Delayed acute vs. chronic rejection

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- **Allograft rejection** is inflammation with specific pathologic changes in the allograft, with (clinical) or without (subclinical) dysfunction of the graft

- Repeated episodes of acute rejection (even well treated) negatively impact graft outcome (by increasing the risk of chronic graft dysfunction) and patient outcome (by increasing the risk of adverse effects of intensified immunosuppressive therapy)

Terminology

Stable graft function (SGF): usually expressed in term of SCR and urine output

Baseline creatinine: average of 3 SCR measurements within last 3 months

Primary graft non-function: dialysis dependence or creatinine clearance≤20 ml/min for 3 months after TX

Delayed graft function (DGF): need for dialysis during the first week after TX

Subacute graft dysfunction (SGD): Elevation of 25%-50% of baseline creatinine (SCR 0.6 …0.8 mg/dl)

Acute graft dysfunction (AGD): Acute impairment of graft function by elevation of baseline by 50% OR ≥0.3mg/dl (SCR 0.5 …0.8)

Acute graft failure (AGF): Sever form of AGD that necessitates dialysis

Terminology

Baseline creatinine: average of 3 SCR measurements within last 3 months

- **Chronic graft dysfunctioncad (CGD):** Slow progressive decline of renal graft function (GFR) that could be immune or nonimmune mediated

- **Chronic allograft nephropathy (CAN):** CGD of not exactly known etiology with characteristic but nonspecific histopathological changes in the graft

Acute rejection (AR) episode

It is an acute graft dysfunction, due to **potentially reversible**, immune-mediated graft injury

Based on **Time of injury**

- Hyperacute R (Immediate)
- Accelerated AR (1st week)
- Early AR (>1st week-3 months)
- Delayed AR (>3 months-years)

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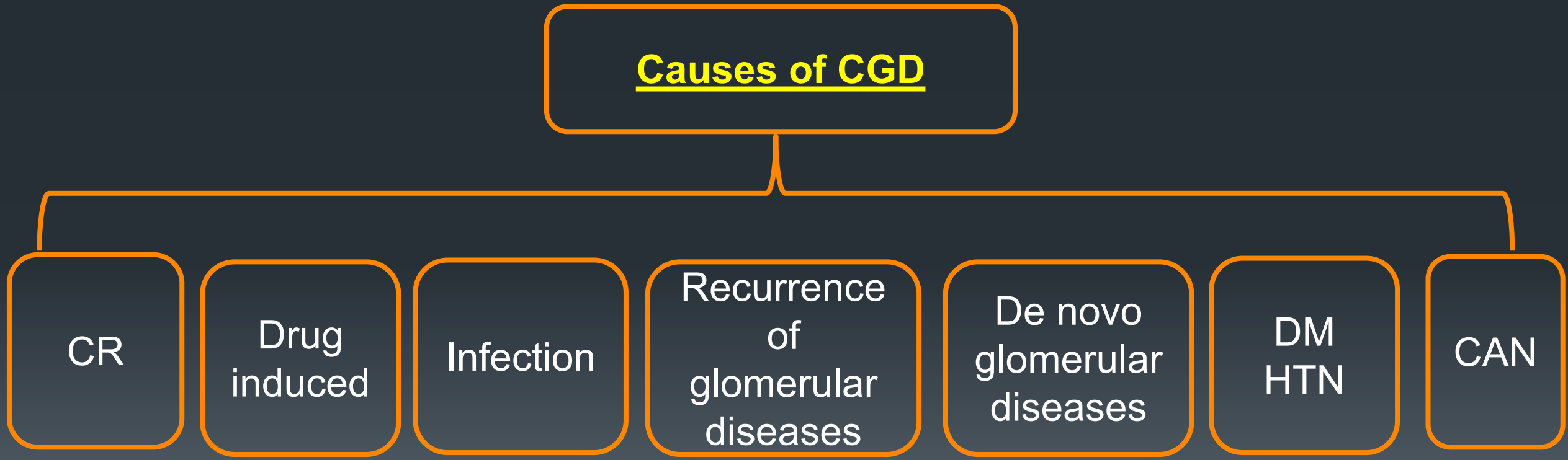
Chronic rejection (CR)

It is immune mediated chronic graft dysfunction (CGD), characterized by a **slow progressive irreversible** decrease of graft function



