Brigham and Women's Hospital
Founding Member, Mass General Brigham

Acute Kidney Injury in Cancer

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DISCLOSURES

Nothing to disclose.

OBJECTIVES

Review clinical cases of Acute Kidney Injury in Cancer Patients

Review basic pathophysiology of cases

Review management pearls of cases

Onconephrology: Introduction

- **The Intersection**
  - Long association between cancer and kidney disease
    - hematological malignancies most frequent cause of Acute Kidney Injury (AKI)
    - Increased appreciation of monoclonal gammopathy of renal significance
  - Precision medicine and the advent of targeted therapeutics (Duggar et al. Nature Reviews, 2017)
    - No longer one size fits all
    - Pathway-based targeted treatment (BCR-ABL imatinib)
    - Immunotherapy (ipilimumab-2011, nivolumab-2014, CAR T, cellular therapy)

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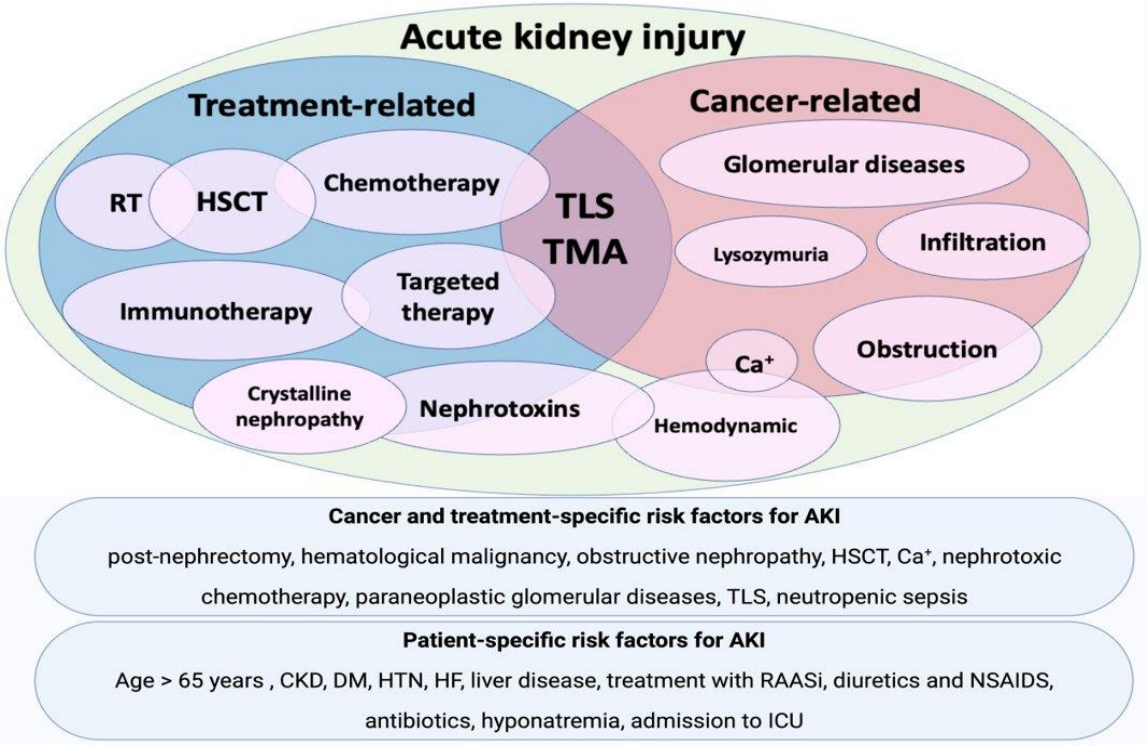
Onconephrology: Scope of Practice



Gupta et al. CJASN 2022.

1	Electrolyte disorders of malignancy (both common and rare)
2	Secondary glomerular diseases of malignancy (treatment strategies)
3	Cancer-related kidney complications such as acute kidney injuries
4	Chemotherapy-related kidney complications
5	Paraproteinemias including monoclonal gammopathy of kidney significance
6	AL and AH amyloidosis (treatment strategies and pretransplant and posttransplant planning)
7	Thrombotic microangiopathic syndromes
8	Bone marrow transplant–related kidney diseases
9	Radiation nephropathy
10	Tumor lysis syndrome
11	Kidney dosing of chemotherapy agents
12	Obstructive kidney disease
13	Kidney cancers
14	Chronic kidney disease after nephrectomy
15	Targeted therapy and immunotherapy-associated kidney toxicities (how to recognize and treat them)

Sachdeva et al. ACKD 2020

Brigham and Dana Farber Cancer Institute?

- Inpatient Onconephrology Service (Fellow)
- Outpatient Onconepherology clinic at BWH and DFCI
- Focus: Oncology collaboration, Education, and Research (multiple landmark papers in Onconephrology)

Epidemiology: Acute Kidney Injury

- 37,267 patients with Cancer from 1999-2006, 27% developed AKI[1]
- 163,071 patients undergoing cancer treatment 2007-2014, 10% developed AKI needing RRT.
- MM, Bladder Cancer, and Leukemia highest 5-year risk of AKI
- Cancer patients who develop AKI requiring RRT, mortality can be as high as >80%
- AKI in cancer patients has morbidity, mortality, and substantial health care cost implications.

AKI: Back to the Basics

62-year-old F with fatigue and chills is referred to outpatient Nephrology for progressively worsening Cr of 1.3 (baseline 0.6-0.7), 10g/d of proteinuria (9.5g/d albuminuria), and worsening edema. Urine microscopy was bland and all serologies were negative. A CT was recently done for her non-specific symptoms showing bulky mediastinal lymphadenopathy, she is awaiting a biopsy of the mass.

What is the renal diagnosis?

