevention?

#NephJC



CONCLUSION: Among patients with recurrent kidney stones, the incidence of recurrence did not appear to differ substantially between HCT or placebo.

Dhayat NA, Bonny O, Roth B, et al. Hydrochlorothiazide and Prevention of Kidney-Stone Recurrence. *N Engl J Med.* 2023; 388(9):781-791

Visual Abstract by: Renz Pasilan @RenzPasilan

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ESA HYPORESPONSIVENESS

Introduction

- People with ESA Hyporesponsiveness are at increased risk for cardiovascular events, kidney failure, and death.

- ESA hyporesponsiveness can be Acute or Chronic (>4 months).

- Its prevalence varies by geographical region ranging from 12.5% to 30.3% as reported in recent studies.

- The most common causes of ESA Hyporesponsiveness are inflammation and iron deficiency.

Guideline	Definition of ESA resistance
ERBG 2004	Increase in erythropoietin dose ≥25% to maintain the same Hb level or < 1 mg/dL gain in Hb after 2–4 weeks
KDIGO 2012	Initial ESA resistance: No increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing
	Subsequent ESA resistance: If after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable HgB concentration
KDOQI/NKF guidelines on anemia in CKD	As per KDIGO 2012 (refer to KDOQI US commentary on KDIGO 2012 Clinical Practice Guideline for Anemia in CKD)
NICE 2021 and BRA 2017	An aspirational Hb range is not achieved despite treatment with 300 IU/kg/week or more of subcutaneous epoetin or 450 IU/kg/week or more of intravenous epoetin or 1.5µg/kg/week of darbepoetin. Or, **There is a continued need for the administration of high doses of ESAs to maintain the aspirational Hb range**

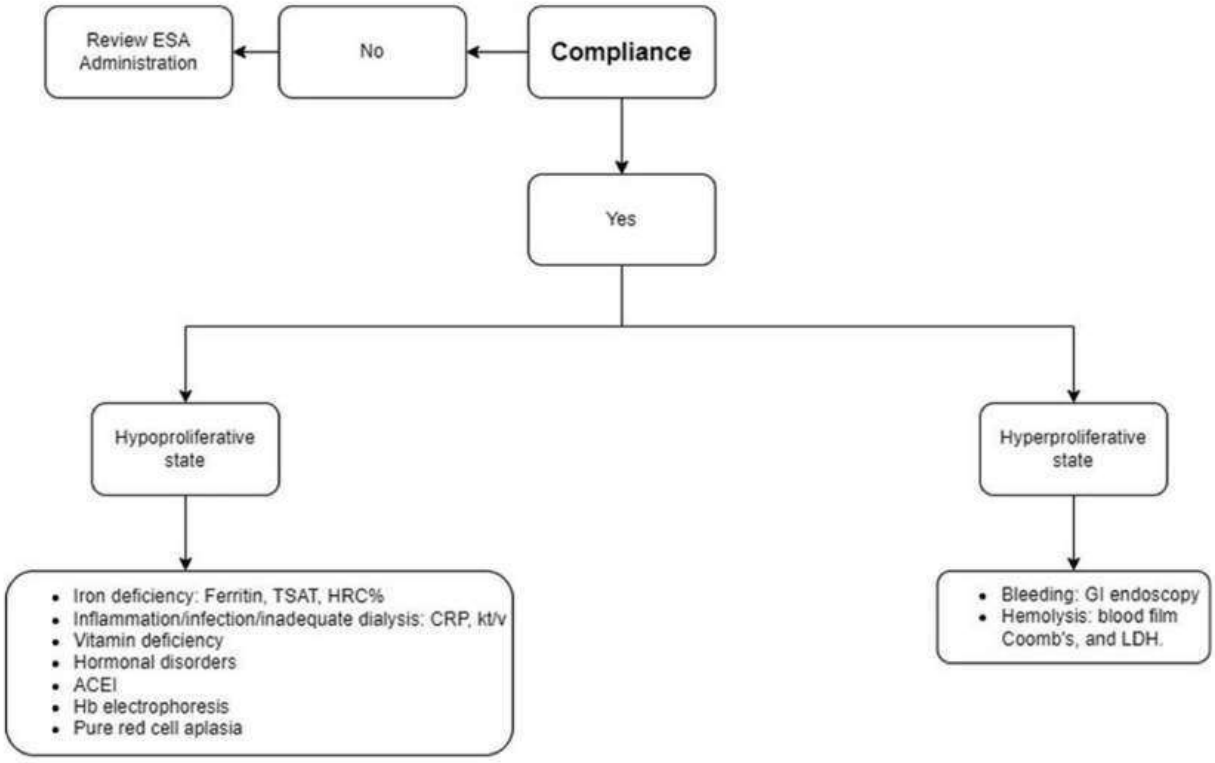
KDIGO 2025

- 3.7.1: In people with Anemia and CKD G5D and CKD not receiving Dialysis with initial orsubsequent ESA Hyporesponsiveness, identify and treat the underlying causes of ESA Hyporesponsiveness, if possible.

- Practice Point 3.7.2: In people with CKD, Anemia, and ESA Hyporesponsiveness, if there is a desire to raise the Hb to avoid a transfusion or improve symptoms attributable to Anemia, a trial of HIF PHI may be considered after discussion of potential risks and benefits prior to treatment.

- Practice Point 3.7.4: In patients with CKD, anemia, and ESA hyporesponsiveness, if a desired Erythropoietic response has not been achieved after 3–4 months of initiating a trial of HIF-PHI, discontinue treatment.

Approach to ESA Hyporesponsiveness



Tests	Finding and action
1. Check adherence	If poor, attempt to improve (if self-injection)
2. Reticulocyte count	If >130,000/μl, look for blood loss or hemolysis: endoscopy, colonoscopy, hemolysis screen
Serum vitamin B_{12}, folate	If low, replenish
Iron status	If low, replenish iron
Serum PTH	If elevated, manage hyperparathyroidism
Serum CRP	If elevated, check for and treat infection or inflammation
Underdialysis	If underdialyzed, improve dialysis efficiency
ACEi/ARB use	If yes, consider reducing dose or discontinuing drug
3. Bone marrow biopsy	Manage condition diagnosed e.g., dyscrasia, infiltration, fibrosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CRP, C-reactive protein; PTH, parathyroid hormone.

HIF PHI in ESA Hyporesponsiveness

- HIF-stabilizers suppresses hepcidin and other pro-inflammatory Cytokine production.
- Regulating iron homeostasis: increase transferrin, transferrin Receptor concentration, Duodenal Cytochrome B, divalent metal transporter-1, and Ceruloplasmin levels.
- DREAM ND and DREAM D trials prove efficacy similar to EPO in increasing Hb levels and also positive reduction in Hepcidin levels and LDL levels.
- Avoid drug in patients with proliferative Diabetic Retinopathy, ADPKD, suspected Malignancy and having Thrombotic events.
- Administer drug on empty stomach or 2 hours after food.
- No desired response after 3-4 months – discontinue HIF-PHI

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PROTON PUMP INHIBHITORS [PPI] AND KIDNEY

Introduction

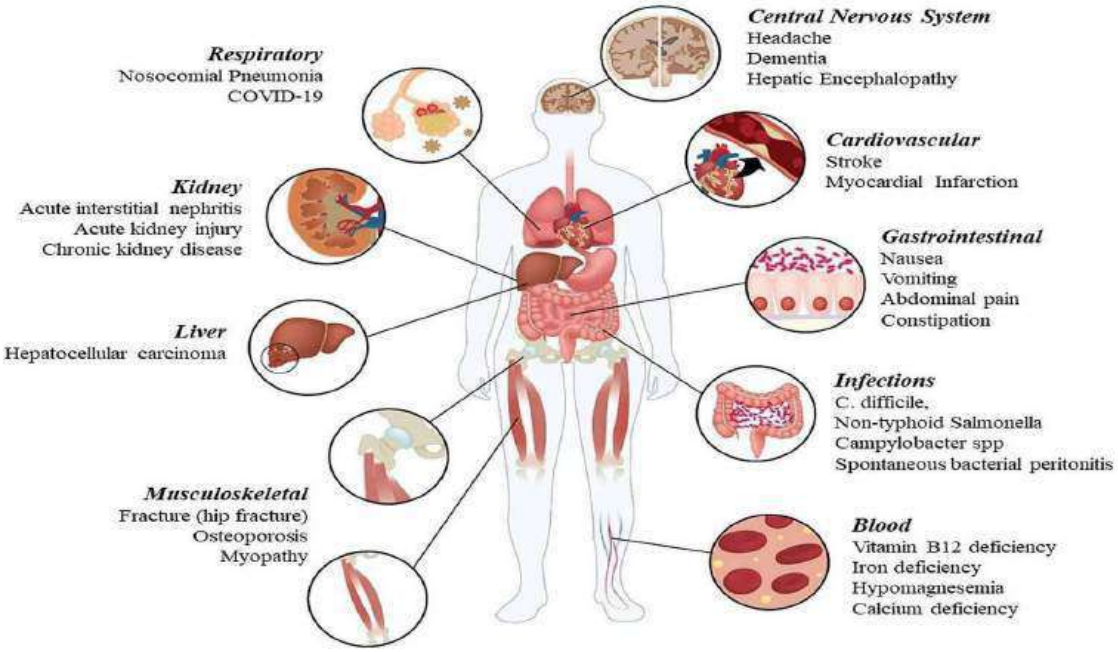
- PPI use is associated with increased risk for Hypomagnesemia,AKI, AIN, incident CKD, CKD progression.

- Acute interstitial nephritis (AIN) is the most well-documented PPI associated kidney injury.

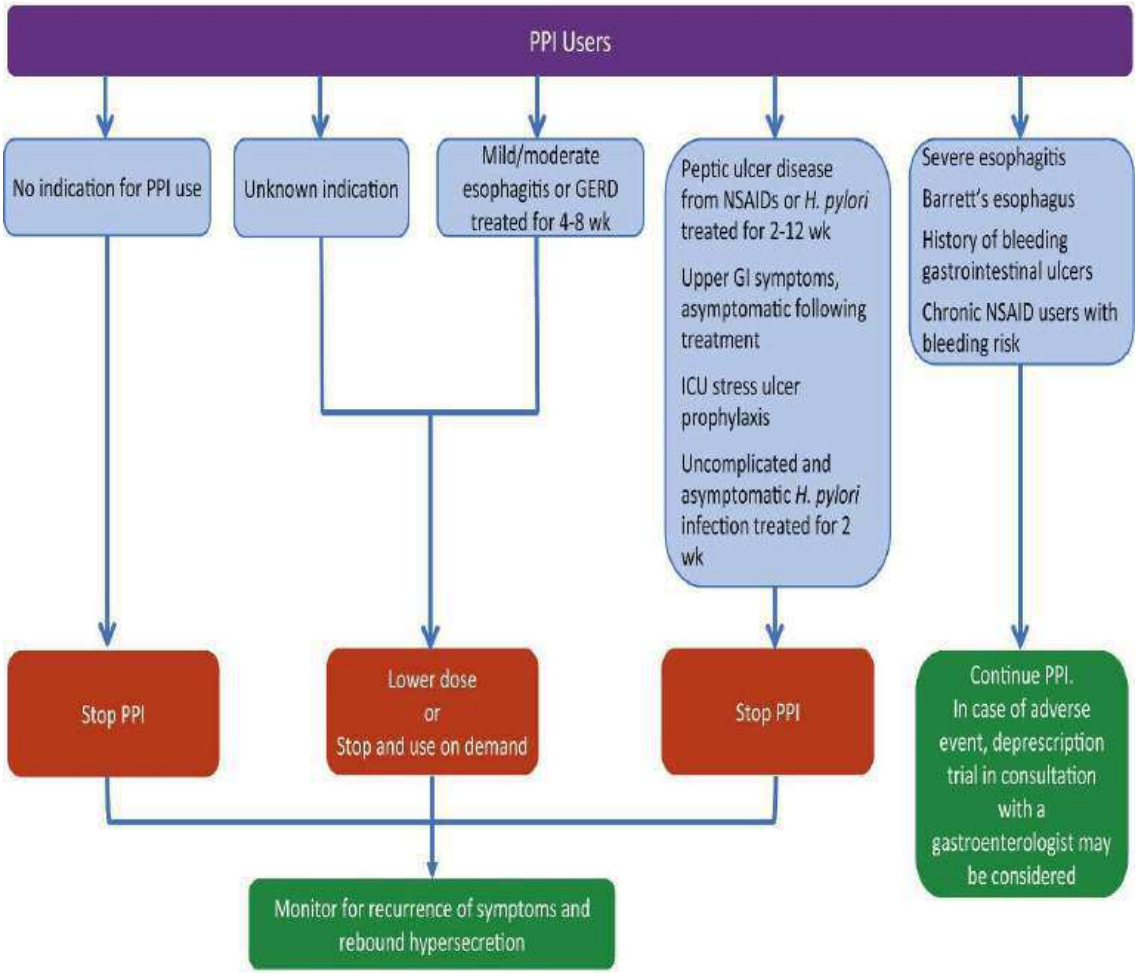
- CKD mechanism: - Undiagnosed/recurrent AIN leading to fibrosis, altered magnesium and calcium absorption contributing to renal injury and potential effects on gut microbiota and inflammation.

- Risk factors: - long term use, high dose of PPI, elderly and patients with renal disease.

Adverse effects associated with Proton Pump Inhibitors



Deprescription Protocol For PPI



Treatment

- Deprescribe PPI in suspected case of kidney involvement due to PPI and when not indicated.
- Use short course of PPI when prescribed for mild symptomatic dyspepsia.
- H2 blockers can be considered as an alternative.

- Potassium-Competitive Acid Blockers (P-CABs) – Vonaprazan, reversibly blocks the H^+/K^+ ATPase (proton pump) in parietal cells, but at the potassium-binding site (unlike PPIs that block the proton binding site irreversibly).

- Monitor patients on PPI for renal involvement.

- Acid peptic disease: Lifestyle changes, exercise, diet modification and eating 2 hours before sleep to avoid symptoms and reduce use of PPI.

- Acute Interstitial Nephritis – BIOPSY and treat with steroids

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NEWER ANTIBIOTIC PLAZOMICIN

Beta lactamase classification

Class A:

- KPCs that confer resistance to cephalosporins and to all Carbapenems, and extended-spectrum Beta-lactamases (ESBLs) that confer resistance to Cephalosporins.

Class B

- Metallo-beta-lactamases (MBLs), such as NDM, VIM, and IMP, which can lead to resistance to all Carbapenems except monobactam.

Class C

- AmpC (mostly chromosomal but can also be Plasmidal), which confer resistance to cephalosporins.

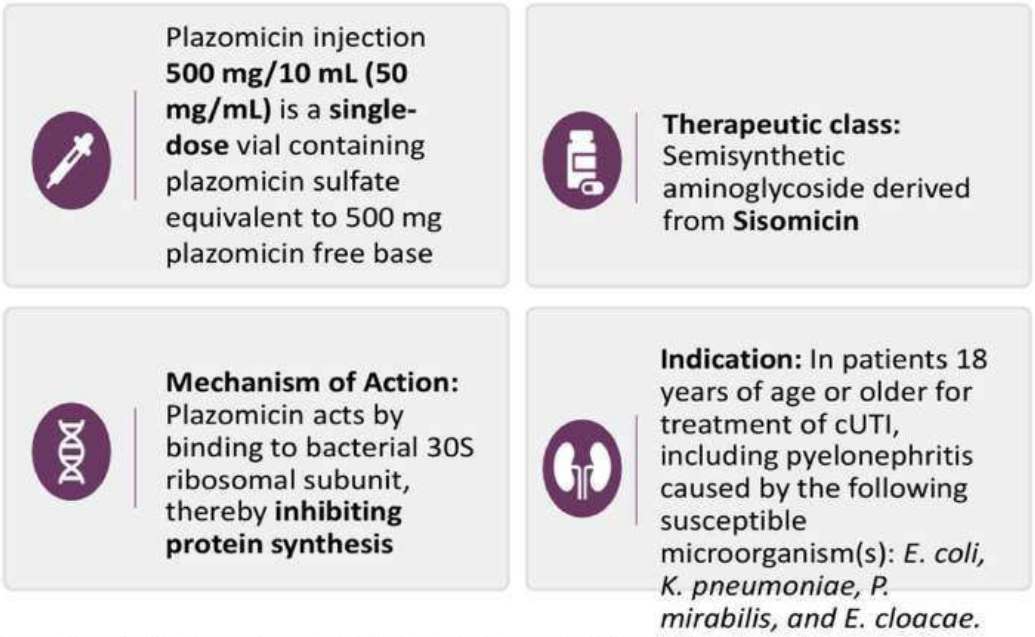
Class D

- OXAs that confer resistance mostly to carbapenems.

	ESBL and AmpC	KPC	OXA-48	MBL	Carbapenem Nonsusceptible *A. baumanii*	Carbapenem Nonsusceptible *P. aeruginosa*
Plazomicin	++	++	++	+/- a	-	-
Eravacycline	++	++	++	+b	++	-
Temocillin	++ (urine breakpoint only)	++ (urine breakpoint only)	-	-	-	-
Cefiderocol	++	++	++	++	++	++
Ceftazidime/avibactam	++	++	++	-	-	+/-
Ceftolozane/tazobactam	++	-	-	-	-	+/- c
Meropenem/vaborbactam	++	++	-	-	?	?
Imipenem/relebactam	++	++	-	-	-	+/- d

Table 1- Possible applications of new antibiotics against Gram-negative bacteria based on resistant mechanisms.

Plazomicin



Ther Adv Infect Dis. 2020 Sep 4;7:2049936120952604. doi: 10.1177/2049936120952604.

Potential Activity against PBP3 inserts

Antibiotic	Target; Mechanism of Action
Ceftazidime Avibactam	**PBP**/β-lactamase enzyme; Cell wall synthesis inhibition
Meropenem- Vaborbactam	**PBP**/β-lactamase enzyme; Cell wall synthesis inhibition
Cefiderocol	**PBP**; Cell wall synthesis inhibition
Imipenem + Cilistatin/ Relebactam	**PBP**/β-lactamase enzyme; Cell wall synthesis inhibition
Aztreonam –Avibactam	**PBP**/β-lactamase enzyme; Cell wall synthesis inhibition
Plazomicin	**30S ribosomal subunit; Protein synthesis inhibition**

Medicina **2024**, 60, 214. https://doi.org/10.3390/medicina60020214

Spectrum of Activity

Gram negative	Enterobacteriaceae family, such as *E. coli, K. pneumoniae, Enterobacter spp., and Proteus spp*
Gram-positive	*S. aureus*, including MRSA, VRSA, heteroresistant vancomycin-intermediate *S. aureus* and *coagulase-negative staphylococci*
Active against Broad range of	✓ AME producing Enterobacteriaceae, ✓ CRE (MBL, Oxa 48, KPC), ESBL producing Enterobacteriaceae ✓ Colistin resistant Enterobacteriaceae ✓ Aminoglycoside resistant

CLSI 2023 Breakpoints

Pathogen	MIC (mcg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
Enterobacteriaceae	≤2	4	≥8	≥16	14-15	≤13

Plazomicin Dosing

Plazomicin has once-daily dosing, administered through a 30-minute IV infusion[1]

Dosage regimen in adults with CrCl ≥90 mL/min

cUTI Infection	Dosage Regimen[b]	Duration of Treatment
cUTI including Pyelonephritis	15 mg/kg every 24 hours	4 to 7 days[c]

Dosage adjustments may be required based on change in renal function in adults with CrCl <90 mL/min;

Estimated CLcr	Recommended Dosage	Dosing Interval
>60 mL/min	15 mg/kg	q24h
>30 to 60 mL/min	10 mg/kg	q24h
>15 to 30 mL/min	10 mg/kg	q48h

Plazomicin is substantially excreted by kidneys, care should be taken in dose selection, and renal function should be monitored.

Synergistic Bactericidal Activity vs CRE

Key Results

- **Plazomicin (0.5 × MIC)** in combination with colistin or fosfomycin, **synergy was observed as well as a >3 log10 decrease in CFU/mL** at 24 h
- When **1 × MIC of plazomicin** was combined with **colistin, meropenem or fosfomycin, bactericidal and synergistic activity** was observed by 24 h for both isolates
- **Plazomicin alone at 2 × MIC was rapidly bactericidal, achieving a 3 log decrease in CFU/mL by 3 h** of exposure, and the bactericidal activity was **sustained up to the 6 h and 24 h time points** against the two isolates tested

Combination of plazomicin with colistin, meropenem or fosfomycin showed in-vitro synergistic activity against carbapenemase-producing K. pneumoniae isolates despite high MICs to comparator antibiotics

Summary

- **Once Daily Dosing** unlike other AGs
- Activity against **resistant Pathogens (PBP3 inserts, AME** producers, **ESBL, CRE**, Colistin resistant Enterobacteriaceae)
- Better activity against CRE & Colistin resistant **Enterobacteriaceae** than other AGs

- Proven efficacy in phase III trial - **Noninferior to Meropenem**

- Acceptable **tolerability profile** (Less nephrotoxicity than colistin)

- Synergy with meropenem, fosfomycin and colistin in CRE isolates

- WHO has categorized it as **Reserve Antibiotic**

- Useful **targeted therapy for cUTI** and Acute Pyelonephritis caused by resistant Pathogen