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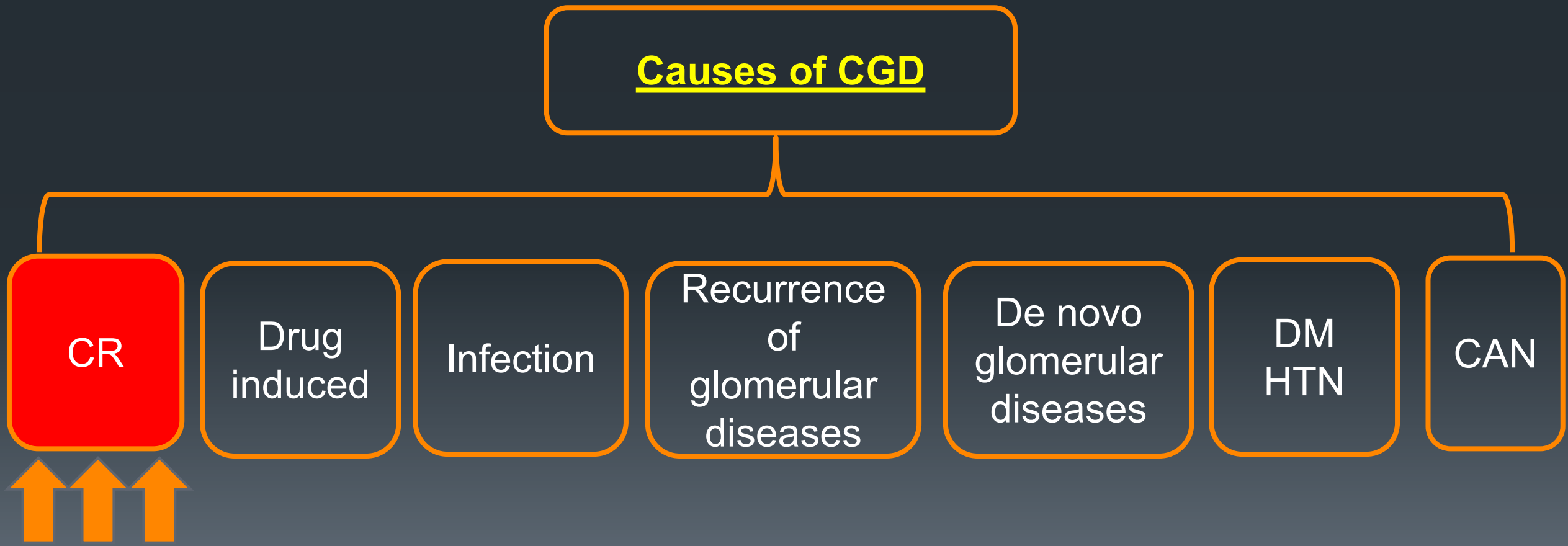
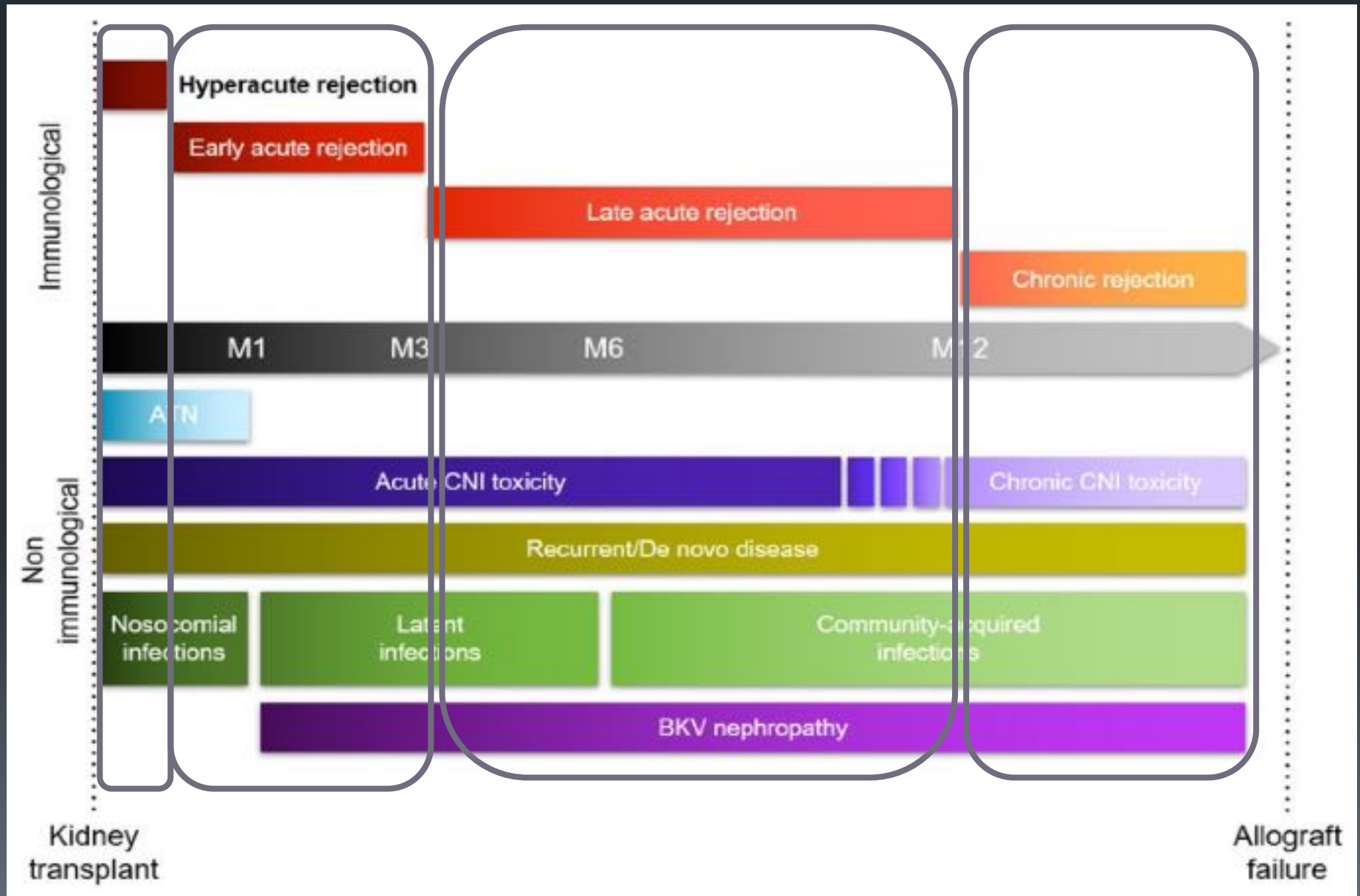


Commonly used time frame for Immune mediated graft injury



- **Delayed AR has been variably defined in some literature;**

2 months after TX (Transplantation. 1993; 55(5): 993-995)

6 months after TX (Transplantation proceedings.2009; 41(10): 4150-4153)

1 year after TX (Kidney Res Clin Pract, 2015; 34: 160-164)

- **Chronic rejection has been diagnosed before 1 year of TX**

At 1-year post-transplant, > 81% of the kidneys have minimal lesions of IF/TA that tend to progress over time; these lesions affect > 50% of transplanted kidneys with severe lesions at 5 years.

