The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

In the name of GOD

TEHRAN 2023

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Immunosuppressive Tx after KT Failure

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Introduction

- ✓ The long-term survival of kidney allografts has significantly increased.
- ✓ Despite this success, a substantial number of KT recipients finally require the permanent KRT because of allograft failure.
- ✓ The survival of such patients on dialysis appears to be relatively poor.

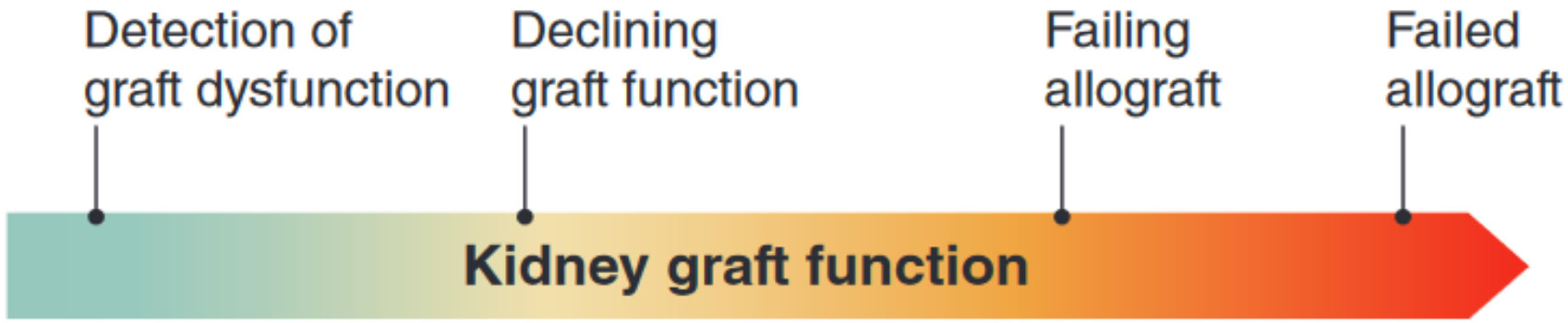

Figure 1 | Spectrum of kidney allograft function.

KDIGO executive conclusions.Challenges in the management of the kidney allograft from decline to failure::KI (2023) 104, 1076–1091

MANAGEMENT OF IMMUNOSUPPRESSION

One of the most important aspects of managing the patient with a failing kidney allograft is deciding when and how to safely stop maintenance IST.

1. The primary goal is to withdraw the IST without precipitating rejection, causing any adverse effects related to drug withdrawal, or exacerbating allosensitization.
2. The impact of sensitization should be considered for those patients follow another transplant.
3. Continuation of IST might be necessary in patients who can not tolerate a transplant nephrectomy.