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ANTICOAGULATION IN CKD

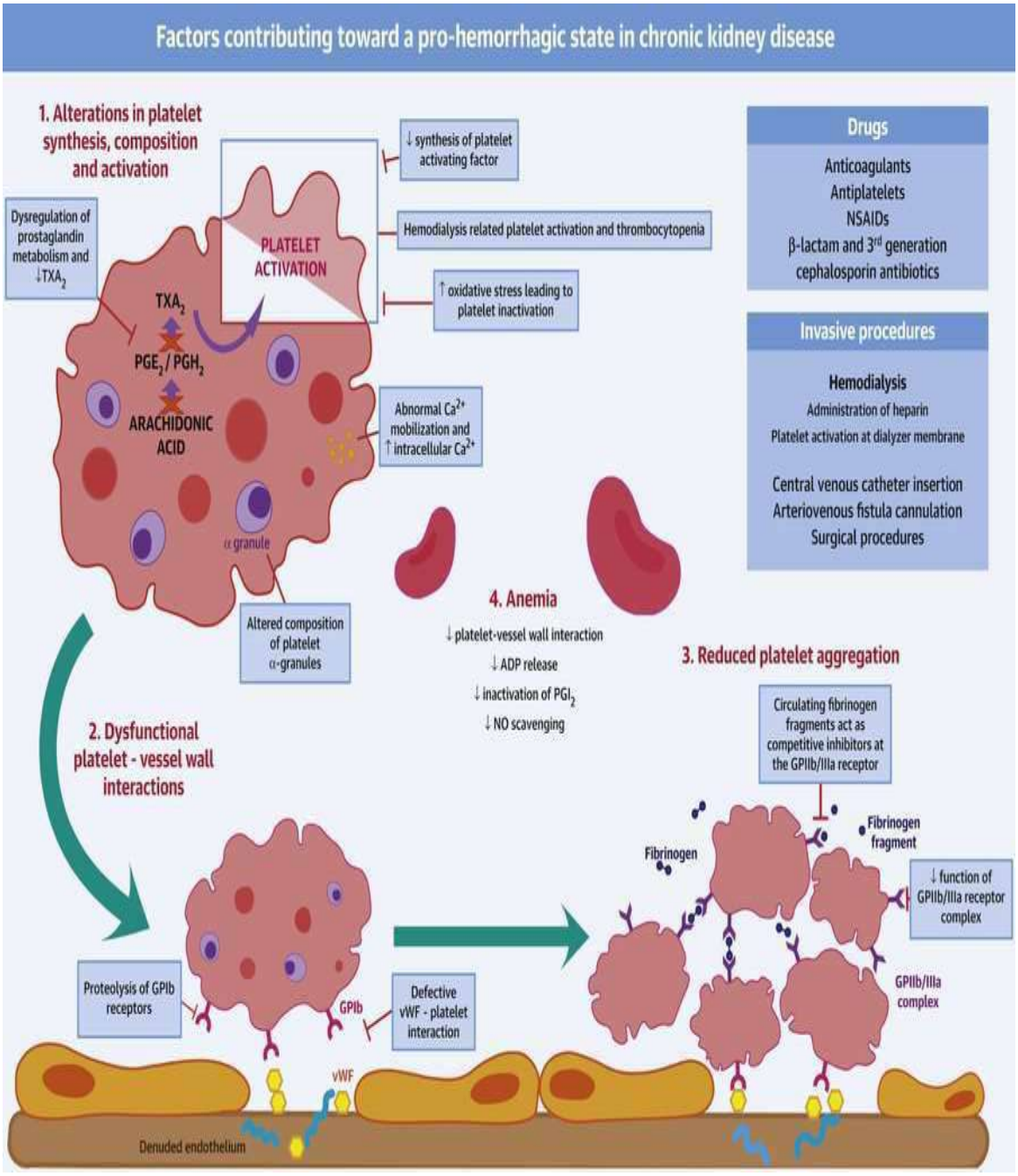
Introduction

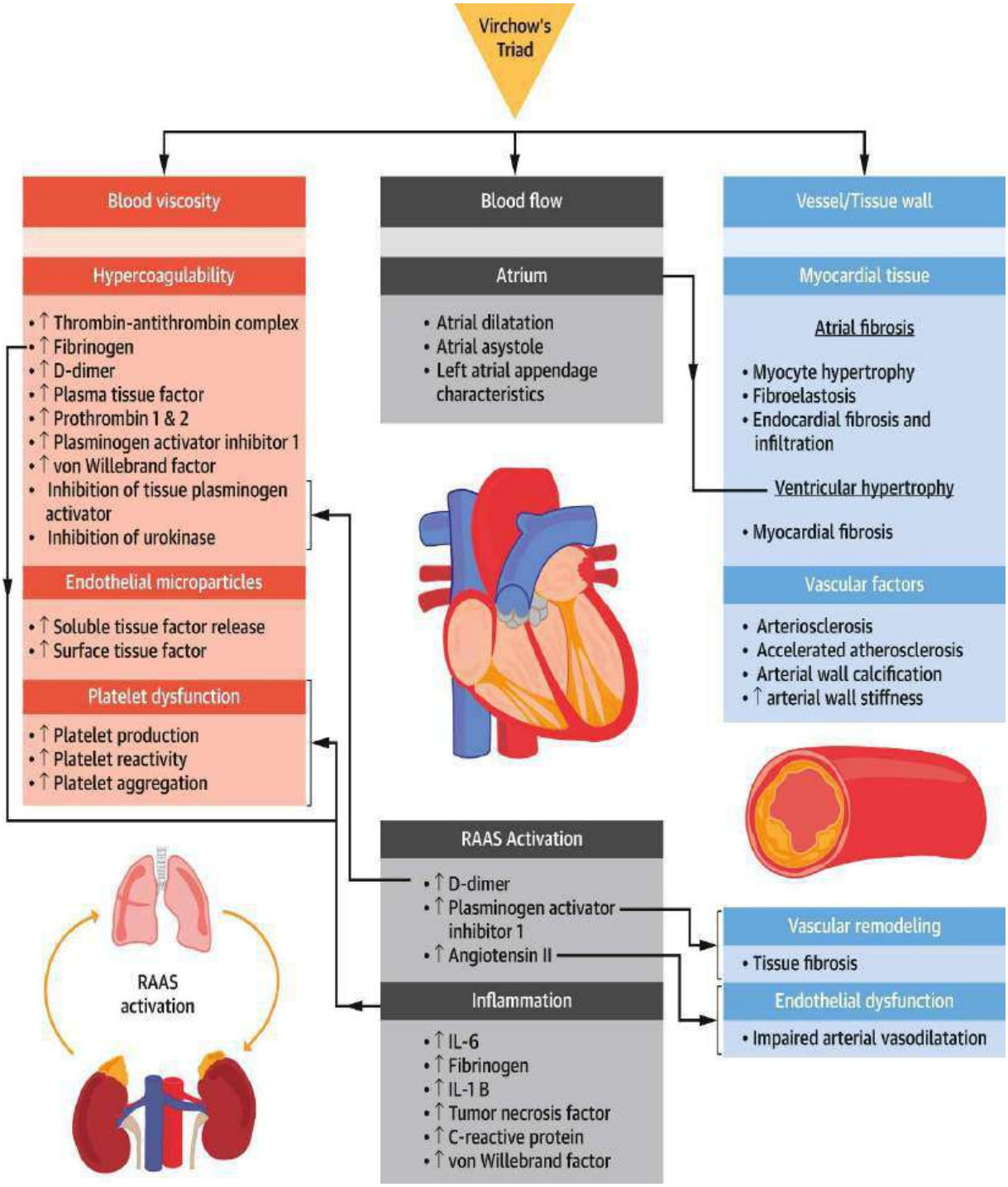
- The risk for venous thromboembolism (VTE) is two to three times greater in patients with CKD.

- The risk for atrial fibrillation (AF) is also 10 to 20 times greater in patients with CKD and ESKD.

- Paradoxically, patients with CKD, and especially those with ESKD are not only at a higher risk of thrombosis, they are also at increased risk of bleeding even without anticoagulant treatment.

- The pathophysiological mechanisms of the increased bleeding risk associated with uremia are diverse and include increased vascular Prostaglandin I_2, decreased Von Willebrand factor, Hyperparathyroidism, Chronic inflammation, decreased Nitric Oxide Bioavailability, Anaemia and Platelet Abnormalities leading to abnormal adhesion and aggregation.


Factors contributing toward a pro-hemorrhagic state in chronic kidney disease
1. Alterations in platelet synthesis, composition and activation
↓ synthesis of platelet activating factor
Dysregulation of prostaglandin metabolism and ↓TXA2
PLATELET ACTIVATION
Hemodialysis related platelet activation and thrombocytopenia
↑ oxidative stress leading to platelet inactivation
TXA2
PGE2 / PGH2
ARACHIDONIC ACID
Abnormal Ca2+ mobilization and ↑ intracellular Ca2+
α granule
Altered composition of platelet α-granules
Drugs
Anticoagulants
Antiplatelets
NSAIDs
β-lactam and 3rd generation cephalosporin antibiotics
Invasive procedures
Hemodialysis
Administration of heparin
Platelet activation at dialyzer membrane
Central venous catheter insertion
Arteriovenous fistula cannulation
Surgical procedures
4. Anemia
↓ platelet-vessel wall interaction
↓ ADP release
↓ inactivation of PGI2
↓ NO scavenging
3. Reduced platelet aggregation
Circulating fibrinogen fragments act as competitive inhibitors at the GPIIb/IIIa receptor
Fibrinogen
Fibrinogen fragment
↓ function of GPIIb/IIIa receptor complex
GPIIb/IIIa complex
2. Dysfunctional platelet - vessel wall interactions
Proteolysis of GPIb receptors
GPIb
Defective vWF - platelet interaction
vWF
Denuded endothelium


Virchow's Triad
Blood viscosity
Hypercoagulability
• ↑ Thrombin-antithrombin complex
• ↑ Fibrinogen
• ↑ D-dimer
• ↑ Plasma tissue factor
• ↑ Prothrombin 1 & 2
• ↑ Plasminogen activator inhibitor 1
• ↑ von Willebrand factor
• Inhibition of tissue plasminogen activator
• Inhibition of urokinase
Endothelial microparticles
• ↑ Soluble tissue factor release
• ↑ Surface tissue factor
Platelet dysfunction
• ↑ Platelet production
• ↑ Platelet reactivity
• ↑ Platelet aggregation
Blood flow
Atrium
• Atrial dilatation
• Atrial asystole
• Left atrial appendage characteristics
Vessel/Tissue wall
Myocardial tissue
Atrial fibrosis
• Myocyte hypertrophy
• Fibroelastosis
• Endocardial fibrosis and infiltration
Ventricular hypertrophy
• Myocardial fibrosis
Vascular factors
• Arteriosclerosis
• Accelerated atherosclerosis
• Arterial wall calcification
• ↑ arterial wall stiffness
RAAS Activation
• ↑ D-dimer
• ↑ Plasminogen activator inhibitor 1
• ↑ Angiotensin II
Inflammation
• ↑ IL-6
• ↑ Fibrinogen
• ↑ IL-1 B
• ↑ Tumor necrosis factor
• ↑ C-reactive protein
• ↑ von Willebrand factor
Vascular remodeling
• Tissue fibrosis
Endothelial dysfunction
• Impaired arterial vasodilatation
RAAS activation

	Normal renal function or stage 1–2 CKD (eGFR ≥60 mL/min/1.73 m²)	Stage 3 (eGFR 30–59 mL/min/ 1.73 m²)	Stage 4 (eGFR 15–29 mL/min/ 1.73 m²)	Stage 5 (eGFR <15 mL/min/ 1.73 m² OR dialysis)
$P2Y_{12}$ inhibitors				
Clopidogrel	300–600 mg orally, then 75 mg a day	No dose adjustment	No dose adjustment	Use only for selected indications (e.g. stent thrombosis prevention)
Prasugrel	60 mg orally then 10 mg a day	No dose adjustment	No dose adjustment	NOT recommended
Ticagrelor	180 mg orally then 90 mg twice a day	No dose adjustment	No dose adjustment	NOT recommended
Cangrelor	30 µg/kg bolus and 4 µg/kg/min infusion	No dose adjustment	No dose adjustment	No dose adjustment
Anticoagulants				
Unfractionated heparin	Prior to coronary angiography: 60–70 IU/kg iv (max 5000 IU) and infusion (12–15 IU/kg/ hour) (max 1000 IU/hour), target aPTT 1.5–2.5× control During PCI: 70–100 IU/kg iv (50–70 IU/kg if concomitant with GPI)	No dose adjustment	No dose adjustment	No dose adjustment
Enoxaparin	1 mg/kg sc twice a day	No dose adjustment	1 mg/kg sc once a day	NOT recommended
Bivalirudin	Bolus 0.75 mg/kg iv, infusion 1.75 mg/kg/hour		No adjustment of bolus, reduce infusion rate to 1 mg/kg/hour	On dialysis, no adjustment of bolus, reduce infusion rate to 0.25 mg/kg/hour
Fondaparinux	2.5 mg sc daily	No dose adjustment	NOT recommended if eGFR <20 mL/min/1.73 m²	NOT recommended
Glycoprotein IIB/IIIA inhibitors				
Eptifibatide	Bolus 180 µg/kg iv, infusion 2 µg/kg/min	No adjustment of bolus, reduce infusion rate to 1 µg/kg/min if eGFR <50 mL/min/1.73 m²	NOT recommended	NOT recommended
Tirofiban	Bolus 25 µg/kg or 10 µg/kg iv, infusion 0.15 µg/kg/min	No dose adjustment	No adjustment of bolus, reduce infusion to 0.05 µg/ kg/min	NOT recommended
Abciximab	Bolus 0.25 mg/kg iv, infusion 0.125 µg/kg/min (max 10 µg/ min)	No specific recommendations for the use of abciximab or for dose adjustment in the case of renal failure. Careful evaluation of haemorrhagic risk is needed		

	Warfarin	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Routine dose	Adjusted to INR	150 mg, 2×/d	5 mg, 1×/d	60 mg, 1×/d	20 mg, 1×/d
CKD dose adjustment	Adjusted to INR	None	2.5 mg, 2×/d, if Scr > 1.5 mg/dL + age ≥ 80 y or weight < 60 kg	30 mg, 1×/d, if CL_{cr} 15-50 mL/min	15 mg, 1×/d, if CL_{cr} 15-50 mL/min
Mechanisms of action	Inhibits synthesis of vitamin K–dependent clotting factors (II, VII, IX, X)	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
4-h dialysis removal	<1%	50%-60%	7%	9%	<1%
Volume of distribution, L	8	50-70	21	107	50
Excretion	Nonrenal	50%-60% renal	CYP3A4/5 (P-glycoprotein liver enzyme); 27% renal	CVP3A4 (liver enzyme); 50% renal; 40% bile	CYP3A4/5 and CYP2J2 (liver enzymes); 36% renal
Reversal agents	Vitamin K, fresh frozen plasma, 4-factor prothrombin complexes	Idarucizumab	4-factor prothrombin complexes	4-factor prothrombin complexes	4-factor prothrombin complexes
FDA approved for CKD-5D	Yes	No	Yes	No	No
Concerns for use in CKD-5D[a]	Requires frequent monitoring, high interindividual variability in drug response, may increase risk for calciphylaxis and vascular calcification	Reversal agent may not be readily available, lack of data for safe dosing in CKD-5D	Reversal agent may not be readily available, dosing in CKD-5D based on pharmacokinetic data only	Reversal agent may not be readily available, lack of data for safe dosing in CKD-5D	Reversal agent may not be readily available, dosing recommendations in CKD-5D based on pharmacokinetic data only

Note: Data in table based on references 89-91, 93-95, 97, 98.

ATRIAL FIBRILLATION

Assess CHA_2DS_2-VASc score
Anticoagulation recommended if score is 1+ (males) or 2+ (females)

	CrCl 80+ mls/min	CrCl 50-79 mls/min	CrCl 30-49 mls/min	CrCl 15-29 mls/min	CrCl <15 mls/min, or dialysis-dependent **
Apixaban	5mg BD	5mg BD	5mg BD	Consider 2.5mg BD	Consider
Rivaroxaban	20mg OD	20mg OD	15mg OD	15mg OD	Contraindicated
Edoxaban	60mg OD	60mg OD	30mg OD	30mg OD	Contraindicated
Dabigatran	150mg BD	150mg BD	110mg BD***	Consider 75mg BD	Contraindicated
VKA *	INR 2-3	INR 2-3	INR 2-3	INR 2-3	Consider

* Data favours the use of DOACs over VKA regarding bleeding risk. VKA should be used in patients with metallic heart valves or other CI to DOACs

** consider alternative options eg. LAA closure, anti-platelets, or no anti-thrombotic agent

*** 110mg BD dabigatran used in Europe; 75mg BD for CrCl 15-30 ml/min approved in US

VENOUS THROMBOEMBOLISM

	CrCl 80+ mls/min	CrCl 50-79 mls/min	CrCl 30-49 mls/min	CrCl 15-29 mls/min	CrCl <15 mls/min, or dialysis-dependent **
Apixaban	Loading then 5mg BD	Loading then 5mg BD	Loading then 5mg BD	Loading then 5mg BD	Consider
Rivaroxaban	Loading then 20mg OD	Loading then 20mg OD	Loading then 20mg OD	Loading then 20mg OD	Contraindicated
Edoxaban*	60mg OD	60mg OD	30mg OD	30mg OD	Contraindicated
Dabigatran*	150mg BD	150mg BD	150mg or 110mg BD	Contraindicated	Contraindicated
VKA *	INR 2-3	INR 2-3	INR 2-3	INR 2-3	Consider

* At least 5 days of parenteral anticoagulation required prior to commencement of Dabigatran and Edoxaban in VTE; When commencing VKA, parenteral anticoagulation is required until the INR is >2 for 2 consecutive days, or for 5 days, whichever is longer.

** Data favours the use of DOACs over VKA regarding bleeding risk. Very limited data in ESRD

Future considerations may include FXI inhibitors

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Trial Characteristics				
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Year of publication	2009	2011	2011	2013
Study doses	110 mg, 2×/d; 150 mg, 2×/d	20 mg daily (15 mg daily for eCL_{cr} 30-49 mL/min)	5 mg, 2×/d[a]	60 mg daily (30 mg daily for eCL_{cr} ≤ 50 mL/min)
N	18,113	14,264	18,201	21,105
Patients With CKD				
No. with moderate CKD	3,554 (20%)	2,950 (21%)	3,017 (17%)	2,740 (19.5%)
Definition/cutoff for moderate CKD	eCL_{cr} 31-49 mL/min	eCL_{cr} 30-49 mL/min	eCL_{cr} 25-50 mL/min	eCL_{cr} 30-50 mL/min
Age, y	76 (median)	79 (median)	78 (mean)	79 (median)
Female sex	47%	55%	53%	54%
$CHADS_2$ score[b]	45% had score ≥ 3	3.7 ± 1.0	2.6 ± 1.2	3.1 ± 1.1
Primary Outcome Measure: Stroke and Systemic Embolism				
Study arm	110 mg: 2.3%/y; 150 mg: 1.5%/y	2.3%/100 pt-y	2.1%/y	2.3%/y
Control arm	2.7%/y	2.8%/100 pt-y	2.7%/y	2.7%/y
HR (95% CI)	110 mg: 0.85 (0.59-1.24); 150 mg: 0.56 (0.37-0.85)	0.84 (0.57-1.23)	0.79 (0.55-1.14)	0.87 (0.64-1.19)
Primary Safety Outcome: Major Bleeding				
Study arm	110 mg: 5.5%/y; 150 mg: 5.5%/y	4.5%/100 pt-y	3.2%/y	4%/y
Control arm	5.5%	4.7%/100 pt-y	6.4%/y	5.3%/y
HR (95% CI)	110 mg: 0.99 (0.77-1.28); 150 mg: 1.02 (0.79-1.30)	0.95 (0.72-1.26)	0.50 (0.38-0.66)	0.76 (0.58-0.98)

Abbreviations: ARTISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CI, confidence interval; CKD, chronic kidney disease; eCL_{cr}, estimated creatinine clearance (calculated by Cockcroft-Gault formula); ENGAGE AF-TIMI 48, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction; HR, hazard ratio; NOAC, non–vitamin K–dependent oral anticoagulant; pt-y, patient-years; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

[a]Dose adjustment for apixaban occurred if 2 of 3 factors were met: serum creatinine ≥1.5 mg/dL, age ≥80 years, or weight ≤ 60 kg.

[b]Mean ± standard deviation unless indicated otherwise.

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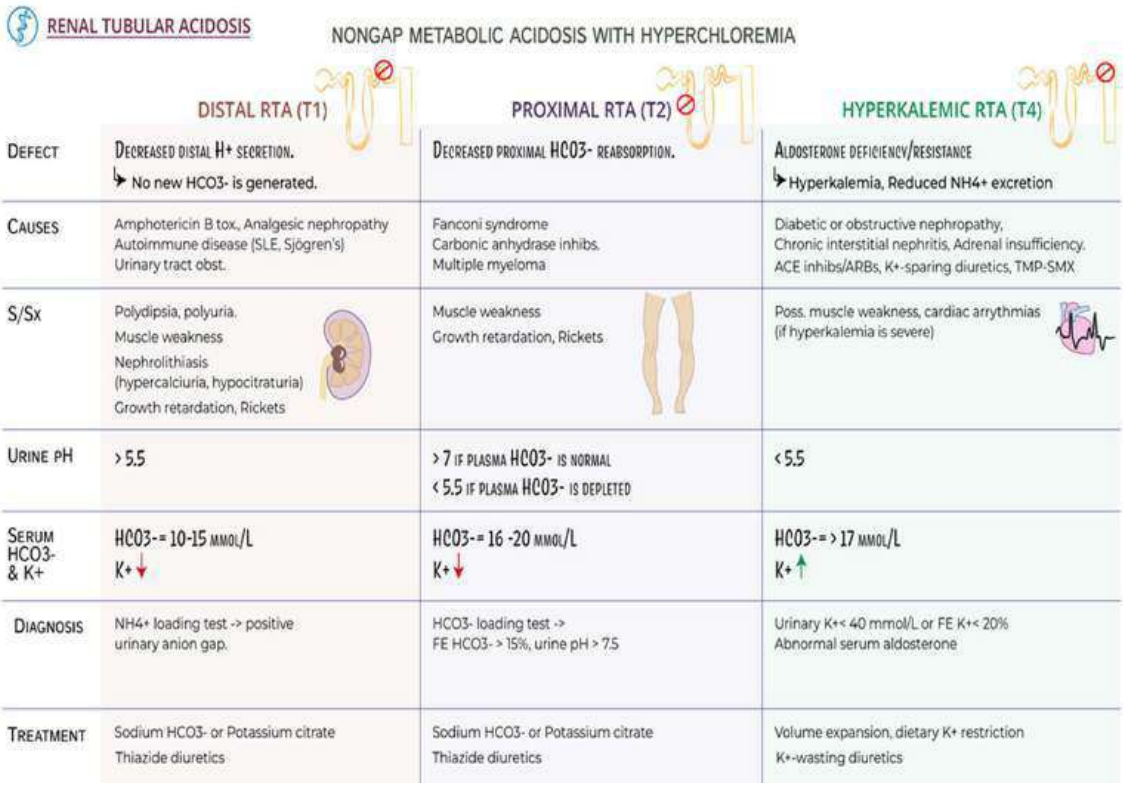
TYPE 4 RTA IN DIABETES MELLITUS

Introduction

- Diabetes mellitus—especially long-standing type 1 or type 2—can cause: Hyporeninemic hypoaldosteronism– **↓ Renin → ↓ Aldosterone → impaired Potassium & Hydrogen ion excretion.**

- Autonomic neuropathy → **↓ Renin release.**

- Diabetic nephropathy → affects juxtaglomerular apparatus → ↓ renin-angiotensin-aldosterone system (RAAS) activation.



Typical biochemical features TYPE 4 RTA

Parameter	Finding
Serum K^+	↑ (hyperkalemia)
Serum HCO_3^-	↓ (mild metabolic acidosis, usually 15–20 mmol/L)
Anion gap	Normal (non-anion gap metabolic acidosis)
Urine pH	< 5.5 (kidneys can acidify urine, unlike type 1 RTA)
Urinary ammonium excretion	Low (despite acidosis)
Trans tubular potassium gradient (TTKG)	Low (inappropriately low in hyperkalemia)

TTKG- Trans-tubular Potassium Gradient

- Formula for TTKG

$$TTKG = \frac{K_{urine} \times Osm_{serum}}{Osm_{urine} \times K_{serum}}$$

- Urine K^+ = Urinary Potassium Concentration (mmol/L).
- Plasma K^+ = Plasma potassium concentration (mmol/L)
- Urine osmolality = Urine Osmolality (mOsm/kg).

- Plasma osmolality = plasma osmolality (mOsm/kg).

TTKG Interpretation

- Normal TTKG values:
- In hyperkalemia: TTKG should be >7–10 → indicates appropriate renal K^+ excretion.
- In hypokalemia: TTKG should be <3 → indicates appropriate Renal K^+ conservation.