(Naik & Shawer, Renal Transplantation Rejection; 2022)

Acute and chronic renal graft rejection can coexist in many graft pathology reports

Incidence

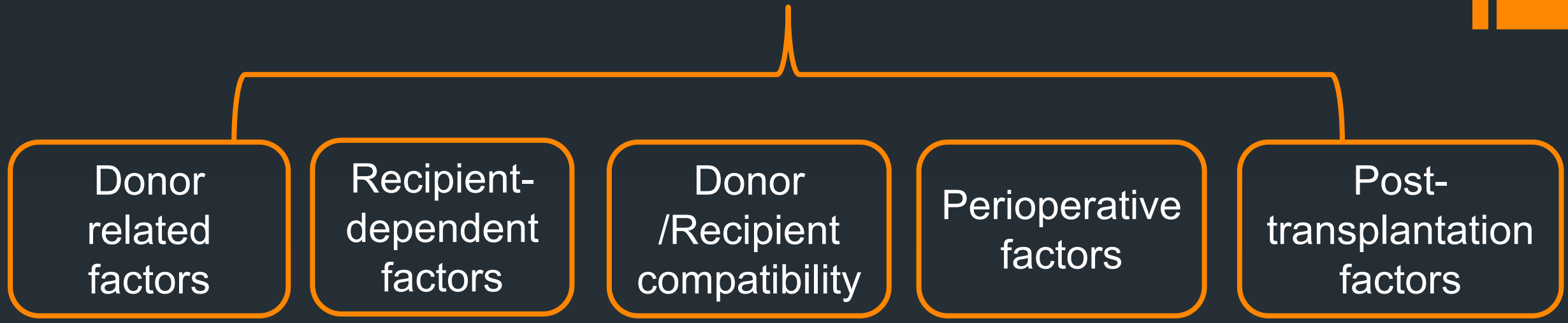
- **Delayed AR:**

Overall the incidence & prevalence of AR whether early or late have **decreased** due to advances in immunosuppression therapy

- **Chronic rejection:**

Currently chronic rejection represents the **most prevalent cause of renal transplant failure**…even with the use of advanced immunosuppression.

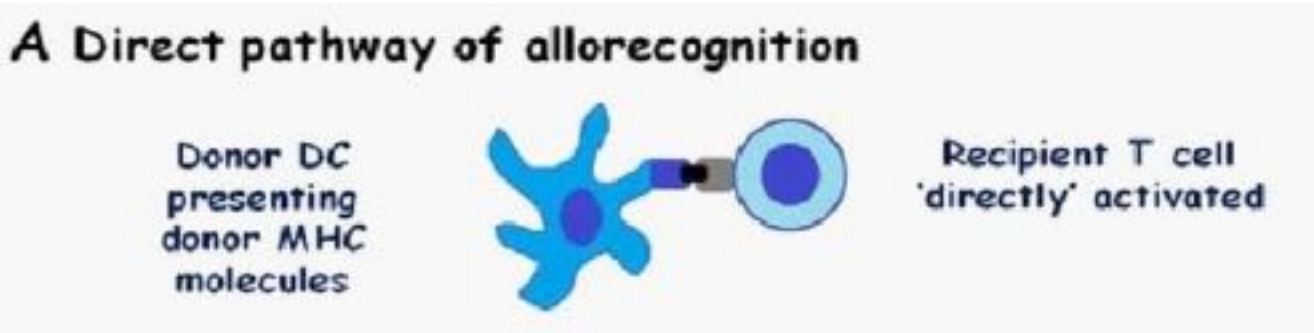
Risk Factors of renal graft rejection

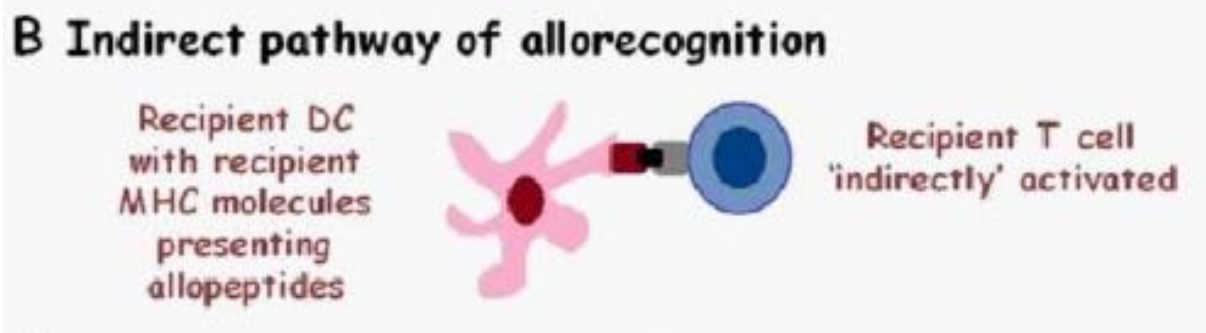


Risk Factors of renal graft rejection

Donor related factors	Recipient-dependent factors	Donor /Recipient compatibility	Perioperative factors	Post-transplantation factors
1- Donor gender 2- Donor age 3- Living or Deceased donor 4- Non marginal or marginal donors	1- Race 2- Age 3- Concomitant disease 4- Re-transplantation	1- ABO blood group type 2- HLA antigen type	Ischemia/ Reperfusion injury	1- Delayed graft function 2- IS Drugs/Regimen

