Kidney Disease Associated With HSCT

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Introduction

- Hematopoietic stem cell transplantation (HSCT) has emerged as one of the most popular therapies for management of neoplastic disorders primarily lymphoproliferative disorders and bone marrow failure states including aplastic anemia and thalassemias

- Various types of HSCT are currently being used in today's era.

Type Of HSCT

- myeloablative allogeneic: use of a conditioning regimen composed of chemotherapy and radiation prior to the infusion of human leucocyte antigen matched donor cells .

cyclophosphamide, busulfan, cytarabine, and total body irradiation.

- Non myeloablative allogeneic: the use of a reduced intensity-conditioning regimen prior to the infusion of the donor cells. This modality of HSCT is better suited for patients with significant comorbidities .
  fludarabine, busulfan, and cyclosporine
- Autologous HSCT: involves extraction of patient's own stem cells prior to administration of chemotherapy and radiation followed by infusion of the same stem cells after processing

AKI

- Most patients undergoing HSCT develop AKI within the course of 1 year.
- the incidence of AKI has been reported any where from 20% to 73% . However, some studies have reported statistics as high as 92%.
- AKI after HCT is usually defined as a doubling of base-line serum creatinine and/or decline in glomerular filtration rate (GFR) of at least 50% within the first 100 days after HCT. This stands for Stage 2 of AKI according to Acute Kidney Injury Network (AKIN) and (KDIGO)

Dx:

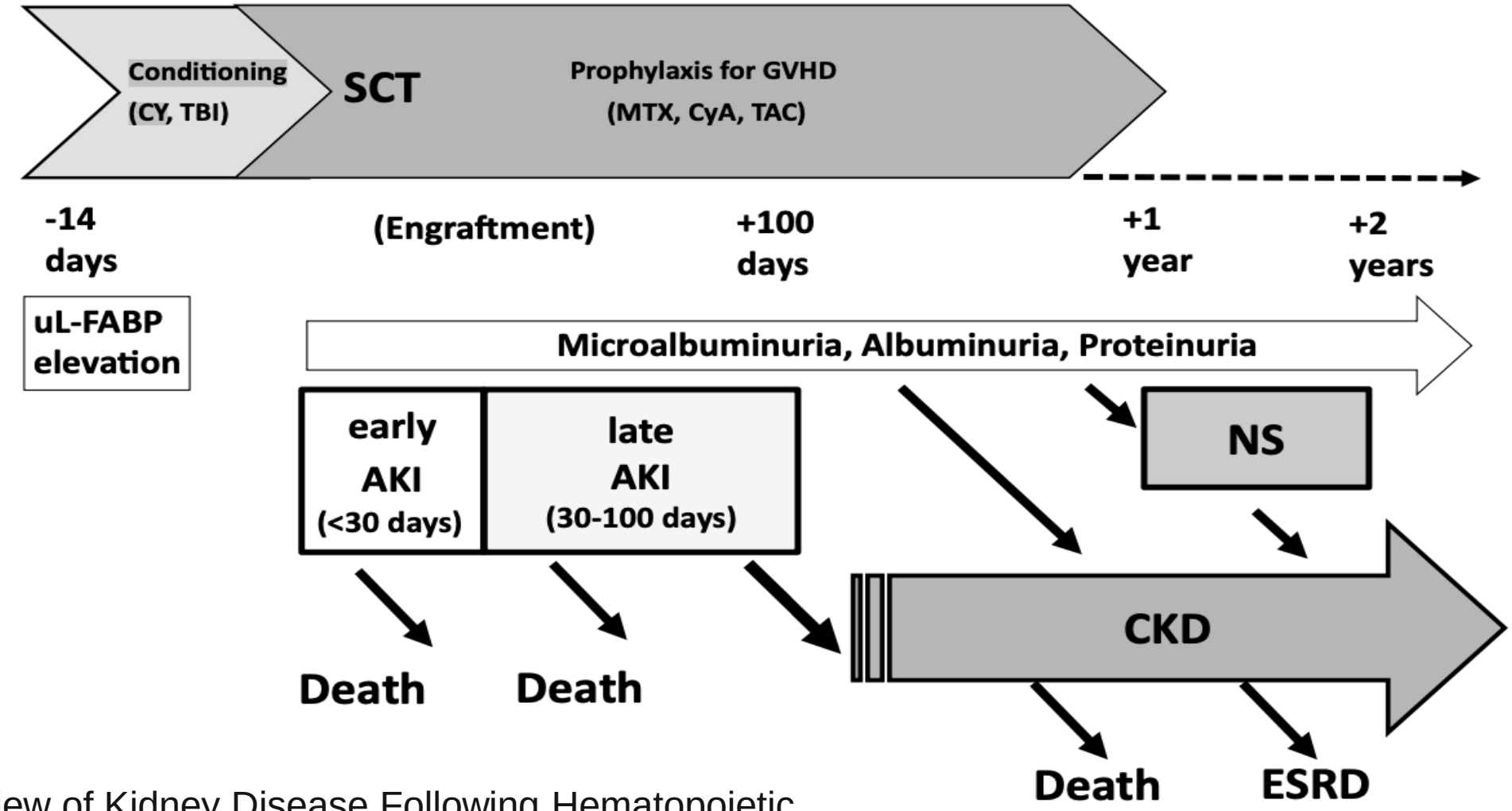
- Diagnosis of AKI after HCT may be challenging. Serum concentration of creatinine depends on muscle mass, hydration, and increases with latency1–3 days after injury of a nephron has occurred. Similarly, GFR estimation based on the creatinine level is prone to errors.
- Comparisons of estimated GFR and GFR measured via radioisotopic methods (involving iohexol, Tc-99m-DTPA) showed significant differences among patients qualified for HCT In consequence, under- and overestimation of GFR carry a risk of toxic or inadequate dosage of chemotherapeutics, as well as delayed AKI diagnosis.
- Since radioisotopic methods are expensive and time consuming, new more sensitive and specific markers of kidney function are urgently needed.

- The incidence of AKI reported in myeloablative Allogeneic Transplant Recipients is considerably higher in comparison to other subclasses such as non myeloablative allogeneic or autologous transplant recipients

- Some survivors of AKI develop nephrotic syndrome within several years after allogeneic SCT , and some develop a gradual loss in the

glomerular function, ultimately resulting in chronic kidney disease (CKD)

Time Course of Kidney Disease Development Following Allogeneic SCT



An Overview of Kidney Disease Following Hematopoietic Cell Transplantation, oi: 10.2169/internalmedicine.9838-17
Intern Med 57: 1503-1508, 2018

Kidney injury before HCT

- Patients qualified for HCT frequently have impaired kidney function prior to transplantation. This may be caused by underlying diseases, comorbidities, or both.
- Glomerulonephritis develops in many hematological malignancies as a paraneoplastic syndrome and resolves with remission of the underlying disease .