In Type 4 RTA, despite hyperkalemia:

- The TTKG is low (<7), showing impaired K^+ secretion.
- This suggests either: –
    - ♦ Low aldosterone levels (hypoaldosteronism)
    - ♦ Aldosterone resistance (Tubular Dysfunction)

Treatment

- Dietary Potassium restriction.
- Loop or Thiazide Diuretics (enhance K^+ excretion).
- Fludrocortisone (Mineralocorticoid replacement, if no contraindications like Hypertension or fluid overload).
- Sodium Bicarbonate to correct Acidosis

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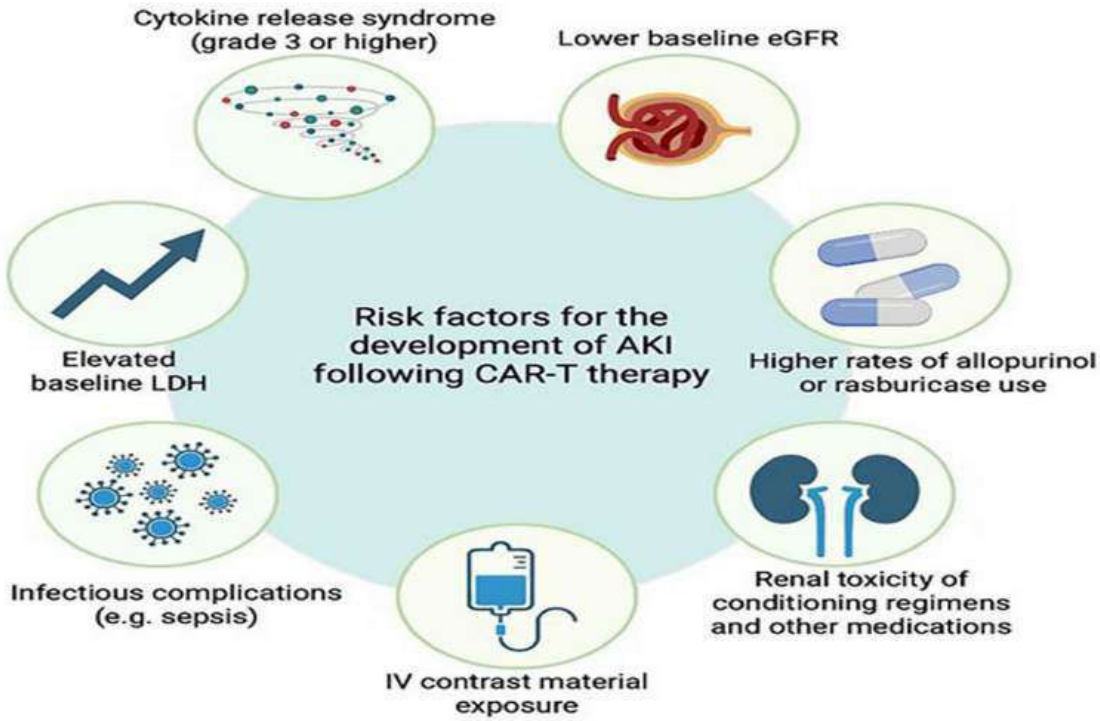
CAR–T CELL THERAPY AND AKI

Introduction

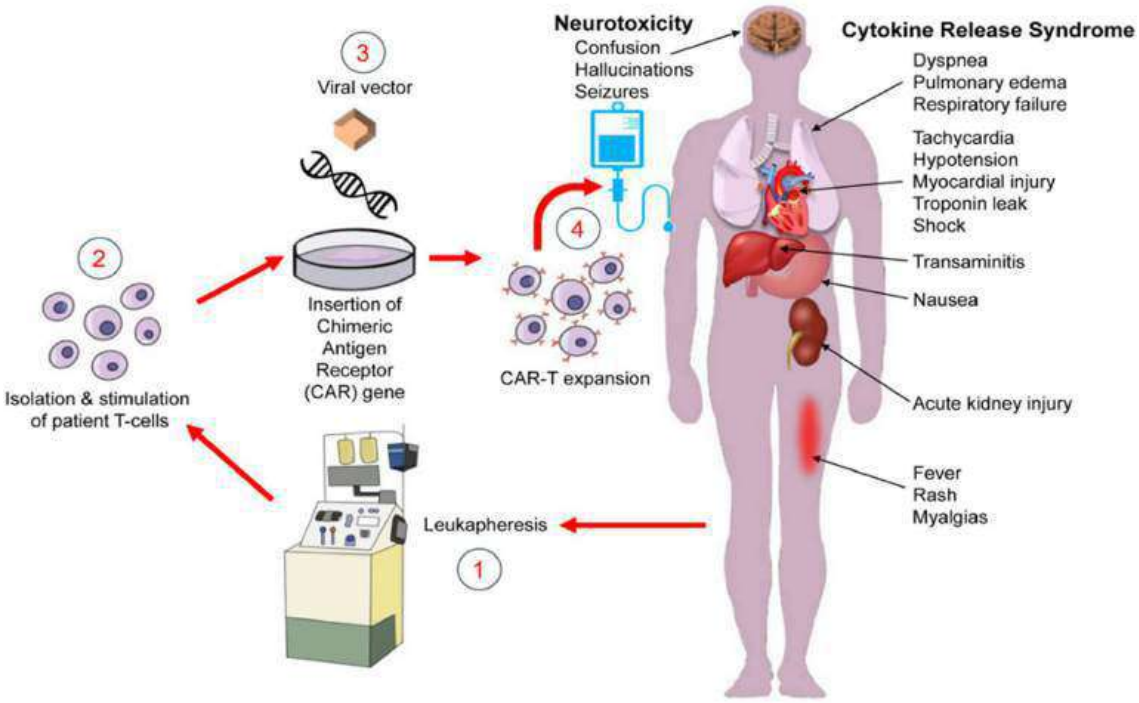
- Chimeric antigen receptor T (CAR-T) cell therapy, personalized immunotherapy for various hematologic malignancies, autoimmune diseases and other conditions, involves the modification of patients ’T cells to express a chimeric antigen receptor that recognizes tumour or autoimmune cell antigens, allowing CAR-T cells to destroy cancerous and other target cells selectively.

- Studies report AKI incidence following CAR T-cell therapy ranging from 5% to 46% - cumulative incidence of any grade AKI around 30% within 100 days post-infusion.

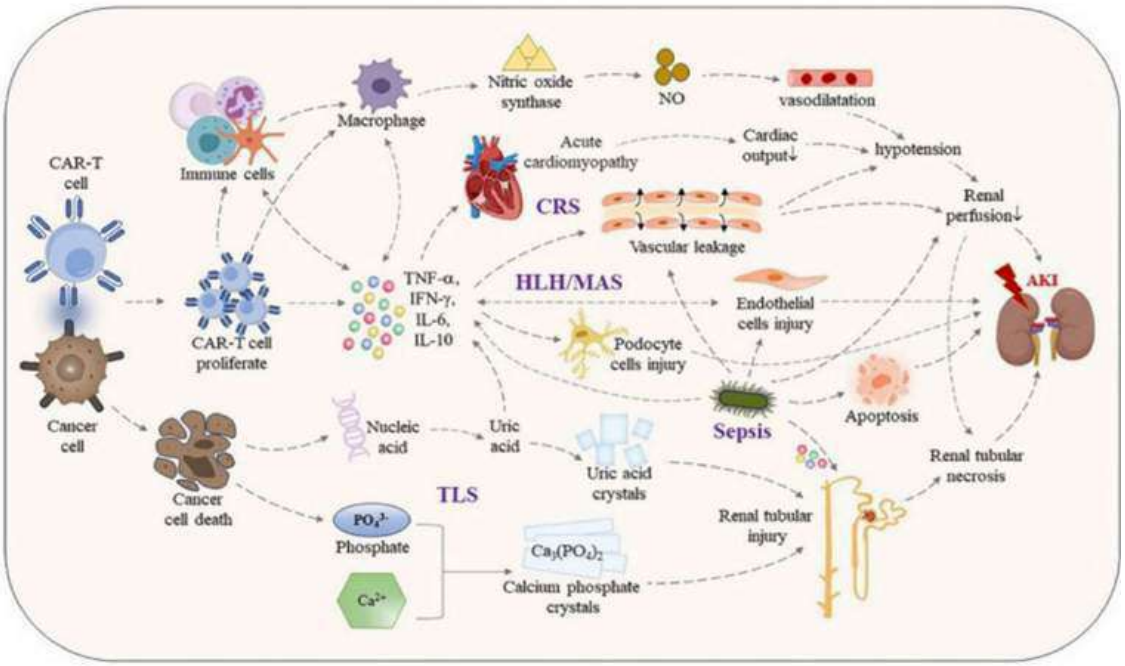
Risk Factors



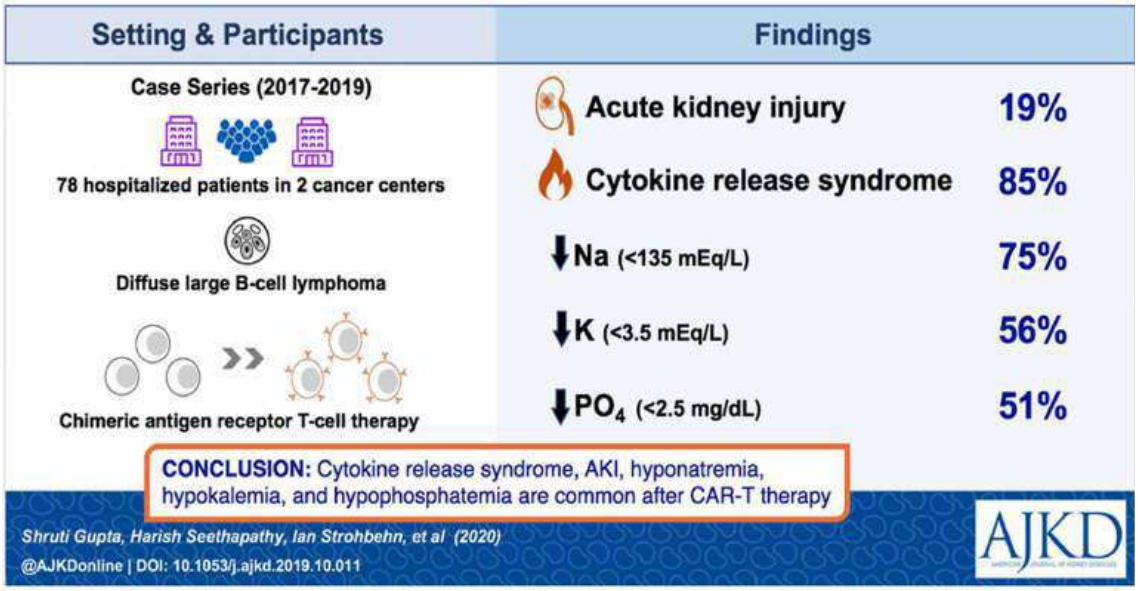
CAR T Cell Therapy –Preparation and Common Side Effects



Mechanism of AKI with CAR T Cell Therapy



AKI and Electrolyte abnormalities after CAR-T Therapy



Electrolyte disorders seen with CAR T cell therapy -The most common was Hypokalemia (47%), followed by Hypophosphatemia (37%), and finally Hyponatremia (5%).

Treatment

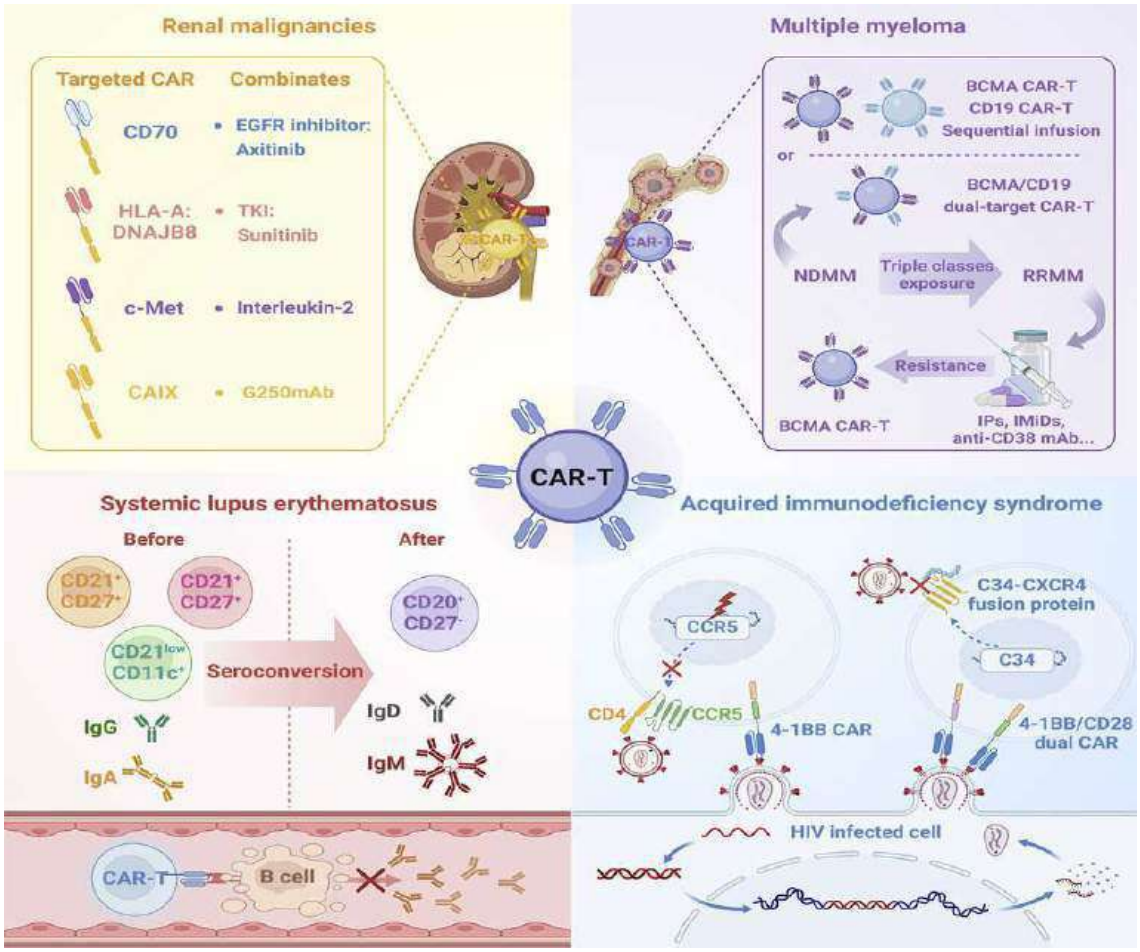
Cytokine storm-related toxicities:

1. Anti-cytokine therapy such as anti-IL-6 agent Tocilizumab. It can quickly reverse the Cytokine storm in most patients.
2. Methylprednisolone 1–2 mg/kg intravenous every 12 hours can be tried in Cytokine release Syndrome that is refractory to tocilizumab.
3. Pretreatment with chemotherapy to reduce Tumor burden and steroids is also considered to be important

in the prevention of cytokine release syndrome.

- Tumor lysis related AKI: aggressive hydration, Rasburicase , dialysis in refractory and severe cases.
- Sepsis: antibiotics, fluids and Vasopressors.
- Discontinue Nephrotoxic drugs. Electrolyte correction.
- Renal replacement therapy [RRT] whenever indicated.

CAR-T Cell Therapy in other Condition



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PREGNANCY – AKI [PRAKI]

Introduction

- Pregnancy-related acute kidney injury (Pr-AKI) is a Heterogeneous disease entity due to varying underlying Etiologies.

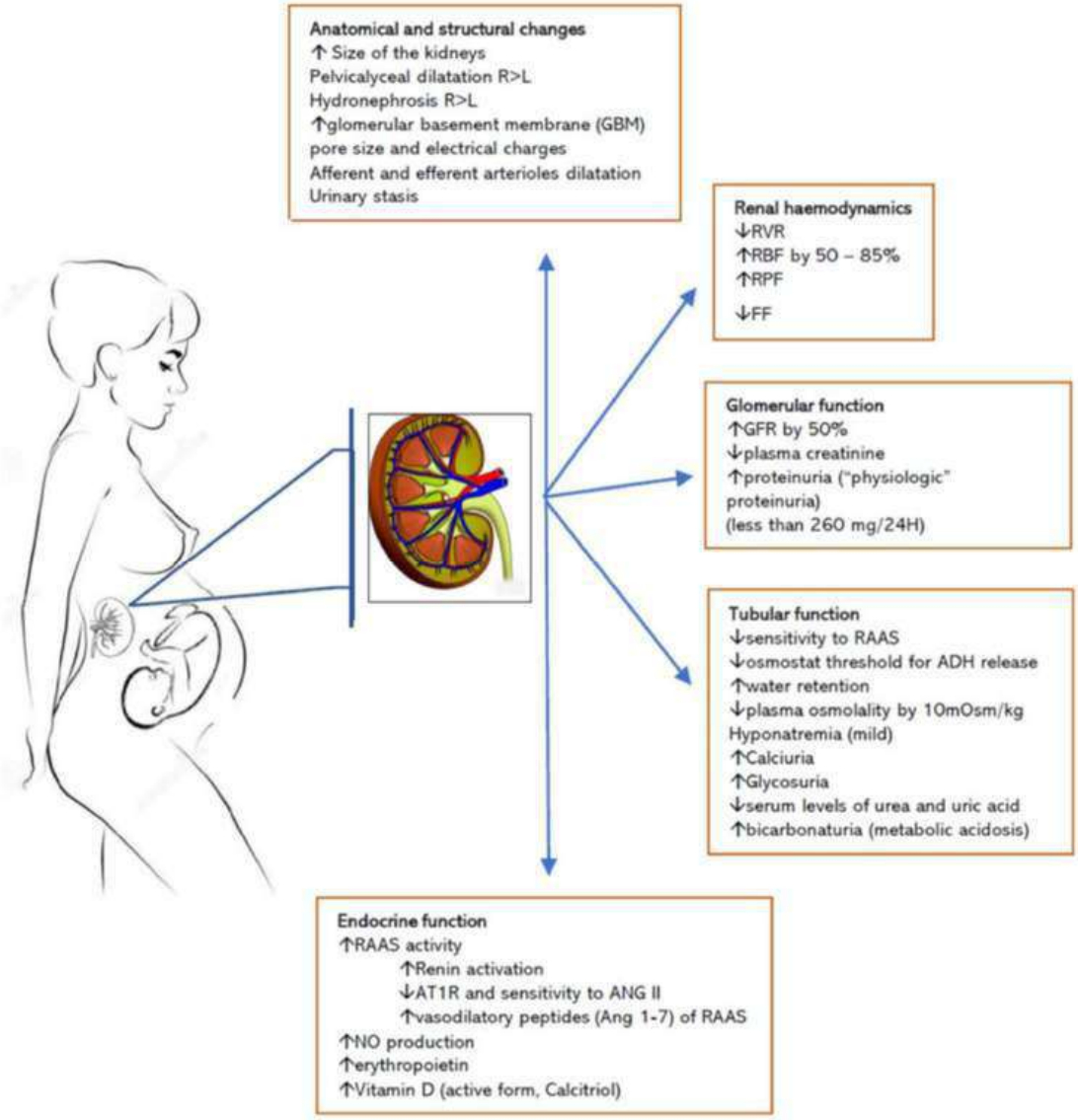
- P-AKI in developing countries accounts for 5%–20% of total AKI population.

- Pr-AKI commonly occur in postpartum rather than the post- abortal period, reflecting a decline in septic abortions.

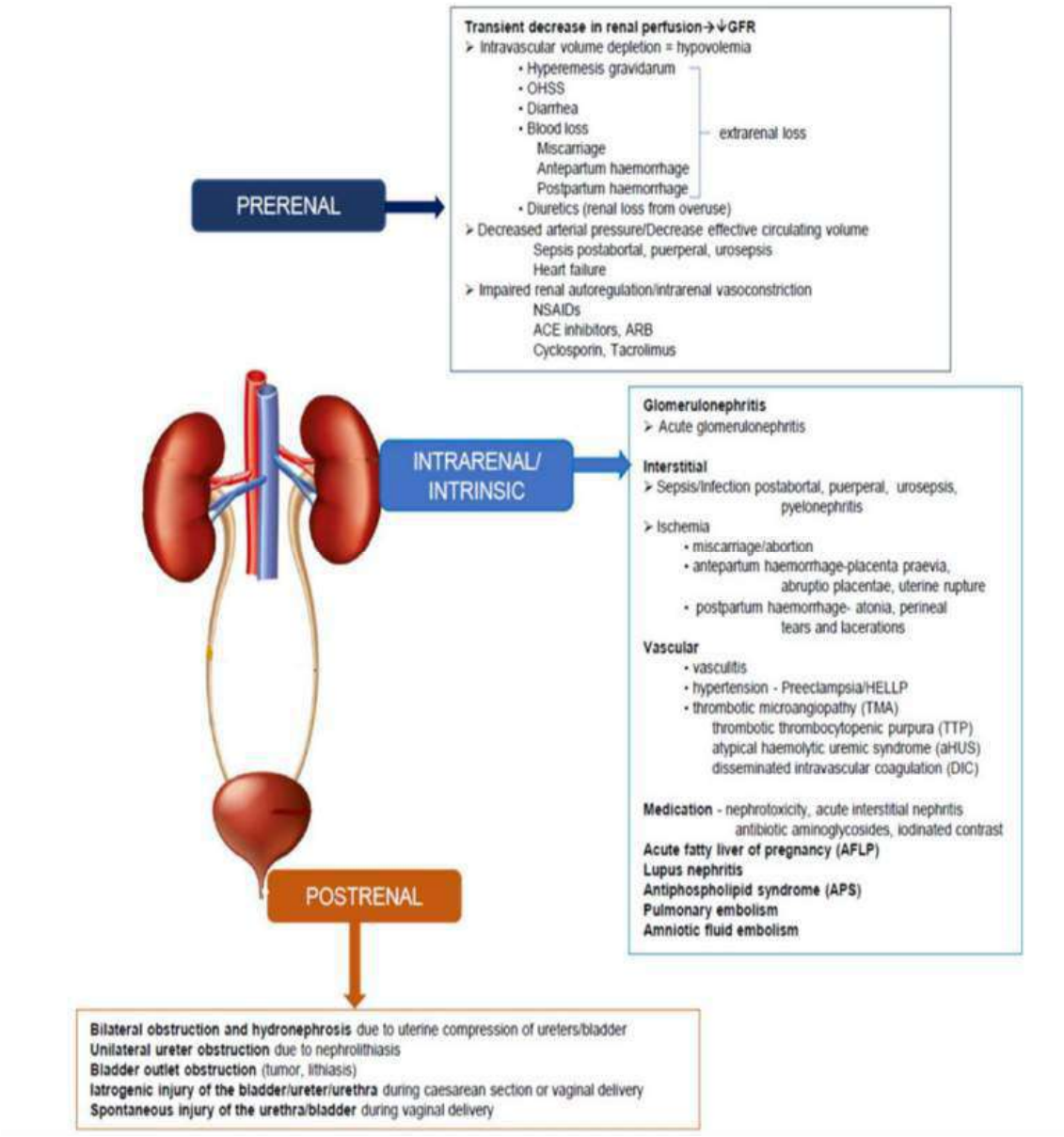
- 24 hr creatinine clearance is closest estimate of GFR in pregnancy.