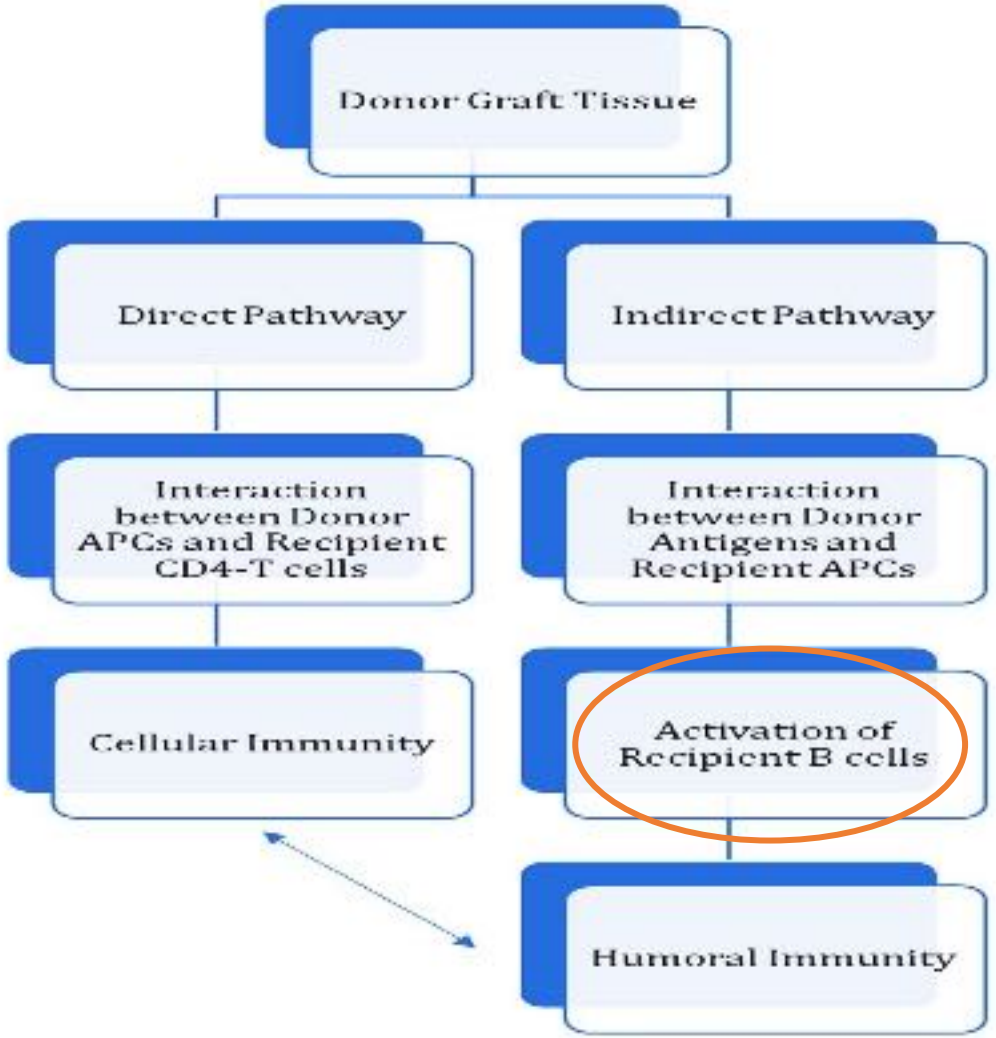
(J Clin Med. 2022 Mar 3;11(5):1392)





Responsible for the activation of the immune system in **acute rejection**

Rapid but not permanent



Presented by APCs in a self-MHC context. Responsible for **chronic rejection**

Takes time but persistant

Both delayed AR and chronic rejections are, in term, immune mediated graft injury that could be cell mediated, antibody mediated or mixed form of rejection

Any pathological type of rejection can occur any time after TX

However

- **Commonly…..T cell mediated rejection occurs early while Ab mediated occurs late after TX**
- **Chronic rejection is frequently Ab mediated (usually related to circulating DSA) and rarely cell mediated**

Risk Factors of chronic rejection

Delayed AR has a detrimental impact on chronic rejection than early AR…….It is associated with MHC I incompatibility, whereas early AR is correlated with HLA-DR mismatches with a better prognosis if adequately treated

Table 1. Risk and progression factors of chronic rejection

Risk factors	Progression factors
Young recipient age	Cadaveric donor
Sensitization pretransplantation	Old donor age
Sensitization posttransplantation	Recipient smoking
Histoincompatibility	Renal insufficiency
Therapy noncompliance	Proteinuria
Acute vascular rejection	Hypertension
Late acute rejection	Hyperlipidemia
	Overweight
	Drug nephrotoxicity

Patient non compliance to immunosuppressive medications is a major risk factor of chronic rejection

(Kidney International, Vol. 68 (2005), pp. 1–13)

Donor/Recipient Tissue typing mismatch

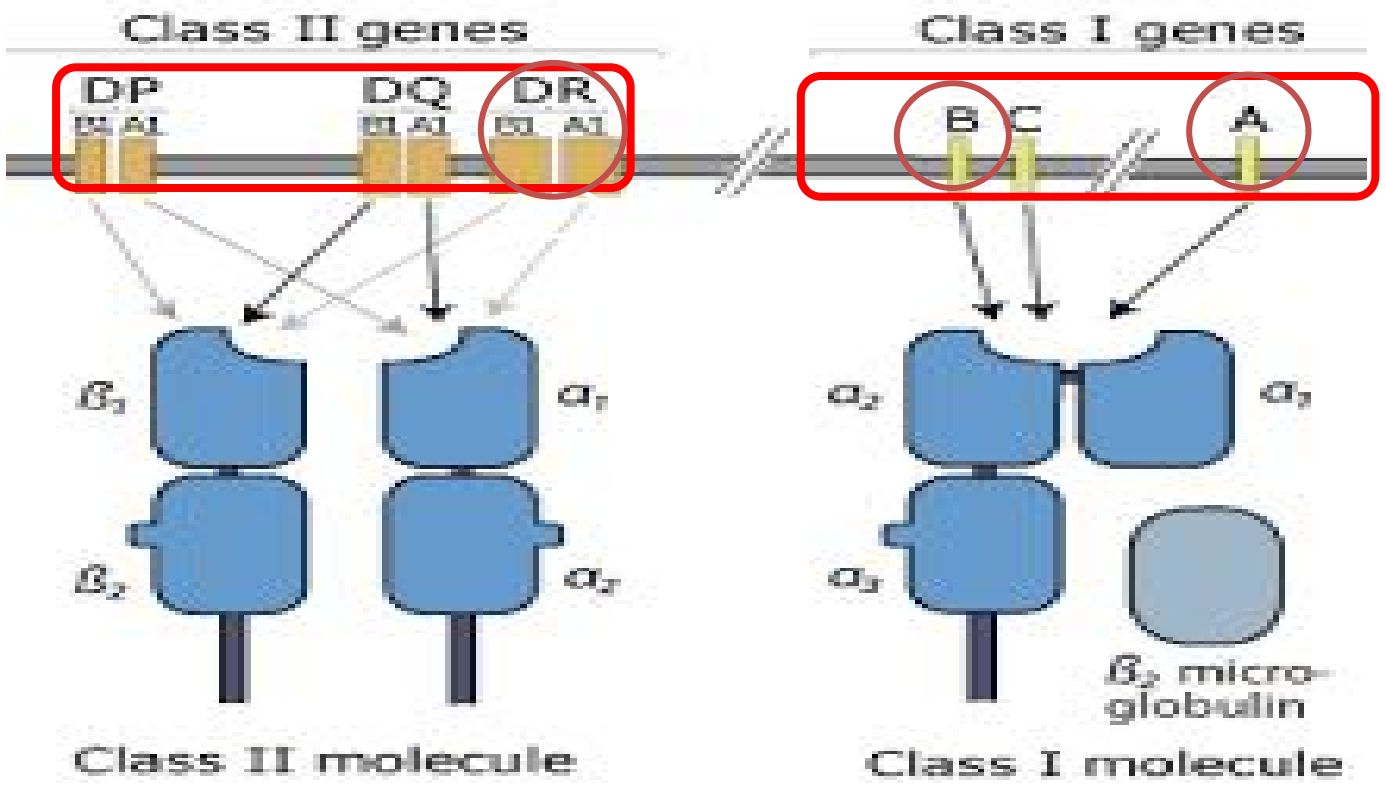
Donor HLA antigens that **not** present in the recipient