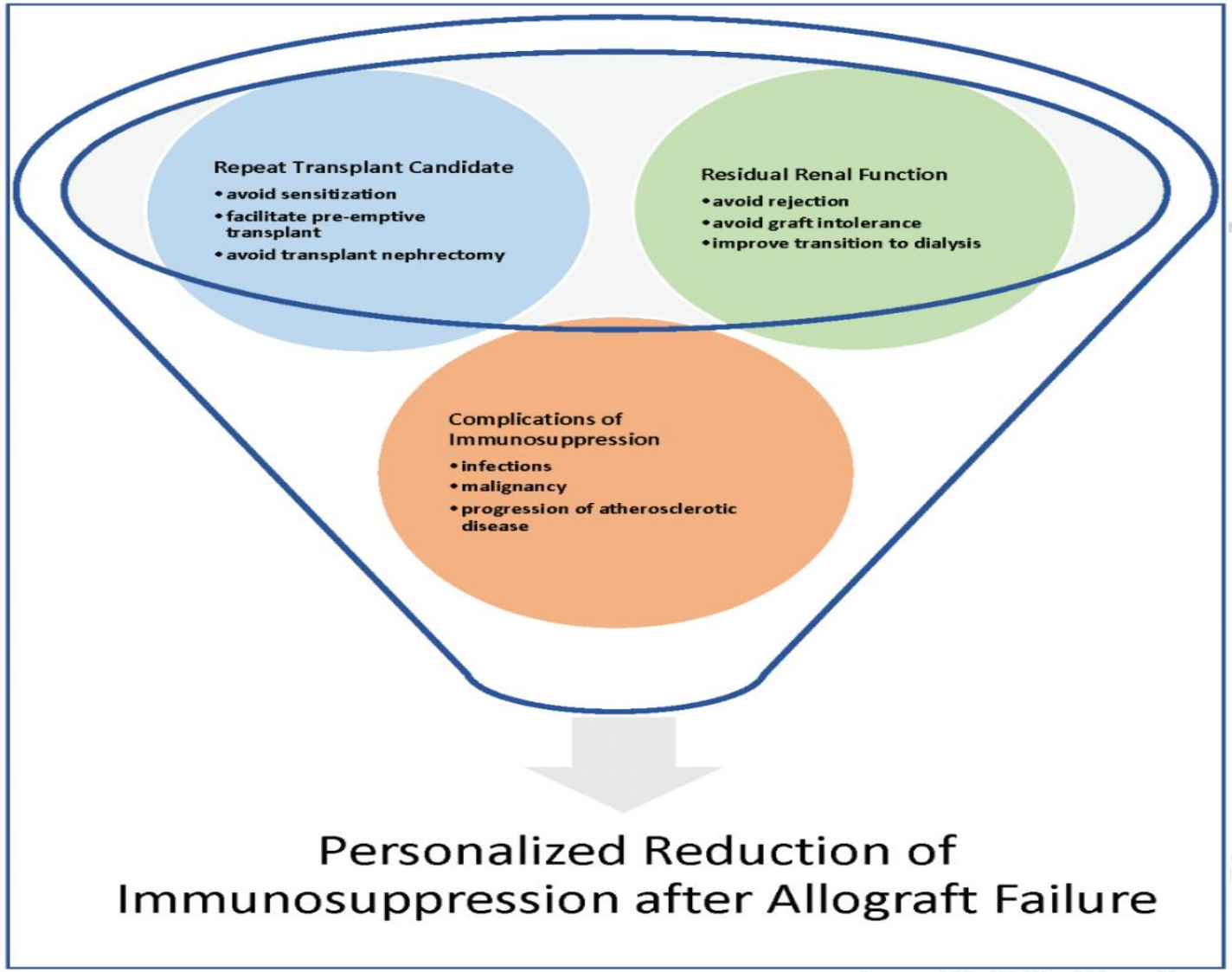

FIGURE 1 Juggling the complexities of a failing allograft. This figure highlights factors for clinicians to consider in immunosuppression management of the failing allograft