In multiple myeloma and other plasma-cell dyscrasias, accumulation of monoclonal protein in nephrons leads to cast nephropathy, glomerulonephritis, or less frequently, to amyloidosis.

- hypercalcemia causes direct damage to the renal interstitium

- Other mechanisms of kidney injury in the course of malignancy include: tumor lysis syndrome, cytokine release syndrome (CRS), infiltration by cancer cells, and obstructive uropathy caused by lymphadenopathy.

- Iatrogenic injury via chemotherapy and radiation also should not be overlooked.

- Comorbidities such as diabetes mellitus, hypertension, and arteriosclerosis also contribute to pretransplant kidney insufficiency.

TBI(T0tal Body irradiation)

- TBI-induced kidney injury has a particular tendency to develop late, even several years after exposure. Animal models and autopsy studies show features of glomeruloscle-rosis, clots in the glomerulus vessels, and scarring of the kidney parenchyma.
- Clinical presentation varies from asymptomatic course, proteinuria, to thrombotic microangiopathy and end stage renal disease .
- Fractionation of the radiation dosage into five to 12 sessions and partial shielding of kidneys may decrease renal toxicity, however, it comes with the price of higher relapse rates .
- Animal studies and small cohort observations suggest a protective role of angiotensin convertase inhibitors for kidney function during TBI, but further studies are needed to draw clear conclusions.

Conditioning Regimens

Table 2 Requirement for dose reduction of chemotherapeutics used in conditioning regimens [23,38,39].

Chemotherapeutic	Clinical presentation	Recommended dosage reduction for general population	Recommended dosage reduction for HCT recipients
Busulfan	AKI, electrolyte disturbances, (hypomagnesemia, hypocalcemia, hypophosphatemia)	NO	NO
Cyclophosphamide	Hemorrhagic cystitis[a] Urinary-bladder fibrosis	25% for GFR < 10, 50% for HD	Consider in moderate to severe renal impairment
Fludarabine	—	25% for GFR 10—50, 50% for GFR <10 and HD	20—25% in moderate to severe renal impairment
Melphalan	AKI	25% for GFR 10—50, 50% for GFR <10 and HD	100—140 mg/m^2 in renal impairment and HD
Carmustine	AKI	No data for GFR 10—50, avoid in GFR <10 and HD	
Clofarabine	-		50% for GFR 30—60
Thiotepa	Hematuria Dysuria Urinary retention	YES	NO in moderate and severe renal impairment.
Etoposide	Metabolic Acidosis	25% for GFR 10—50, 50% for GFR <10. HD: no reduction	No data

Note. AKI = acute kidney injury; GFR = estimated glomerular filtration rate (mL/min/m^2); HCT = hematopoietic cell transplantation; HD = hemodialysis; MESNA = sodium 2-mercaptoethane sulfonate.

[a] Risk significantly decreases with use of adequate hydration and prophylaxis with MESNA [29].

Table 1 Etiology of kidney dysfunction after Hematopoietic Cell Transplantation (HCT) [23].

Prerenal	Intrarenal	Post-renal
• Decreased renal blood flow following heavy fluid loss (vomiting, diarrhea, dehydration, mucosal damage, bleeding) • Septic shock • CLS • ES • VOD/SOS	• Acute tubular necrosis (sepsis, nephrotoxic drugs, contrast agents, CRS, ES, VOD/SOS) • Interstitial nephritis (induced by: drugs, infections such as BK virus, adenovirus, fungal infection) • TAM • Complex origin: GvHD • Tumor lysis syndrome	• Crystal nephropathy • Retroperitoneal fibrosis associated with radiotherapy • Tumor infiltration of urinary tract • Hemorrhagic cystitis

Note. CLS = capillary leak syndrome; CRS = cytokine release syndrome; ES = engraftment syndrome; GvHD = graft versus host disease; SOS = sinusoidal obstructive syndrome; TAM = transplant-associated microangiopathy; VOD = veno-occlusive disease.

Kidney dysfunction after hematopoietic cell transplantation—Etiology, management, and perspectives
Dorota Jagus ´a, Karol Lis b, Longin Niemczyka, Grzegorz W. Basak b,2016

capillary leak syndrome (CLS) and engraftment syndrome

- Both of them cause AKI in the early post-transplant period . Both are caused by release of pro inflammatory cytokines and may manifest after auto HCT and allo HCT as fluid retention and non infectious fever.
- The mechanism of kidney injury is prerenal—secondary to intravascular volume depletion and possibly also direct impact of inflammation on kidney tissue .

❖CLS

- CLS often presents within 2 weeks post HCT as peripheral edema and serosal effusion resistant to diuretics

Clinically significant renal failure was found in 14% of severe CLS .

- Treatment options are steroids and currently investigated anti-interleukin-6 therapies

❖ Engraftment syndrome

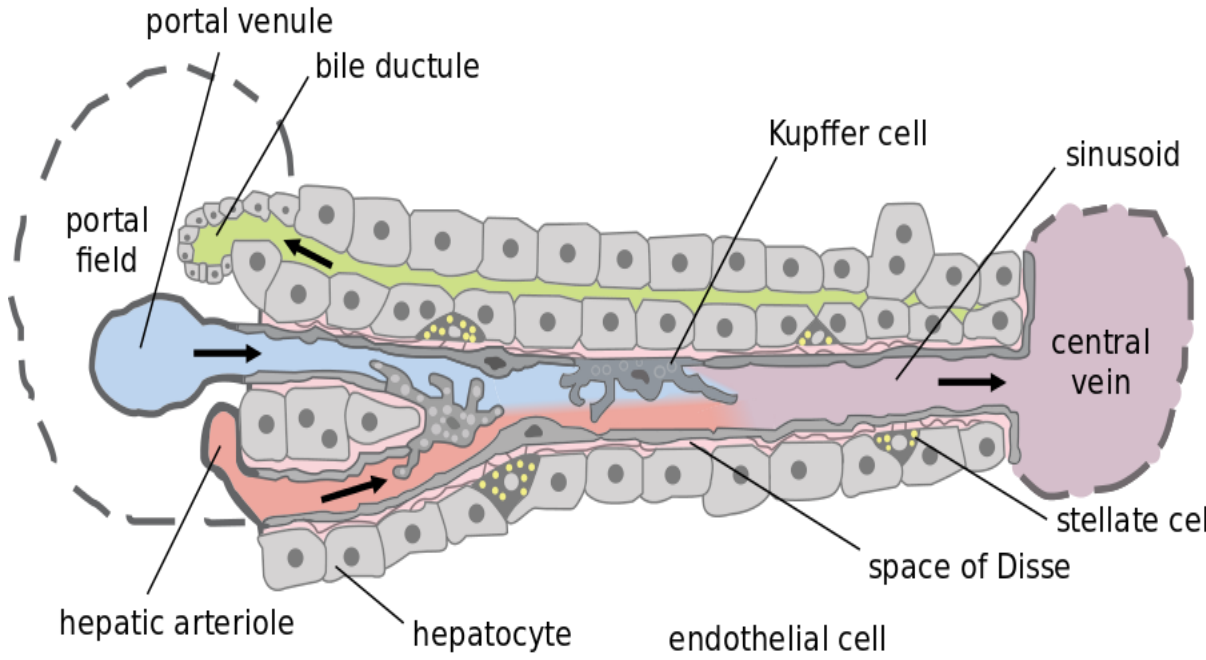
- Engraftment syndrome presents similarly to CLS but it occurs mainly during neutrophil regeneration and is often accompanied by fever and rash with multiorgan dysfunction.
- Kidney dysfunction in engraftment syndrome was found in 8% of allo HCT recipients and 27% of auto HCT recipients .
- Engraftment syndrome responds well to glucocorticoid treatment provided that the treatment is implemented early.