1) AL Amyloidosis
2) PLA2-r Positive Membranous Nephropathy
3) THSD7A Positive Membranous Nephropathy
4) FAT1 Positive Membranous Nephropathy
5) Minimal Change Disease

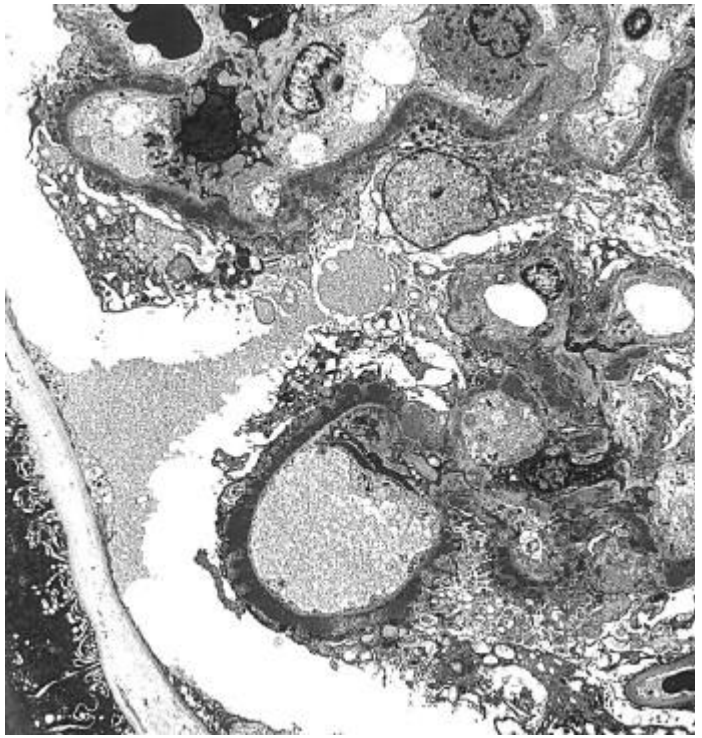


Figure 01 . Reproduced from ADJKD Atlas of Renal Pathology.

AKI: Intrinsic Renal Disease

Paraneoplastic GN

P-GN Solid Tumors

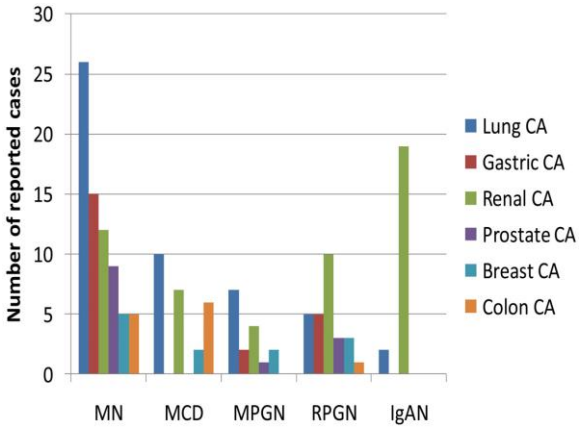


Fig 2. P-GN in Solid Tumors. Lien et al. Nat Rev, 2011.

P-GN Lymph Malignancy

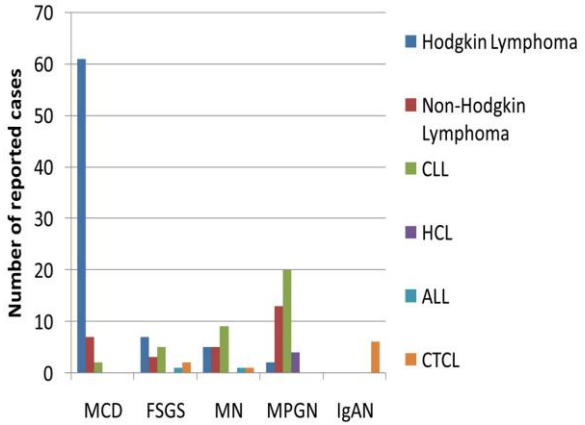


Fig 3. P-GN in Lymph Malignancy. Lien et al. Nat Rev, 2011.

P-GN Myeloid Malignancy

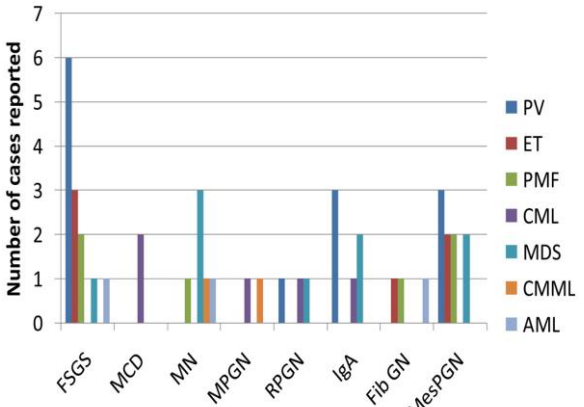


Fig 4. P-GN in Heme Malignancy. Lien et al. Nat Rev, 2011.

Fig 2-4. Reproduced from P-GN in Malignancy. Lien et al. Nat Review, 2011.

AKI: Intrinsic Renal Disease
Paraneoplastic GN

- Membranous Nephropathy
  - Consider solid tumors, lung[2]
  - THSD7A-IgG4 15-20% cases of MN + Cancer[26]
  - NELL1-IgG1/IgG 3 33% have cancer
  - Unclear pathophysiology, likely involves tumor factors and antigen interaction
- Minimal Change Disease
  - Consider Liquid Tumors = MCD
  - Consider colorectal and thyroid cancer as well
  - Podocytopathy mechanism unclear, possibly VEGF-mediated IL-13[2]?
- Treat underlying malignancy with renal supportive care. Target B or plasma cell clone. Consider Rituxan

Paraneoplastic Membranous Nephropathy

Antigen	Disease	IgG	Prevalence
PLA2R	Primary Membranous, Cancer?	IgG 4	~80%
THSD7A	Malignancy (colon lung)	IgG 4	~3%
NELL1	Malignancy	IgG 1	3%
FAT 1	Stem Cell	IgG 4	Unclear

Sethi, Fervenza. NDT 2024

AKI: Intrinsic Renal Disease

A 62-year-old business executive presents with a three-week history of fatigue and back pain

VS: 125/ 75 HR: 95 Temp 99.0F on Room Air.

BMP: Ca 14 mg/dl , Cr 2.9 mg/dl (bsl 1.7-1.s)

CBC: Hgb 7g/dl, rest WNL

SPEP: M spike 3.9 g/d

FLC: L 3000 mg/l K 30 mg/l R 100

UA: bland, pr/cr 8g, albumin/cr 500

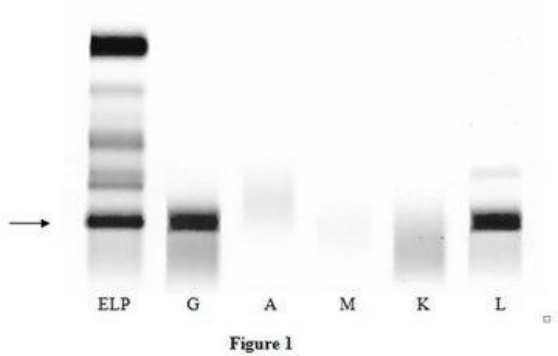


Fig 7. Serum Electrophoresis-Immunofixation, Reproduced from UCSD Laboratory Medicine. http://ucsdlabmed.wikidot.com/chapter-7-laboratory-diagnosis-of-protein-abnormalities

AKI: Intrinsic Renal Disease, Myeloma Diagnosis

Criteria 1: Clonal Proliferation of >10% or Biopsy Proven Extramedullary Plasmacytoma

AND

≥ 1 CRAB

OR

≥ 1 SLIM

OR MDE

Which of the following can precipitate cast formation?