The degree of HLA mismatch between donor and recipient plays a role in determining the risk of chronic rejection

Donor:
HLA A21,24
HLA B 4, 51
HLA Dr2, 10

Recipient
HLA A1,24
HLA B 5, 51
HLA Dr2, 17

3/6 mismatched HLA alleles



The commonly tested 3genes with 6 allels are A, B, DR

Delayed AR could be clinical or subclinical

Clinical AR

Generally presents as AGD (rising creatinine) after 3 months of TX.
Other manifestations include new-onset proteinuria or hypertension.
Fever and graft tenderness are rare except in the context of low CNI.

Subclinical rejection

Histologic changes compatible with AR in the absence of graft dysfunction diagnosed by protocol/ survillence biopsy

Both clinical & subclinical AR should be adequately treated
Both clinical & subclinical AR increase the risk of chronic rejection

Chronic rejection clinically present with…..

- Slow progressive decline of graft function that is usually start to manifest after 1 year and often accompanied by hypertension and proteinuria

Again….

Delayed AR and chronic rejection frequently coexist.

Suspected clinically : acute rise of serum creatinine in a patient previously diagnosed with/ or has a base line compatible with chronic rejection

Confirmed pathologically

Diagnostic approaches

Most patients with either delayed AR episode or chronic rejection are **asymptomatic** and have abnormal graft dysfunction (rising serum creatinine) as evidence by the routine blood workups

In subclinical graft injury; even rising serum creatinine is not present & diagnosis is made only by protocol biopsy

In delayed AR:

The patient has AGD with normal (his own known base line) serum creatinine in the last follow up visit (≤3 months)

In chronic rejection:

The patient has graft dysfunction with already impaired (increased base line) serum creatinine in the last follow up visit (>3 months)

Graft biopsy is mandatory for diagnosis of all types of rejection

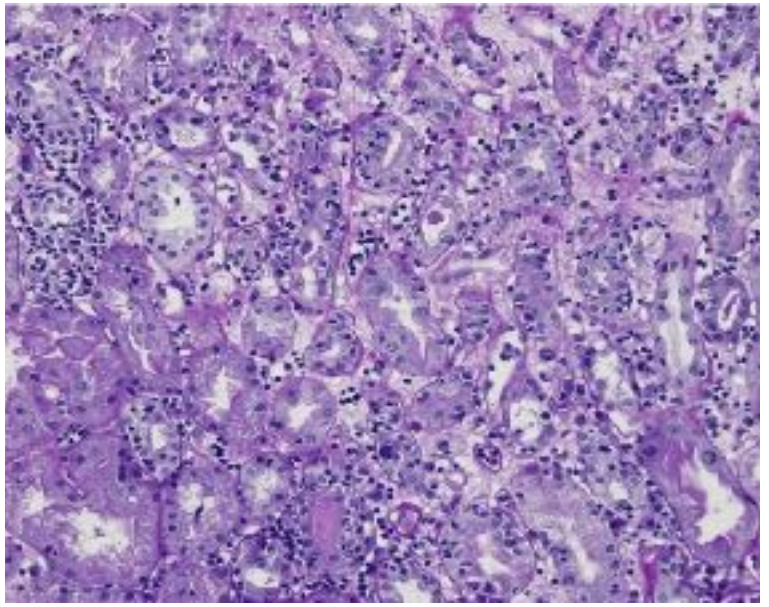
Pathological types of AR

- **Acute cell mediated rejection**:

Tubulo-interstial /vascular

Up to 90% of early rejection episodes

Vascular involvement reflects a more severe variant with poorer response to therapy and more risk to chronic rejection



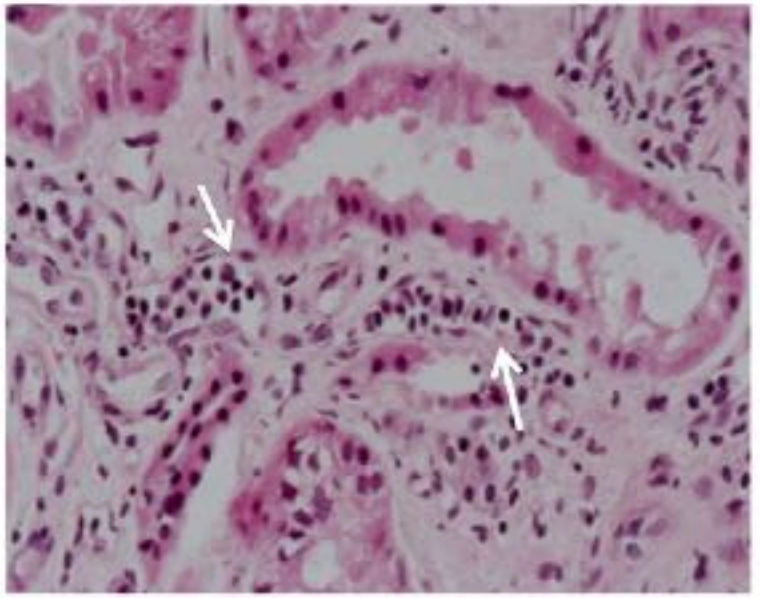
- **Acute Ab mediated rejection:**

Usually > 3-6 mo.