COMPREHENSIVEREVIEW

The failing kidney allograft: Am J Transplant. 2021;21:2937–2949

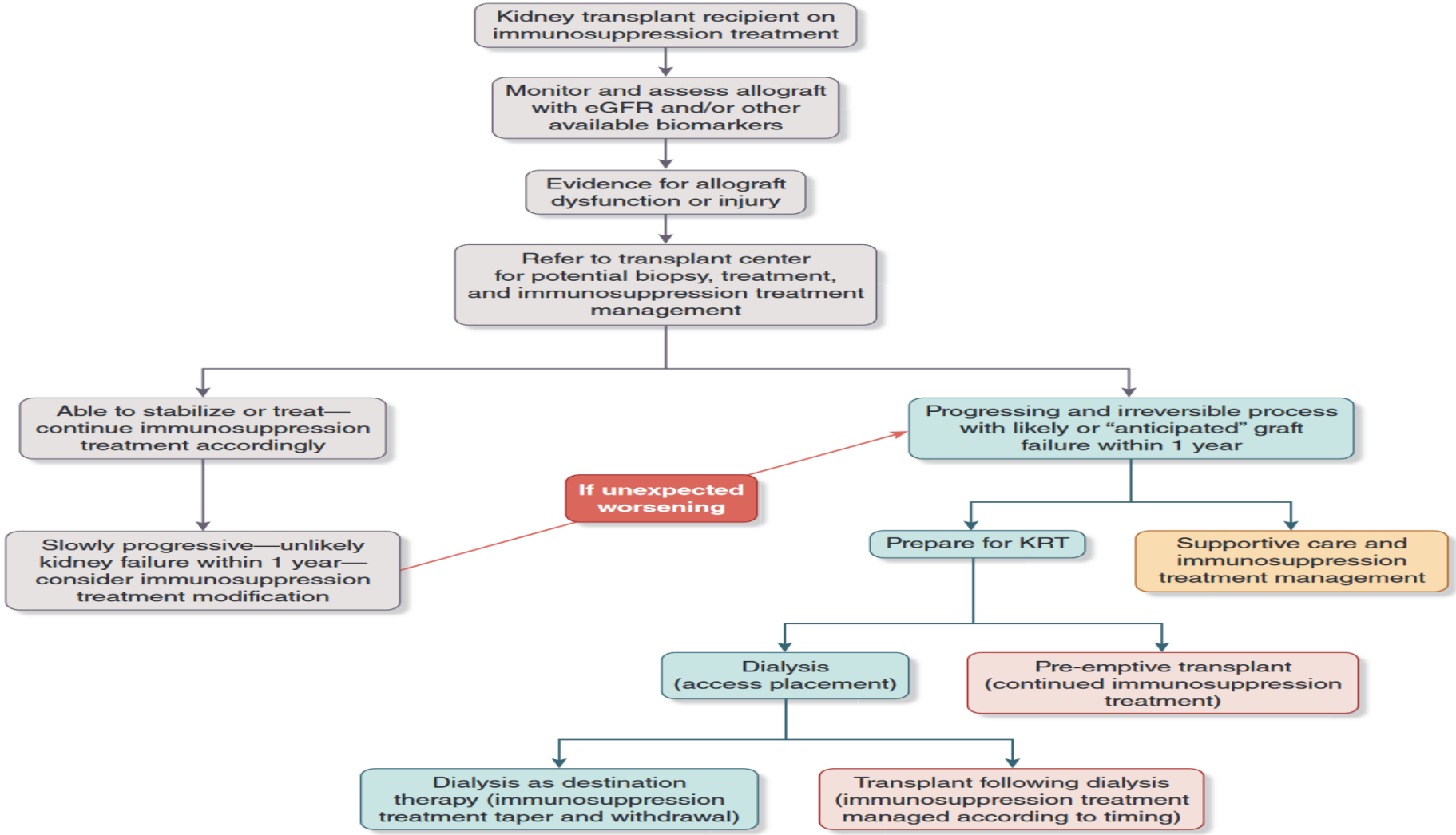

Figure 2 | Integrated management and shared decision-making for a declining and failed kidney allograft. eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy.

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Table 3 | Five key considerations for IST management in recipients with allograft functional decline

Circumstance	Intent
Intended kidney replacement therapy mode following graft failure	
Preemptive transplantation	Avoid DSAs to facilitate next transplant; retain IST to merge into induction for next allograft
Dialysis and wait-listing for retransplantation	Need to balance dialysis safety, residual graft function, and development of DSAs; may be impacted by plans for graft nephrectomy
Dialysis, but not candidate for retransplantation	Imperative to minimize IST to reduce risks of infection and morbidity Risk of allosensitization less of a factor, balanced by need for graft nephrectomy
Supportive care	Need to maximize graft longevity and function
Cause of graft failure	
Non-alloimmune cause	
Recurrent glomerular disease	Does IST have a role in the recurrent disease management?
BK polyomavirus nephropathy	Need for IST reduction and/or graft nephrectomy
Interstitial fibrosis/tubular atrophy	Concurrent comorbidities should be considered to tailor management
Early surgical failure	Likely graft nephrectomy and IST withdrawal
Alloimmune cause	
Acute rejection	May require nephrectomy, as IST failed
Chronic rejection	Complex decision about control of rejection vs. safety
Comorbid considerations impacting safety of IST	
Sepsis, congestive heart failure, malignancy, diabetes, frailty, older age	Tailor to condition
Past history of immunosuppression-associated adverse effects	Previous or ongoing adverse events may direct therapeutic management
Presence of another transplanted solid organ	Protection of the other allograft takes precedence for IST management

DSA, donor-specific antibody; IST, immunosuppression treatment.

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MANAGEMENT OF IMMUNOSUPPRESSION

1. Reasons for withdrawal of immunosuppression
2. Approach to withdrawal of immunosuppression
3. Monitoring during withdrawal of immunosuppression
4. Complications of withdrawal

Reasons for withdrawal of immunosuppression

1. Increased risk of infection
2. Increased risk of malignancy
3. Complications of glucocorticoid therapy
4. Altered drug dosing

Reasons for withdrawal of immunosuppression

Increased risk of infection

- ✓An increased risk of serious infections is observed in both groups:
- ✓1)transplant recipients (because of the direct effects of IST)
- ✓2)dialysis patients (because of immune system disorder from uremia and access-related problems)

Reasons for withdrawal of immunosuppression
Increased risk of malignancy

- ✓ An increased risk of malignancy may occur in patients exposed to IST and is decreased by IST withdrawal.