1)ACE/ARB
2)Diuretics
3)NSAID
4)All of the above

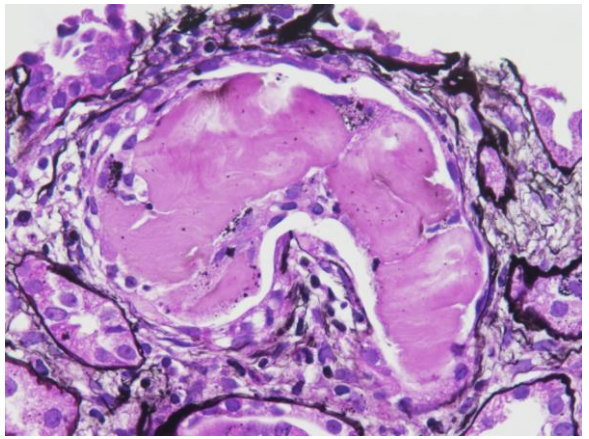


Fig. 7 Cast Nephropathy, LM, Reproduced from AJKD atlas of Renal Pathology.

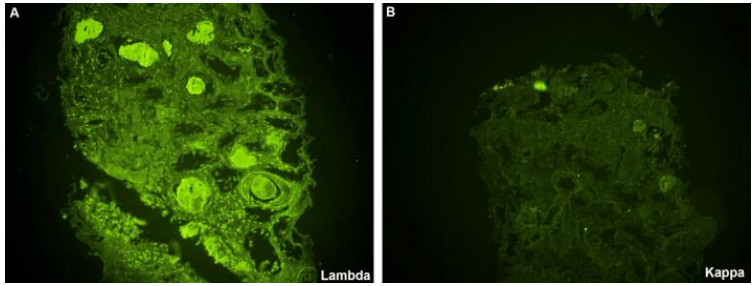


Fig. 8 Cast Nephropathy, IF, Reproduced from AJKD atlas of Renal Pathology.

AKI: Cast Nephropathy

Can occur as a presenting feature or later in the course

Incidence varies from 16-31% in Myeloma Patients[6].

50% of all Myeloma patients will develop some form of kidney disease

Renal impairment has the highest impact on survival in Myeloma Patients

Risk factors

- degree of sFLC elevation. Rare <50 mg/dl (500 mg/l)
- ACE/ARB/Diuretics/NSAIDS can precipitate cast formation

AKI: Cast Nephropathy

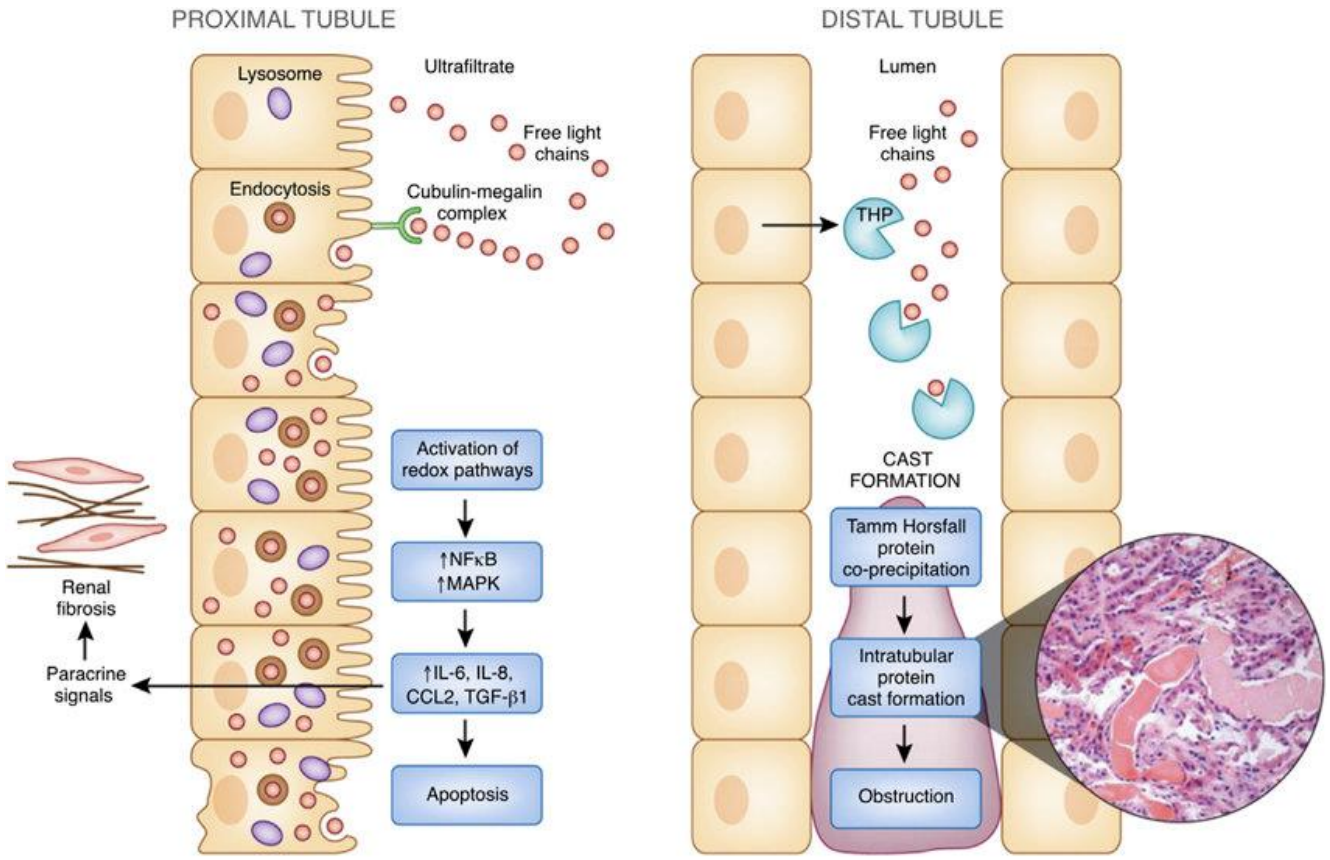


Fig 9. Mechanism of Cast Nephropathy. Reproduced from Lam, A.Q., Humphreys, B.D. (2012). CJASN

Renal Impact:

-Decrease OS, response rates[7]

-MM patients requiring RRT have median OS 0.91 vs 4.46 MM non-RRT

AKI: Cast Nephropathy

Goal = reduce light chain burden, suppress further light chain formation, address precipitating causes (volume depletion, hypercalcemia)