The veno-occlusive disease/sinusoidal obstruction syn-drome (VOD/SOS)

- It is the effect of pathological activation of endothelium and coagulation that results in obstruction of hepatic sinuses and consequently portal hypertension . The mechanism of kidney injury is analogical to hepato-renal syndrome , but the pathophysiology of hepato-renal syndrome also remains puzzling. Currently, it is thought to be a result of hypoperfusion of kidneys, secondary to splanchnic vasodilatation and reduced effective blood volume.
- Kidney specimens typically

show no structural changes,

which confirms the above hypothesis .



- Clinical presentation of AKI secondary to VOD/SOS is:

oliguria, ascites, peripheral edema, low mean arterial pressure with a relatively high pulse pressure, and tachycardia.

DX:

- In laboratory testing, creatinine concentration may be inadequately normal or only slightly increased. Other findings include hyponatremia, hyperkalemia, urine sodium exertion less than 10 mEq/L and urine osmolality greater than plasma osmolality .

RX:

Treatment is based on fluid and sodium restriction, albumin infusion together with vasoconstrictors, preferably terlipressin, and in severe cases RRT . Apart from the above symptomatic measures, defibrotide is considered as an effective causative treatment

Pathophysiology and management of AKI in HSCT

Etiology	Pathophysiology	Management/potential therapeutic options
Sepsis	Vasodilatation and reduced renal blood flow resulting in ischemia and direct renal tubular insult by inflammatory cytokines	Treatment of sepsis with appropriate medication
Nephrotoxic medication		
Amphotericin B	Vasoconstriction of renal vasculature resulting in hypoperfusion and renal tubular epithelial damage	Measurement of urinary UNGAL levels may serve as early biomarker of AKI. Restricting amphotericin use only for documented fungal infections. Use of antifungals with minimal nephrotoxicity such as itraconazole, fluconazole, and voriconazole.
Acyclovir	Formation of crystals in renal tubules and collecting ducts resulting in obstruction especially with IV administration in high doses	Demonstration of birefringent needle shaped crystals in urinary sediment under polarizing microscopy helps in diagnosis. Slower IV administration, hydration, and renal dose adjustments are recommended

Aminoglycosides	Intracellular accumulation in proximal tubules and change in cellular permeability	Measurement of alanine aminopeptidase and N-acetyl-beta-D glucosaminidase in urine may serve as an early biomarker of nephrotoxicity. Reduction in dosage frequency is the mainstay of management
Cyclosporine A	Renal vasoconstriction secondary to renin-angiotensin system activation. Increased production of VEGF. Downregulation of renal Klotho and increased oxidative stress causing renal endothelial damage. Thrombotic microangiopathy. Impaired glucose metabolism	Potential treatment options are aliskiren, valsartan, and switching to alternative immunosuppressant such as sirolimus

Hepatic SOS	Damage to hepatic sinusoidal endothelial cells by chemotherapeutic agents and subendothelial deposition of fibrin and other blood products resulting in venular obstruction. Glutathione depletion due to chemotherapeutic drug detoxification by glutathione pathway resulting in hepatocellular necrosis and fibrosis	Circulating endothelial cells (CECs) and plasminogen activator inhibitor-1 are potential biomarkers. Modification of conditioning regimens and use of defibrotide
Thrombotic microangiopathy	Renal endothelial injury by cytokines released in GVHD. Decreased levels of VEGF. Exposure to calcineurin inhibitors, TBI, and infections	Measurement of serum NETs level may serve as early biomarker for TMA. Continuing acute GVHD treatment may be of benefit. Plasma exchange has a limited role. Eculizumab may be a potential treatment option
Marrow infusion toxicity	Exposure to cryoprecipitants causes hemolysis and heme precipitation in distal renal tubules resulting in tubular obstruction	Alkalinization of urine and mannitol induced diuresis

Tumor lysis syndrome	Lysis of tumor cells releasing intracellular products into circulation resulting in hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. Precipitation of calcium phosphate and urate crystals causes damage to renal tubules. Vasoconstriction of renal arterioles and exposure to inflammatory cytokines causes injury to renal tubules	Mainstay of management involves IV hydration, rasburicase, and allopurinol. Low phosphate diet and phosphate binders for hyperphosphatemia. Medical management of hyperkalemia and renal replacement therapy in resistant cases and severe AKI
Infections		
BK virus	Immunosuppression reactivates dormant virus in urinary tract causing renal tubular injury and hemorrhagic cystitis	Reducing immunosuppression is the mainstay of treatment. Supportive care for cystitis.
Adenovirus	Tubulointerstitial nephritis and cystitis	Supportive care. Intravesical cidofivir is potential treatment option for cystitis