Early in highly sensitized patients

At any time in patients who develop de novo DSAs.

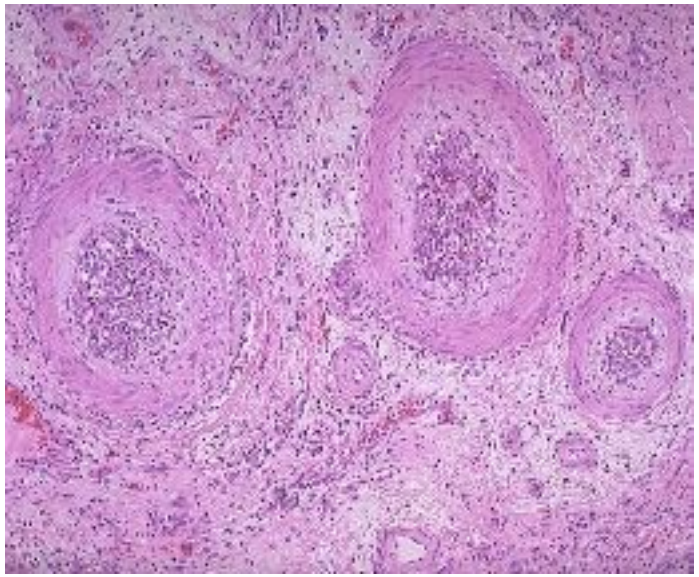
Non adherence is the cause in up to 50% of cases



- **Mixed rejection**

Pathology of chronic rejection

- **Isolated findings of IFTA** may be due to nonimmune mechanisms: hyper filtration injury or the toxic CNIs
- **arteriolar hyalinosis, and hyaline arteriolar thickening**
- **Transplant glomerulopathy (TG):** vascular fibrous intimal thickening, GBM double contouring occurs more commonly in patients with chronic active ab mediated rejection.



The degree of IF classify chronicity into mild (<25%), moderate (25-50%) and sever (>50%)

Presence of IFTA/ TG together with active cellular infiltrates of interstium/ tubules (in cell mediated) or glomerular capillaries, glomerulitis, peritubular capillaritis (in ab mediated) diagnose chronic active rejection

Case (1)

11 year male patient transplanted 1.5 years ago, presented with rising serum creatinine (2.1 with base line 1.5 mg/dl) associated with proteinuria 1.5 gm/ 24 hr urine. Graft biopsy revealed IFTA 25% with glomerular capillaritis and negative staining for C4d.

Acute on top of chronic graft dysfunction……Chronic active Ab mediated rejection

Case (2)

- 8 year female transplanted 2 years ago. Her BP was 150/90 with no signs of infection or dehydration. Laboratory work up revealed rising serum creatinine (1.5 with last visit 2 month before was 0.7 mg/dl). FK level 3.2 ng/dl, 24 hour urine protein was 1.2 gm

Delayed acute rejection episode ……..
Graft biopsy & pulse methylprednisolone advised till report is available

Case (3)

- 16 year male patient transplanted 5 years ago. He stopped being committed to follow up visits 1 year ago with denial of any non compliance to his immunosuppressive medications. He had history of repeated episodes of AR that were adequately treated with partial response (Previous baseline creatinine was not regained). Presented with serum creatinine 3.6 with last reported baseline was 3.2mg/dl, FK level 2 ng/l associated with proteinuria 1 gm/24 hr

Chronic graft rejection….To be confirmed with graft biopsy

Acute Rejection (AR)

It is a **potentially reversible** immune mediated graft injury

Delayed AR is commonly AB mediated

- Pulse methylprednisolone is the first line ART in all types of AR (biopsy done)

  Steroid resistant AR: No response 5-7 days after first dose (pathology report received)

T – cell depleting therapy (ATG) in steroid resistant acute TCMR

Options for ABMR: PE, RTX and IVIG
Baseline IS therapy are recommended to be intensified after treatment of AR

- Outcomes of AR vary depending on baseline renal function and the extent of injury

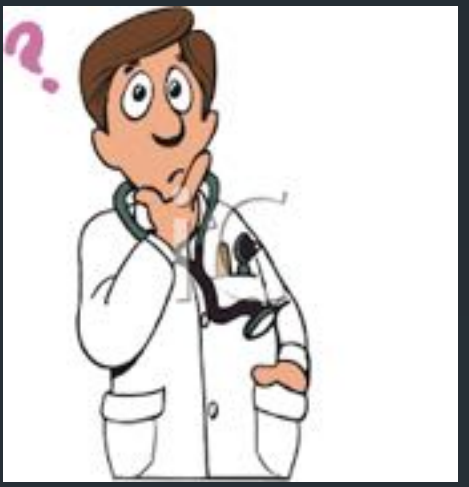
Chronic rejection

Prevention is much more better than treatment

- Proper selection of pediatric patients fit for TX
- Medical counselling of the child & the family to outline the importance of commitment to medications & follow up visits before TX
- Proper donor selection (ABO, HLA)
- Proper manipulation of the immune system at TX (selection of IS protocol & desensitization protocols if needed)
- Early detection and adequate treatment of acute rejection episodes

Chronic rejection

It is a **potentially irreversible** graft injury



Do you recommend to treat (immunologically) this form of immune mediated graft injury ??????????????