Volume Expansion =2-3L UOP

Clone Directed Therapy (PI) + Alkylating Agent (Cytoxan) + Steroids +/- Daratumumab

Bortezomib

- Proteosome inhibitor that induces apoptosis, decreases tumor growth/angiogenesis of myeloma cells in BM[8].
- VISTA Trial: Bortezomib increased ORR, CR, and renal recovery rate[9]
- Phase II Trial by Ludwig et al. Bortezomib arm better ORR, eGFR improvement correlated with depth of heme response
- Is Bortezomib nephrotoxic?[10]
- 5 Landmark trials, >2000 patients, significant renal adverse events extremely sparse

AKI: Cast Nephropathy

Extracorporeal Management

High Cut Off Dialyzers

- 50kd pore size vs ~15Kd
- H+L 150 Kd vs IgM >1000 Kd
- MYRE Trial[11]
  - High cut off Dialyzers vs conventional dialysis
- **trends towards higher hematological response and renal recovery**
- Most experts will favor the use of High Cut off Dialyzers

AKI: Cast Nephropathy, Plasmapheresis

No Benefit

- Clark et Al, 2005[12]
- 104 patients with AKI and MM
- Conventional therapy vs 5-7 sessions of PLEX
- No difference in death, dialysis dependence, or eGFR improvement >30

Benefit

- Leung et al. 2008[13]
- 14 patients with biopsy proven LCCN treated with PLEX
- Renal response 78% in PLEX treated patients.
- FLC reduction >50% had a renal response rate of 71%
- Survival higher in renal response group

Expert Opinion: involved FLC >150 mg/dl with bence jones proteinuria > Dara+Bort+Cytoxan+Dex + daily PLEX.

Goal: target 50% reduction by the end of cycle 1

This may change!

My Approach:

- First episode vs relapsed?

- Diagnosis Correct?
  - Prior LCCN?
    - What is the rate of Light Chain and Cr Rise
  - Biopsy?

- Do they meet Criteria for LCCN?
  - Involved Light Chain >1500 mg/L (150mg/dl)
  - bence jones proteinuria

- Risk of PLEX
  - DIC
  - Infectious
  - Electrolytes

- Next line of therapy?
  - Discussion with Myeloma Team

Post Stem Cell Transplant AKI

AKI: Intrinsic Renal Disease

58 yo M with a diagnosis of AML is s/p allogenic myeloablative HSCT. He was felt to be engrafting well; However, on day 18, he was persistently hypertensive with a new AKI and proteinuria. His CBC was notable for worsening thrombocytopenia and anemia. His urine microscopy revealed 2-3rbc/HPF. Kidney biopsy is planned after platelet transfusion.

LDH 1200
Hapto <10
Peripheral Smear with Schistocytes

Which of the following is NOT a cause of Thrombotic Microangiopathy (TMA) post stem cell transplant?

1. CNI use for GVHD prophylaxis
2. Active GVHD
3. Complement Activation
4. Drugs
5. All of the above can cause TMA post stem cell transplant.

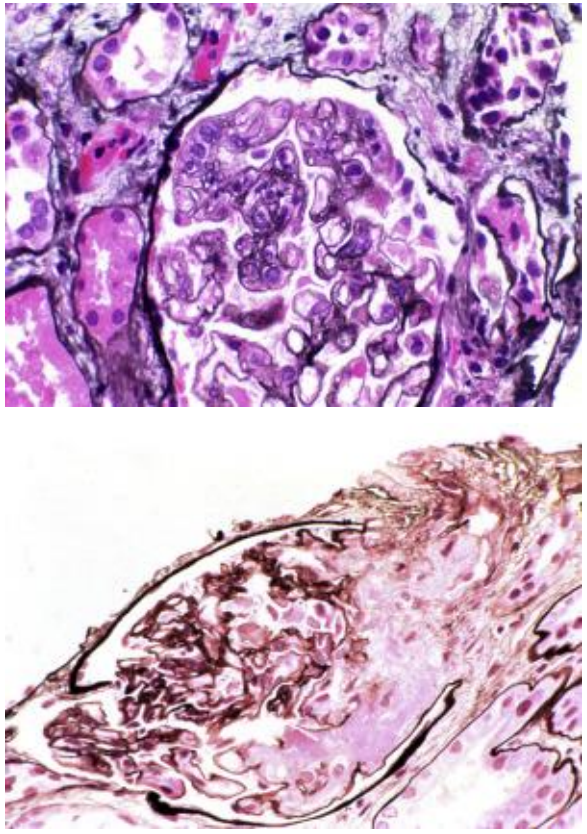


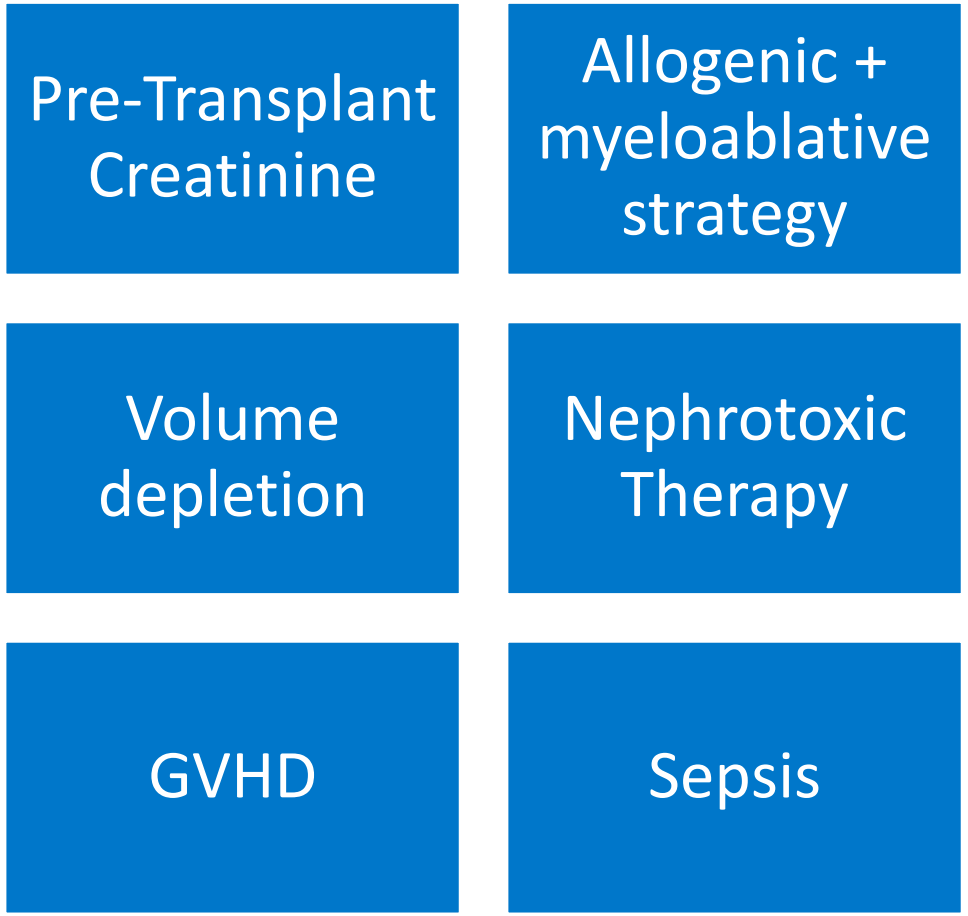
Fig 13. TMA, Reproduced from AJKD Atlas of Renal Pathology.

