Renal Transplant Rejection: How To Approach?

Doaa M. Salah; MD

Associate Prof. of Pediatrics & Pediatric Nephrology

Cairo University

Logically speaking;

Transplantation of renal graft from a **genetically different donor** to the recipient

Alloantigen of the donor induces an **immune response** in the recipient against the graft

This is called allograft rejection

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

This response can destroy the graft if not controlled

Repeated episodes of acute rejection (even well treated)

- Negatively impact **graft outcome** (by increasing the risk of chronic graft dysfunction).
- Negatively impact **patient outcome** (by increasing the risk of adverse effects of intensified immunosuppression)

The good new:
Overall the incidence & prevalence of acute rejection have decreased

The Bad new:
Chronic rejection remains unsolved problem

Agenda

- Is it Rejection or Not?
- Pathophysiology & Risk factors of rejection
- Types and classifications
- Diagnostic & Therapeutic approaches
- Home message

Graft Dysfunction

(The broad term)

So; although acute rejection is the most common; still it falls between a long list of differential diagnosis of AGD

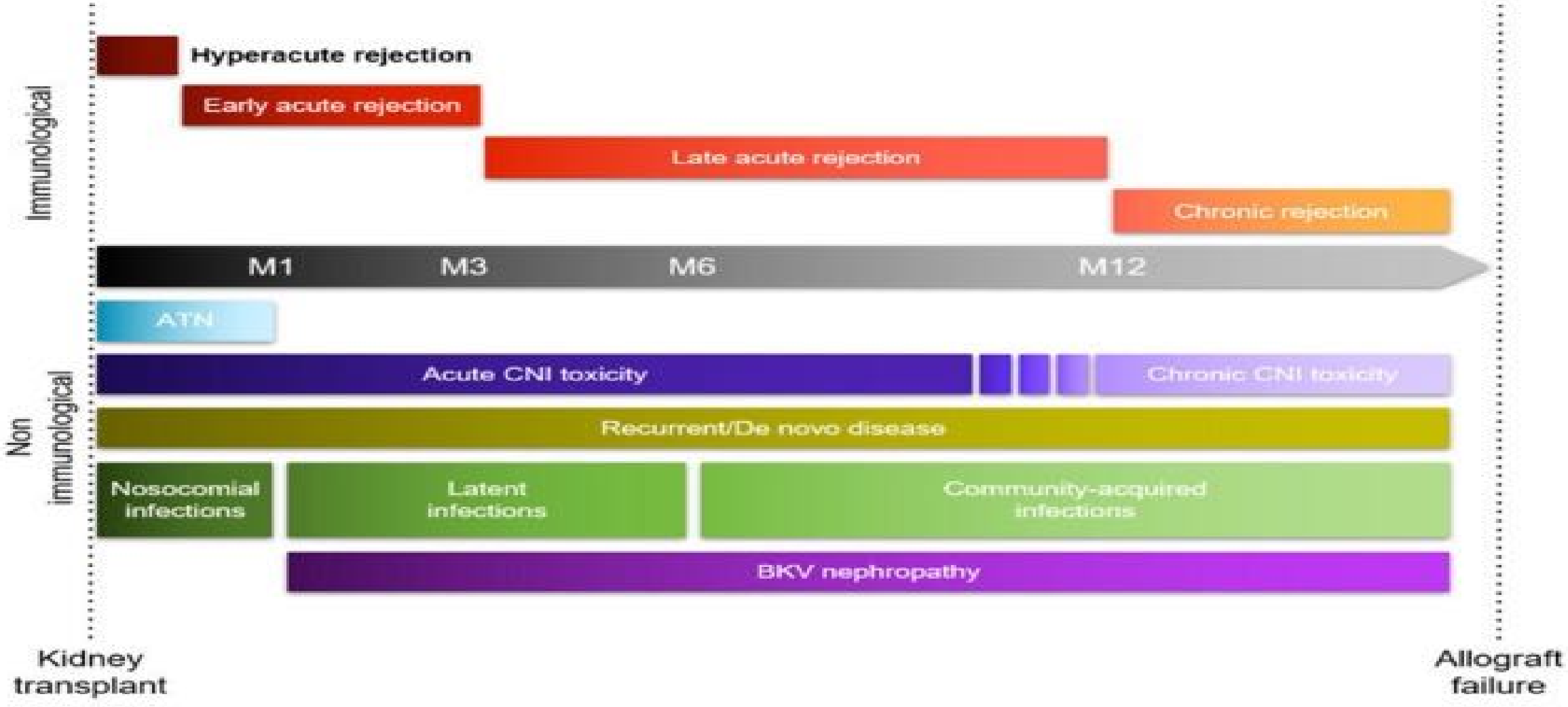
Pre renal dehydration ,volume depletion or sepsis.

