
In The Name
of
GOD

Antibody-mediated rejection: prevention, monitoring and treatment

	Active AMR
Histopathology[a]	Acute tissue injury, including one or more of the following: Microvascular inflammation (glomerulitis and/or peritubular capillaritis) in the absence of recurrent or de-novo glomerulonephritis Intimal or transmural arteritis Acute TMA, in the absence of any other apparent cause Acute tubular injury, in the absence of any other apparent cause
Evidence of antibody interaction with the endothelium[b]	C4d deposition in peritubular capillaries, OR At least moderate microvascular inflammation, OR Molecular markers of endothelial activation
DSA[c,d]	Detectable serum anti-HLA DSA If anti-HLA DSA is undetectable, non-HLA antibody testing should be considered
Clinical presentation	Acute kidney injury, hypertension ± proteinuria
Prognosis	It may respond to prompt therapy
Treatment	Under investigation in clinical trials Plasma exchange, intravenous immunoglobulin, and corticosteroids

Chronic active AMR

Chronic tissue injury, including one or more of the following:
- Transplant glomerulopathy (glomerular basement membrane duplication in the absence of subendothelial immune complex deposits) if no evidence of chronic TMA in the absence of recurrent or de-novo glomerulonephritis
- Severe peritubular capillary basement membrane multilayering (requires EM)
- Transplant arteriopathy (arterial intimal fibrosis of new onset)

AND

Mild to moderate acute tissue injury (microvascular inflammation)

- C4d deposition in peritubular capillaries, OR
- At least moderate microvascular inflammation, OR
- Molecular markers of endothelial activation

Detectable serum anti-HLA DSA

If anti-HLA DSA is undetectable, non-HLA antibody testing should be considered

Subacute. Commonly observed on for-cause biopsies in patients with deteriorating renal function and proteinuria, or on protocol biopsies from patients with normal graft function, with or without proteinuria, ranging from 3 months to 5 years posttransplant

Typically, more guarded prognosis

Under investigation in clinical trials

It is unclear how patients with microvascular inflammation, with or without early transplant glomerulopathy, should be treated

Chronic (inactive) AMR

Chronic tissue injury:
- Transplant glomerulopathy, and/or
- Severe peritubular capillary basement membrane multilayering (requires EM)

Significant loss of peritubular capillaries (capillaries simply no longer exist to show capillaritis)

C4d negative

There may be prior evidence of antibody interaction with the endothelium

Anti-HLA DSA may be undetectable

However, there should be prior evidence of anti-HLA or non-HLA DSA

Progressive kidney allograft dysfunction, progressive proteinuria, hypertension

Poor prognosis with almost universal graft lost

Optimization of baseline immunosuppression

WHAT IS THE BEST STRATEGY TO PREVENT THE DEVELOPMENT OF DENOVO DONOR-SPECIFIC ANTIBODIES?

Risk factors for dnDSA formation are non adherence

or reduced immunosuppression, higher eplet mismatch,younger age and preceding T-cell mediated rejection(TCMR).

immunosuppression

Induction immunosuppression consisted of Thymoglobulin (6 mg/ kg total) or the humanized anti-CD25 monoclonal antibody (basiliximab), and methylprednisolone (500 mg) followed by a 7-day prednisolone taper.

Most patients receive a calcineurin inhibitor (cyclosporine or tacrolimus), typically in combination with an antimetabolite (azathioprine, mycophenolate mofetil, or mycophenolic acid) and a glucocorticoid.

Mycophenolate mofetil has largely replaced azathioprine; however, azathioprine can be substituted during pregnancy, when mycophenolate mofetil is contraindicated, or if gastrointestinal intolerance of mycophenolate mofetil develops.

Transitional B cell cytokines risk stratify early borderline rejection after renal transplantation
Kidney International (2023)
Long-Term Survival after Kidney
Transplantatinejm.org August 19, 2021

immunosuppression

Adequat tacrolimus exposure(trough levels of 7 to 12 ng per milliliter during the first year after transplantation and

>5 ng per milliliter after the first year),with low-dose glucocorticoids and an antimetabolite , is central to the prevention of early acute rejection .

Acute antibody- mediated rejection was treated with glucocorticoids, plasmapheresis and i.v. IgG

Long-Term Survival after Kidney
Transplantatinejm.org August 19, 2021
Antibody-mediated rejection: prevention, monitoring

immunosuppression

Maintaining adequate baselineimmunosuppression,particularly a calcineurin inhibitor (CNI), is a key to preventing dnDSA formation.

When comparing CNIs, recipients treated with cyclosporin-based therapy have a 2.7-fold higher incidence of dnDSA development compared with tacrolimus-based therapy .