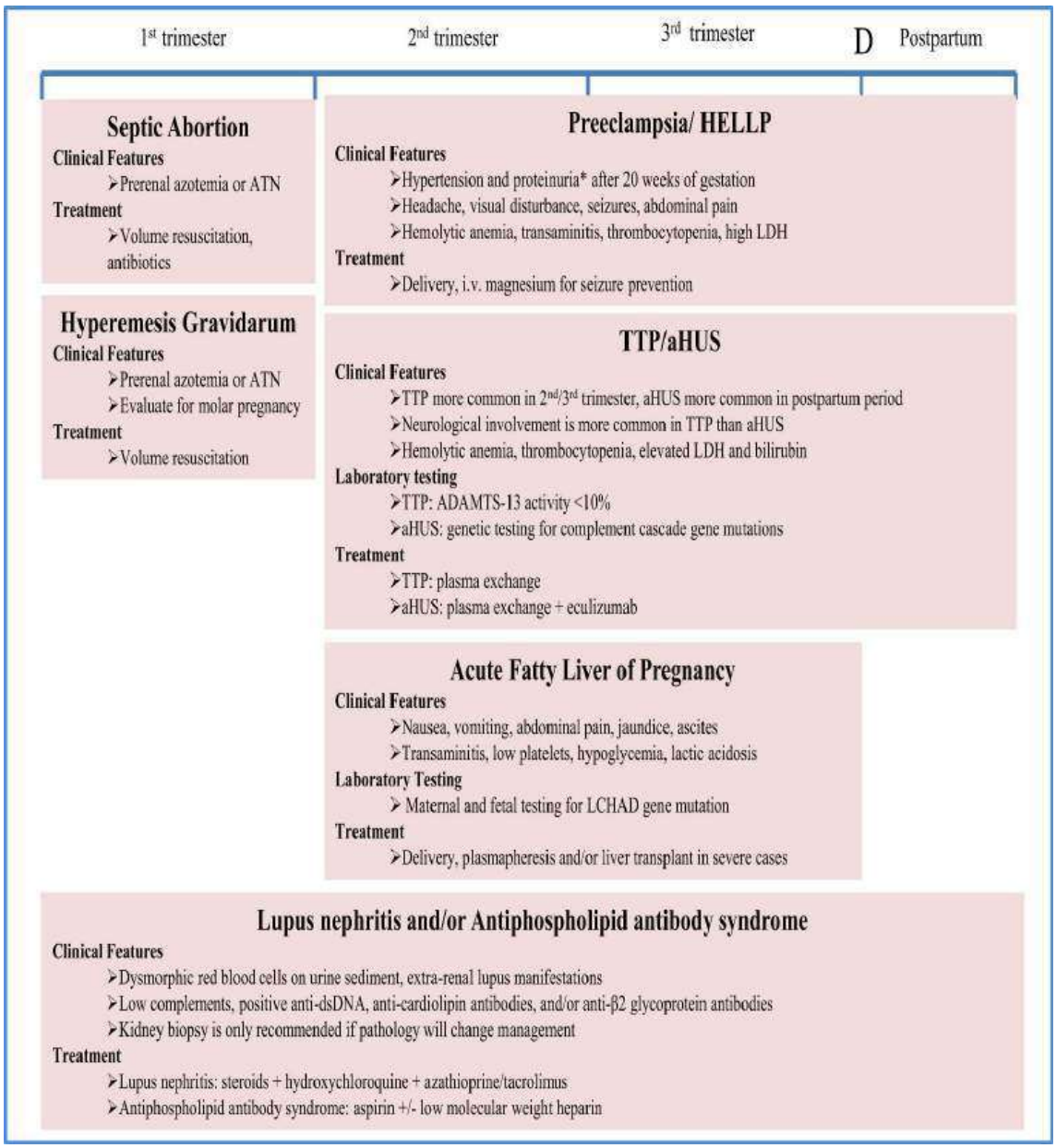
- Diagnosis of AKI in pregnant women (any one of the three)
    1. Sudden increase in serum creatinine >1 mg/dl,
    2. Oliguria/anuria
    3. Need for dialysis.

Physiological Changes in Pregnancy



Causes of P-AKI




1st trimester
2nd trimester
3rd trimester
D
Postpartum
Septic Abortion
Clinical Features
➢Prerenal azotemia or ATN
Treatment
➢Volume resuscitation, antibiotics
Hyperemesis Gravidarum
Clinical Features
➢Prerenal azotemia or ATN
➢Evaluate for molar pregnancy
Treatment
➢Volume resuscitation
Preeclampsia/ HELLP
Clinical Features
➢Hypertension and proteinuria* after 20 weeks of gestation
➢Headache, visual disturbance, seizures, abdominal pain
➢Hemolytic anemia, transaminitis, thrombocytopenia, high LDH
Treatment
➢Delivery, i.v. magnesium for seizure prevention
TTP/aHUS
Clinical Features
➢TTP more common in 2nd/3rd trimester, aHUS more common in postpartum period
➢Neurological involvement is more common in TTP than aHUS
➢Hemolytic anemia, thrombocytopenia, elevated LDH and bilirubin
Laboratory testing
➢TTP: ADAMTS-13 activity <10%
➢aHUS: genetic testing for complement cascade gene mutations
Treatment
➢TTP: plasma exchange
➢aHUS: plasma exchange + eculizumab
Acute Fatty Liver of Pregnancy
Clinical Features
➢Nausea, vomiting, abdominal pain, jaundice, ascites
➢Transaminitis, low platelets, hypoglycemia, lactic acidosis
Laboratory Testing
➢ Maternal and fetal testing for LCHAD gene mutation
Treatment
➢Delivery, plasmapheresis and/or liver transplant in severe cases
Lupus nephritis and/or Antiphospholipid antibody syndrome
Clinical Features
➢Dysmorphic red blood cells on urine sediment, extra-renal lupus manifestations
➢Low complements, positive anti-dsDNA, anti-cardiolipin antibodies, and/or anti-β2 glycoprotein antibodies
➢Kidney biopsy is only recommended if pathology will change management
Treatment
➢Lupus nephritis: steroids + hydroxychloroquine + azathioprine/tacrolimus
➢Antiphospholipid antibody syndrome: aspirin +/- low molecular weight heparin

Preeclampsia

- Definition: Characterized by
  - ✓ New-onset hypertension (blood pressure >140/90 mmHg)
  - ✓ Proteinuria (>300 mg/dl) after 20 weeks of gestation.

- Eclampsia is defined as preeclampsia with the presence of seizure.

Table 5: Severe feature of preeclampsia (one or more of these findings)

Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg on two occasions at ≥4 h apart while the patient is on bed rest
Platelet count <100,000/mm^3
Elevated liver enzymes (twice normal concentrations)
Renal insufficiency (serum creatinine concentration >1.1 mg/dl or doubling of serum creatinine concentration) or oliguria (<500 ml in 24 h)
Pulmonary edema or cyanosis
New-onset cerebral or visual disturbances
Severe persistent right upper quadrant or epigastric pain

Clinical feature	HELLP*	AFLP**	aHUS***	TTP
Time of onset	3T	3T	Postpartum	2T/3T
Hypertension	80%-100%	25%-50%	+	0/+
AKI	Mild/moderate	Moderate	Severe	Mild/moderate
Renal prognosis	Recovery	Recovery	76% ESRD	Fair
CNS findings	+	Absent	Absent	Dominant
Hemolytic anemia	+	0/+	+	++
Thrombocytopenia	+	0/+	++	++
Coagulopathy	0/+	+	0	0
Liver transminases increase	++	++	0	0
LDH (IU/L)	+	0/+	++	++
Ammonia	Normal	High	Normal	Normal
ADAMTS-13 activity <10%	0	0	+	++
Alternative complement pathway	0/+	0/+	++	0
Management	Support measures/ delivery	Support measures/ delivery	Plasma infusion/ exchange	Plasma infusion/ exchange
Effect of delivery on diseases	Recovery	Recovery	None	None

*Urine sediment is bland in preeclampsia/HELLP syndrome, **Coagulopathy, hepatic injury, and hypoglycemia are the key feature of AFLP, ***Isolated LDH increase with normal hepatic transaminase is characteristics of HUS/TTP (P-TMA). 0: Absence, 0/+: Occasionally present, +: Sometimes present, ++: Always present, HELLP: Hemolysis, elevated liver enzymes, and low platelet count, AFLP: Acute fatty liver of pregnancy, aHUS: Atypical hemolytic-uremic syndrome, TTP: Thrombotic thrombocytopenic purpura, AKI: Acute kidney injury, CNS: Central nervous system, LDH: Lactate dehydrogenase, ESRD: End-stage renal disease, P-TMA: Thrombotic microangiopathy of pregnancy

Renal Cortical Necrosis

- Rare condition resulting from severe reduction of renal perfusion caused by vascular spasm, microvascular injury, or intravascular coagulation.

- Abrupt onset of Oliguria, gross Hematuria, flank pain and Hypotension.

- Causes: Placental abruption, Placenta previa, Septic abortion. Prolonged intrauterine fetal death and Amniotic fluid embolism.

- Hypercoagulable state with increased level of coagulation factors with repressed fibrinolytic state.

- Prognostic factors: extent of necrosis, duration of oliguria, and severity of associated conditions.

- Ultrasound: Hypoechoic Rim and Renal Cortical Rim Sign: The hypoechoic rim seen on ultrasound, potentially with an echogenic (brighter) layer outside the rim.

- CT scan: Lack of Cortical Enhancement and Reverse Rim Sign: A specific CT finding where the cortex appears hypo attenuating (darker) and non-enhancing, while the medulla enhances.

- Dialysis as indicated and treatment of the underlying diseases.

HD Prescription during Pregnancy

Frequency	5–6 time/week
Duration of dialysis	>36 h/week (>6 h/day)
Dry weight	Increase by 0.5 kg/week during the second and third trimesters
UF rate	6–8 mL/kg/h
Dialysate	K = 3 mmol/L, Ca = 1.5 mmol/L, HCO3 = 28–32 mmol/L
Anticoagulation	Low-dose unfractionated heparin

HD: hemodialysis; UF: ultrafiltration.

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RENAL ABSCESS

Introduction

- Renal abscesses are collections of walled-off, infected, and Purulent fluid in the Renal Parenchyma that are commonly associated with underlying Pyelonephritis.

- Risk factors: Diabetes Mellitus, Anatomical Abnormalities such as Vesicoureteral Reflux, Neurogenic Bladder, Polycystic Kidney disease, and Ureteral calculi.

- Clinical manifestations of renal abscesses include fever and chills, flank pain with radiation to the abdomen and costovertebral tenderness.

Investigations

- Laboratory findings: Leukocytosis with elevation of Erythrocyte sedimentation rate and C-reactive protein.

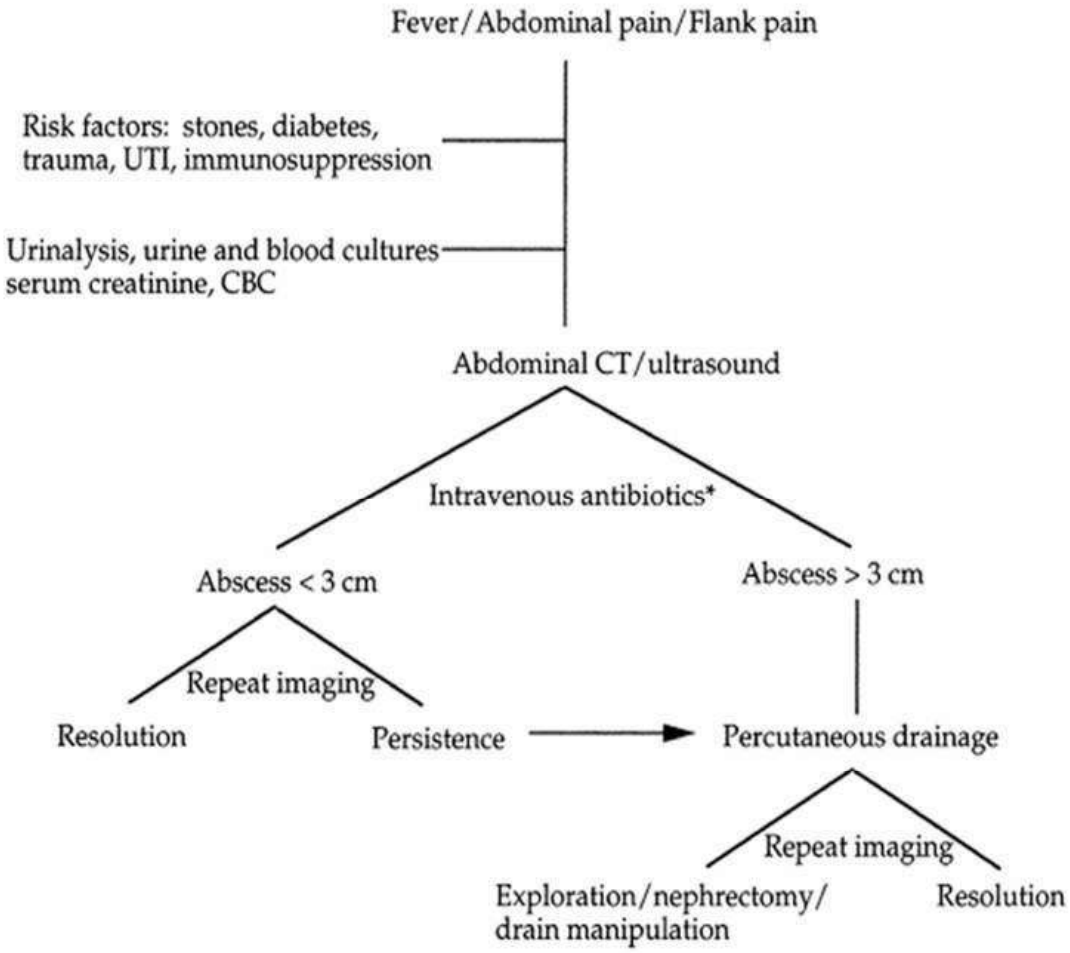
- Contrast enhanced CT is gold standard.

- CT findings of renal abscesses are a focal collection of fluid with a thickened, irregular enhancing wall.

- Other findings: gas within the central fluid, Fascial and Septal changes, and Perinephric fat Plane Dissipation.

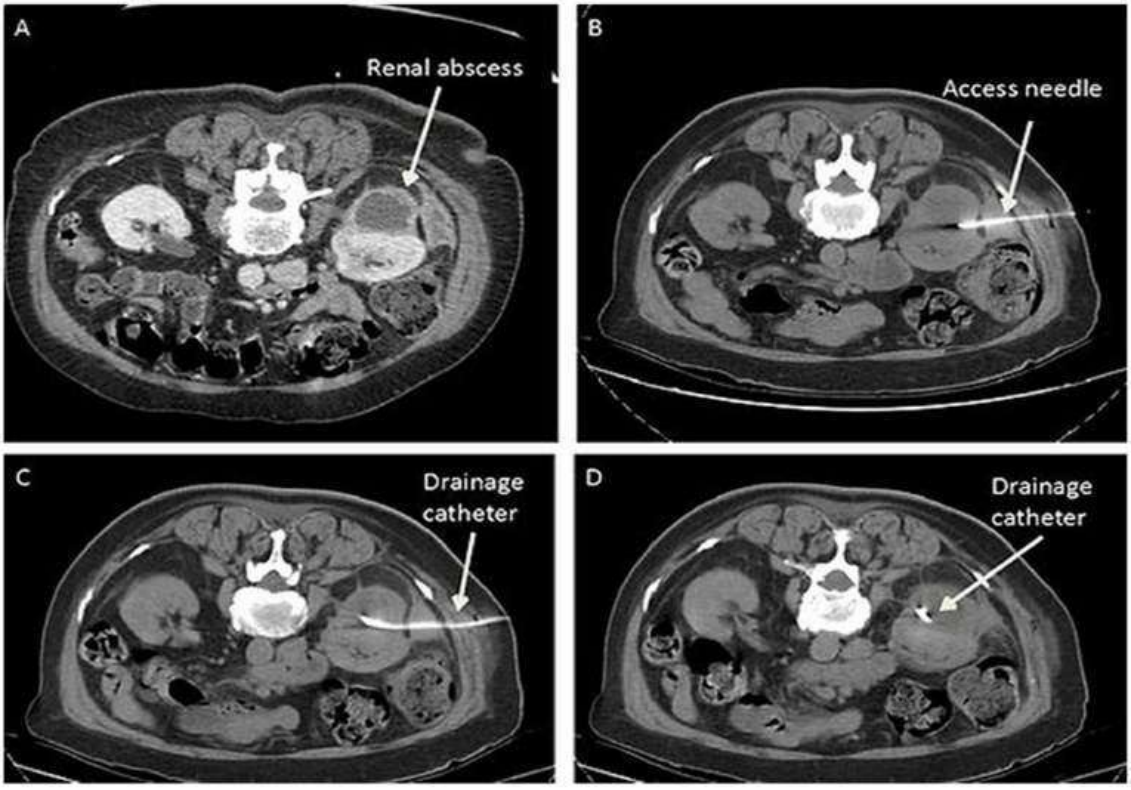
- Ultrasound findings show a Hypoechoic or Cystic mass with lack of vascular flow indicating an infectious process rather than Neoplasm.

Approach To Renal Abscess



*consider urinary drainage if obstruction present

Percutaneous Renal Abscess Drainage



Axial CT images of the abdomen with contrast highlighting right renal abscess with subsequent drainage. A. Right Renal Abscess (white arrow) with ring of Hyperdensity surrounding the fluid collection. B. Percutaneous access needle entering the Renal Abscess (white arrow). C. Insertion of drainage catheter into the abscess (white arrow). D. Drainage catheter coiled in the abscess (white arrow)

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VASCULAR CALCIFICATION [VC]

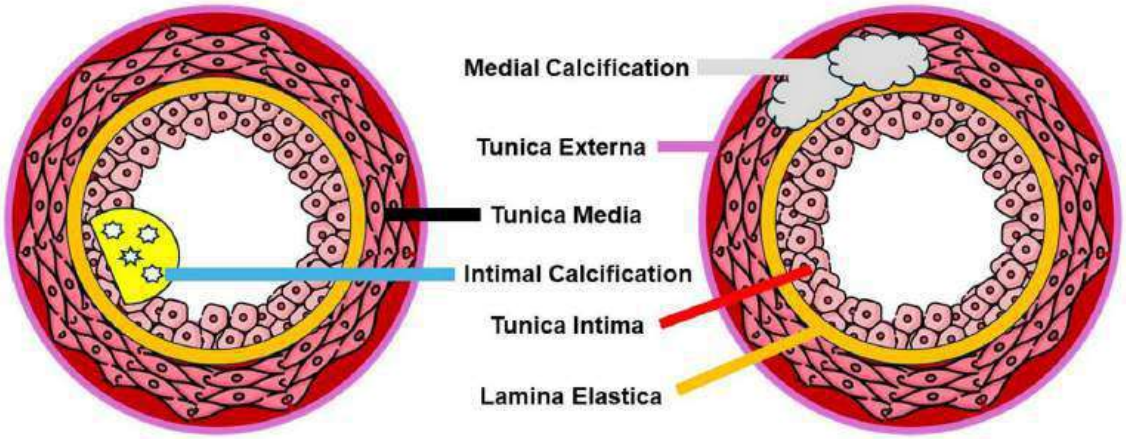
Introduction

- Vascular calcification (VC) is a common Pathological condition in patients with chronic kidney disease (CKD), characterized by the accumulation of Calcium and Phosphate deposits in the walls of blood vessels.

- CKD patients exhibit a significantly higher risk of Cardiovascular mortality compared to the general population, primarily due to their increased predisposition to vascular calcification.

- Risk Factors: Age, Sex, Smoking, Hypertension, Diabetes, Dyslipedemia, Dialysis vintage, Disordered Mineral Metabolism, Calcium, Phosphate, Oxidative stress and inflammation.

- Other risk factors: FGF-23 soluble Klotho, Osteopontin, Calprotectin, Sclerostin, Osteoprotegerin, Bone morphogenic proteins, Matrix Gla protein gene, Fetuin-A, Calciprotein particles (CPP), Magnesium, Zinc, Microbiome, Uremic toxin, and Advanced glycation end-products.



Intimal Calcification

Vessel stenosis
Atherosclerosis
Occlusive arterial disease

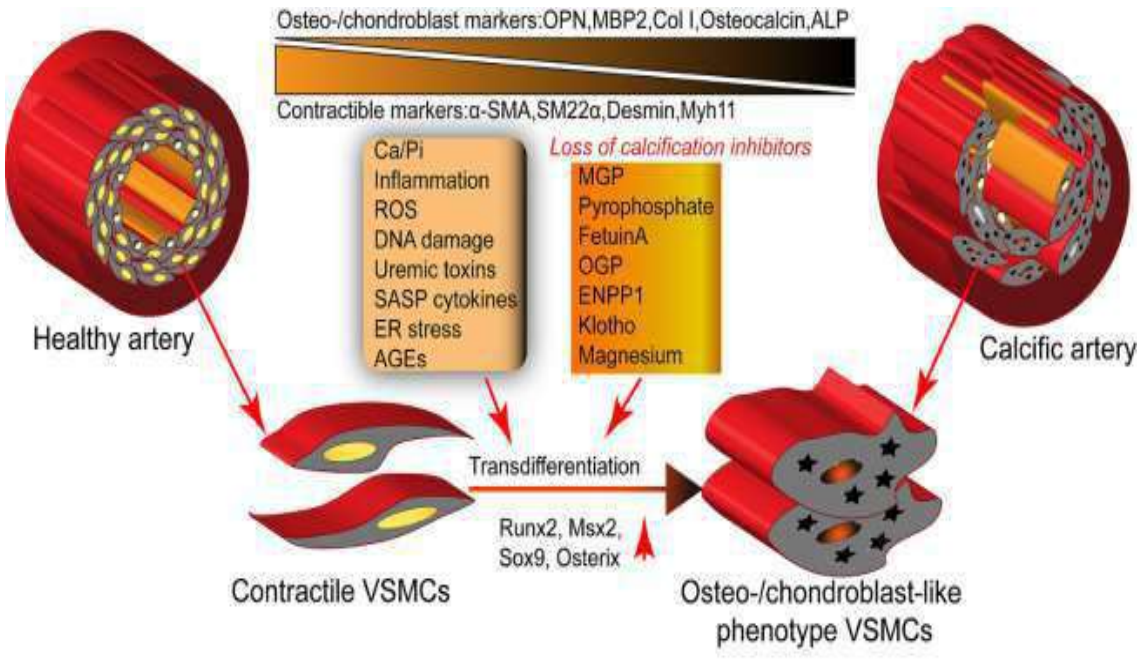
Medial Calcification

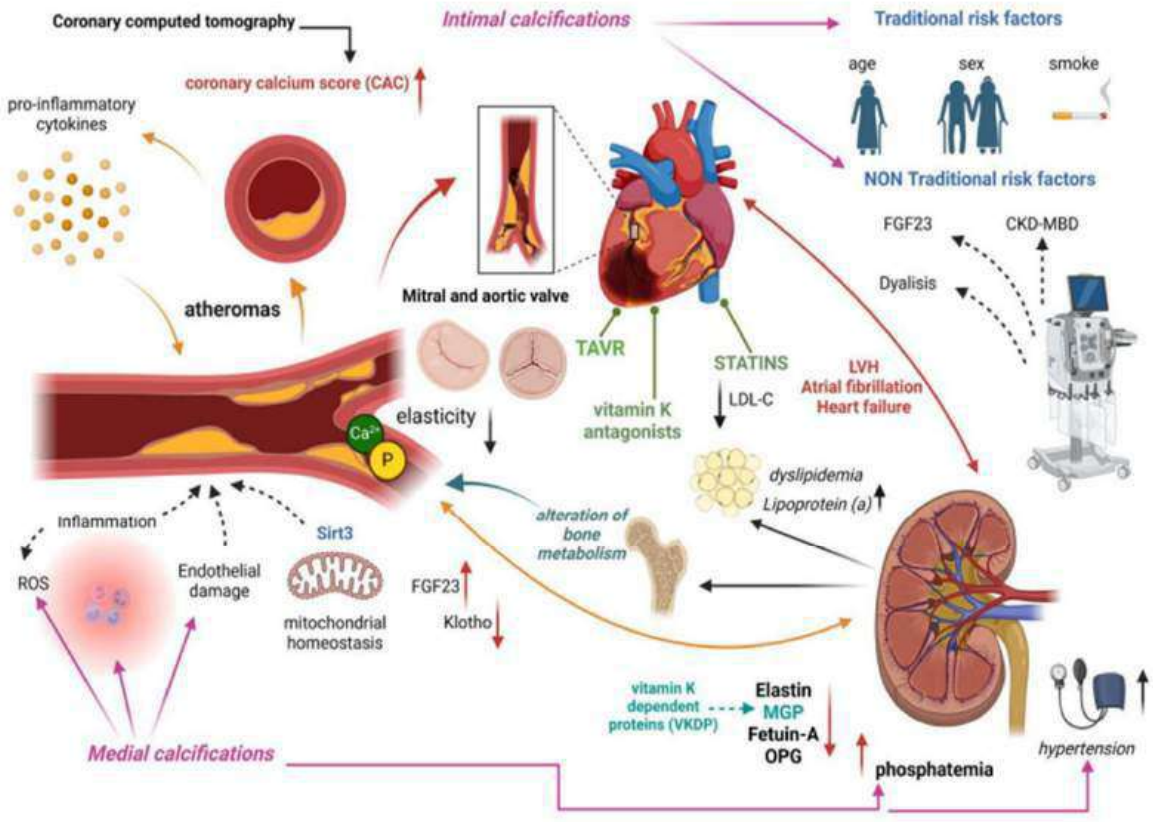
Vessel wall stiffness
Hypertension
Ventricle Hypertrophy