- ✓The incidence of cancers after allograft failure in KT recipients was highly variable, the incidence of Kaposi sarcoma and non-Hodgkin lymphoma decreased markedly on restart of dialysis, as did the incidence of lip cancer and melanoma.

Reasons for withdrawal of immunosuppression

Complications of glucocorticoid therapy

✓ Patients on long-term glucocorticoid therapy are at risk for infectious as well as noninfectious complications, including osteoporosis, muscle wasting, cataracts, and hyperglycemia.

Reasons for withdrawal of immunosuppression

Altered drug dosing

Standard immunosuppressive agents have special considerations in patients with severe kidney function impairment.

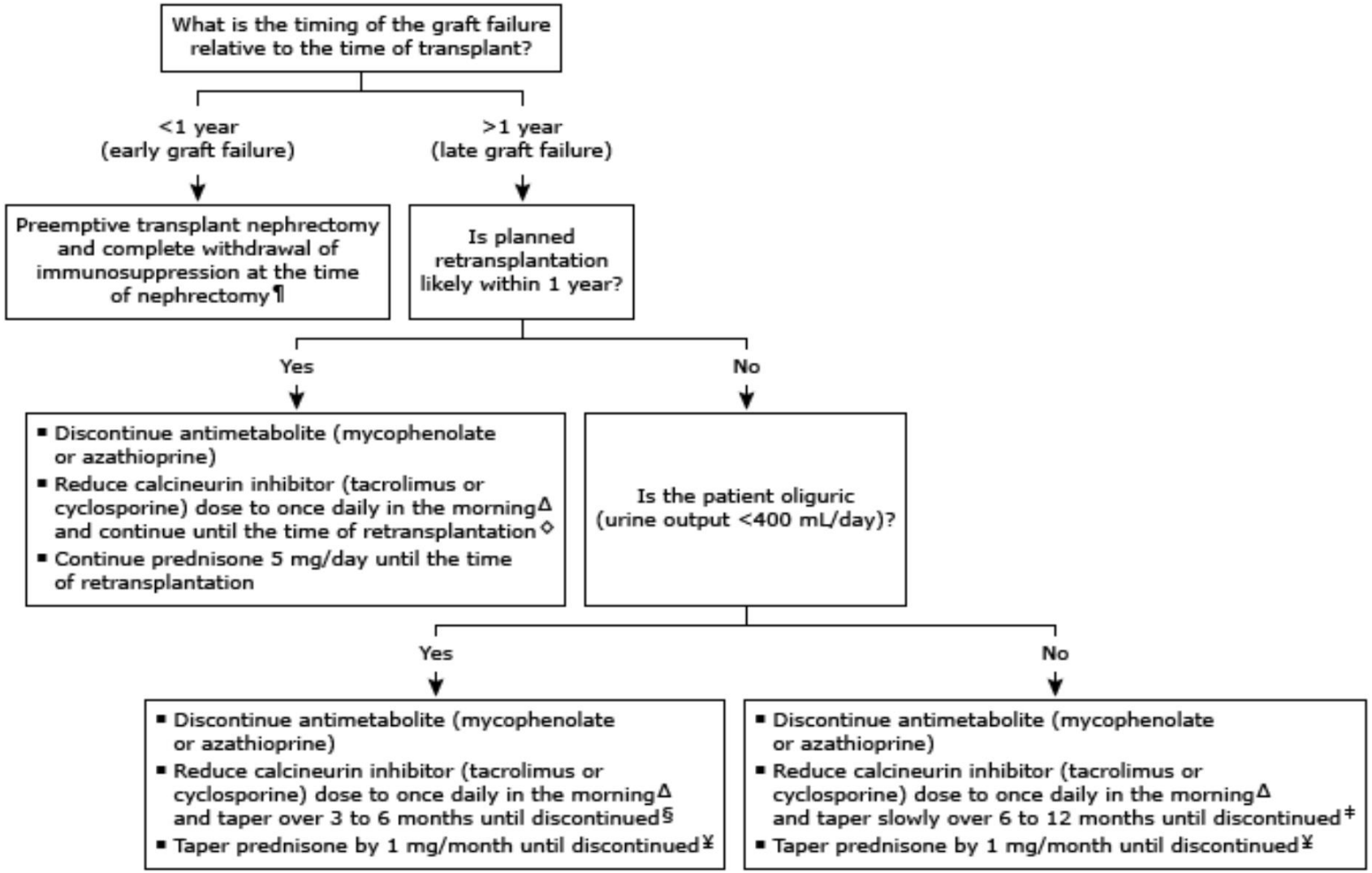
- ✓ As an example, although calcineurin inhibitors are not metabolized or excreted by the kidney, their neurotoxicity may compound the neurologic effects of uremia
- ✓kidney failure can result in changes in the pharmacokinetics of mycophenolate, which may result in higher blood levels of active drug.