Antibody-mediated rejection: prevention, monitoring and treatment dilemmas 2022 The Author(s). Published by Wolters Kluwer Health

Belatacept

a selective T cell costimulation blocker has been FDA-approved based on noninferiority for biopsy- proven *acute rejection* relative to cyclosporine .and lower cumulative event rates for dnDSA development vs cyclosporine.

Comparing belatacept with *tacrolimus* did not observe any difference in dnDSA formation or AMR rates at 1 year.

The estimated glomerular filtration rate (eGFR) was significantly higher with belatacept compared with tacrolimus, *but so was the incidence of biopsy-proven TCMR.(higher rates of TCMR)*

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immunosuppression

Long-term use of mTOR inhibitors, with or Without a calcineurin inhibitor, has been Associated with an increased incidence of acute rejection , worsening renal function, and increased long term mortality.
Use of a combination of mycophenolate mofetil and *belatacept* has been limited because of high rates of acute rejection, high cost, concerns about post-transplantation lymphoma, and the logistics of the required monthly belatacept infusions.

Long-Term Survival after Kidney
Transplantatinejm.org August 19, 2021

immunosuppression

The combination of mycophenolate mofetil, tacrolimus, and low-dose prednisoneremains the most common immunosuppressive regimen for kidney transplant recipients worldwide.

Long-Term Survival after Kidney
Transplantatinejm.org August 19, 2021

Decreasing human leukocyte antigen eplet mismatches

each HLA antigen contains a unique set

of epitopes.a higher number of mismatched eplets is associated with a higher risk of developing DSA post transplantation , transplant glomerulopathy and graft loss .

Recipients of a low-risk HLA-DR/DQ molecular

Mismatch appear to tolerate lower CNI trough levels and lower rates of dnDSA.

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HOW SHOULD DE-NOVO DONOR-SPECIFIC ANTIBODIES BE MANAGED IN KIDNEY TRANSPLANT RECIPIENTS WITH STABİE GRAFT FUNCTION?
IS DE-NOVO DONOR SPECIFIC ANTIBODIES PATHOGENIC OR AN INNOCENT BYSTANDER?

Not all DSAs are pathogenic or associated with AMR. Several characteristics of DSA are associated with worse outcomes, such as certain IgG subclasses' (IgG3 subclass

Of immunodominant DSA and C1q-binding ability of DSA)higher titers and complement-binding ability.

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Acute rejection in the first year after transplantationis primarily T-cell–mediated rejection,with fewer cases of antibody-mediated rejection,

whereas after the first year, acute rejection is often a combination of antibody-mediated and T-cell–mediated rejection.

Long-Term Survival after Kidney
Transplantatinejm.org August 19, 2021

antibody mediated rejection

Early antibody mediated rejection is treated with glucocorticoids,plasmapheresis, and intravenous immune globulin.

Other therapies (anti-CD20 antibodies, proteasome inhibitors,and anticomplement therapy) are being investigated.[61][5]

Late antibody-mediated rejection may be treated By augmenting maintenance immunosuppressive Therapy, but the benefit of plasmapheresis with intravenous immune globulin, proteasome inhibitors, and anti-CD20 antibodies remains questionable.

Long-Term Survival after Kidney
Transplantatinejm.org August 19, 2021

WHAT IS THE BEST TREATMENT STRATEGY FOR PATIENTS WITH DONOR SPECIFIC ANTIBODY POSITIVE ANTIBODY-MEDIATED REJECTION?

Evidence for the combination of IVIg and plasmapheresis to improve allograft outcomes

in AMR only comes from observational studiesa .

dose of rituximab (375mg/m2) to glucocorticoids,

plasma exchange and IVIg was not associated with

improvement in allograft function or survival .

Remarkably,the coadministration of IVIg with rituximab can shorten the half-life of anti-CD20 mAb and lead to quicker recovery of B cells, potentially affecting anti-CD20 efficacy.

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TPE prescription

Plasma volume: 1-1.5 estimated plasma volume (EPV).

EPV = ***(0.065 × weight) × (1 – hematocrit).***

- Frequency: Daily or every other day
- Replacement fluid: Albumin or frozen plasma plus IV Immunoglobulin 100-200 mg/kg
- Duration: For AMR, TPE is usually daily or every other day for 5 or 6 sessions or based on clinical outcomes and decrease in donor-specific antibody titers; for those receiving TPE for desensitization, TPE is performed until cross-match is less than institution-dependent thresholds or postoperatively for a minimum of 3 procedures.

Therapeutic Plasma Exchange: CoreCurriculum 2023
AJKD Vol XX | Iss XX | Month 2023

bortezomib

In terms of proteasome inhibitors,

the largest randomized clinical trial of bortezomib

in decreasing the production

of donor-specific anti-HLA antibodies (by targeting B cells and plasma cells, respectively) and *late AMR* showed no Improvement in allograft function.