Post renal Urinary tract obstruction

Reno-vascular renal artery stenosis and renal vein thrombosis.

Renal intrinsic Acute rejection, Acute CNIs toxicity, Infection (UTI, CMV or BK virus) Others (recurrent and de novo renal disease presenting acutely)

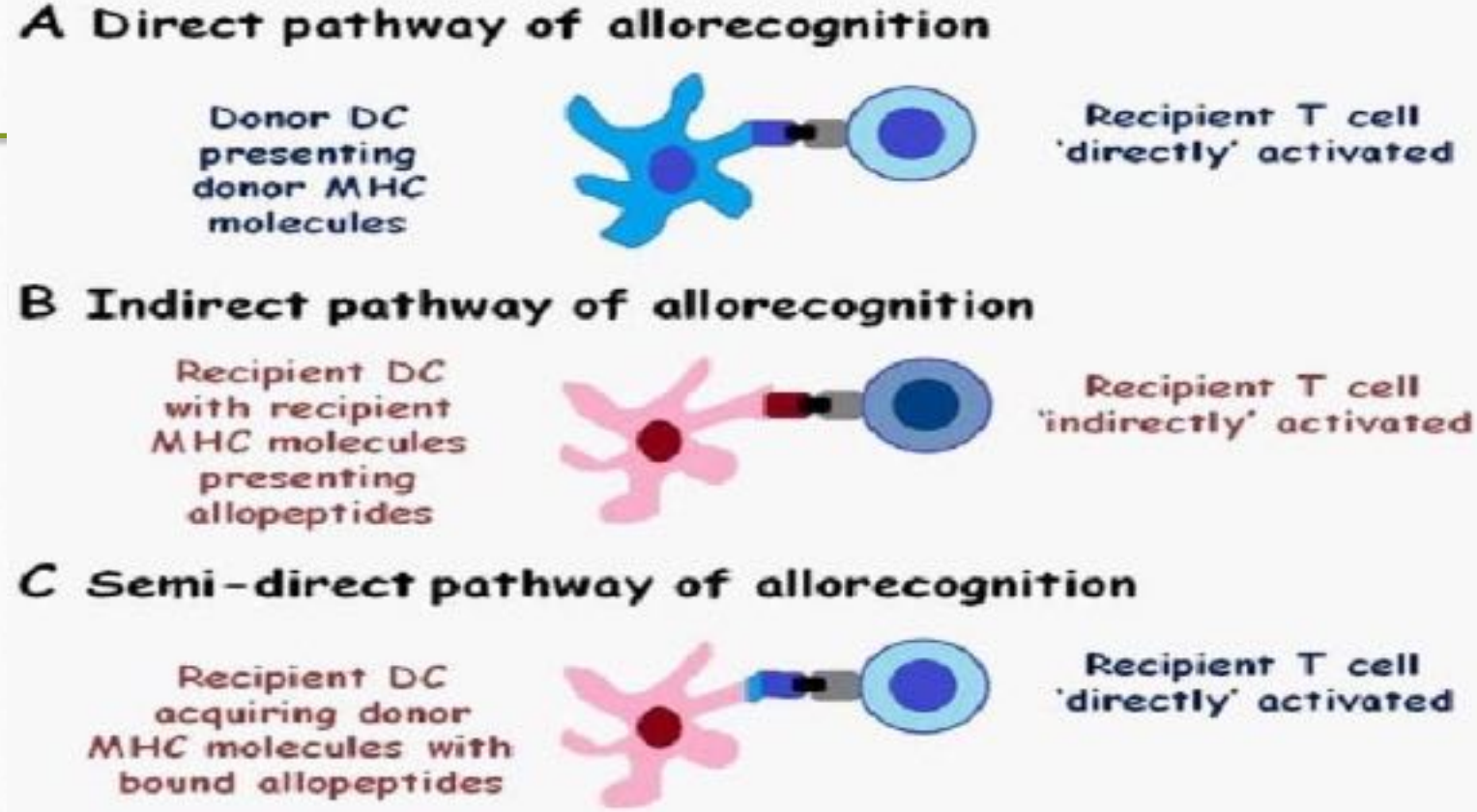
Common causes of AGD based on time after TX