Acute Kidney Injury in Hematopoietic Stem Cell Transplantation: A Review, 2016

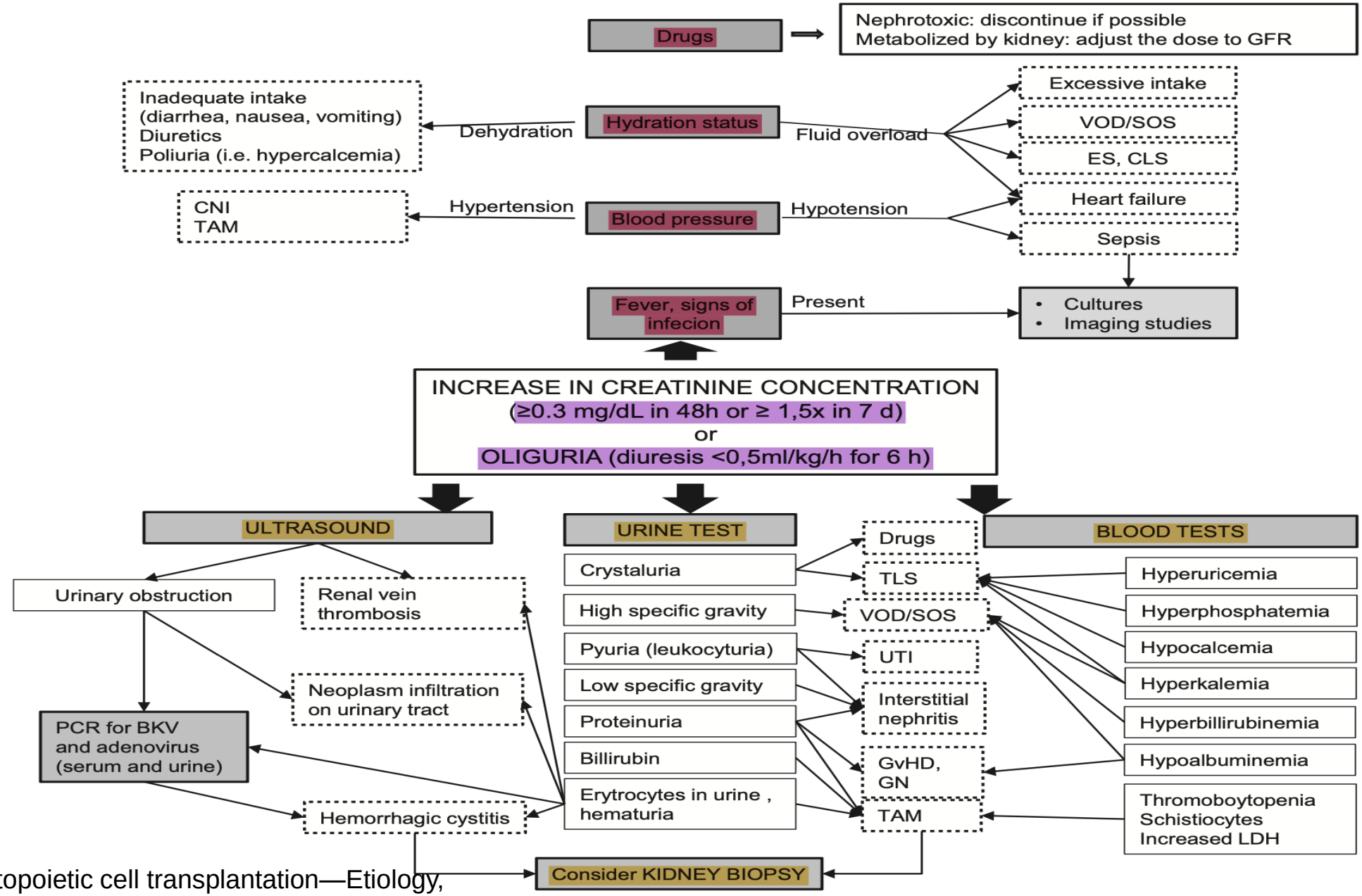
Novel Markers of Acute Kidney Injury in HSCT

- Elafin : increased urinary elafin levels were found to be associated with the development of albuminuria, AKI, progression to chronic

Kidney disease, and death in HSCT recipients

- Urinary Liver-Type Fatty Acid Binding Protein (L-FABP)
- Urinary Alpha 1M : It is a urinary biomarker for predicting severe AKI.

AKI Workup



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Management of Acute Kidney Injury

- (a) Use of the reduced intensity-conditioning regimen wherever possible
- (b) Closer monitoring of nephrotoxic medications such as amphotericin or use of liposomal preparations
- (c) Use of alternative antifungals such as fluconazole and voriconazole for prophylaxis against infection
- (d) Early identification and management of sepsis
- (e) Use of diuresis and alkalinization of urine in conditions such as tumor lysis syndrome or marrow infusion toxicity
- (f) Early identification and management of hepatic SOS with defibrotide
- (g) More importantly, early involvement of the nephrologist in the disease course is helpful in prevention of AKI and related complications.

Table 4 Suggested Management Options of AKI after hematopoietic cell transplantation (HCT).

Dehydration	Hydration guided by fluid balance and electrolyte concentration
VOD/SOS	Albumins RRT defibrotide
ES, CLS	Steroids, diuretics
Heart failure	Diuretics, vasopressors, inotropes, specific cardiologic treatment
Tumor lysis syndrome	Hydration, allopurinol, rasburicase, febuxostat, RRT
TAM	Consider discontinuation of CNI Plazmapheresis Rituximab[a] Eculizumab[a]
Hemorrhagic cystitis	Urinary bladder irrigation, Cidofovir[a] Leflunomid Immunoglobulin infusions[a] Hyperbaric oxygen[a]
Obstruction in urinary tract	Urethral and ureteral catheterization Nephrostomy
Interstitial nephritis	Discontinue drugs, steroids
GVHD, GN	Immunosuppression