AKI: Post Stem Cell

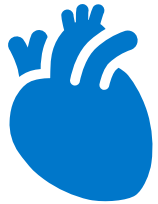
- 2002: Parikh et al. 2002: 88 patients who received HSCT at the University of Colorado[18].
  - Allogenic Transplant + Myeloablative strategy associated with an incidence of ~92% of AKI.
  - Allogenic + myeloablative group had a 4x increase in the need for RRT vs nonmyeloablative group.
  - RRT conferred a **mortality of ~82.6%**
  - Autologous transplants have incidence of AKI ~20%.

- 2021: Abramson et al.
  - Single center retrospective review
  - 616 allogenic HSCT 2014-2017
  - Incidence of AKI ~64%
  - Those requiring dialysis, 5/21 (~24%) survived

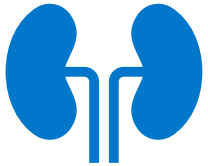
- 2024: Kim et al.
  - 87.4% 90-day mortality
  - If low serum albumin, high total bilirubin, mortality 100%



AKI: Intrinsic Renal Disease, TMA



Incidence varies 2%-39% post HSCT, mortality as high as 75% [19]



Can present with subclinical AKI and lead to CKD.

Proteinuria

HTN

Worsening Anemia

Diagnostic Criteria

>2 Schistocytes/HPF on peripheral smear

Increase in serum LDH above baseline. Hapto low.

Concurrent renal or neurological dysfunction

Negative Coombs

Does not always correlate with histological findings.

AKI: Intrinsic Renal Disease, TMA

- Causes
  - Complication of HSCT
  - Medications
  - Complication of GVHD?
    - Changsirikulchai et al. Biopsy from 314 patients[20]
    - correlation between GVHD II-IV
  - Complement Mediated?
    - Alternative pathway mediated Atypical HUS
  - GVHD beyond TMA
    - MN
    - MCD

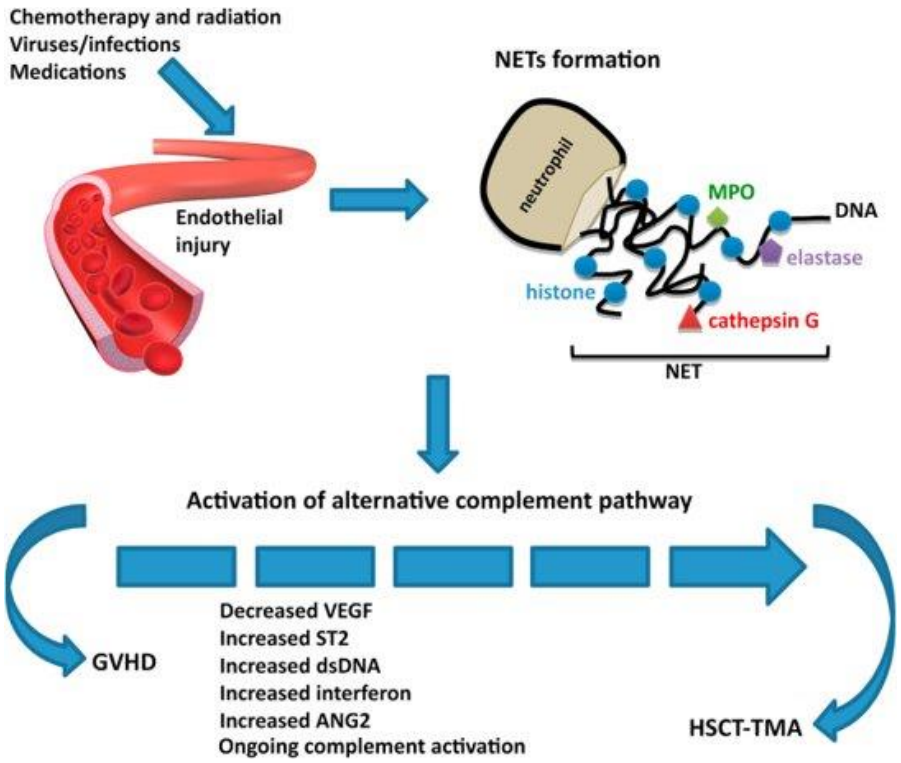


Figure 14. GVHD and TMA. Wanchoo et al AJKD 2018.