Types of Cascular Calcification

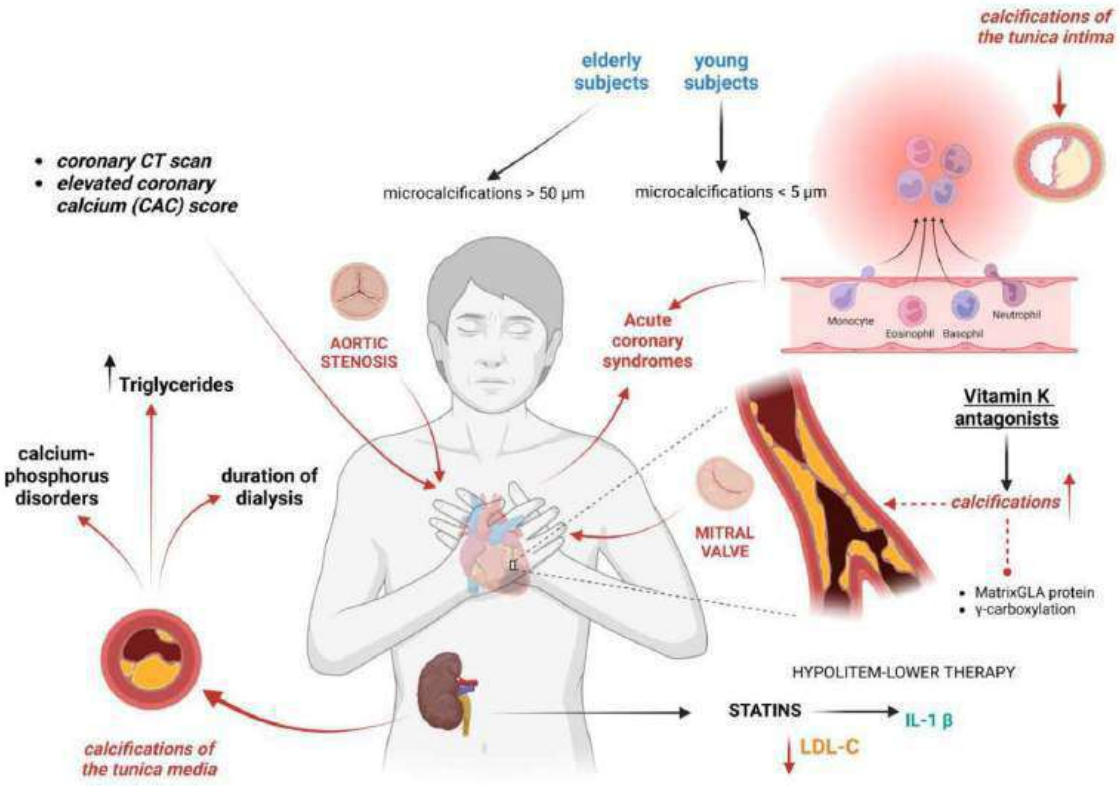
	Intimal calcification	Medial calcification
Distribution	Focal	Diffuse
Mechanism	Associated with lipid deposition and inflammatory infiltration	Can occur without lipid deposition and immune cell infiltration
Deposits	Cholesterol	Hydroxyapatite
Type of ossification	Endochondral	Intramembranous
Pathogenic mechanism	Atherosclerosis Plaque rupture	Arteriosclerosis Increased Cardiac after load
Risk factors	Hypertension DM Hypercholesteremia Smoking.	More prevalent in patients with CKD

Mechanism of Vascular Calcification

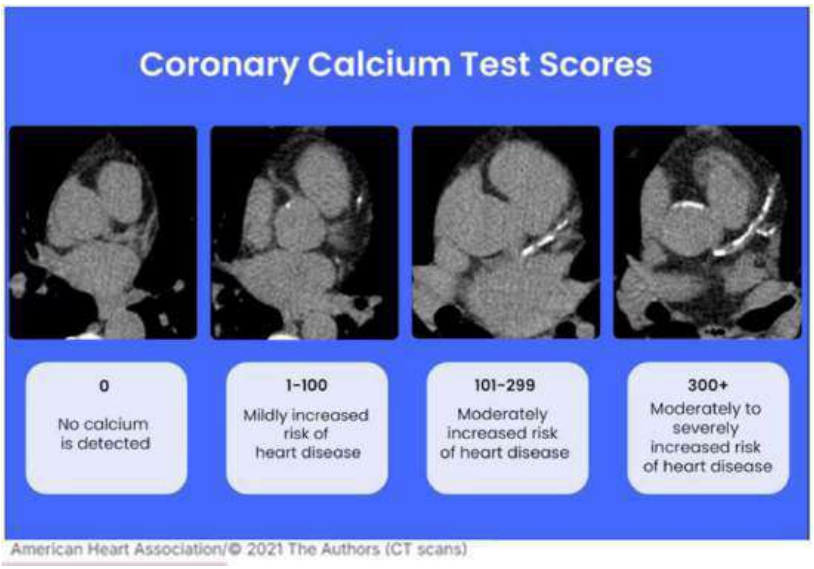




Pathogenic mechanisms of vascular calcification (VC) in chronic kidney disease (CKD). Hyperphosphatemia and hypercalcemia with loss of calcification inhibitors such as fetuin A, Osteoprotegerin, and matrix GLA protein (MGP) promote Osteochondrogenic differentiation of vascular cells. VC is, furthermore, influenced by traditional risk factors (e.g., aging, smoking) and non-traditional factors related to calcium-phosphorus metabolism dysfunction and increased FGF23. The accumulation of minerals in the arterial walls and the degradation of elastin lead to progressive vascular stiffness.



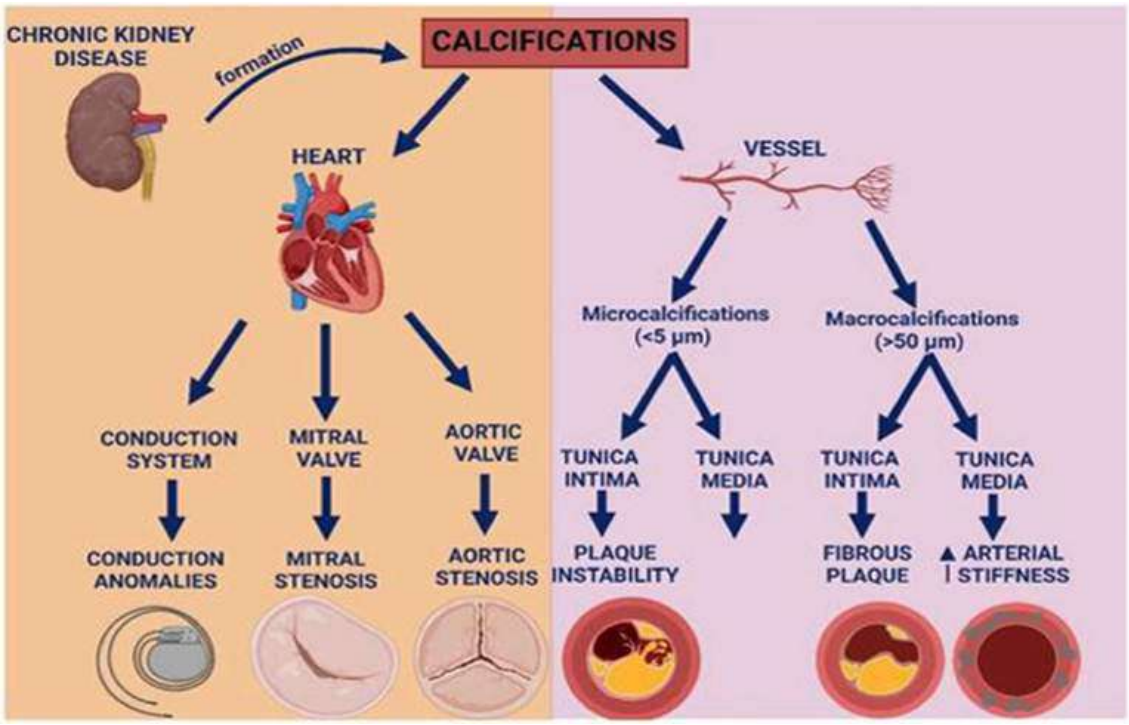
Clinical management of vascular calcifications in CKD patients and intervention strategies to delay the progression.



Investigations

- Plain Xray- lateral abdominal Xray.
- Coronary Artery Calcification scoring using CT (Agatson, Adragao, Kaupilla)
- Echo

Role of micro- and macro calcifications in the large vessels, heart valves, and cardiac conduction system.



Role of micro- and macro calcifications in the large vessels, heart valves, and cardiac conduction system.

Treatment

- No specific therapy to reverse vascular calcification in Chronic Kidney Disease.
- Controlling hyperphosphatemia and optimising CKD-MBD therapies.
- Tenapanor - Reduces intestinal phosphate absorption by inhibiting sodium/hydrogen exchanger 3 (NHE3). Lowers serum phosphate - potentially slows VC.
- Micro RNA therapies and gene therapies [experimental]
- Denosumab - Inhibits osteoclast activity and may reduce vascular osteogenic signalling. [investigational for VC].
- Intensification of dialysis
- For Calciphylaxis:
- Wound care- antibiotics for infected wound, Debridement of necrotic wounds.
- Replace warfarin with LMWH or DOACs.
- Stop vit D analogues
- Sodium Thiosulphate.
- Hyperbaric oxygen therapy

Newer therapies

- Vitamin K- Cofactor for Matrix Gla Protein (MGP) activation, an endogenous inhibitor of vascular calcification. Vitamin K2 (menaquinone) is most effective. Trials ongoing (VitaVasK, VIKTORY).

- SNF472 (Myo-inositol hexaphosphate / Phytate): Direct inhibitor of hydroxyapatite crystal growth (a key step in calcification) without interfering with calcium and phosphorus metabolism. CaLIPSO trial (in hemodialysis patients) showed reduced coronary artery calcification progression. Phase 3 trials ongoing with promising results.

- Magnesium: Competes with calcium; inhibits phosphate-induced calcification of VSMCs. [ongoing trial –DIALMAG- Canada].

- Etelcalcetide: Suppress PTH → reduce Calcium/Phosphate release from bone. May slow progression of VC in dialysis patients (EVOLVE trial – secondary outcomes)

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ATHEROEMBOLIC RENAL DISEASE [AERD]

Introduction

- Cholesterol crystal embolism (CCE) is an under recognized multisystemic disease caused by the displacement of cholesterol crystals from atheromatous aortic plaques to distal vascular beds, leading to ischemic injury of target organs, particularly the kidneys, i.e., atheroembolic renal disease.

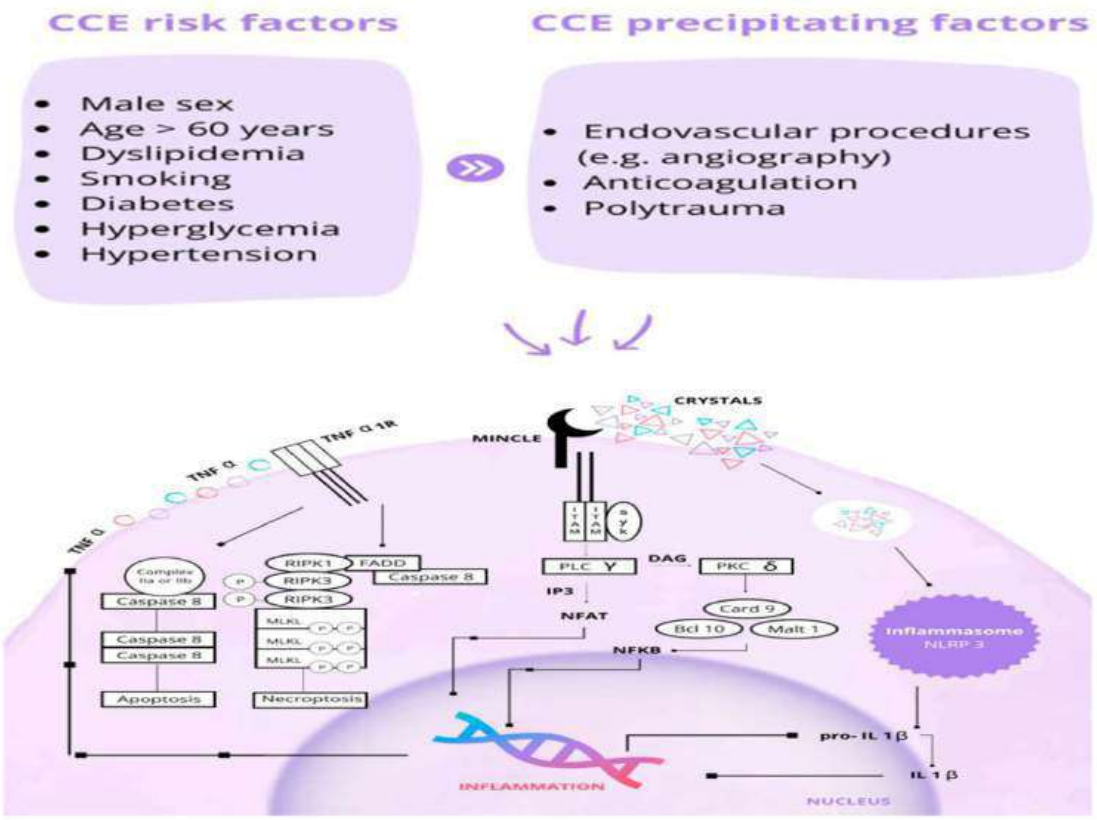
- AERD- Renal failure secondary to occlusion of renal arteries, arterioles, and glomerular capillaries with cholesterol crystals originating from atheromatous plaques of the aorta and other major arteries.

- Atheromatous material can be dislodged spontaneously or after intravascular trauma or anticoagulation.

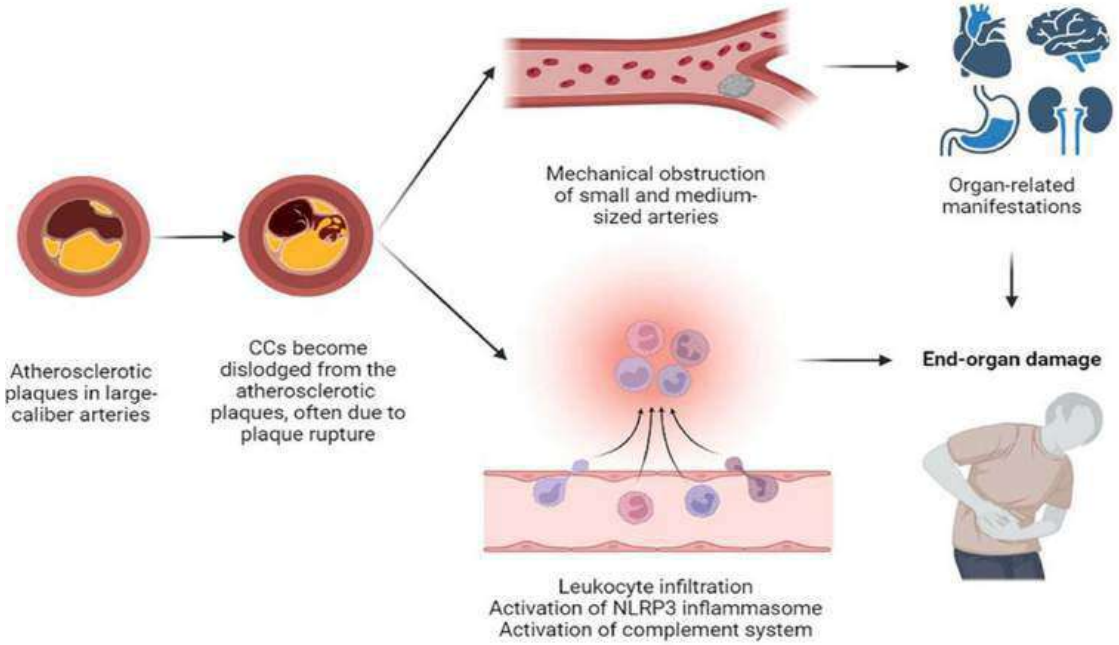
- The exact prevalence of atheroembolic renal disease is unknown- an under-diagnosed condition.

- AERD is often associated with irreversible organ damage with a poor prognosis

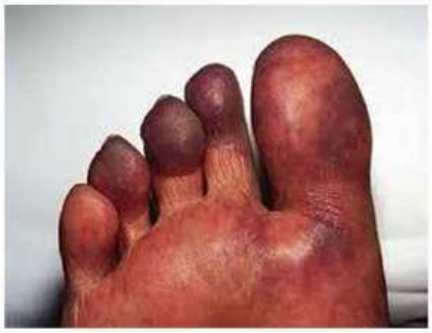
Risk Factors and Patterns of Injury



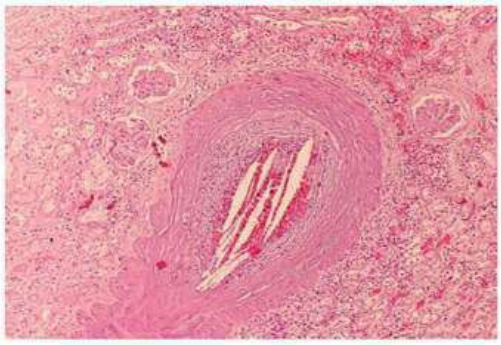
Pathogenesis



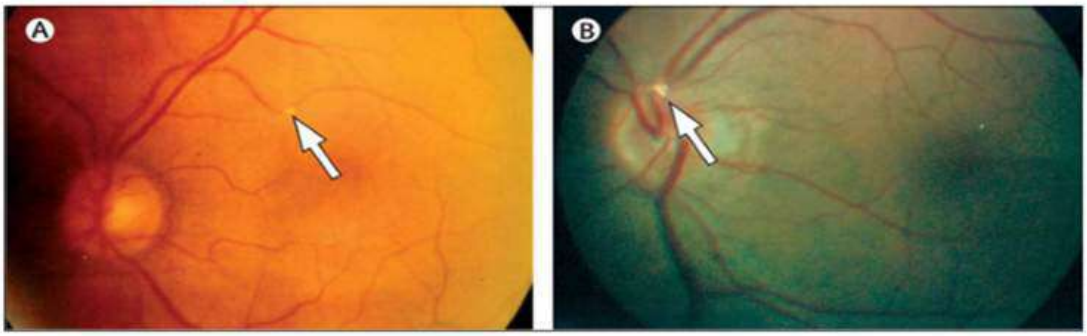
Clinical And Biopsy Indicators



BLUE TOES



BICONVEX ,NEEDLE SHAPED CHOLESTEROL CLEFTS IN RENAL ARTERIES



HOLLENHORST PLAQUES

Renal Involvement

- Acute kidney injury - acute onset, arising within 1 week of a clear causal event, affects 20–30% of patients.
- Sub-acute kidney injury- most common form in which progressive kidney dysfunction occurs 3-8 weeks after the inciting event in staggered
- steps, separated by periods of stable kidney function resembling a staircase pattern.
- Chronic stable renal failure -May mimic ischemic nephropathy and often coexists with it.

- Dialysis is needed in 28–61% of patients with acute or subacute disease, with 20–30% partly recovering kidney function after a variable period of dialytic support.

Lab Tests

- Anemia, leukocytosis, thrombocytopenia, and raised concentrations of inflammatory markers (ESR or C-reactive protein).
- Results of urinalysis are typically benign, with few cells and a minimum amount of proteinuria, occasionally microscopic hematuria.
- Proteinuria and urinary sediment abnormalities are more likely to occur in patients who have glomerular capillary embolization than the more typical arterial involvement.
- Eosinophilia, Eosinophiluria and Hypocomplementemia.

Treatment

- No definitive treatment has been established.
- Therapeutic measures are mostly preventive and supportive.
- Restriction of exposure to precipitating factors.
- Withdrawal of anticoagulant therapy and avoidance of any additional radiological or aortic surgery procedure.

- Steroid use is still controversial, although it could have a role in patients with multi-system involvement, recurrent and progressive disease, and systemic inflammation.
- Statin therapy was independently associated with decreased risk of ESRD.
- During endovascular procedures, use of proper and cautious techniques, including a so-called no touch technique avoiding direct trauma of the catheter tip.
- Renal replacement therapy when indicated.
- The most important predictors of end-stage renal disease needing permanent dialysis therapy were pre-existing chronic renal insufficiency and longstanding hypertension.

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DARATUMUMAB

Introduction

- CD38 is a transmembrane glycoprotein expressed at high levels on plasma cells and NK cells.

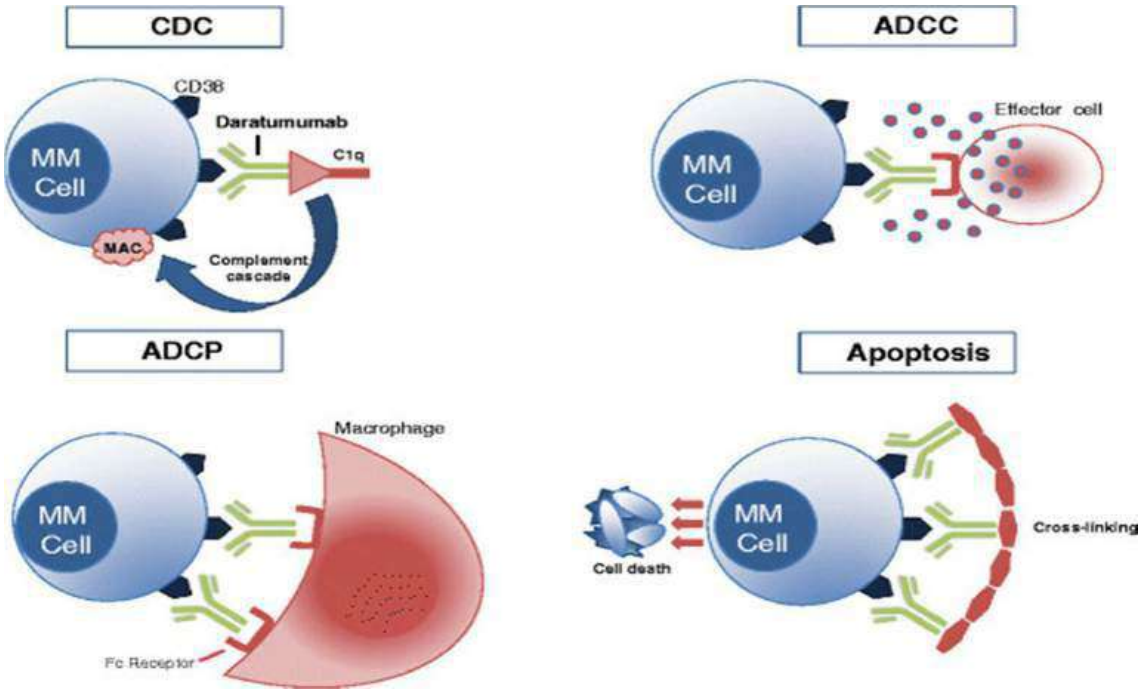
- Daratumumab, a humanized Ig G1-kappa, targets CD38 on plasma and NK cells, is an approved treatment for multiple myeloma and for autoimmune diseases.