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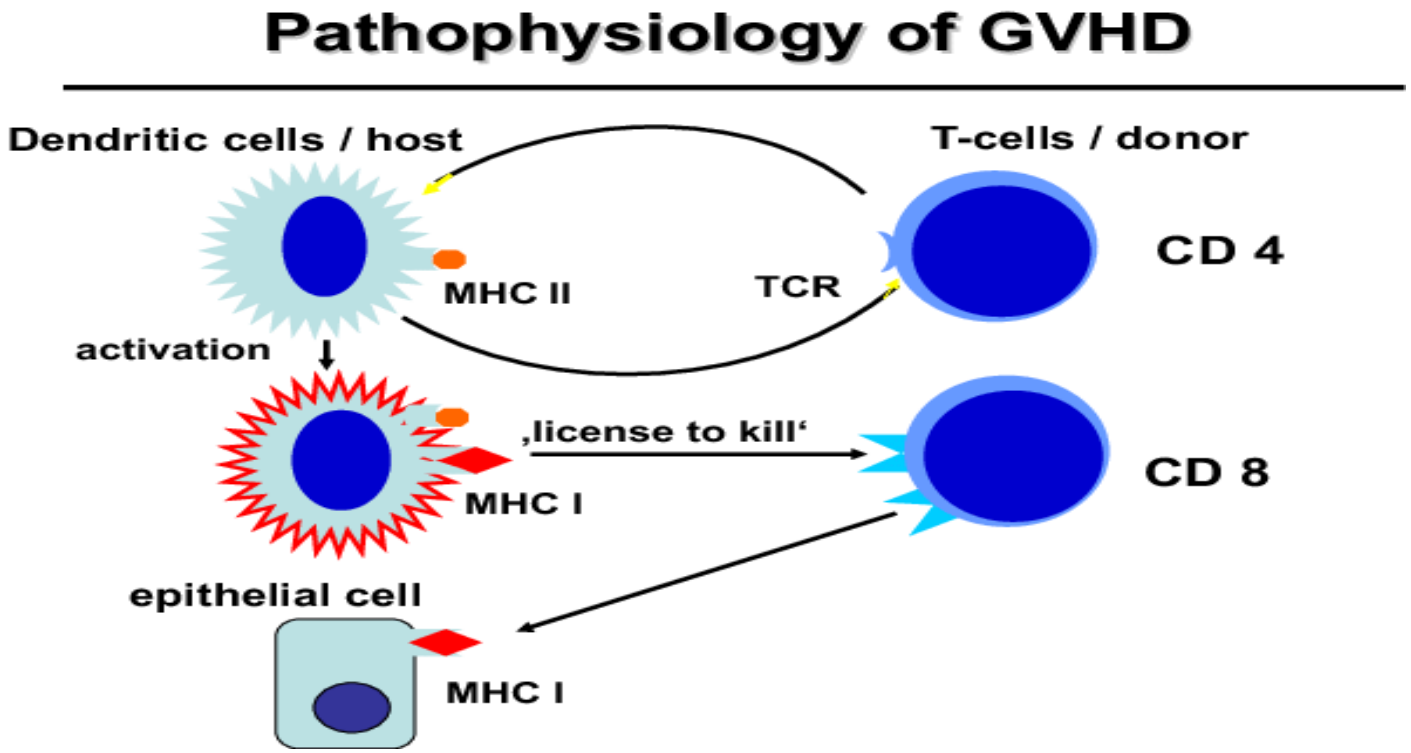
GVHD

- GVHD is an immune-mediated disorder believed to be driven by allo specific lymphocytes, as it does not occur after autologous HSCT. GVHD develops when donor-derived T cells respond to recipient tissues.



Prophylaxis against Graft-versus-Host Disease and Infections

- All allogeneic transplant recipients receive prophylaxis against graft-versus-host-disease (GVHD).
- Regimens for prophylaxis include cyclosporine A (CsA), mycophenolate mofetil(MMF), tacrolimus(FK), or even short-termmethotrexate(MTX). However, the use of the above regimens

For prophylaxis against GVHD is limited to allogeneic transplants.

- Furthermore, most of the patients discussed in various

Studies received prophylaxis against infections with acyclovir and azoles.

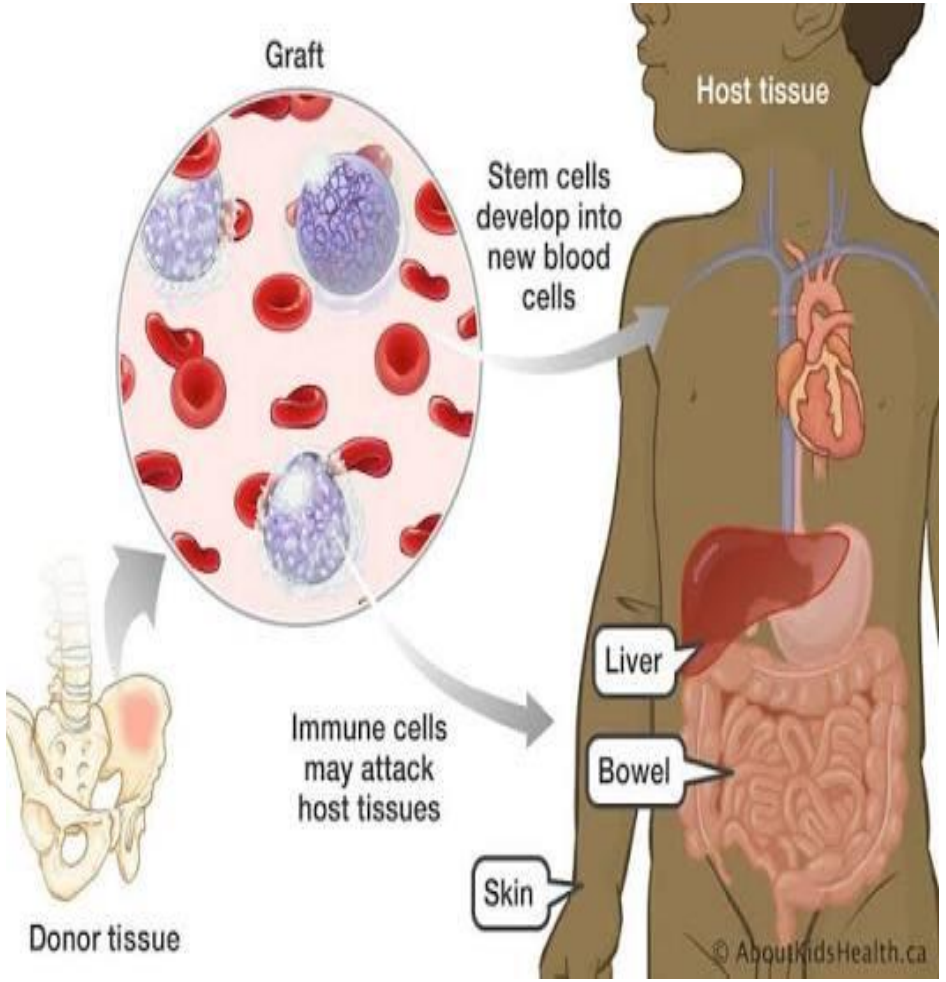
Acute GVHD:

- acute GVHD is a severe but normal inflammatory response mediated by donor lymphocytes infused into the recipient. Second, recipient tissues that stimulate donor lymphocytes are usually vulnerable because they have been damaged by the underlying disease, chemotherapy, prior infection, and/or the HSCT conditioning regimen. As a result, these tissues produce inflammatory cytokines that promote activation and proliferation of donor immune cells

chronic GVHD

- The pathophysiology of chronic GVHD is more complicated. Recent studies of chronic GVHD have increasingly focused on the importance of B cells, while earlier studies focused on T cells

- In general, GVHD involves epithelial tissues of the skin, gastrointestinal tract, and lungs. GVHD can also damage endothelial cells, and transplant-associated microangiopathy (TA-TMA) may represent GVHD.