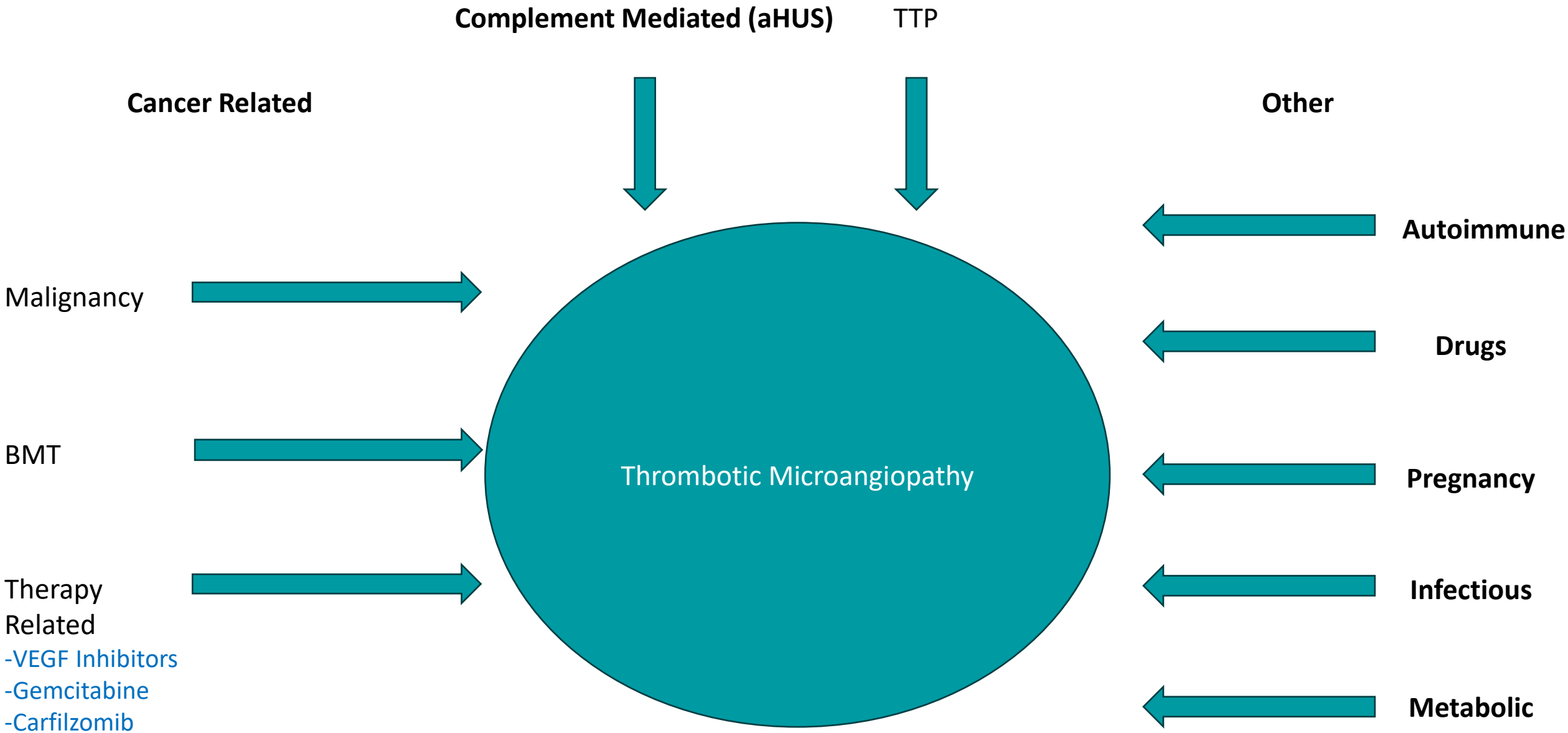
AKI: Intrinsic Renal Disease, TMA

Management

- BP and Stop offending agents
- Terminal Complement Inhibition?

Complement Inhibition?

- Jodele et al. Reported 64 pediatric cases of HSCT with high-risk TA-TMA32 [21].
  - 66% 1-year survival in treated group vs 16.7% untreated
  - 56% achieved complete remission
  - Only 23% required RRT
  - In survivors median eGFR was 20% lower than pre HSCT.
- Consider Adams TS, C5B-C9 (MAC) and CFH testing.


Complement Mediated (aHUS)
TTP
Cancer Related
Other
Malignancy
BMT
Therapy Related
-VEGF Inhibitors
-Gemcitabine
-Carfilzomib
Thrombotic Microangiopathy
Autoimmune
Drugs
Pregnancy
Infectious
Metabolic

The Complement System:

Classical Pathway

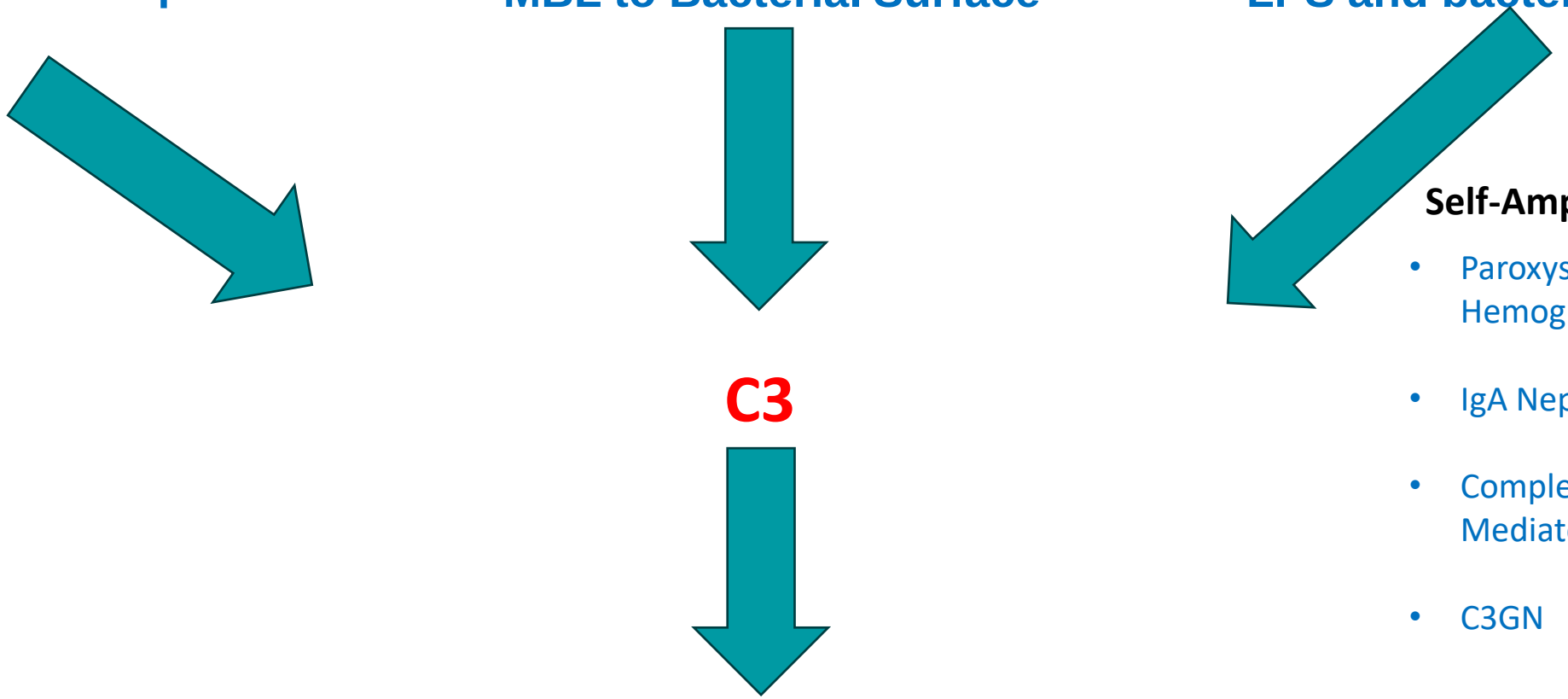
IgG and IgM AB complex

Lectin Pathway

MBL to Bacterial Surface

Alternative Pathway

LPS and bacterial toxins



C3

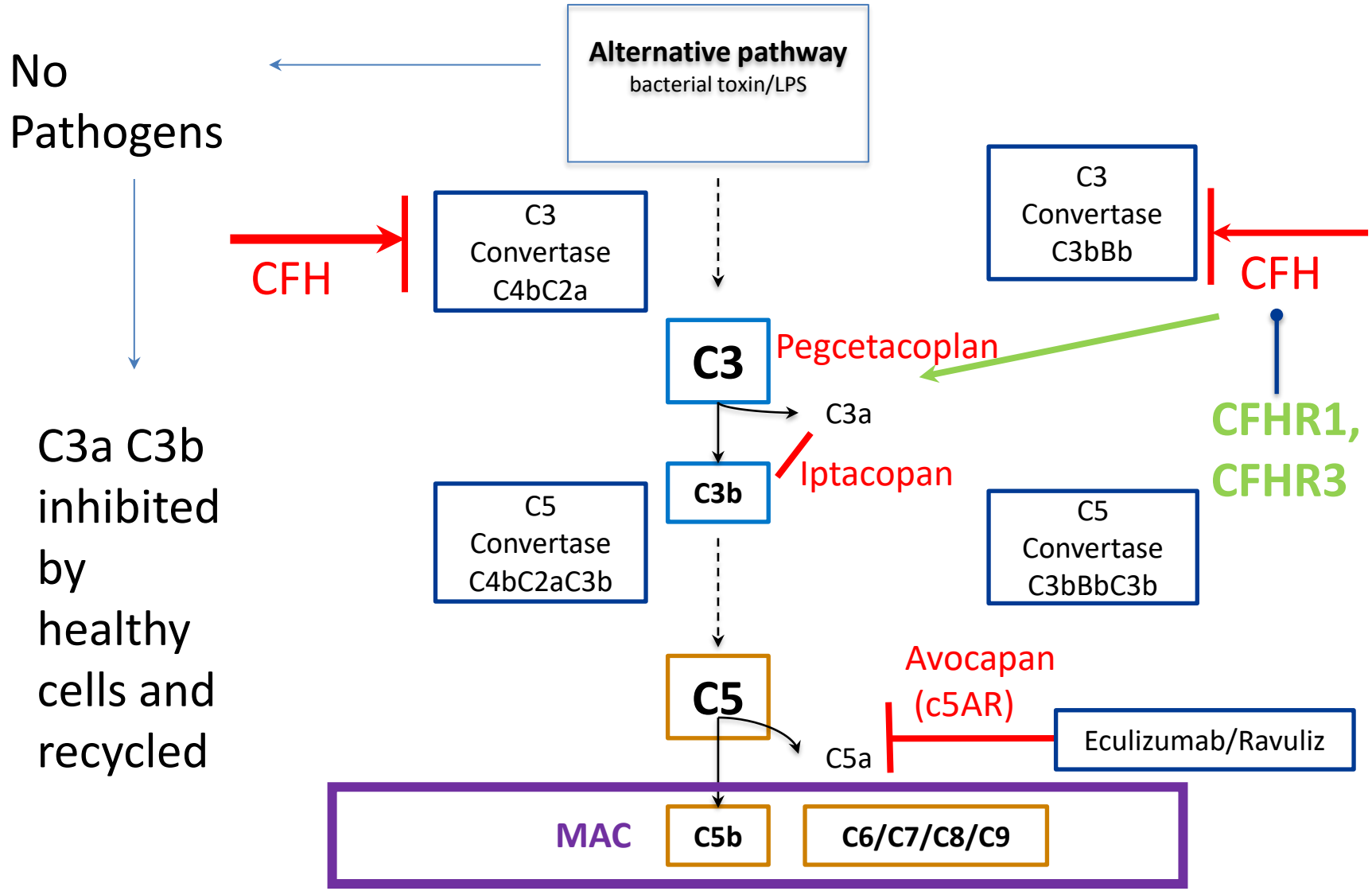
Self-Amplification

- Paroxysmal Nocturnal Hemoglobinuria
- IgA Nephropathy
- Complement Mediated TMA
- C3GN

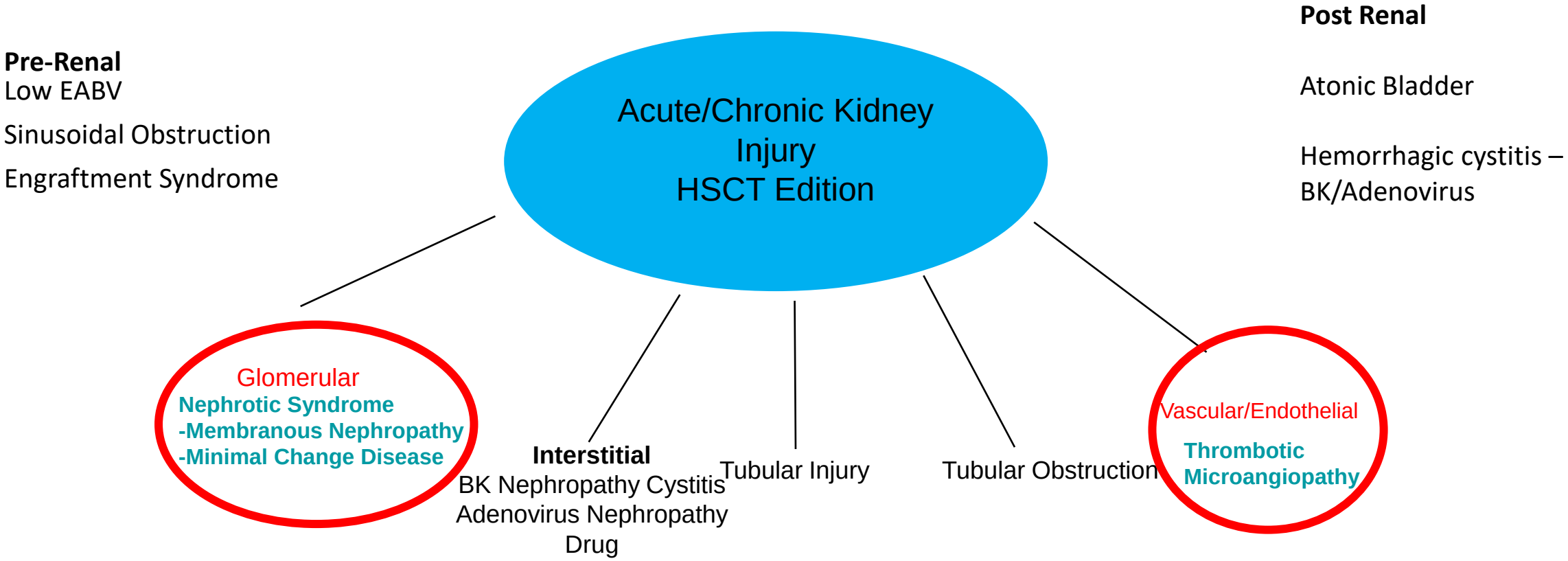
MAC : C5b-C9

Opsonization
Bacterial cytotoxicity

The Complement System:



Stem Cell and Renal Impact



Courtesy of Raad Chowdhury

HARVARD MEDICAL SCHOOL

Complement Mediated TMA

Genetic Variants not always causative, environmental trigger necessary (pregnancy, drugs)

- Factor H most common ~25% of cases.
- Activating mutations of C3 can occur

Plasmapheresis vs C5 inhibition or both?