Approach to withdrawal of immunosuppression

1. Early graft failure (<1 year posttransplant)

2. Late graft failure (>1 year posttransplant)

Management of immunosuppression in the patient with a failed kidney transplant*



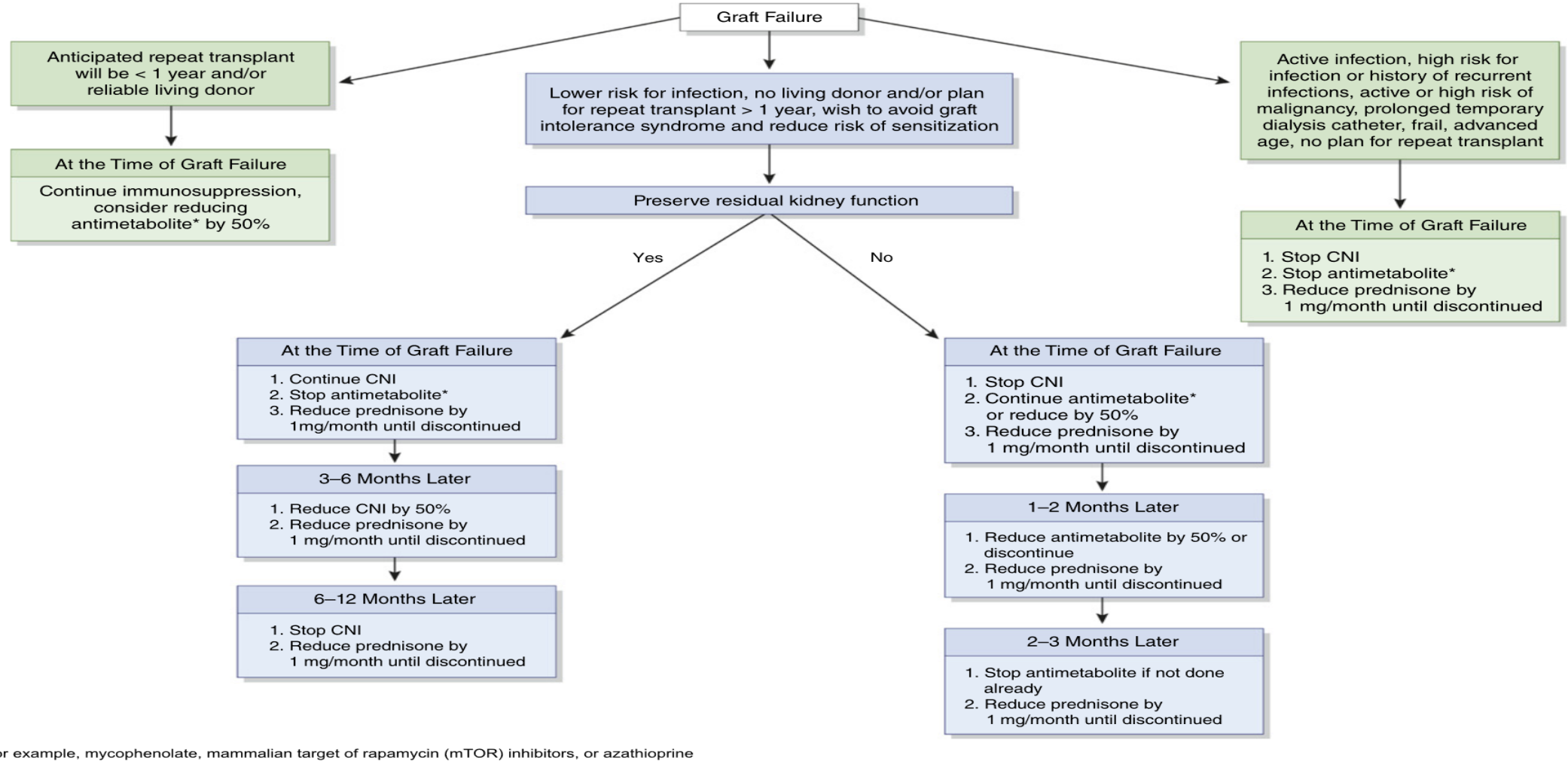


Figure 3. | A suggested approach to immunosuppression weaning upon allograft failure. CNI, calcineurin inhibitor.