Treatment of Graft-versus-Host Disease

- it can independently serve as a risk factor for the development of AKI in HSCT recipients . The contribution of GVHD to AKI can be two fold. It could either be related to cytokine-mediated inflammation affecting the tubules/glomeruli or indirectly Related to the use of medications such as cyclosporine, which by itself can predispose to nephrotoxicity.
- Furthermore, the presence of GVHD promotes viral reactivation such as cytomegalovirus (CMV), which can also contribute to AKI.

- Medical treatment options for GVHD include prednisone, anti thymocyte globulin, sirolimus, and mycophenolate mofetil

Renal TMA-associated GVHD after HSCT

- It is thought that damage of vascular endothelium triggers platelet aggregation in the microvasculature and excessive activation of the complement leading to thrombosis and fibrin deposition
- Plasma levels of markers of endothelial cell injury and the coagulation

system are elevated in patients with acute GVHD after HSCT, suggesting an association of endothelial injury, acute GVHD, and subsequent development of TMA

- diagnostic criteria for TA-TMA :

(1) hemolytic anemia
(2) thrombocytopenia
(3) elevated lactate dehydrogenase level
(4) presence of schistocytes in peripheral blood or a blood smear.

- In addition, elevated circulating C5b-9 (a marker of terminal complement activation), elevated blood pressure, and proteinuria may be indicators of TA-TMA.

Renal Complications after Hematopoietic Stem Cell Transplantation: Role of Graft-Versus-Host Disease in Renal Thrombotic Microangiopathy

Akiko Mii[1], Akira Shimizu[2], Hiroki Yamaguchi[3] and Shuichi Tsuruoka[1]

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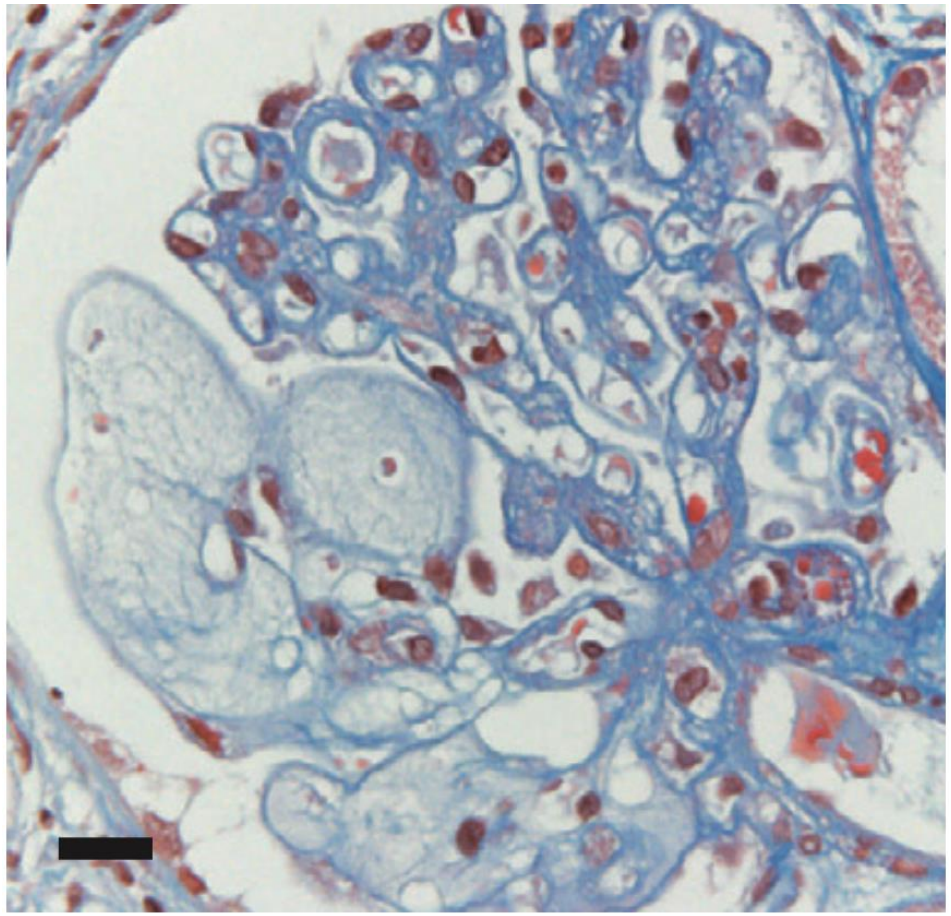
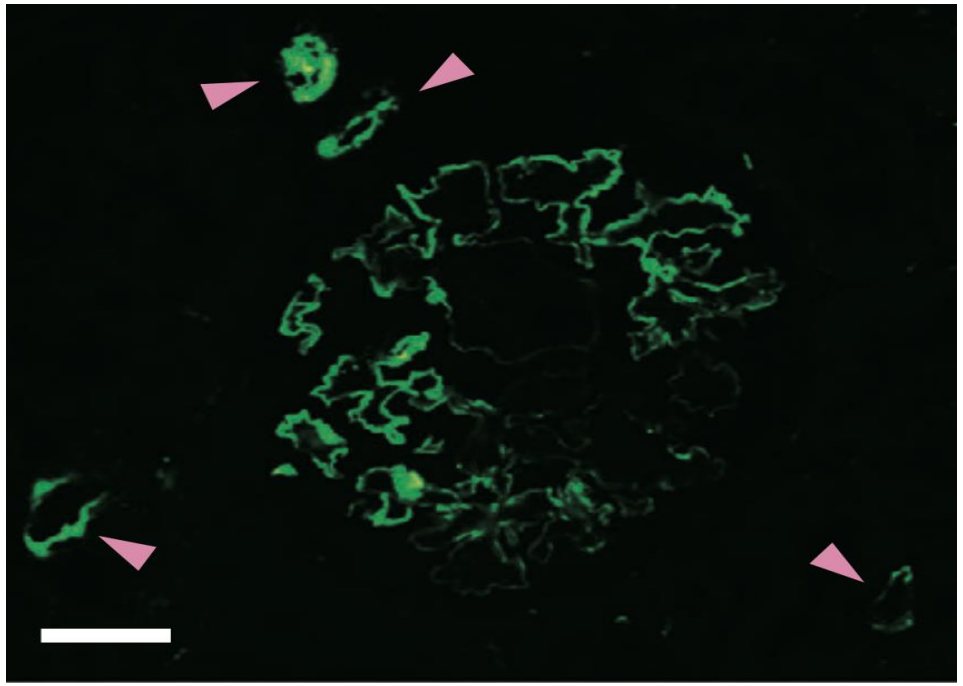
(J Nippon Med Sch 2020; 87:7—12)