OR

To manage as conservative approaches for CKD patients

The therapeutic effectiveness of PE, RTX, IVIG, Boretzomab, Eclizumab (single or in combination) in treatment of chronic active ABMR have been evaluated in a randomized controlled trials and results have been extensively reviewed

(Am J Transplant (2017) 17:2381–9).

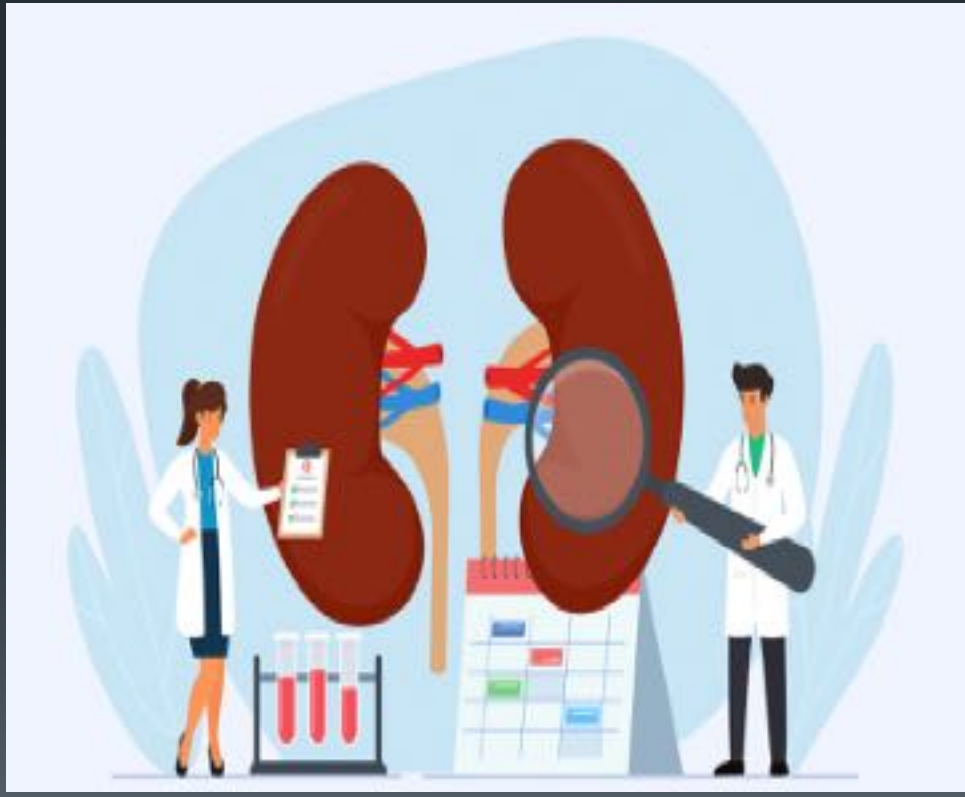
limited success being achieved by using these agents was suggested despite their effectiveness in treating acute ABMR

Considerations while taking a decision in a patient with chronic rejection….To treat Or Not to treat

1- Treatment could **interrupt the progressive process** rather than to restore the previous graft function (a new baseline creatinine will be set for this patient after treatment)

2- The **extend of interstial fibrosis** largely affects the decision (mild <25%, moderate 25-50%) or sever (>50%)

3- The **extend of acute changes** (potentially reversible) on top of chronic that is frequently present in pathology report