Managing Patients with Failing Kidney Allograft. Many Question remain. CJASN 17: 444–451, 2022

IST tapering based on allograft failure

COMPREHENSIVEREVIEW.The failing kidney allograft: Am J Transplant.

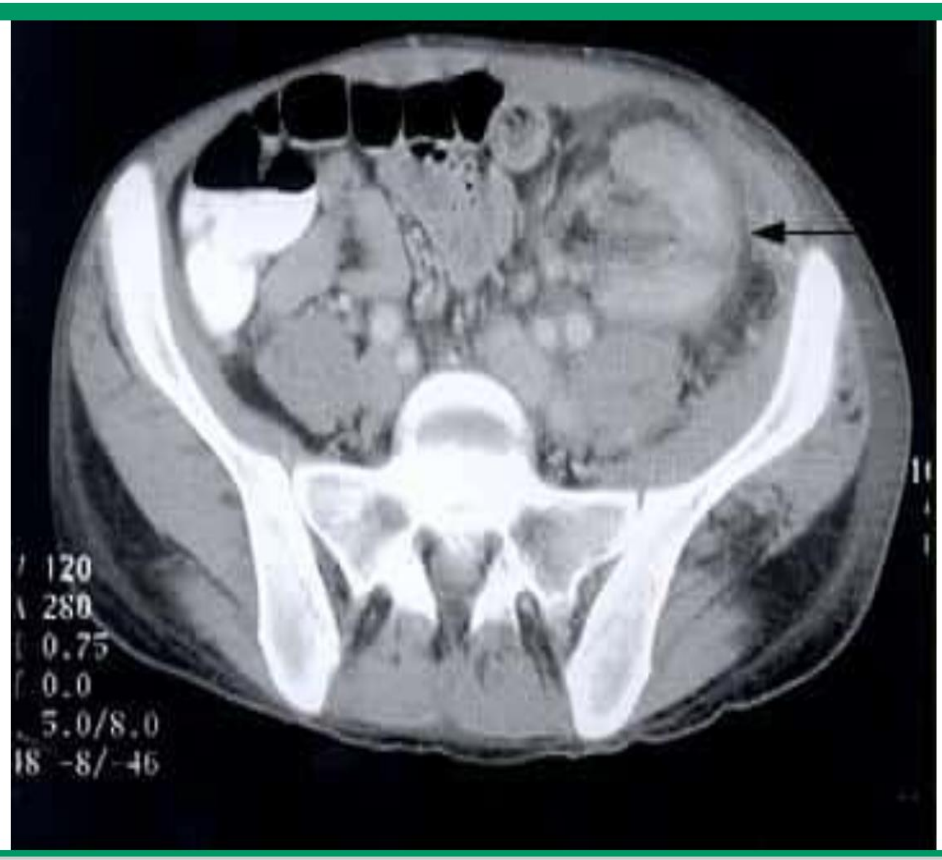
Failed Allograft with Residual Renal Function	• stop anti-metabolite • taper CNI/prednisone to low dose as tolerated (consider Tacrolimus trough 3-5ng/mL)* • follow DSA/PRA, monitor for infectious complications
Failed Allograft Without Residual Renal Function	• stop anti-metabolite • slow taper of CNI/prednisone over 6 months (see Table 1) • consider low dose of CNI alone or prednisone if planned future transplant
Graft Intolerance Syndrome on Dialysis	• pulse steroids for graft intolerance syndrome, followed by slow taper over 6 months • if no response to steroids consider referral for nephrectomy or embolization • consider immunosupression reduction as follows* • target CNI trough of 4-6ng/mL • reduce anti-metabolite by 50% for 4-6 weeks then stop

Monitoring during withdrawal immunosuppression

- ✓All patients who are undergoing withdrawal of their immunosuppression should be closely monitored for complications of withdrawal, including:

- ✓rejection (fever, graft pain and/or tenderness, oliguria)
- ✓secondary adrenal insufficiency