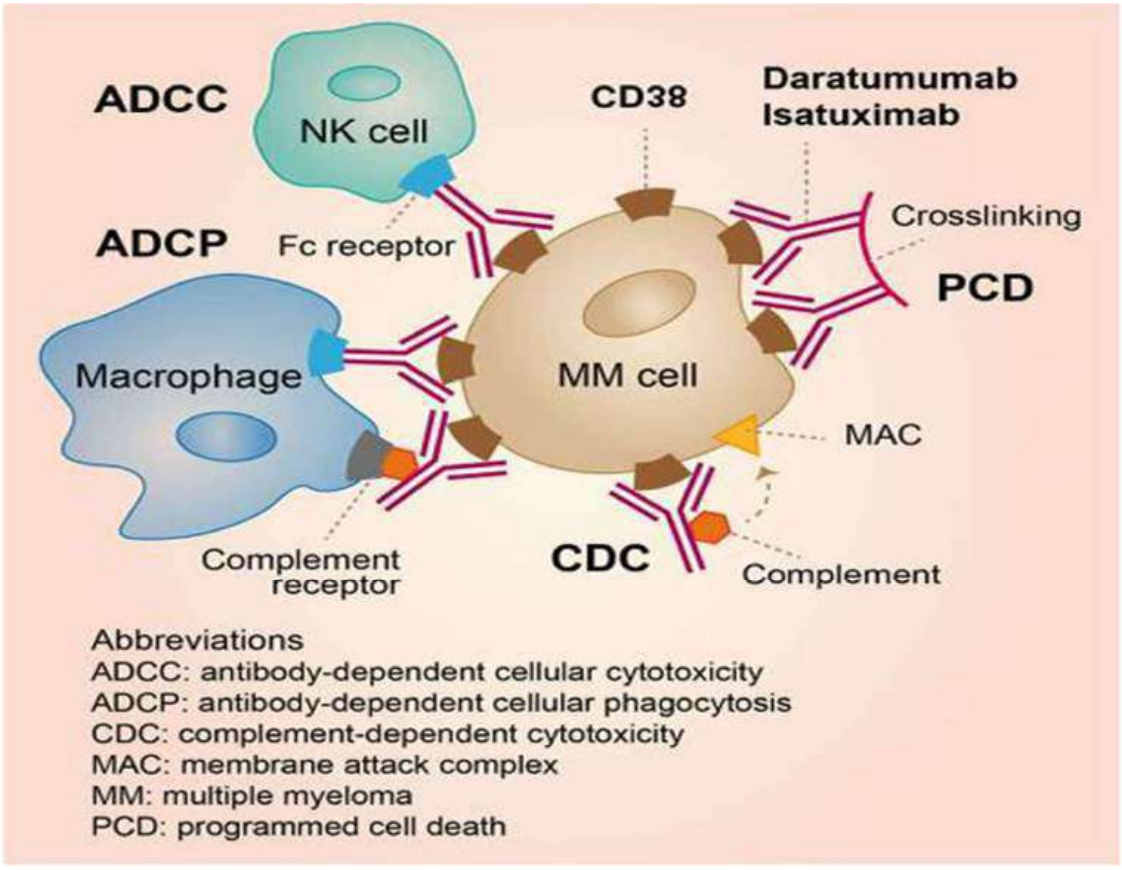
- New role in desensitization and chronic active ABMR.[needs more RCTs].

- Daratumumab reduced total and activated NK cells, which play a role in ABMR

Mechanism of Action

The therapeutic effects of daratumumab in **multiple myeloma** are mainly based on the mechanism that daratumumab **binds to CD38** expressed on the surface of multiple myeloma cells to **induce rapid cell death** of multiple myeloma cells through complement dependent cytotoxicity **(CDC),** antibody dependent cell-mediated cytotoxicity **(ADCC)**, antibody-dependent cellular phagocytosis **(ADCP)**, **apoptosis** upon secondary crosslinking, and **immunomodulatory effects** via a decrease in immune suppressive cells.





Abbreviations
ADCC: antibody-dependent cellular cytotoxicity
ADCP: antibody-dependent cellular phagocytosis
CDC: complement-dependent cytotoxicity
MAC: membrane attack complex
MM: multiple myeloma
PCD: programmed cell death

Daratumumab Reduces Risk of Progression in High-Risk Smoldering Multiple Myeloma

SMOLDERING MULTIPLE MYELOMA: does daratumumab slow progression to active disease?

Randomized Controlled Trial

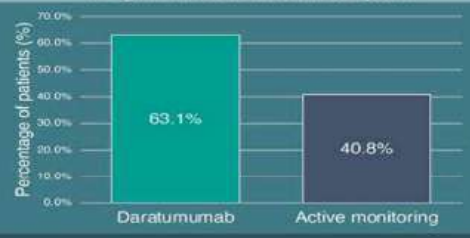
Active monitoring
Continued for 36 months or until confirmation of disease progression

390 patients with high-risk smoldering multiple myeloma randomized in a 1:1 ratio

Daratumumab
1800 mg subcutaneous monotherapy for 39 cycles

PRIMARY OUTCOMES

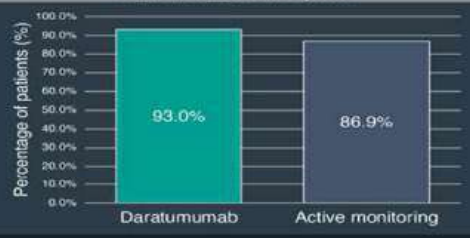
Progression-free survival at 5 years



Hazard ratio 0.49 95% CI, 0.36-0.67 p < 0.001

SECONDARY OUTCOMES

Overall survival at 5 years



Hazard ratio 0.52 95% CI, 0.27-0.98

Subcutaneous daratumumab monotherapy led to significantly lower risk of progression to active multiple myeloma or death among patients with smoldering multiple myeloma.

@2minmed

Dimopoulos, *et al. NEJM*. December 9, 2024.

Anti-CD38 Daratumumab Treatment of Chronic Active Antibody-mediated Kidney Allograft Rejection

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Study Design & Cohort

Retrospective Review

Adult KTR
Feb 2022 – Aug 2023

KTR with cABMR diagnosed > 6 months post-transplant

Monitored Outcomes: eGFR, uACR, dd-cfDNA, DSA, renal biopsy, adverse events

Intervention

Subcutaneous Daratumumab

Flat dose 1,800 mg

Weekly for 4 weeks, followed by 3 quarterly doses

Findings

N=16
Adults with KTR diagnosed with cABMR
Median time transplant to treatment = 9 years

Biopsy Histology, 10 months After Treatment

13/16 showed improved microvascular inflammation scores

8/16 showed ABMR score decline (median ↓74%)

eGFR levels remained stable

11/16 showed uACR improvement

dd-cfDNA significantly decreased (median ↓85%)

eGFR, estimated glomerular filtration rate; uACR, urine albumin/creatinine ratio; DSA, donor-specific antibody

KIREPORTS
Kidney International Reports

Lye WC et al, 2025

Visual abstract by:
Jade Teakell, MD PhD
@jmteakell

Conclusion Subcutaneous daratumumab may be an effective treatment for chronic active antibody-mediated rejection (cABMR); larger randomized trials are warranted to study its role in the treatment for cABMR in kidney transplant recipients (KTR). Donor-derived cell-free (dd-cfDNA) may be a useful monitoring tool to predict and detect relapses.

Table 1 Daratumumab Premedication Protocol Used at Cedars-Sinai Medical Center Before This Study

Administer the following medications 1-3 hours before every infusion of daratumumab:

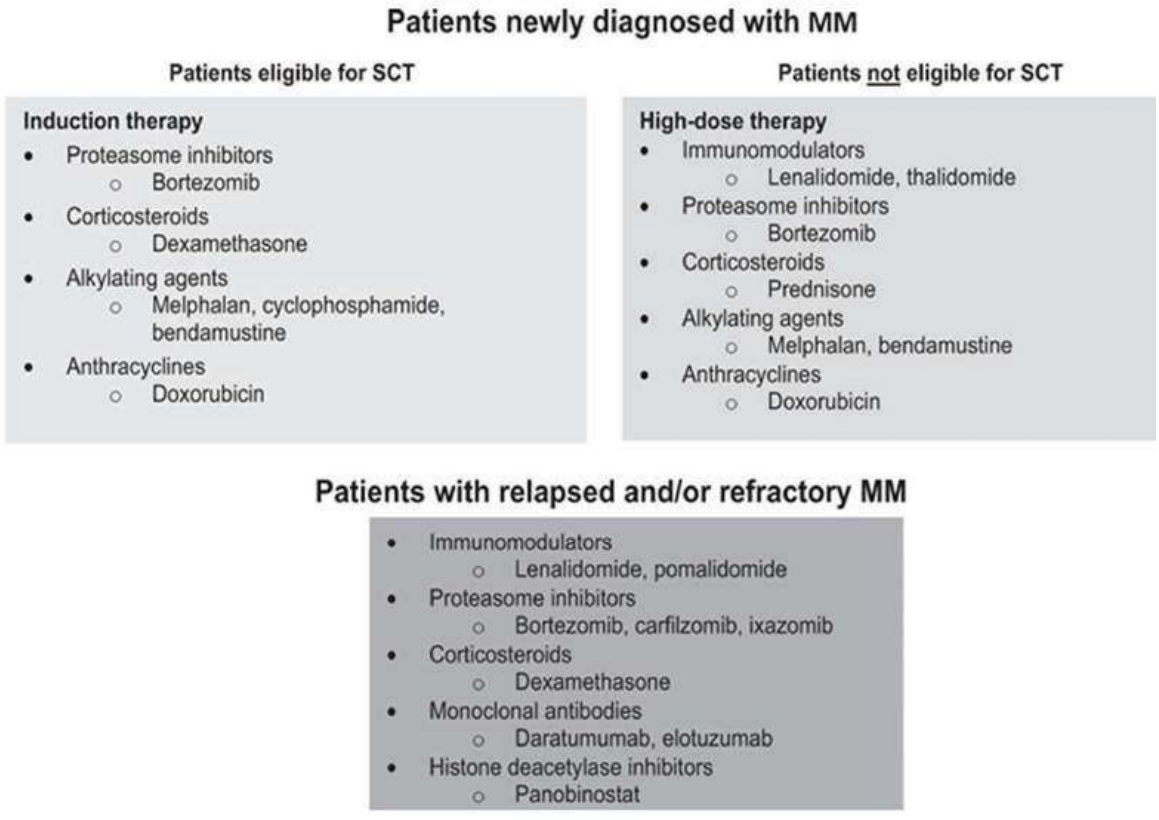
Acetaminophen 650 mg, orally

Diphenhydramine 50 mg, via intravenous push

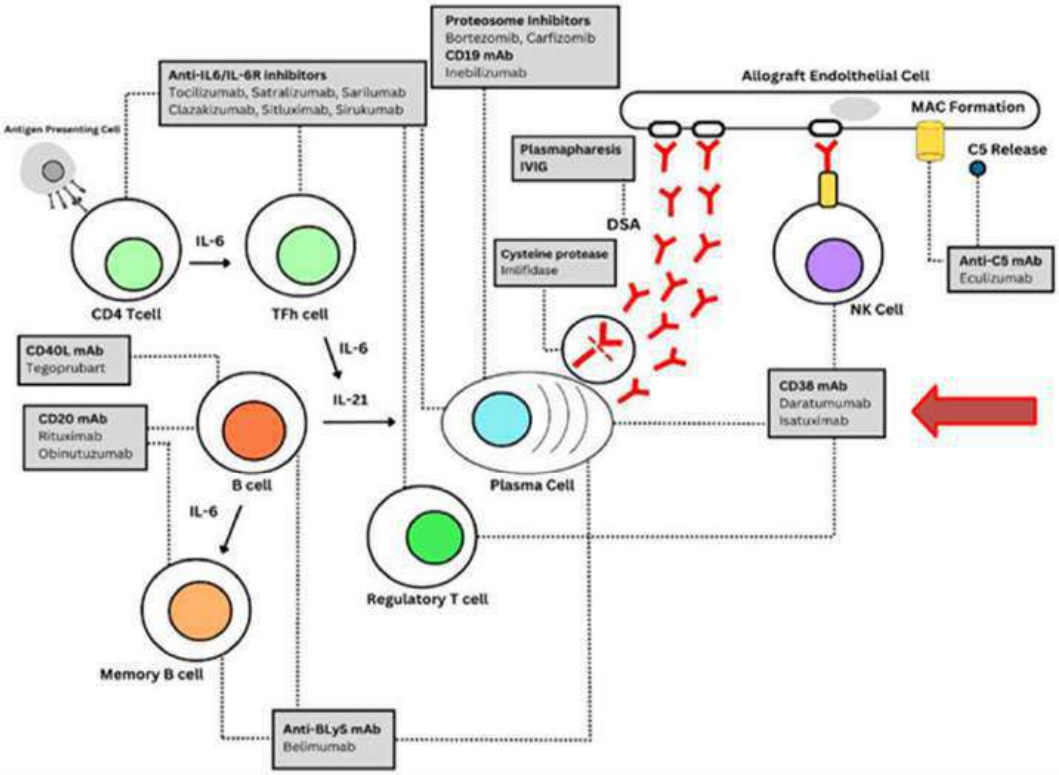
Dexamethasone 20 mg, given intravenously before first infusion, then orally for subsequent infusions, if tolerated

Montelukast 10 mg, orally, before the first infusion only

Famotidine 20 mg, intravenously, before the first infusion only



Emerging therapies in ABMR



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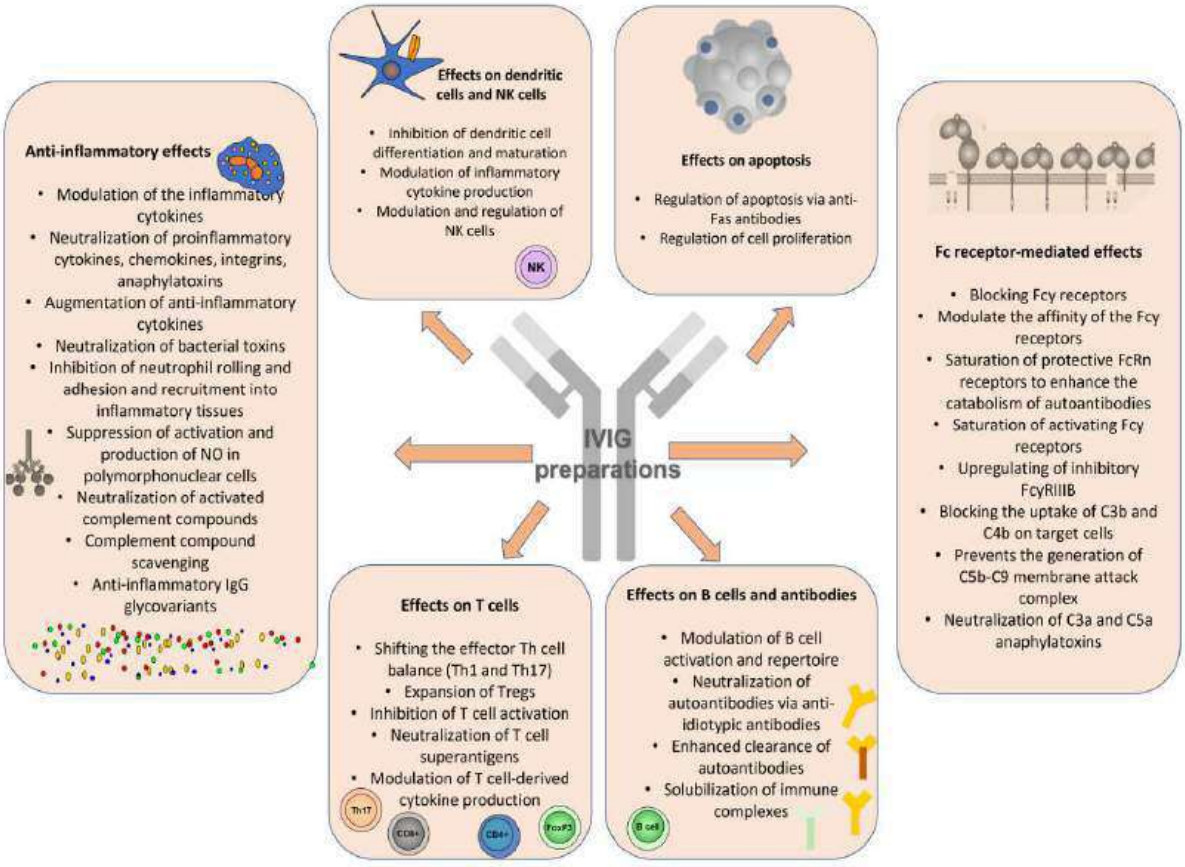
IV
IMMUNOGLOBULIN IN NEPHROLOGY

Introduction

- First commercial immunoglobulin product for IVIG was approved in 1980.
- Uses in nephrology:- Desensitization, ABMR, ABOi kidney transplantation, Post transplant infections [BKV].
- Components IV IG: - Immunoglobulin G (IgG) constitutes 95-98% of the preparation. Mainly IgG1 IgA and IgM - present in small amounts, cytokines and soluble receptors

Actions and Effects



Desensitization using IVIG alone for living-donor kidney transplant: impact on donor-specific antibodies

BRAZILIAN JOURNAL OF NEPHROLOGY
JORNAL BRASILEIRO DE NEFROLOGIA

METHODS AND RESULTS

Retrospective study

Medical record data

Single center

From January, 2003 To December, 2014

45 sensitized patients

33 patients continued in the study

Positive cross-match (CDCXM ou FCXM) against potential living donor

Median 6 infusions

Monthly IVIG infusions (2 g/kg) only until they had a negative T-cell and B-cell FCXM

66.7% Living donor transplant

12.1% Did not undergo transplant

21.2% Deceased donor transplant

Antibody-mediated rejection 27.3%

Graft survival

1 year 86.4% | 3 years 86.4% | 5 years 79.2%

Patient survival

1 year 95.5% | 3 years 95.5% | 5 years 83.7%

Conclusions: Desensitization using IVIG alone is an effective strategy, allowing successful transplantation in these highly sensitized patients.

Referência: Ulisses LRS, et al. Braz J Nephrol. 2022. DOI: https://doi.org/10.1590/2175-8239-JBN-2021-0200.

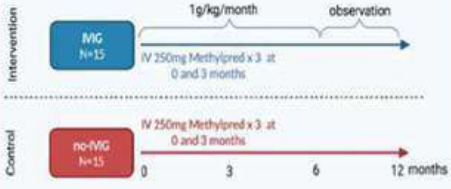
Visual abstract by Jenyffer Ribeiro Bandeira

A randomized controlled trial of intravenous immunoglobulin vs standard of care for the treatment of chronic active antibody-mediated rejection in kidney transplant recipients

kidney INTERNATIONAL
ISN

Cohort/Methods

- Kidney transplant recipients with chronic active antibody mediated rejection were randomized 1:1 to intravenous immunoglobulin (IVIG) or standard of care.

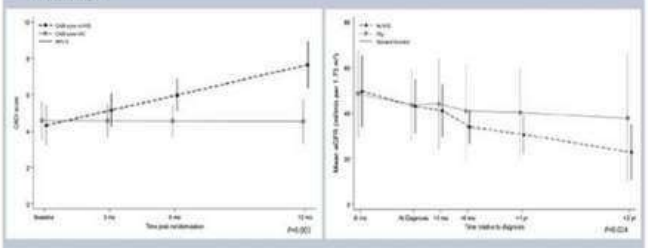


Investigations (clinical, biopsy, serology) performed at 0,3,6,12 months

Endpoints:

- **Primary** – chronic allograft damage index (CADI)
- **Secondary** – estimated glomerular filtration rate (eGFR), donor specific anti-HLA antibodies (DSA), allograft & patient survival and intragraft mRNA expression.

Findings:



1. IVIg stabilized histological damage
2. IVIg stabilized eGFR
3. IVIG did not reduce donor specific antibodies or proteinuria
4. Patient and allograft survival was similar at 12 months
   - At 5 yrs, 0 deaths in IVIG and 5 deaths in no-IVIG group
5. IVIg stabilized/reduced intragraft gene transcripts – particularly B-cell, T-cell, NK-cell and fibrosis associated transcripts.

Mulley et al, 2025

CONCLUSION: In kidney transplant recipients with chronic active antibody mediated rejection, IVIG therapy stabilized allograft histology, function and intragraft gene transcripts.

IV IG in post-transplant infections

- Treating Parvovirus B19, Polyoma BK virus and Cytomegalovirus (CMV).
- Mechanisms:
    - Broad-spectrum neutralizing antibodies against viruses.
    - Complement inhibition (↓ MAC, ↓ C3 convertase activity).
    - Anti-inflammatory modulation of immune responses in infected tissues.
    - In BKVN: - Combining immunosuppression reduction with IVIG therapy showed the most significant benefit for viral clearance.
- Parvo –B19:- IVIG therapy contains neutralizing antibodies against HPV-B19. Dose: IVIG 2 g/kg over 2–5 days

Complications of IVIG

Adverse effect	Predisposing factors
Flu-like symptoms	High dose, rapid infusion rate, accompanying infection, previous adverse effects
Dermatological adverse effects	High dose, rapid infusion rate, accompanying infection, male patients with chronic inflammatory demyelinating polyneuropathy
Arrhythmia and hypotension	History of heart disease
Transfusion-related acute lung injury	Rapid infusion rate
Thrombotic events	High dose, rapid infusion rate, advanced age, being bedridden, diabetes mellitus, hypertension, dyslipidemia, prior/current thrombosis, preexisting atherosclerotic disease, elevated serum viscosity, oral contraceptive use, hereditary hypercoagulable state, idiopathic thrombocytopenic purpura
Aseptic meningitis	High dose
Renal impairment	Rapid infusion rate, advanced age, renal insufficiency, nephrotic syndrome, diabetes mellitus, dehydration, sepsis paraproteinemia, nephrotoxic drugs, hemolysis, sucrose-containing preparations
Hemolysis	High dose, rapid infusion rate, non-O blood group, underlying inflammatory state

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CONTINUOUS GLUCOSE MONITORING

Use of CGM

Indications

- HbA1c unreliable in CKD due to altered RBC lifespan, ESA/transfusions.
- Glycemic variability and hypoglycemia under-recognized in dialysis.
- Use CGM when:
    - ♦ Recurrent hypo/hyperglycemia.
    - ♦ Insulin-treated CKD or transplant patients.
    - ♦ Suspected “glycemic blindness” in dialysis.
    - ♦ Research or audit of glycemic trends.

Clinical Goals •

- Identify hidden dysglycemia.
- Optimize insulin/diet/dialysis timing.
- Reduce hypoglycemia and variability

CGM Systems Available in India

CGM Systems Available in India

Device	Type	Wear Time	Alarms	Calibration
Freestyle Libre Pro / 2	Professional & Real-time	14 days	Optional (Libre 2)	None
Medtronic Guardian Connect	Real-time	7 days	Yes	2/day
Dexcom G7		10 days	Yes	Factory-calibrated
Eversense (Implantable)	Long-term	90 days	Yes	Yes

Procedure, Key Metrics, and Interpretation

Clinic protocol

- Identify patient & explain CGM purpose.
- Apply sensor (arm/abdomen); record start date/time.
- Advise normal diet & activity; note dialysis days.
- Retrieve data after 14 days → generate AGP (Ambulatory Glucose Profile).
- Review with team → adjust insulin/diet.

Key Metrics

Metric	Target	Clinical Implication
TIR (70–180 mg/dL)	>70%	Optimal control
Time<70mg/dL	<4%	Avoid Hypoglycemia
GV (CV%)	<36%	Minimize oxidative stress
GMI	-	HbA1c equivalent

Benefits and Practical Insights

Advantages	Limitations
• Accurate glycemic assessment when HbA1c unreliable. • Detects intradialytic and nocturnal hypoglycemia. • Enables fine-tuning insulin, diet, and dialysis protocols. • Improves patient safety and confidence.	• Sensor site reactions, data gaps with hypotension. • Cost and data interpretation training needed. • Accuracy may drop with fluid overload or poor perfusion.

CGM bridges the gap le by HbA1c in CKD — a prac cal, data-driven tool to personalize diabetes care in nephrology prac ce.