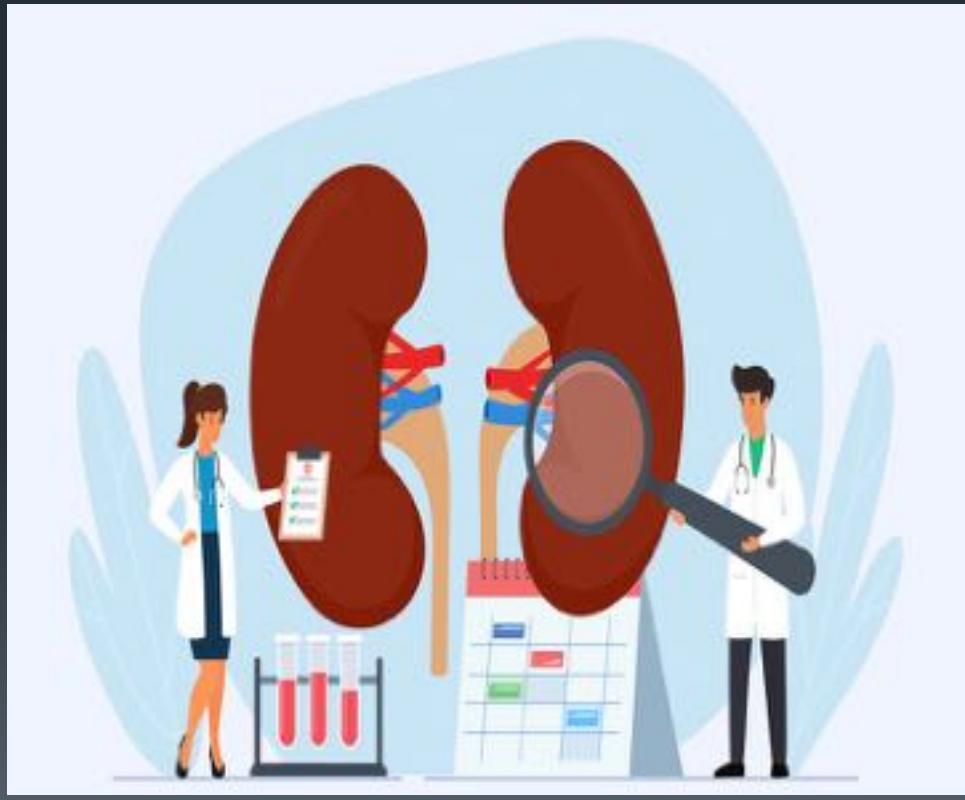


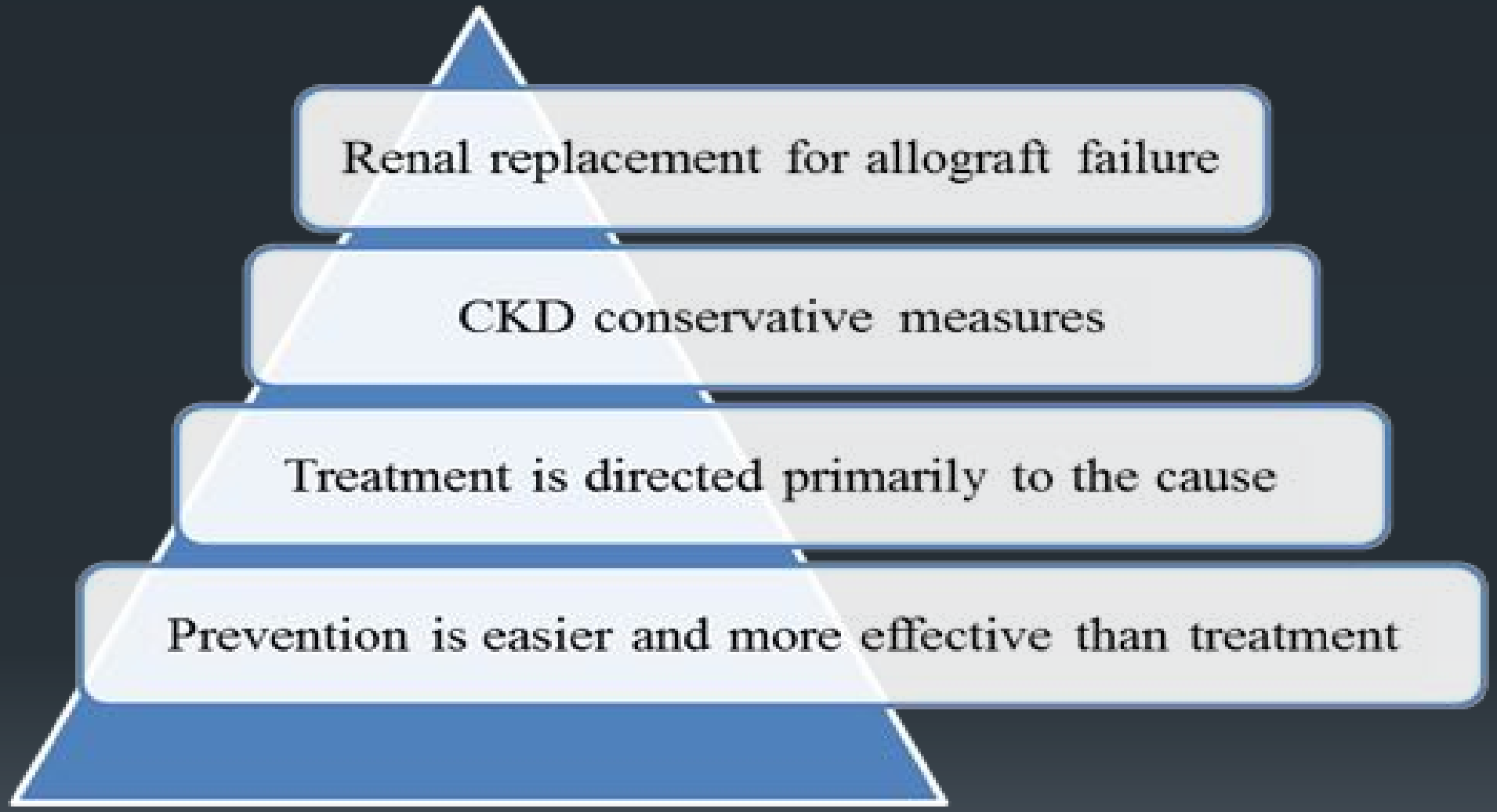
Considerations while taking a decision in a patient with chronic rejection….To treat Or Not to treat

4- Patients with **circulating DSA** could gain benefit of PE and RTX/ IVIG

6- **Treatment is costly** and needs time & human resources and still **associated with the risk** of immunosuppressive intensification, plasma exchange procedure

5- Pathologists insist to call it chronic active ab mediated rejection and NOT chronic ab mediated rejection in order to push the clinicians to treat it





Histological evidence of CNI toxicity is an indication of reducing, withdrawal or replacing CNI

Home message

- Delayed AR incidence have decreased however; chronic rejection represents the most common cause of graft failure
- Delayed AR (particularly repeated episodes) is a major risk factor for chronic rejection
- Graft biopsy has to be performed in any type of suspected rejection
- Delayed acute & chronic rejections frequently coexist
- Delayed AR is a potential reversible graft injury that should be well treated with timely intervention is crucial

Home message

- Although chronic rejection is theoretically irreversible graft injury; adequate treatment could be a wise option in certain circumstances
- Chronic rejection is potentially preventable uncurable (till now) immune mediated graft injury that end up in graft failure
- Immunosuppression modifications (CNI minimization or withdrawal), induction of graft tolerance, stem cell therapy and antifiberotic agents could carry hope for stoppage or potential reversibility of the process of chronic rejection

Thank You

For 8 year female transplant recipient presented with acute graft dysfunction presumably due to acute rejection 8 months after TX

(a) Kidney graft biopsy is controversial

(b) Pulse methylprednisolone therapy is the first line treatment

(c) Base line creatinine inevitably will be resumed after adequate antirejection therapy

(d) Immunosuppression should be minimized for the sake of the patient

The following is true regarding chronic rejection EXCEPT

(a) By far, it is the most common cause of graft failure
(b) It is mediated by indirect pathway of antigen presentation
(c) Can never be diagnosed before the end of the first transplantation year
(d) Treatment with plasma exchange/ Rituximab could be wise choice in some cases

In pathological diagnosis of chronic active antibody mediated rejection, which statement is correct

(a) The extend of acute/ chronic pathological changes does not matter
(b) C4d has to be positive for the patient to be treated
(c) It is a pathological diagnosis with a good prognosis
(d) Testing serology for DSA to guide treatment option is usually needed