Allograft rejection after immunosuppression withdrawal



Abdominal and pelvic CT scan shows ill-defined margins and heterogenous enhancement of kidney allograft (arrow),

Complications of withdrawal

1. Precipitation of rejection possibly requiring transplant nephrectomy
2. Secondary adrenal insufficiency
3. Loss of residual kidney function
4. Potentially adverse immunologic effects among those pursuing another transplantation
5. Worsening anemia due to erythropoiesis-stimulating agent (ESA) resistance

Complications of withdrawal

Rejection possibly requiring Tx nephrectomy

- ✓A major effect of withdrawing IST is the possible precipitation of rejection, an event that may require **allograft nephrectomy**.
- ✓Transplant nephrectomy is relatively safe.
- ✓Main complication being bleeding and a need for transfusion, need tostart dialysis
- ✓In patients who develop rejection during withdrawal of immunosuppression, we and others administer a five- to seven-day course of prednisone at a dose of 0.3 to 1.0 mg/kg per day.
- ✓The use of CNI has been associated with a dramatic increase in the incidence of required transplant nephrectomies

Complications of withdrawal

Secondary adrenal insufficiency

- ✓Most patients returning to dialysis continue to receive long-term glucocorticoid therapy.
- ✓At risk for adrenal insufficiency following glucocorticoid withdrawal
- ✓ Frequently present with subtle findings of isolated glucocorticoid insufficiency .
- ✓These include persistent fever, weakness, fatigability, myalgias, arthralgias, weight loss with subsequent fluid overload because of the lack of adequate ultrafiltration, mild hypercalcemia, and eosinophilia.
- ✓ACTH stimulation test is the "gold standard" for diagnosing secondary adrenal insufficiency

Complications of withdrawal
Loss of residual kidney function

- ✓kidney allograft function deteriorates rapidly after withdrawal of immunosuppression in both HD and PD patients.

- ✓Longer taper of immunosuppression over a year may permit the maintenance of some kidney allograft function while on dialysis .

Complications of withdrawal

Sensitization

- ✓ Kidney transplant recipients with a failing kidney allograft have an increased risk of developing de novo HLA sensitization.

- ✓Most commonly in the setting of restarting dialysis and relisting for transplant, when immunosuppression is frequently modified or withdrawn.

Graft intolerance syndrome

Common clinical findings	Less common clinical findings
• Fever	• Malaise
• Gross hematuria	• Weight loss
• Allograft enlargement and localized edema	• Hematological findings: thrombocytopenia, ESA resistant anemia
• Allograft tenderness	• Elevated inflammatory markers: ferritin, CRP, ESR

Abbreviations: CRP, C-reactive protein; ESA, erythropoietin stimulating agents; ESR, erythrocyte sedimentation rate.

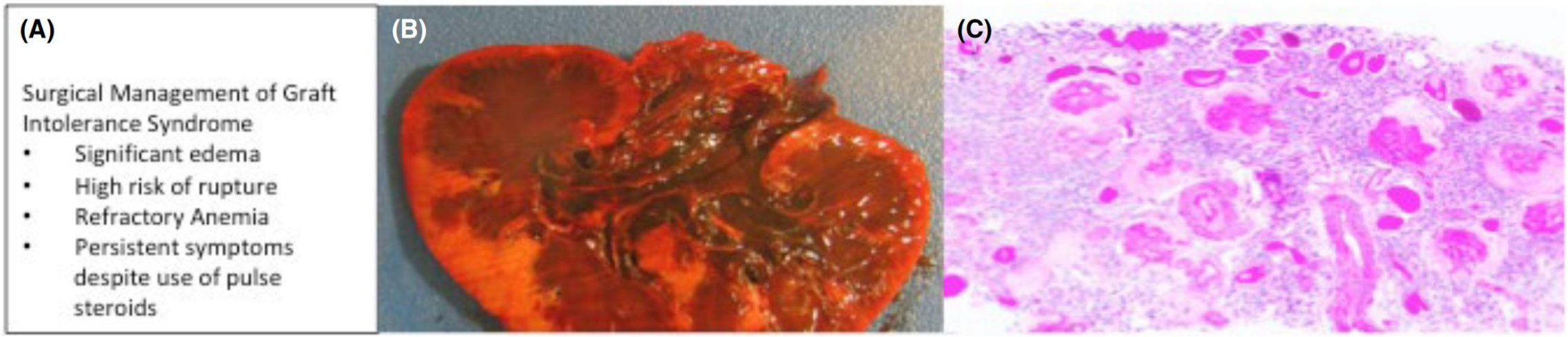


FIGURE 3 Management of graft intolerance syndrome and pathology. (A) Symptoms of graft intolerance syndrome signaling the need for allograft nephrectomy. (B) Gross pathology of nephrectomy specimen showing thrombosis and necrosis (image courtesy of Dr. Surya Seshan

COMPREHENSIVEREVIEW

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Change to belatacept?