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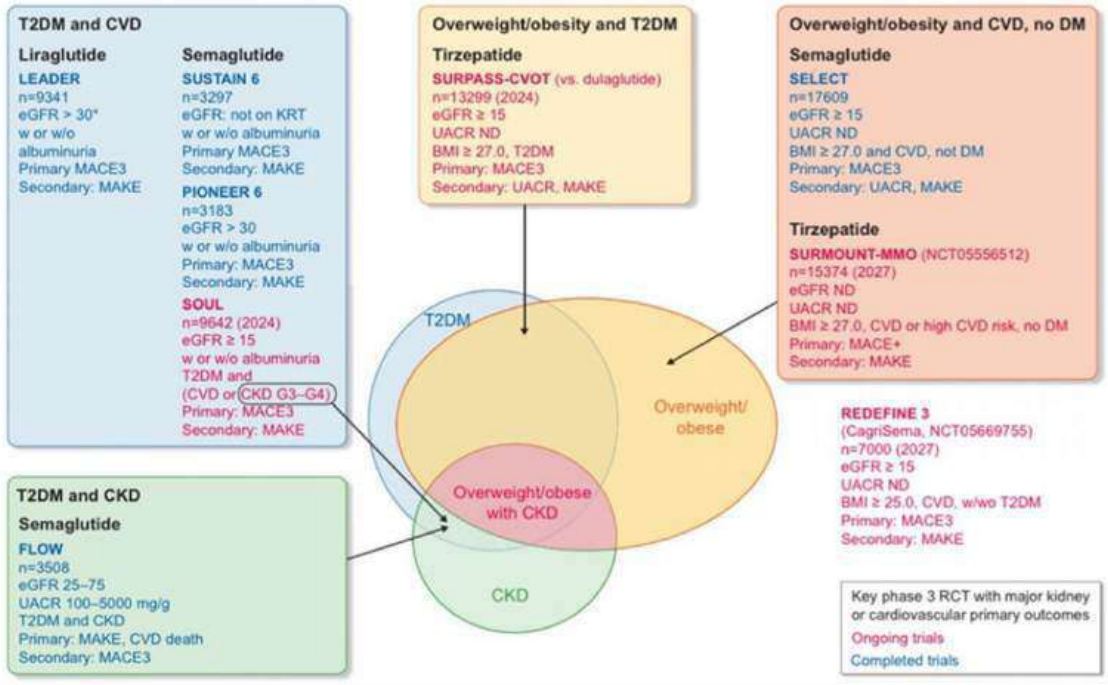
GLP-1 RECEPTOR AGONISTS IN NEPHROLOGY PRACTICE

GLP-1 Receptor Agonists — Overview

- Incretin-based therapy acting via GLP-1 receptor stimulation
- Proven cardio-renal-metabolic benefits beyond glycaemic control
- Agents: Liraglutide, Semaglutide, Dulaglutide, Exenatide, Lixisenatide, Tirzepatide
- Major outcome trials: LEADER, SUSTAIN-6, REWIND, FLOW (2024), SURPASS series (Tirzepatide)
- Now emerging as 4th pillar in diabetic kidney disease (DKD) management

Trials in GLP 1 analogues



Mechanism of Action

- ↑ Glucose-dependent insulin secretion
- ↓ Glucagon secretion
- Delayed gastric emptying → improved post prandial control
- Promotes satiety → weight loss
- Renal effects:
    1. ↓ Intraglomerular pressure
    2. ↓ Albuminuria
    3. Anti-inflammatory and anti-oxidative actions

Dosing & Titration

Agent	Dose Schedule	Renal Consideration
Liraglutide	0.6 → 1.8 mg SC daily	Use with caution in CKD
Dulaglutide	0.75 → 1.5 mg SC weekly	Use with caution
Semaglutide (inj.)	0.25 → 1 mg SC weekly	
Oral Semaglutide	3 → 14 mg daily	Safe in mild–mod CKD
Exenatide	5–10 µg SC BID	Avoid if eGFR < 30
Lixisenatide	10–20 µg SC daily	Avoid if eGFR < 30
Tirzepatide	2.5 → 15 mg SC weekly (increase every 4 weeks)	No dose change needed in CKD

Practical points:

- Not first-line for hyperglycaemia.
- Do not combine with DPP-4 inhibitors.
- Slow titration in patients with diabetic retinopathy (monitor within 6 months).

Contraindications

- Personal/family history of medullary thyroid carcinoma
- MEN 2A/2Bsyndromes
- Prior pancreatitis
- Severe gastrointestinal disease (gastroparesis, obstruction)
- Renal impairment:
- Exenatide, Lixisenatide contraindicated if eGFR <30 ml/min
- Liraglutide, Dulaglutide, Semaglutide, Tirzepatide– use with caution

Adverse Effects & Use in Transplant

Adverse Effects

- Nausea, vomiting, diarrhea, constipation
- Tachycardia, mild injection-site reactions– Usually transient; improve with gradual up-titration

Use in Transplant Recipients

- Useful in post-transplant diabetes and obesity
- May lower insulin requirement and body weight

- No known direct nephrotoxicity
- Monitor tacrolimus/cyclosporine levels if GI absorption issues occur

Take-Home Message

- GLP-1 RAs and Tirzepatide target multiple pathways: glycaemic, renal, cardiovascular, metabolic
- 4th pillar of DKD management alongside RAAS blockade, SGLT2 inhibitors, and MRAs
- Adverse effects manageable with slow titration and patient education
- Cost and access remain major limitations for routine nephrology practice

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TYPE IV RENAL TUBULAR ACIDOSIS

Overview: Type IV RTA

- Most common form of RTA
- Normal anion gap metabolic acidosis with hyperkalemia.
- Urine pH < 5.5, mild renal insufficiency ϖ Impaired ammonia synthesis → ↓ NH_4^+ excretion → Positive UAG.
- Tubular disorder (Chronic tubulointerstitial disease).
- New term: *Hyperkalemic RTA / Tubular Hyperkalemia*

Etiology

Chronic Tubulointerstitial Causes

- Analgesic nephropathy
- Obstructive nephropathy
- Sickle cell nephropathy
- Lead nephropathy
- Diabetes mellitus

~50% of Type IV RTA occurs in diabetic patients

Other Associations

- Chronic kidney disease
- Primary adrenal insufficiency

Genetic causes:

- Congenital hypoaldosteronism (21-hydroxylase deficiency)
- Pseudo hypoaldosteronism type 2 (Gordon’s syndrome)

Pathophysiology

- Hyporeninemic hypoaldosteronism (commonest mechanism)
- ↓ Renin and/or aldosterone → ↓ distal Na^+ reabsorption → ↓ K^+ and H^+ secretion
- ↓ Cortical collecting tubule responsiveness
- Impaired NH_4^+ synthesis → ↓ acid excretion
- **Result**: Hyperkalemia + normal anion gap metabolic acidosis.

Urine Indices

- Urine Anion Gap (UAG):
- $(U\ Na^+ + U\ K^+) - U\ Cl^-$
- Normal: −50 to −20 mEq/L
- Indirect measure of urinary NH_4^+ excretion
- GI HCO_3^-loss → ↑ NH_4^+ → UAG negative
- RTA → ↓ NH_4^+ → UAG positive
- Transtubular K^+ Gradient (TTKG):
- Low in Type IV RTA (↓ distal K^+ secretion)

Drug-Related Causes

ACE inhibitors
ARBs
Mineralocorticoid receptor antagonists (spironolactone, eplerenone)
Direct renin inhibitors
β-blockers
NSAIDs
Calcineurin inhibitors (cyclosporine, tacrolimus)
Heparin & analogues
Trimethoprim, herbal preparations

1. **Management**

- General Measures
- Stop or reduce offending drugs (NSAIDs, ACEi/ARB, MRAs, etc.)
- Manage hyperkalemia: Calcium gluconate, insulin, newer K^+ binders
- Treat hyperglycemia
- Monitor ECG; temporary HD if severe
- Specific Measures
- Fludrocortisone 0.1–0.2 mg/day (selected cases)
    1. Watch for HTN, edema, alkalosis •
    2. Avoid in volume overload or heart failure
- Before RAASi initiation: •
    1. Check eGFR, S. Cr, S. K^+
    2. Review every 2 weeks initially

Type IV RTA is common in diabetics, potentiated by RAAS blockade, and diagnosed via UAG/TTKG — respond well to drug withdrawal, K^+ correction, and cautious fludrocortisone use

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CYTOMEGALOVIRUS NEPHROPATHY IN A TRANSPLANT SETTING

Overview of Cytomegalovirus (CMV) in Transplantation

The Pathogen

- Beta -Herpes virus with the largest genome in the herpes family.
- Double-stranded linear DNA virus that replicates only in human cells.

Clinical Spectrum

- CMV Syndrome: Viral replication + constitutional symptoms (fever, malaise, leukopenia) without tissue invasion.
- Tissue-Invasive Disease: Evidence of end-organ damage (e.g., Nephritis, Colitis, Pneumonitis, Retinitis).

Indirect Effects

- Increased risk of bacterial/fungal infections and Post-Transplant Lymphoproliferative Disorder (PTLD).
- Associated with cardiovascular events and new-onset diabetes.

Epidemiology & Risk Stratification for CMV Nephritis

Prevalence

- Rare complication: Identified in ~0.2% of kidney transplant biopsies.
- Typical Onset: 1–7 months post-transplant.

High-Risk Factors

- Serology: Donor Positive / Recipient Negative (D+/R-) is the highest risk group.
- Immunosuppression:
    1. Induction with Antithymocyte Globulin (ATG).
    2. Maintenance with Mycophenolate Mofetil (MMF).
- Clinical History: Sepsis, neutropenia, and previous acute rejection episodes.

Diagnosis: The Gold Standard

Laboratory Testing

- PCR (Quantitative NAT): First-line systemic test. High viral load supports diagnosis but is not confirmatory for nephritis.

Renal Biopsy (Gold Standard)

- Pathognomonic Feature: "Owl’s eye" intranuclear and intracytoplasmic viral inclusion bodies.
- Location: Primarily tubular epithelial cells; occasionally endothelial cells or podocytes.
- Histological Pattern:
    1. Patchy lymphoplasmacytic infiltrate with tubulitis.
    2. Cytopathic changes: Enlarged tubular epithelial cells with enlarged nuclei.
    3. Most common lesion: Tubulointerstitial nephritis

Differential Diagnosis: CMV vs. Acute Rejection

The Diagnostic Challenge

- CMVtriggers acute cellular rejection (ACR) via HLA upregulation and innate immune activation.
- Differentiation is critical as treatments are opposing (reducing IS for CMV vs increasing IS for Rejection).

Histological Clues

- Favoring CMV Nephritis: Viral inclusions, plasma cell-rich infiltrate, focal necrosis, patchy inflammation.
- Favoring Acute Cellular Rejection: Moderate to severe tubulitis (without inclusions), Endothelitis, Arteritis (Banff v-lesions).

Co-Infection:

- Polyomavirus (BK Virus) can coexist and may induce CMV gene expression.

Antiviral Management Strategies

First-Line Therapy

- IV Ganciclovir: 5 mg/kg every 12 hours. Preferred for severe illness or high viral loads.
- Oral Valganciclovir: Equally effective as IV ganciclovir for solid organ transplants; well-tolerated.

Second-Line / Alternative Agents

- Foscarnet: For resistant strains; highly nephrotoxic (requires hydration).
- Maribavir: Oral agent inhibiting UL97; no kidney toxicity.
- Cidofovir: Nephrotoxic; usually last-line.

Duration of Therapy

- Treat until symptoms resolve AND two consecutive PCRs (1 week apart) are undetectable.
- Typical minimum duration: 21 days

Immunosuppression & Drug Resistance

Modifying Immunosuppression

- Strategy: Stop or reduce antimetabolites (Mycophenolate) depending on severity/drug levels.
- mTOR Inhibitors: Switching to mTORs (e.g., everolimus) reduces CMV incidence due to improved T-cell functionality.

Genotypic Resistance Testing

- Indications: Persistent viremia ≥2 weeks despite therapy, rising viral load, or breakthrough disease on prophylaxis.
- Resistance Profiles:
    1. UL97Mutation: Ganciclovir resistance →Switch to Foscarnet or Maribavir.
    2. UL54Mutation: DNA Polymerase mutation; may confer multi-drug resistance →Foscarnet or combination therapy.

Summarising..

- CMV nephritis is a rare but significant complication, with profound implications on allograft function and outcomes

- CMV nephritis can coexist with rejection/ other viral infections and can be a diagnostic dilemma

- Early identification and treatment is imperative in ensuring graft survival

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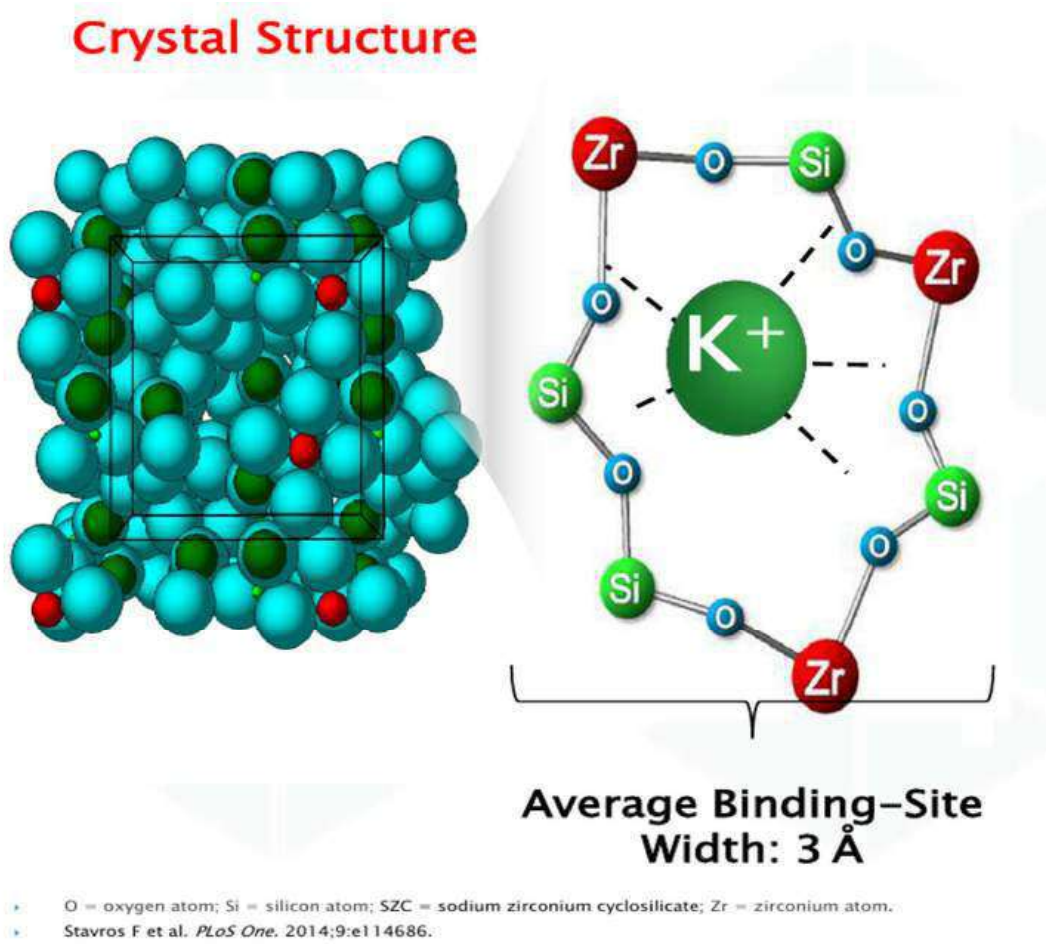
NEW POTASSIUM BINDER

Sodium Zirconium cyclosilicate (SZC)



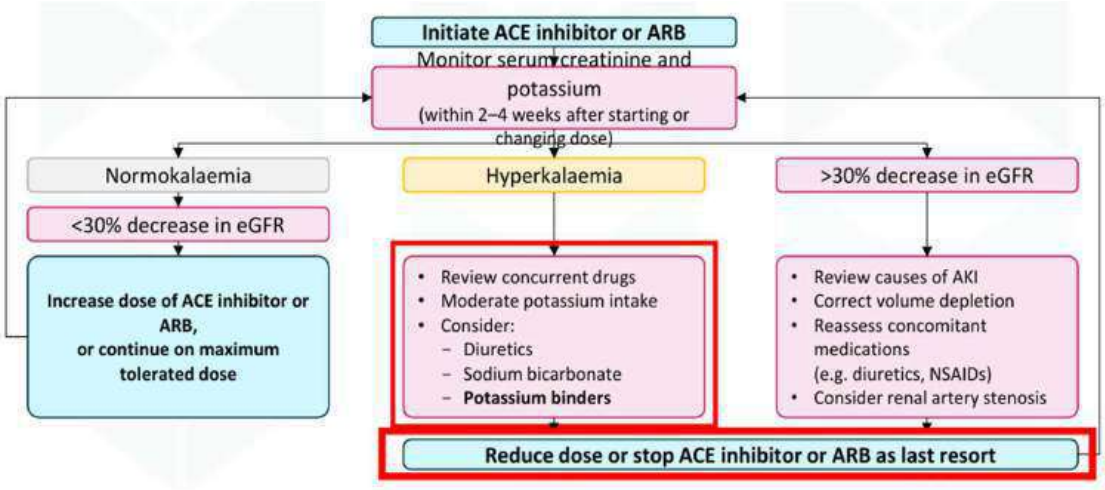
- O = oxygen atom; Si = silicon atom; SZC = **sodium zirconium cyclosilicate**; Zr = zirconium atom.
- Stavros F et al. *PLoS One*. 2014;9:e114686.

- Inorganic crystalline potassium binder; not a polymer.
- Exchanges H+ and Na+ for K+
- Highly selective for K+; binding site width and K+ ionic diameter are similar.
- Insoluble, highly stable, and does not expand in water.
- Not systemically absorbed

	Traditional Potassium Binder	Novel Potassium Binder	Novel Potassium Binder
	Calcium polystyrene sulfonate (CPS)	Sodium zirconium cyclosilicate (SZC)▼	Patiromer
Mechanism	Nonspecific calcium cation–exchange resin[4]	Selective potassium binding in exchange for sodium and hydrogen[6]	Potassium binding in exchange for calcium
Onset	Action may be delayed for 1 to 2 days[4]	1 hour[8]	7 hours
Dosing	15 g orally 3 to 4 times daily[5] 30 g given as retention enema once daily[5]	10 g orally 3 times daily for a maximum of 72 hours (starting dose)[8,b] 5 g orally once daily (recommended starting maintenance dose)[8]	8.4gm QD, titrate upto 16.8gm or 25.2gm
Indication	Treatment of HK associated with anuria or severe oliguria and treatment of HK in patients requiring dialysis[5]	Treatment of HK in adults; there is limited experience in patients with serum K^+ levels greater than 6.5 mmol/L[8]	Treatment of HK in adults and paediatrics
Location	Colon[4]	Entire intestinal tract[6]	Colon
Adverse events	Cases of intestinal necrosis, which may be fatal, and other serious GI adverse events have been reported[5]	Hypokalaemia and oedema-related events[8]	Hypomagnesemia, GI adverse effects
Drug Interactions	Antacids, laxatives, digitalis, sorbitol, lithium, levothyroxine[5] Administer at least 3 hours before or 3 hours after other oral medications[5]	Administer at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH-dependent bioavailability[8]	None

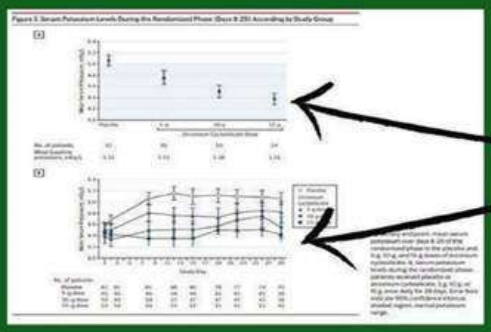
* SPS was FDA approved prior to the Kefauver-Harris Drug Amendments in 1962, which required drug manufacturers to prove effectiveness of their product.[3]
▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.[8] [a]Dose differs for patients on haemodialysis- refer to SmPC for more information.[8] References and abbreviations in slide notes.

Hyperkalaemia associated with use of RAAS inhibitors can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RAAS inhibitors



Note: ACE inhibitor or ARB should only be reduced or stopped after measures outlined above have failed
ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NSAID, non-steroidal anti-inflammatory drug; RAAS, renin–angiotensin–aldosterone system; T2D, Type 2 diabetes
Kidney Disease: Improving Global Outcomes. 2024 Guidelines

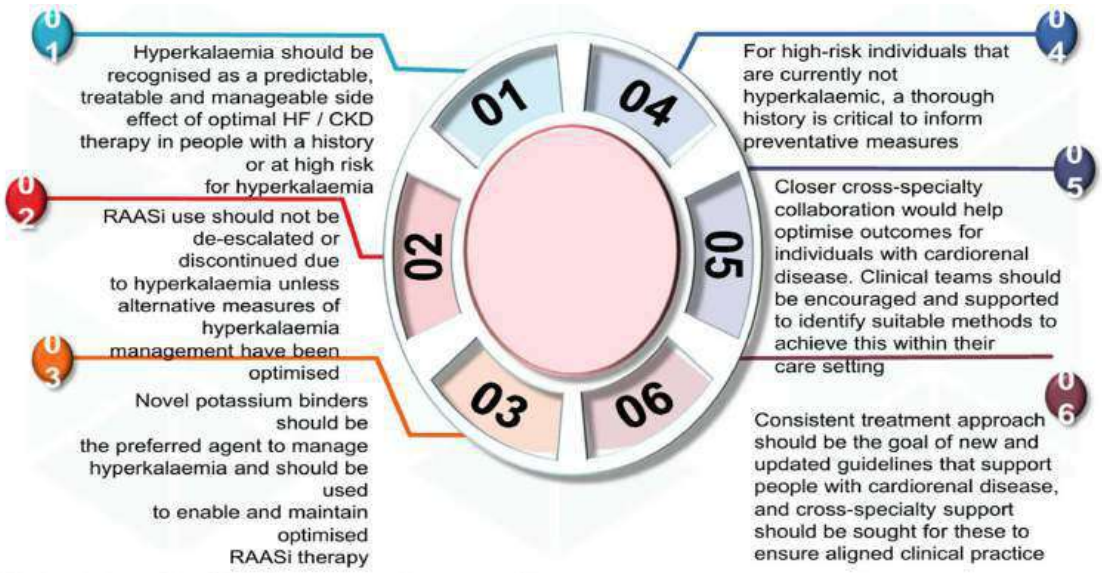
HARMONIZE Trial



- N=237 patients
- Patients with persistent hyperkalemia entered a 48-hour open-label run-in during which they received Sodium Zirconium Cyclosilicate 10g 3 times daily
- K >5.1
- 69% had CKD
- 70% per taking RAASi
- documented hyperkalemia that led to D/C of RAASi or beta-blocker within 6 months.

Results: Sodium Zirconium Cyclosilicate is safe and efficacious in the treatment of asymptomatic hyperkalemia. A dose-dependent relationship was observed, with higher doses achieving greater normalization of hyperkalemia, but with a greater propensity for side effects including hypokalemia.