Pathophysiology of rejection

Types of antigen presentation

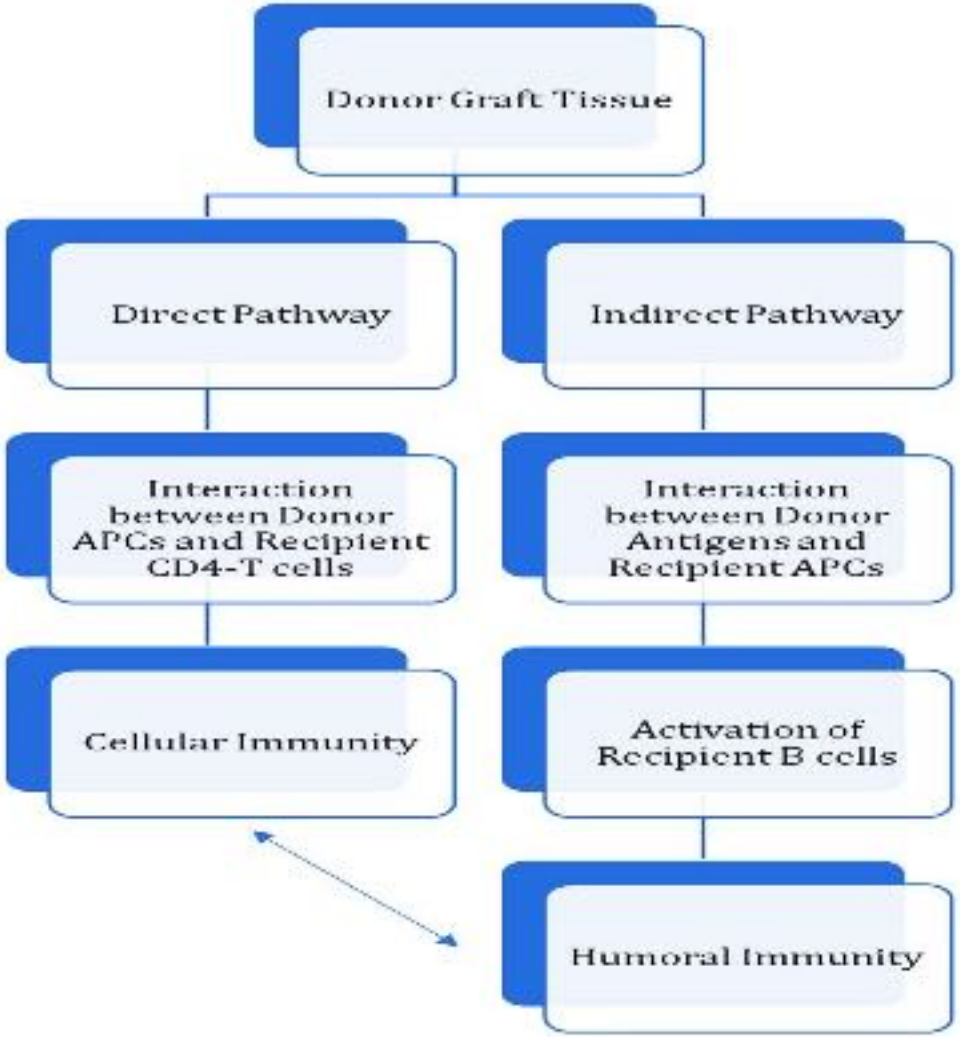
- **Direct presentation**
- **Indirect presentation**
- **Semi-direct presentation**