A kidney biopsy showed severe endothelial cell injury of micro vessels. Renal TMA was diagnosed, even though there were no clinical symptoms of TMA, except for hypertension .
We initially thought that kidney injury was caused by use of CNI for GVHD prophylaxis. However, renal function deteriorated when CNI was gradually reduced and stopped. The patient ultimately required dialysis.

diffuse global enlarged subendo-thelial spaces, double contouring of the glomerular basement membrane, and post-mesangiolysis lesions

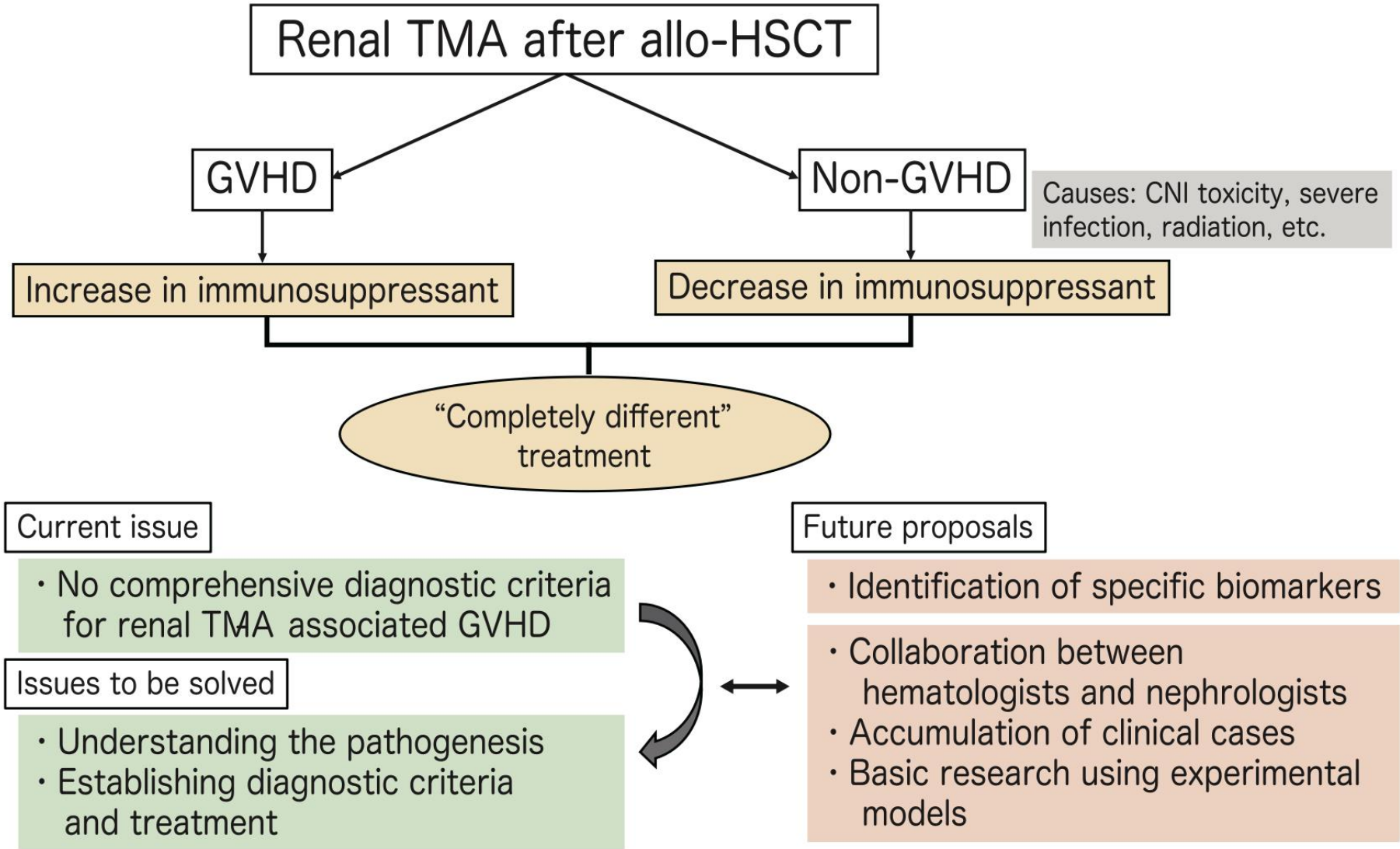


A diffuse, global pattern of C4d deposition was detected on glomerular capillaries. Patchy staining for C4d was also evident in peritubular capillaries

- in addition to vascular endothelial cell injury, there was glomerulitis,PTC-itis, tubulitis, and C4d deposition in the glomerular basement membrane and patchy PTCs. These findings were similar to those seen in images of chronic antibody-mediated rejection in kidney transplantation

- These findings suggested that the cause of renal TMA in this case might be chronic renal GVHD, in which chronic humoral GVHD may have caused antibodies to renal microvascular endothelial cells.

Renal TMA-associated GVHD after HSCT



Renal Complications Associated with GVHD

- Among the renal complications associated with GVHD, nephrotic syndrome is well known but rare.

➢membranous nephropathy with subepithelial deposits.

➢minimal change disease,

➢focal segmental glomerulosclerosis,

➢ IgA nephropathy

- The precise mechanism underlying kidney injury and GVHD is unclear, although the kidney is believed to be a target organ of GVHD.

CKD

- during the late stage after transplantation, renal function gradually deteriorates for various reasons and ultimately progresses to end-stage renal failure.
- The causes of (CKD) :

❖repeated AKI attributable to various causes,

❖long-term use of calcineurin inhibitors (CNIs) for GVHD prophylaxis and treatment,

❖radiation nephropathy,

❖nephrotic syndrome caused by GVHD,

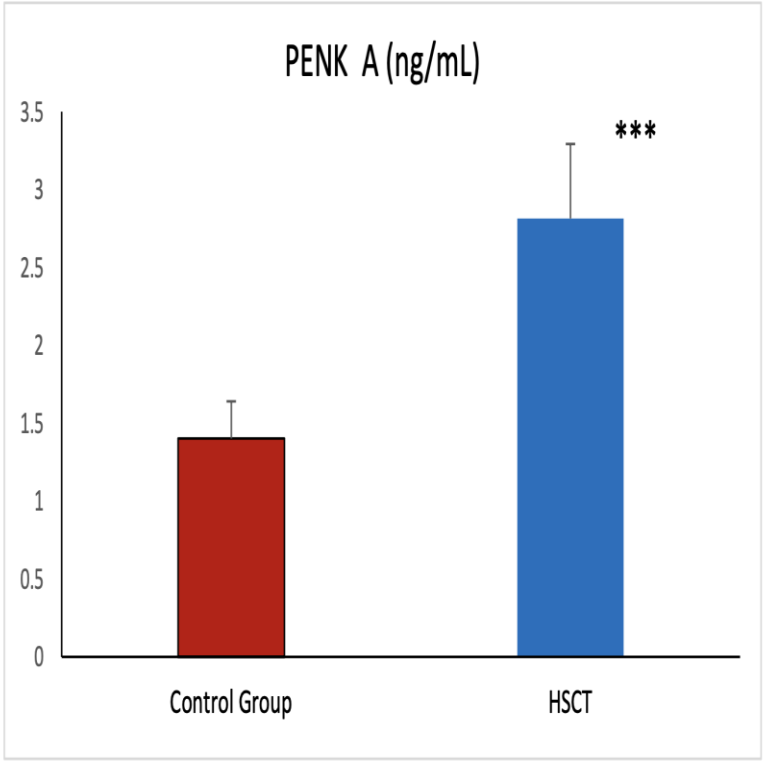
❖renal TMA with or without systemic symptoms