- ✓Reduced immunosuppression is commonly recommended in failing allografts, this approach may be counterintuitive in some individuals such as those with ongoing, chronic ABMR and may contribute to more rapid loss of the allograft.
- ✓ One strategy :is the late conversion to **belatacept** based regimens, which may allow for an improvement in kidney function and retard the rate of decline, primarily from the elimination of CNI coupled with improvement in acidosis and other metabolic parameters .
- ✓ this approach is limited to small observational cohorts and more robust prospective data are needed .
- ✓This strategy may have the additional benefit of lowering the possible development of de novo DSA.

Summary of clinical considerations for patients with a failed allograft	
Immunosuppression considerations	• Consider transition to belatacept to delay/slow decline in kidney function over time • Optimal immunosuppression strategy in patients with failed allograft balancing the potential risks (*e.g.*, infection) and benefits (*e.g.*, avoiding sensitization) • Personalization of immunosuppression taper informed by the anticipated time interval to a subsequent transplant • Strategies to avoid an allograft nephrectomy
Retransplantation considerations	• Initiate discussion about identification of a potential living donor • Preemptive waitlisting on the deceased donor waitlist as soon as the GFR <20ml/min • Immunosuppression management for patients with donors • Timing of preemptive retransplantation relative to GFR when a donor is available • Helping patients advocate for a living donor transplant
Transition considerations	• CKD management including management of anemia of CKD and secondary hyperparathyroidism • Evaluation and timely placement of vascular access or peritoneal dialysis catheter • Educating about role of palliative care and consideration of early referral when appropriate, especially for patients who are not candidates for relisting • Modality counseling including home-based therapies

Figure 4. | Summary of clinical considerations for patients with a failed allograft.

Managing Patients with Failing Kidney Allograft. Many Question remain. CJASN 17: 444–451, 2022

Table 4 | Consensus points for immunosuppression management

Strategy	Consensus points
Maintain IST	• Continue IST in patients considered transplantation candidates who have an identified living donor or a short expected waiting time for a deceased-donor organ (though there is no consensus on what constitutes a "short" waiting time) • Continue IST in patients with other solid-organ transplants • Provide IST at a threshold level to prevent overt rejection, minimize sensitization, and maintain residual function
Taper IST (reduction to minimal or none)	• In patients not considered for retransplantation • In patients with severe complications/side effects, especially infections and malignancies • On dialysis, once graft function ceases, corticosteroids should be maintained and should be the last medication tapered for those on corticosteroids maintenance (i.e., adrenal dependency)
Allograft nephrectomy	• In patients with severe rejection or graft-intolerance syndrome unresponsive to IST

IST, immunosuppression treatment.

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Table 1. Summary of key knowledge gaps in the optimal clinical management of patients with failing allografts

	Key Knowledge Gaps
Immunosuppression	Potential benefit, timing, and strategy of introducing calcineurin inhibitor–avoidance protocols that would prolong the life of a failing allograft
	Timing for reduction of immunosuppression in patients with failing allografts and evidence of ongoing chronic rejection
	Immunosuppression withdrawal strategy after allograft failure and initiation of KRT to minimize the risk of sensitization
	Factors to consider for personalization of the risk/benefit ratio of continued immunosuppression (*e.g.*, infectious risk versus decreased sensitization) in patients on dialysis with different expected intervals before a subsequent transplant
	Determining when the potential benefit of a transplant nephrectomy outweighs the potential risks
Transitions of care	Timing of initiation of discussion for the transition to dialysis in the absence of a living donor
	Timing of modality counseling and appropriate access placement, especially for those patients who are not candidates for a subsequent transplant
	Optimal strategy to offer either preemptive listing while encouraging seeking a living donor
	Timing of preemptive transplantation when available as an option
	Transition of care from transplant clinic to CKD clinic
	Consideration for, and timing of, palliative care referral for patients who are not candidates for a subsequent transplant

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