Pathophysiology of rejection

Direct presentation

- Responsible for the activation of the immune system in acute rejection
- Not permanent



Indirect presentation

- Responsible for chronic rejection and therefore is the main cause of organ loss

Risk Factors of Rejection

-Prior sensitization (high % PRA)

-Type of transplant (Deceased or living donor)

-HLA mismatch

-Positive B cell cross-match

-Younger recipient`s age

-Delayed graft function

-Previous episodes of rejections

-Advanced donor age

-Prolonged cold ischemia time

-ABO incompatibility

-Black Recipient's race

-Therapy non-compliance

-Inadequate immunosuppression

Types & Classifications of Rejection

(1) Based **on timing** after KTX

(2) **Clinical** Classification

(3) **Pathological** Classification

Classification of Rejection Based on timing after KTX

Hyper-acute

-Within **few hours** after allograft is revascularized
-Preexisting circulating abs at time of KTX
-Usually ABO or HLA Abs

Acute

Accelerated: **1st week**

Early: **1st 3month**

Delayed:**3-12 month**

Chronic

-Usually **after 1 year**
Related to both immune and non-immune mediated factors
-Non-compliance to IS is the major risk
-Can be chronic ABMR (DSA) or less common CMR

Acute Rejection

Potentially reversible, immune-mediated graft injury

- Either recipient's lymphocytes become activated by recognition of foreign (non-self) donor antigens in **TCMR**
- Or related to antibodies against foreign (non-self) donor antigens, mainly HLA antigen, which leads to damage to the allograft through activation of the complement-dependent pathway in **ABMR**
- **Mixed TCMR & ABMR**

Clinical Classification of Rejection

- **Clinical acute rejection**

Generally presents as AGD (rising creatinine). 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 acute rejection in the absence of graft dysfunction diagnosed by protocol/survillence biopsy

Clinical Classification of Rejection

- **Presumed acute rejection:**

An episode of acute rejection, which is clinically diagnosed (AGD not attributed to any cause other than acute rejection) and medically treated (by pulse methylprednisolone), but a biopsy sample was not taken

- **Biopsy proven acute rejection:**

AGD associated with pathological evidence of rejection.

Clinical Classification of Rejection

- **Chronic allograft dysfunction:**

Clinically as a progressive deterioration of graft function with ≥ 15% irreversible rise in creatinine within 1 to 3 months and proteinuria ≥1 g/24h together with a histologic diagnosis of interstitial fibrosis and tubular atrophy (IFTA)

Pathological Classification of Rejection

The Banff Classification System

- It is uses scores to assess the **presence & the degree** of histo-pathological changes in the different compartments of renal transplant biopsies
- It focuses mostly, but not exclusively, on the **diagnostic features seen in rejection.**
- Developed as a standardized working classification system in 1991 & Updated every 3 years with last meeting was 2019 meeting report

Pathological Classification of Rejection

Banff diagnostic categories

Category 1	Normal biopsy or non-specific changes
Category 2	Antibody-mediated changes
Category 3	Suspicious (borderline) for acute T cell-mediated rejection
Category 4	T cell-mediated rejection
Category 5	Interstitial fibrosis and tubular atrophy
Category 6	Other non-rejection changes