- CKD is associated with cardiovascular risks and increased incidences of several cancers. Similarly, post-HSCT patients with CKD have a lower overall survival rate than those without CKD.
- The frequency of CKD increases with time after HCT and differs substantially between allogeneic (14%) and autologous transplantation recipients (4%)

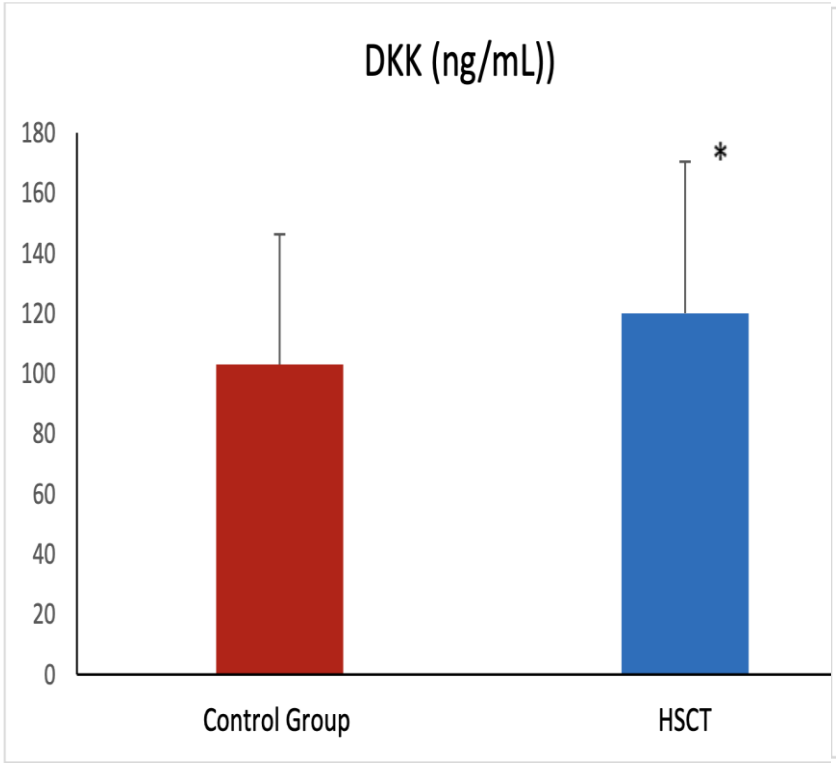
- Albuminuria defined as urinary albumin to creatinine ratio (ACR, 30–300 mg/g) is a negative prognostic marker for survival, progression of CKD, occurrence of GvHD, and bacteremia. There is a linear correlation between the level of ACR and mortality during the first 100 days after HCT: mortality rises about 10% on every 100 mg/g ACR increase

Markers of Kidney Injury: Proenkephalin A and Uromodulin, but Not Dickkopf-3, Are Elevated in Patients After Hematopoietic Stem Cell Transplantation 2025

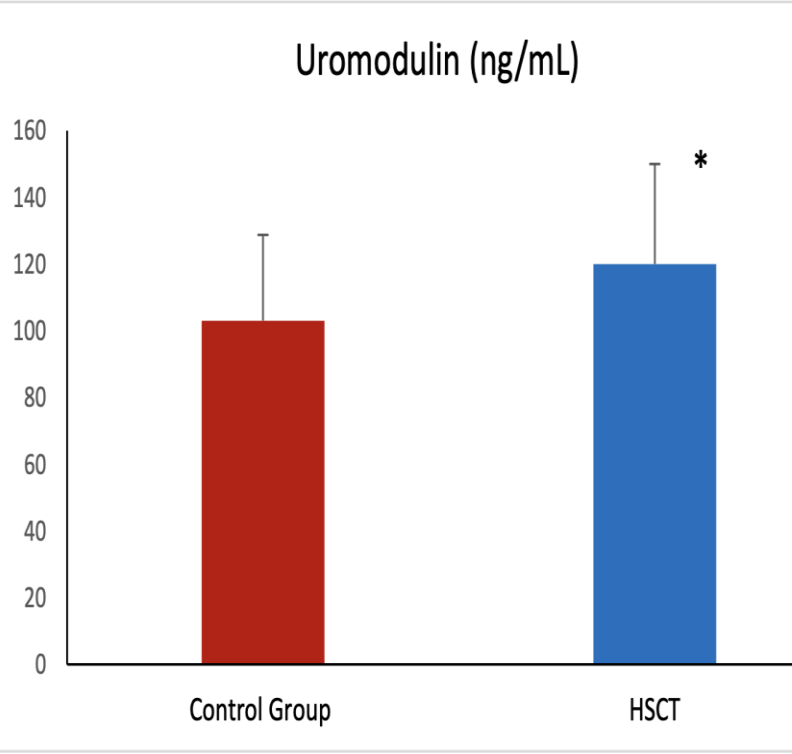
Aleksandra Kaszyńska [1], Małgorzata Kępska-Dzilińska [1], Ewa Karakulska-Prystupiuk [2], Agnieszka Tomaszewska [2],



Proenkephalin A—PENK A



Dickkopf-3 (DKK)



- The results showed that PENK and DKK-3 levels were significantly higher in patients after HSCT compared to healthy volunteers. Furthermore, when patients were divided according to kidney function (below and over 60 mL/min/1.72 m2), it was found that the concentration of PENK and DKK-3 were significantly higher in23 patients with CKD stage 3 relative to patients with eGFR over 60 mL min 1.72 m2
- In univariate correlations, PENK demonstrated an inverse relationship with eGFR ($r:-0.21, p < 0.05$), while DKK-3 exhibited no significant correlation with creatinine or eGFR.

Thanks