Treatment Monitoring

Plasmapheresis: potential benefit if CFH antibody present, but otherwise not first line

Eculizumab

- Non responders: C5 polymorphisms
- Follow CBC, CMP, MAHA, C3/C4, CH50, sc5b-c9 two weeks after initiation
  - Heme response ~2 weeks
  - Renal response 4 weeks and greater
- CFC/C3 mutations high risk of relapse/progression difficult to discontinue

Thompson, Kavanagh. Journal of Laboratory Hematology, 2022
Fakhouri et al. Blood, 2023.

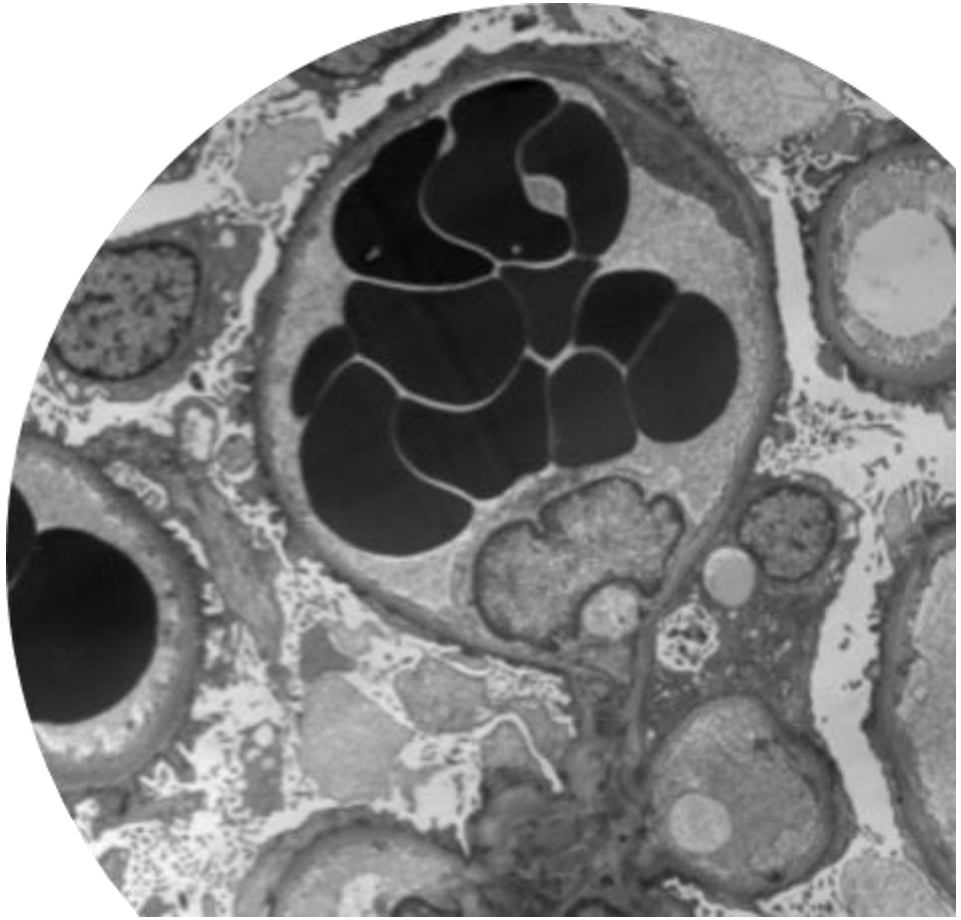
My Approach in HSCT-TMA

- + TMA Screen AND within 100 days
- Eculizumab 900mg weekly x 4 doses. Outpatient: convert to Ravulizumab
- Complete Iowa functional and genetic panel
- Continue till heme and renal remission. (~3-4months)
- Stop if no genetic variant is identified

HSCT and Glomerular Disease

62 yo F with AML is s/p HSCT with appropriate engraftment **day >100.** She is admitted for profound AKI with CR 7mg/dl (baseline 1s) and oligo-anuria. Onconephrology was consulted and proteinuria found to be 9.5g/24-hour urine microscopy was bland, and all serologies were negative. She required dialysis for hypervolemia and anuria.

Kidney biopsy was consistent with Minimal Change Disease and Acute Tubular Necrosis (ATN)



Reproduced from ADJKD Atlas of Renal Pathology.

HSCT and Glomerular Disease

Nephrotic Syndrome

Incidence ~1%. Concomitant AKI, rare28. More commonly occurs >6 months post HSCT.

Nonmyeloablative therapy is more commonly associated.

Graft versus Host Disease

Elafin: a potential plasma biomarker for GVHD

Elevated urinary elafin is associated with AKI. Elevated urinary elafin is associated with micro- and macroalbuminuria.

Beyar-Katz et al. Biology of Blood and Marrow Transplantation, 2016.,

Hingorani et al. CJASN, 2014

HSCT and Glomerular Disease

- Nephrotic Diseases: Membranous Nephropathy vs Minimal Change
  - 116 cases of Nephrotic Syndrome reviewed post HSCT between 1988-2015
  - Median onset 20.5 months
  - 65.5% had Membranous on biopsy and 19% with MCD
  - Developed concomitant to GVHD
  - **How I treat?**
    - Rituximab as first line
    - Consider ace/arb if tolerating
    - Diuretics

Beyar-Katz et al. Biology of Blood and Marrow Transplantation, 2016.,

TAKE HOME MESSAGES

Differentials for intrinsic AKI in cancer patients can go beyond the usual (TLS, Cast Nephropathy, etc.)

Consider the type and activity of cancer when formulating renal differentials

Consider renal manifestations of GVHD in stem cell AKI (MN, MCD, TMA)

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CLINICAL TRIALS

Clinical Trials	Change in Management	
None Specific as this topic was a gross overview		