Diagnostic & Therapeutic approaches

Most patients who have acute rejection episodes are asymptomatic

Abnormal allograft function by the routine blood workups is the evidence of acute rejection in those patients

Patients with **subclinical rejection** do not even have abnormal graft function & **diagnosed only by protocol biopsy**

Case 1

A mother of 12 year male transplanted 4 years ago came complaining that her child is non compliant to his medications and does not want to come for follow up. His labs revealed rising serum creatinine to 1.8 mg/dl (last visit creatinine 1.1 mg/dl 5 months earlier. FK level 3.5 ng/ml and 24 hr Urine protein was 2.5 gm. US and Doppler unremarkable

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Most probably…Chronic graft rejection…..To be confirmed with graft biopsy

Case 2

Apparently healthy 8 year girl transplanted 6 months ago presented with serum creatinine 1.1 mg/dl rising from 0.7 on her last visit. FK level was 16 ng/ml and 24 hour protein 200 mg. US and Doppler are unremarkable.

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AGD….Most probably…Acute CNI Toxicity…..To be confirmed with graft biopsy

Case 3

5 year boy transplanted 1 year ago presented by GE with mild dehydration, leucopenia and elevated liver enzymes together with impaired graft function (serum creatinine 1 with his baseline 0.6). FK level was 7 ng/ml and 24 hour urine protein was 250 mg. US and Doppler are unremarkable

Case 3

5 year boy transplanted 2 month ago presented by GE with mild dehydration, leucopenia and elevated liver enzymes together with impaired graft function (serum creatinine 1 with his baseline 0.6). FK level was 7 ng/ml and 24 hour urine protein was 250 mg. US and Doppler are unremarkable

Acute graft dysfunction most probably secondary to infection (CMV???) & dehydration…..To be confirmed with therapeutic correction of dehydration & CMV PCR

Approaches as recommended by guidelines of ESPNT

All transplant recipients be **regularly monitored for graft function**

Any patient presenting with AGD have the following factors assessed and corrected:

- Volume and hydration status
- Vascular lesion or urinary tract obstruction **(graft ultrasound with Doppler)**

Approaches as recommended by guidelines of ESPNT

All transplant recipients be **regularly monitored for graft function**

Any patient presenting with AGD have the following factors assessed and corrected:

- Drug level (CNI)

If CNI level has been too high, check creatinine response to reducing dose.

A low CNI level may be associated with AR that may not be corrected simply by increasing the dose.

- Systemic or UT infection or other obvious causes

Approaches as recommended by guidelines of ESPNT

Graft biopsy is recommended to be performed in any patient presenting with unexplained AGD

It is suggested that first-line antirejection therapy not be delayed awaiting extensive evaluation when AR is likely

Therapeutic Approaches (ESPNT)

- Subclinical Rejection should be treated

All AR episodes be initially treated with pulse methylprednisolone (250 mg/m2–10 mg/Kg for 3 successive days).

1st AR episode & response 5-7 days of 1st dose
rapid tapering of oral steroids to or just above the maintenance dose, with optimizing trough CNI levels

Rebound, recurrent, Steroid resistant episodes
Consider increasing IS & perform graft biopsy

Therapeutic Approaches (ESPNT)

- AR is considered **steroid resistant** if there is no response 5-7 days after the first dose…….**Further management based on biopsy result**
- It is better to perform graft biopsy **before starting** steroid therapy if logistics will not cause therapeutic delay.
- ATG is recommended in all steroid-resistant acute TCMR, and its use is advised in very early, severe (Banff IIb or above) or rebound cases
- Options for ABMR include steroids, plasma exchange, Rituximab and IVIG