The recent Delphi consensus resulted in the following recommendations regarding Hyperkalemia



CKD, chronic kidney disease; HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitor
Burton JO, et al. *Eur J Heart Fail* 2022;24:1467-1477

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POST TRANSPLANT DIABETES MELLITUS [PTDM]

Introduction

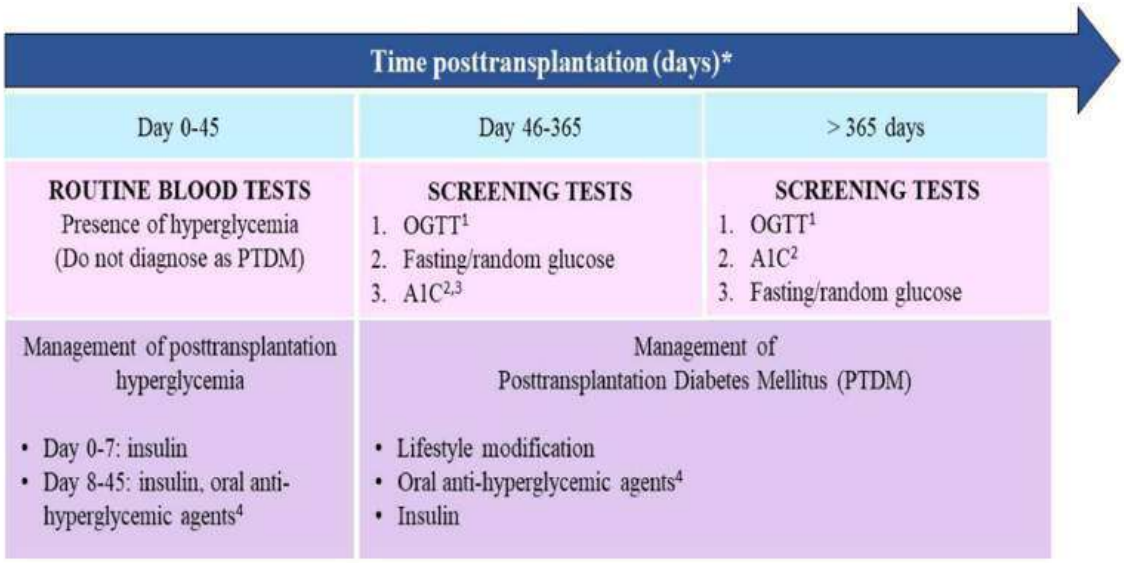
• 15-20% of non-diabetic kidney transplant recipients develop PTDM by 6 months.

• PTDM - Includes all post-transplant diabetes first recognised after transplant regardless of prediabetic pre transplant, but excludes transient post-transplant hyperglycemia in 1st 6-week post-transplant.

• HbA1c should not be used for 3-month post Tx (False low HbA1c levels due to anaemia (erythropoietin treatment or blood cell transfusions).

• Fasting glucose has a low sensitivity for diagnosing PTDM.

• OGTT is considered gold standard for diagnosis of PTDM and for screening preTx (2024 international consensus).



Pham PT , Sindhu HS et al. PTDM after SOT 2019

Risk Factors

Non-modifiable	Potentially modifiable	Modifiable[4]	End-organ specific diagnosis
African American, Hispanic Age > 45 years Male recipient Family history of diabetes mellitus Human Leukocyte Antigen (HLA) mismatches HLA A30, B27, B42 Acute rejection history Deceased donor Male donor Genetic polymorphism [e.g. TCF7L2 variant (rs7903146), PPAR-α variant (rs4253728),	Hepatitis C virus[1] Cytomegalovirus[2] Pretransplant IGT/IFG Proteinuria Hypomagnesemia[3]	Obesity (body mass index ≥ 30) LDL cholesterol Steroids, tacrolimus, cyclosporine, sirolimus Vitamin D deficiency	End stage kidney disease due to polycystic kidney disease End stage liver disease due to HCV infection or non-alcoholic steatohepatitis (NASH)[5] End stage lung disease due to cystic fibrosis

Pham PT , Sindhu HS et al. PTDM after SOT 2019

Trials/meta analysis

• 2004 meta-analysis showed PTDM in 9.8% with tac vs CsA (DIRECT study).

• In ELITE study at one-year higher rates of PTDM in low dose tacrolimus (8.4%) compared to std. dose of CSA (6%), low dose CSA (4.2 %) and low dose sirolimus.

• Recent meta-analysis of 56 randomized controlled trials demonstrated less PTDM and better overall graft survival with CNI minimisation strategies using new agents such as Belatacept or Tofacitinib

Immunosuppressants -PTDM

Cyclosporine vs tacrolimus

• Tacrolimus 2-3 times more diabetogenic.

• Marked beta cell toxicity, calcineurin inhibition, insulin hyposecretion.

• Trough level > 15 ng/ml first month high risk for PTDM.

• PTDM incidence with CNIs: 10–25% in 36 months post-transplant.

Prednisone

• >10mg/day dose -- 1.8-fold increased risk (increases with further increase in dose).

• 5 percent per 0.01 mg/kg per day increase in prednisolone dose - PTDM risk increases.

Adjusting Immunosupression

Steroids

• Steroid minimisation as early as possible.

• Prednisolone dose reduction to 5 mg at one year (PTDM from 55 to 34%). • Few studies have found that there is no significant difference between 5mg prednisolone compared to complete steroid withdrawal at 5 years posttransplant (CSWD 22.5% vs. CCS 21.5%).

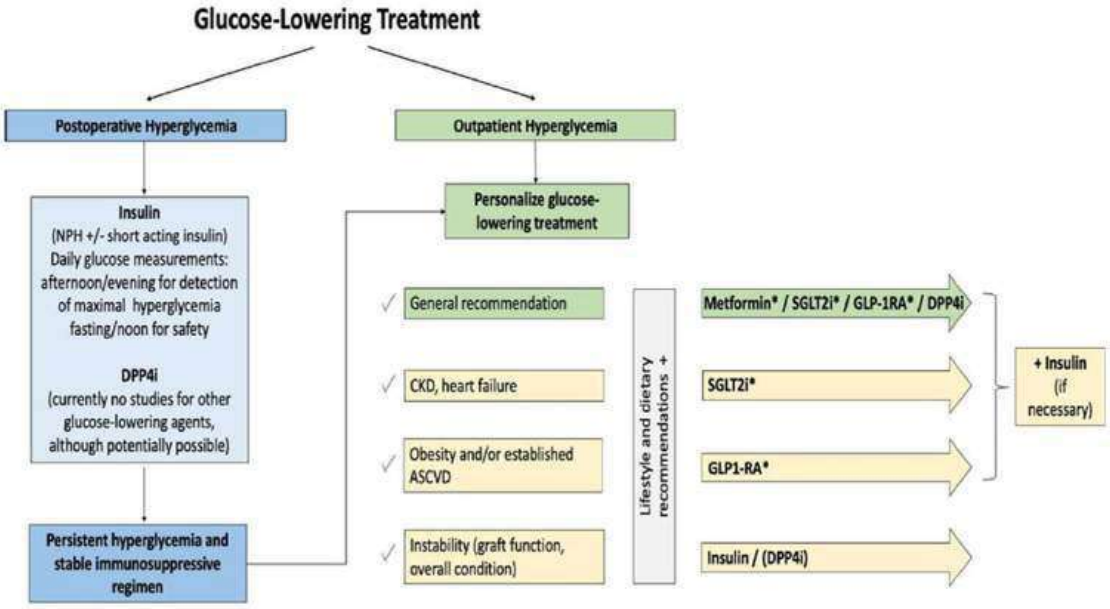
• No controlled data on the effect of late withdrawal of low dose steroids in patients with established PTDM.

CNI

- Dose reduction without increasing risk for rejection.
- Change from tacro to Cyclosporin for PTDM is not recommended
- Effect of tacrolimus on glucose may be reversible even if agent is not discontinued
- Conversion to sirolimus may worsen insulin resistance, not recommended.

Newer onset diabetes after transplantation, 2003 International consensus guidelines

Glucose-lowering treatment in KTRs: suggested algorithm



Nephrol Dial Transplant, Volume 39, Issue 3, March 2024, Pages 531–549.

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ONCE DAILY TACROLIMUS

Introduction

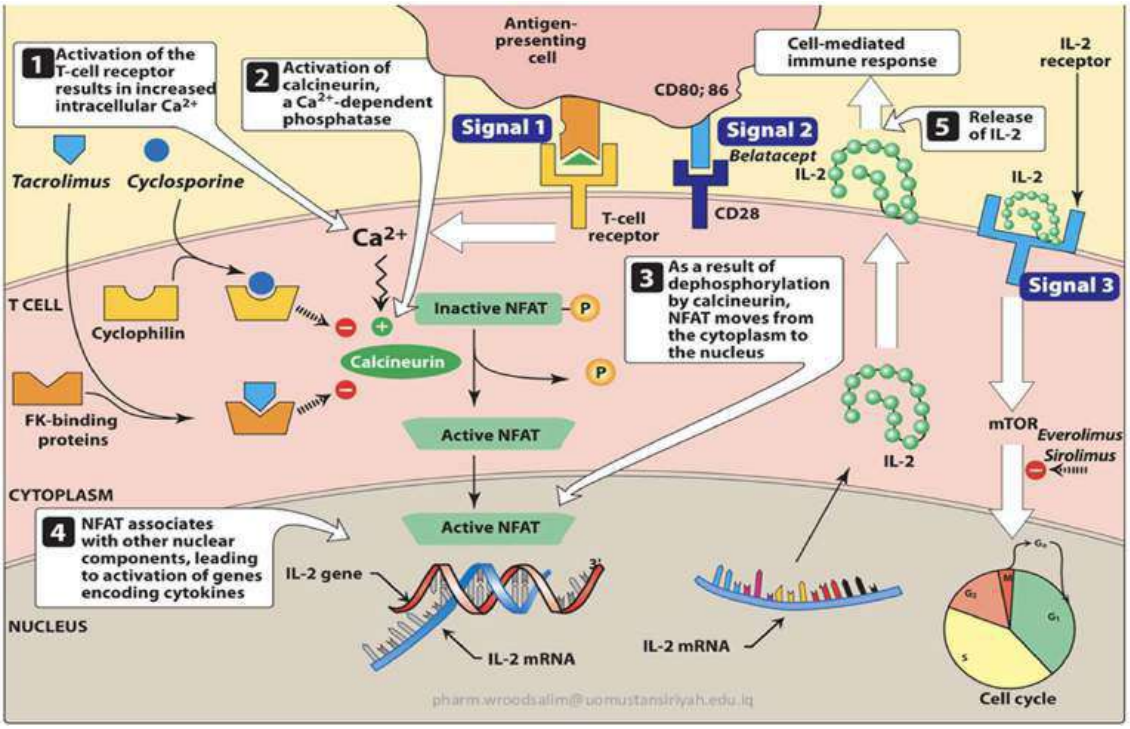
•Once daily tacrolimus is designed to deliver the same 24-hour immunosuppressive effect with OD dosing and more stable exposure — but conversion requires brand-specific knowledge and close therapeutic drug monitoring.

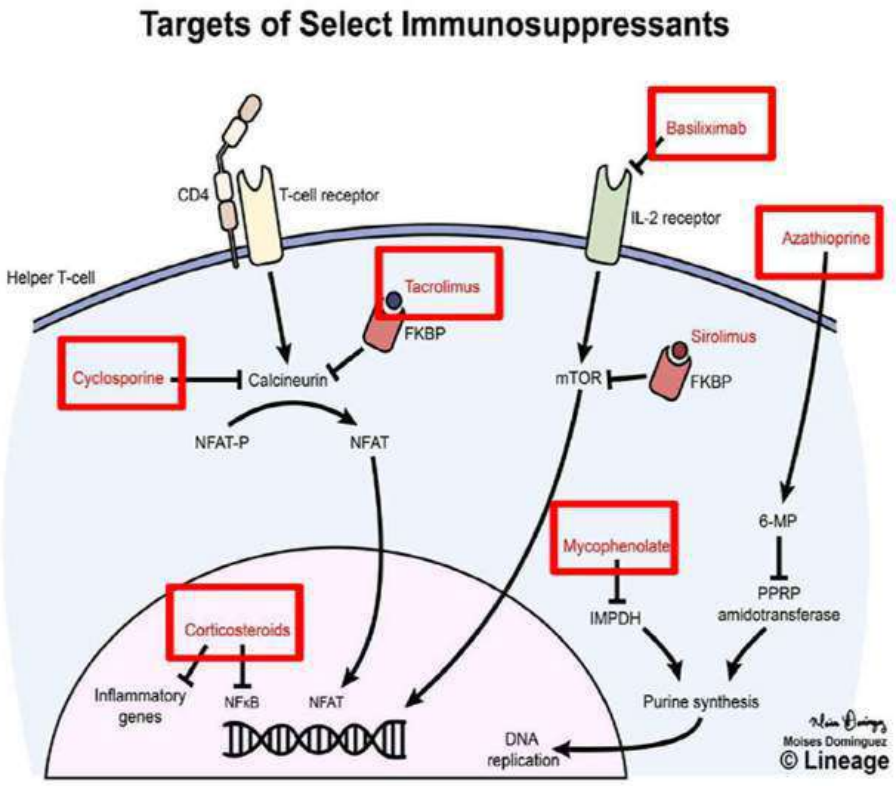
•The pharmacokinetic differences between the two formulations come from the difference in excipients.

•Replacing croscarmellose by ethyl cellulose slows down the diffusion rate of tacrolimus, leading to a prolonged release.

•Tacrolimus OD compared to BD provides - lower intra patient variability, improved compliance, similar rates of patient survival, graft survival, renal function, and adverse effects.

Mechanism of action of CNIs





Pharmacokinetics of Tacrolimus

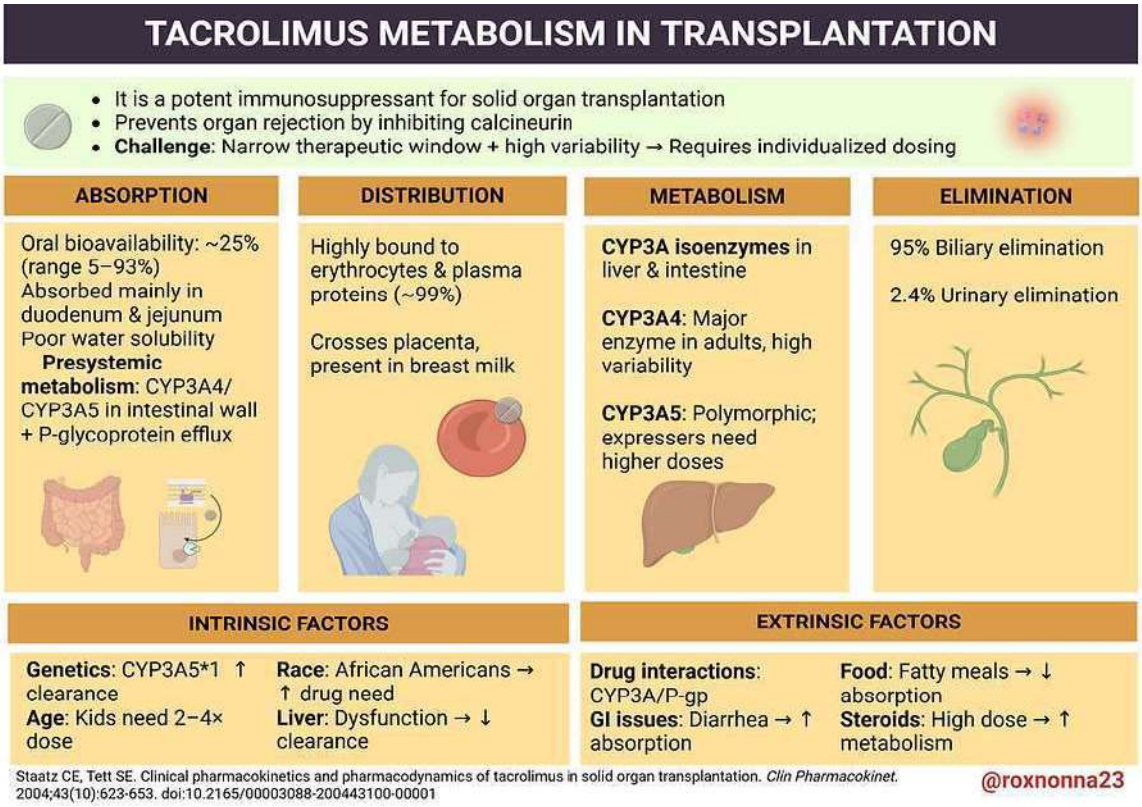
•The rate of absorption of tacrolimus is variable with peak blood or plasma concentrations being reached in 0.5 to 1 hours; approximately 25% of the oral dose is bioavailable.

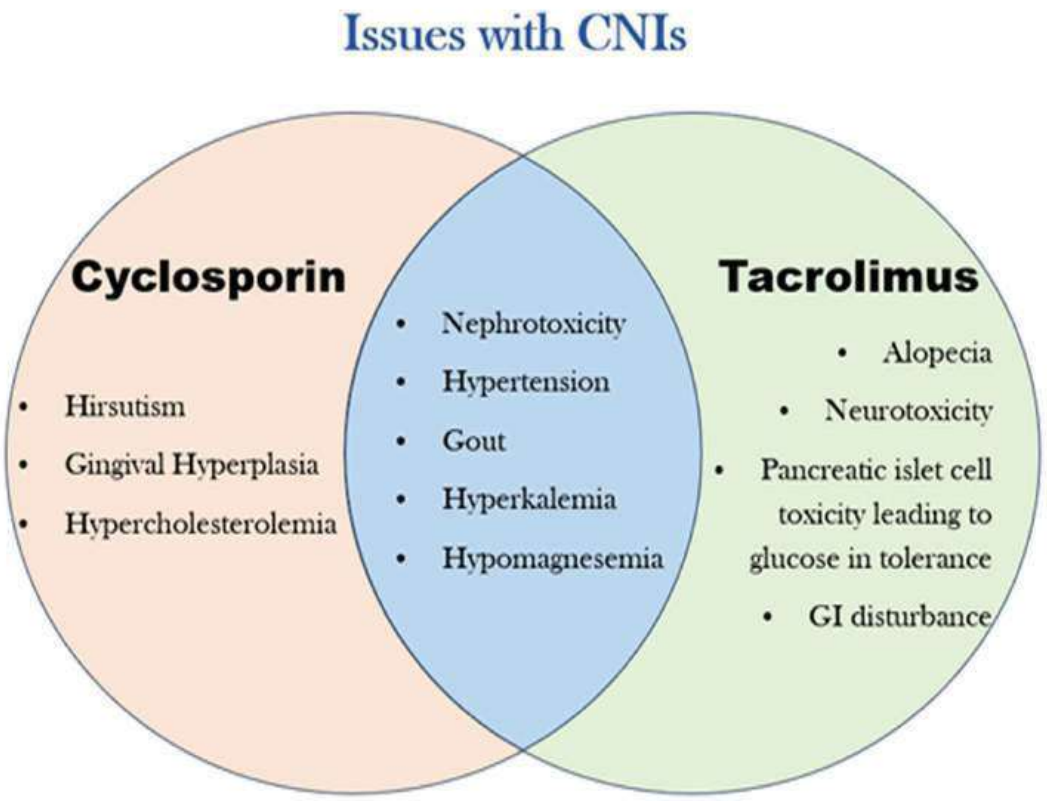
•Tacrolimus is extensively bound to red blood cells, with a mean blood to plasma ratio of about 15; albumin and α1-acid glycoprotein appear to primarily bind tacrolimus in plasma.

• Tacrolimus is completely metabolised prior to elimination.

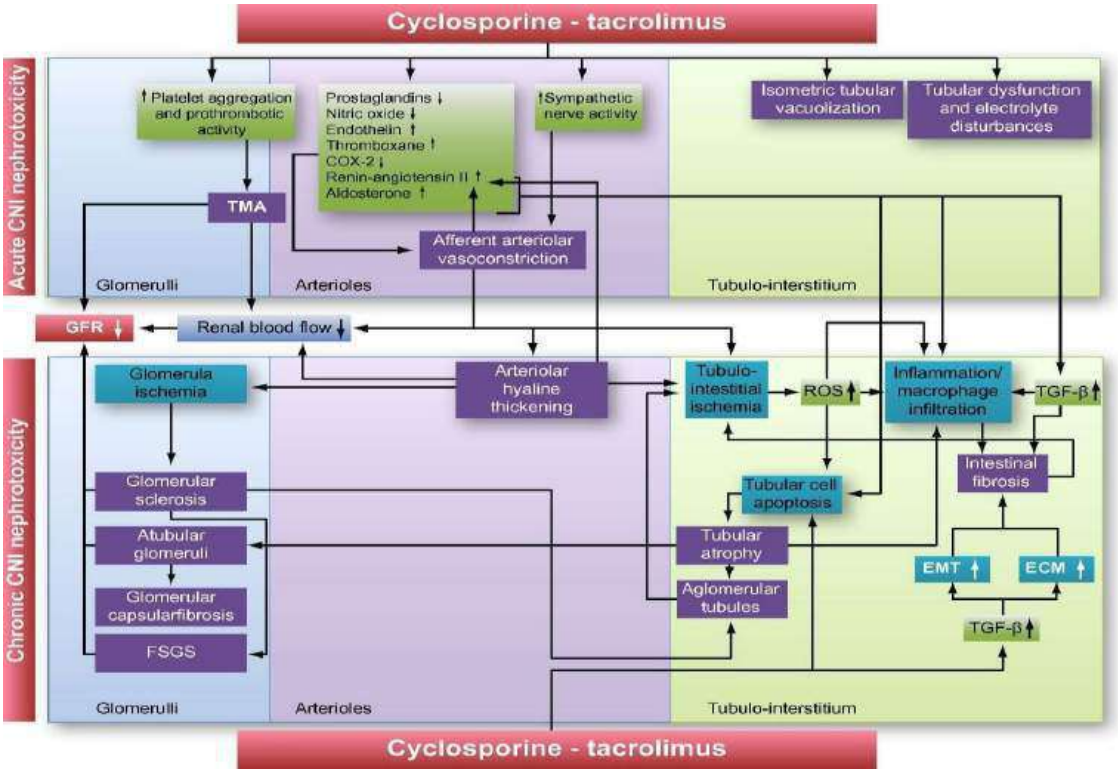
•The mean disposition half-life is 12 hours and the total body clearance based on blood concentration is approximately 0.06 L/h/kg.

•The elimination of tacrolimus is decreased in the presence of liver impairment and in the presence of several drugs.





CNI Nephrotoxicity



Genes and Tacrolimus dosing

1) CYP3A5 —primary determinant

• Enzyme: metabolizes tacrolimus in liver & intestine

• Variants:

– **CYP3A5*1 (expressor)** → fast metabolism → **needs higher doses**

– **CYP3A5*3, 6, 7 (non-expressor) → slow metabolism →

standard / lower doses

• Common in many Asian and African populations; less common in

Europeans.

• **Clinical impact**: CYP3A5 expressors often need ~1.5–2× higher starting

dose (but always titrate to trough levels).

2) CYP3A4 —secondary contributor

• Also metabolizes tacrolimus, especially when CYP3A5 is absent.

• Variants:

– CYP3A4*22→ ↓ activity → ↑ tacrolimus levels

–CYP3A4*1G (common in Asians) → may ↑ clearance in some studies

3) ABCB1 (MDR1 / P-glycoprotein)

- Affects absorption (gut) and distribution (Kidney, Brain).
- Polymorphisms **(like 3435C>T, 2677G>T/A)** may modestly influence dose needs and nephrotoxicity, but findings are inconsistent.

4) POR (P450 oxidoreductase)

- Transfers electrons to CYP3A enzymes → influences activity.
- Some variants modify tacrolimus dose requirements (often subtle).

5) PXR (NR1I2 — Pregnane X Receptor)

- Regulates CYP3A4/5 expression.
- Variants can change induction response (e.g., Rifampicin, Phenytoin).

6) CAR (NR1I3 — Constitutive Androstane Receptor)

- Another regulator of CYP3A expression and induction

Tacrolimus — BID → OD Conversion

Formulation Conversion Rules

- Dose to target trough + clinical context (do not rely on trough alone).

- CYP3A5 expressers may need higher OD doses.
- Avoid unsupervised formulation switching.
- Consider AUC in unstable/high-risk patients.

FEATURES	IR (Prograf)	Advagraf OD	Envarsus XR
Release	Fast	Slow	Very slow, distal
Absorption site	Proximal small bowel	Proximal → mid	Distal intestine
CYP3A exposure	High	Moderate–high	Lower
Bioavailability	Variable	Similar to IR	↑ Higher
Dose change	—	~1:1	↓ ~30%
Technology	Conventional capsule, rapid dissolution Absorbed mainly in the **proximal small intestine**	**Extended-release granules** inside the capsule Slower dissolution → prolonged absorption along intestine	LCPT / MeltDose Tacrolimus is micronized and dispersed on carriers → **dramatically increases surface area** Releases **distally** in the intestine (where there is less CYP3A) Slower, more controlled absorption

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