Therapeutic Options for ABMR

Plasma exchange:1.5 plasma volume daily x3, followed by 3 treatments per week at 1 plasma volume for a minimum total of 8 sessions Additional treatments may be indicated based on condition

IVIG may be replaced at 100 mg/kg/dose given after each PE, 400 mg/Kg after the third PE session and/or be given in a total dose of 1-2g/Kg. The latter dose should be given after, not before, PE

Therapeutic Options for ABMR

Rituximab :375 mg/m2/ dose for 2-4 doses at weekly- 2wk intervals. The first dose may be given after the third PE session; however, wait for a minimum of 24 hrs (ideally 48 hrs) before resuming PE after dosing Rituximab.

Intensification of **baseline immunosuppression** after treatment for ABMR

Pre-medications for therapeutic interventions of AR

- Steroids (100 mg/m2 methylprednisolone) 30 minutes before Rituximab or first (& possibly second) dose of ATG
- Premedicating Rituximab with (in addition to steroids) paracetamol and diphenhydramine (oral or IV) and continuing these medications for 24-48hrs
- Premedicating ATG (1st and 2nd doses) with (in addition to steroids) paracetamol and diphenhydramine (oral or IV)
- IVIG may be premedicated with diphenhydramine and acetaminophen

Chronic Rejection
(Chronic Graft Dysfunction)

Progressive loss of renal graft function

Renal biopsies show characteristic but nonspecific histopathological changes in the vascular, glomerular and tubule-interstitial compartments of the kidney.

By far the most common cause of graft loss

Causes of Chronic Graft Dysfunction

Causes	Examples
Immunological causes	T-cell- and antibody-mediated rejection
Drug toxicity	Calcineurin inhibitor toxicity
Infections	CMV, BK Polyoma virus infections, repetitive urinary tract infections with an accompanying pyelonephritis of the graft
Recurrent glomerular disease	Focal segmental glomerulosclerosis, IgA nephropathy, MPGN, anti-GBM disease, HUS or ANCA associated vasculitis
De novo glomerular disease	
Diabetes mellitus	
Arterial hypertension	
Non- compliance to immunosuppressive medications	
Graft senescence	

Management of Chronic Graft Dysfunction

Kidney allograft biopsy is recommended for all patients with declining kidney function of unclear cause, to detect potentially reversible causes.

Histological evidence of CNI toxicity is an indication for reducing, withdrawing, or replacing the CNI.

Home Message

- Although AR incidence has been decreased; **chronic rejection** remains unsolved major obstacle and represents the major cause of graft failure
- Before assuming the patient having AR; you should **exclude other known causes of AGD** (commonly infection & dehydration).
- Graft biopsy should be done **for any patient** with unexplained AGD

Home Message

- Pulse methylprednisolone is the **first line antirejection** therapy with further management based on pathological diagnosis.
- **Temporary intensification of immunosuppression** during AR is recommended as long as no side effects or infection exist.
- **Early therapeutic intervention** for AR is very important & repeated AR episodes **predispose to chronic rejection** and carry worse patient/ graft outcomes.

Thank You

1-In Acute antibody mediated rejection

(a) Pulse methylprednisolone is not the first line therapy

(b) Plasma exchange is an important therapeutic option to remove antibodies

(c) Rituximab should never interrupt plasma exchange sessions

(d) IVIG may be needed in 1 g/kg after each plasma exchange session

2-Performing graft biopsy

(a) Is not recommended in patients with Known cause of AGD

(b) Of minor importance in diagnosis of AR

(c) Is a safe procedure free of complication and used as protocol in all centers for diagnosis of subclinical rejection

(d) It makes no therapeutic difference in presence of fibrosis in chronic rejection

3-Steroid Resistant Acute rejection

(a) Considered when there is no response at the 3rd day of pulse steroid therapy

(b) Usually associated with better outcome than steroid sensitive acute rejection

(c) Is an indication for ATG administration

(d) Graft biopsy is mandatory for any further management