AMR treatment responses can be monitored by evaluating changes in serum creatinine, Proteinuria , DSA levels, histopathologic findings and other new potential approaches.

Studies have shown that an improvement in serum creatinine to *less than 1.5 mg/dl* after treatment in kidney transplant recipients with rejection and allograft dysfunction is associated with better allograft.

sensitization

Desensitization may be an option for transplantation candidates considered to be close to receiving an offer of a kidney from a deceased donor.

Desensitization protocols involve the use of intravenous immune globulin,anti-CD20 antibody, and plasmapheresis, with the goal of achieving a negative cross-match.

Desensitized patients , however, remain at risk for the development of denovo donor-specific antibodies, antibody-mediated rejection, and Graft loss.

Long-Term Survival after Kidney
Transplantatinejm.org August 19, 2021

Imlifidase

Administration of imlifidase, an enzyme that cleaves IgG, reduces the degree of sensitization, permitting a negativecross-match,yet antibody-mediated rejection develops in roughly 40% of patients who have undergone desensitization with imlifidase.

Long-Term Survival after Kidney
Transplantatinejm.org August 19, 2021

Imlifidase

Imlifidase is a promising agent that has conditional approval from the European Medicines Agency for desensitization in kidney transplant recipients of a deceased donor with a positive cross match.

Because imlifidase non-specifically degrades IgG , therapeutic monoclonal antibodies

or rabbit ATG (Thymoglobulin) should be administered at least *four days* after treatment.

Imlifidase for the treatment of anti-HLAantibody-mediated processes in kidney transplantation
Am J Transplant. **2022;22:691–697.**

Imlifidase

Imlifidase 0.25 mg/kg was given before transplant with an additional 0.25 mg/kg dose allowed if a negative cross match was not achieved after the first dose.

Imlifidase for the treatment of anti-HLAantibody-mediated processes in kidney transplantation
Am J Transplant. **2022;22:691–697**

TABLE 1 Recommended time intervals for administration of antibody-based medicinal products after administration of imlifidase

Medicinal product	Recommended time interval after imlifidase administration
Equine anti-thymocyte globulin (Atgam®) Eculizumab (Soliris®)	No time interval needed (can be administered concomitantly with imlifidase)
Intravenous immunoglobulin (IVIG)	12 hours
Alemtuzumab (Campath®) Adalimumab (Entyvio®) Basiliximab (Simulect®) Denosumab (Xgeva®) Etanercept (Enbrel®) Rituximab (Rituxan®)[a] Rabbit antithymocyte globulin (rATG, Thymoglobulin®)	4 days
Belatacept (Nulojix®)	1 week

[a]Although not tested, the recommend time interval is recommended for anti-CD20 biosimilars.

Imlifidase for the treatment of anti-HLAantibody-mediated processes in kidney transplantation
Am J Transplant. **2022;22:691–697.**

Tocilizumab

IL-6 is a key cytokine : it regulates inflammation, and the development,maturation,and activation Of T cells, B cells, and plasma cells.

Tocilizumab (TCZ) is the main humanized Monoclonal aimed at IL-6R.

Tocilizumab may be an alternative to SOC (standard-of-care) therapy in DSA positive caABMR or aABMR in kidney transplant recipients, either as a first-line treatment or after failure of SOC therapy.

Tocilizumab and Active Antibody-Mediated Rejection in KidneyTransplantation: A Literature Review
Frontiers in Immunology | April 2022

Tocilizumab

TCZ seems to reduce DSA levels and decrease kidney inflammation and microvascular lesions and seems to have aprotective effect on renal function.

Tocilizumab and Active Antibody-Mediated Rejection in KidneyTransplantation: A Literature Review
Frontiers in Immunology | April 2022

Daratumumab

Daratumumab is an anti-CD38 immunoglobulin G monoclonal antibody commonly used as maintenance therapy for relapsed or refractory multiple myeloma.

Which increased expression of CD80 and CD86 T-cell costimulatory molecules.

This stimulated T-cell expansion through CD28 binding.use of this medication within 27 days or less of transplantation could be detrimental to the allograft and triggering this early and severe acute T cell–mediated rejection event .

Daratumumab Use Prior to Kidney Transplant and T Cell–Mediated Rejection: A Case Report
AJKD Vol XX | Iss XX | Month 2023

Daratumumab

A case report described the use of daratumumab for treatment of *antibody-mediated rejection* following an ABO-incompatible living donor kidney transplant. This patient did not experience acute T cell–mediated rejection after receiving daratumumab. However, he had received various other immunosuppressive agents prior to receiving daratumumab,such as anti-human T-lymphocyte globulins, methylprednisolone pulses, and eculizumab.

Daratumumab was given soon after these therapies, which could have prevented T cell–mediated rejection from occurring

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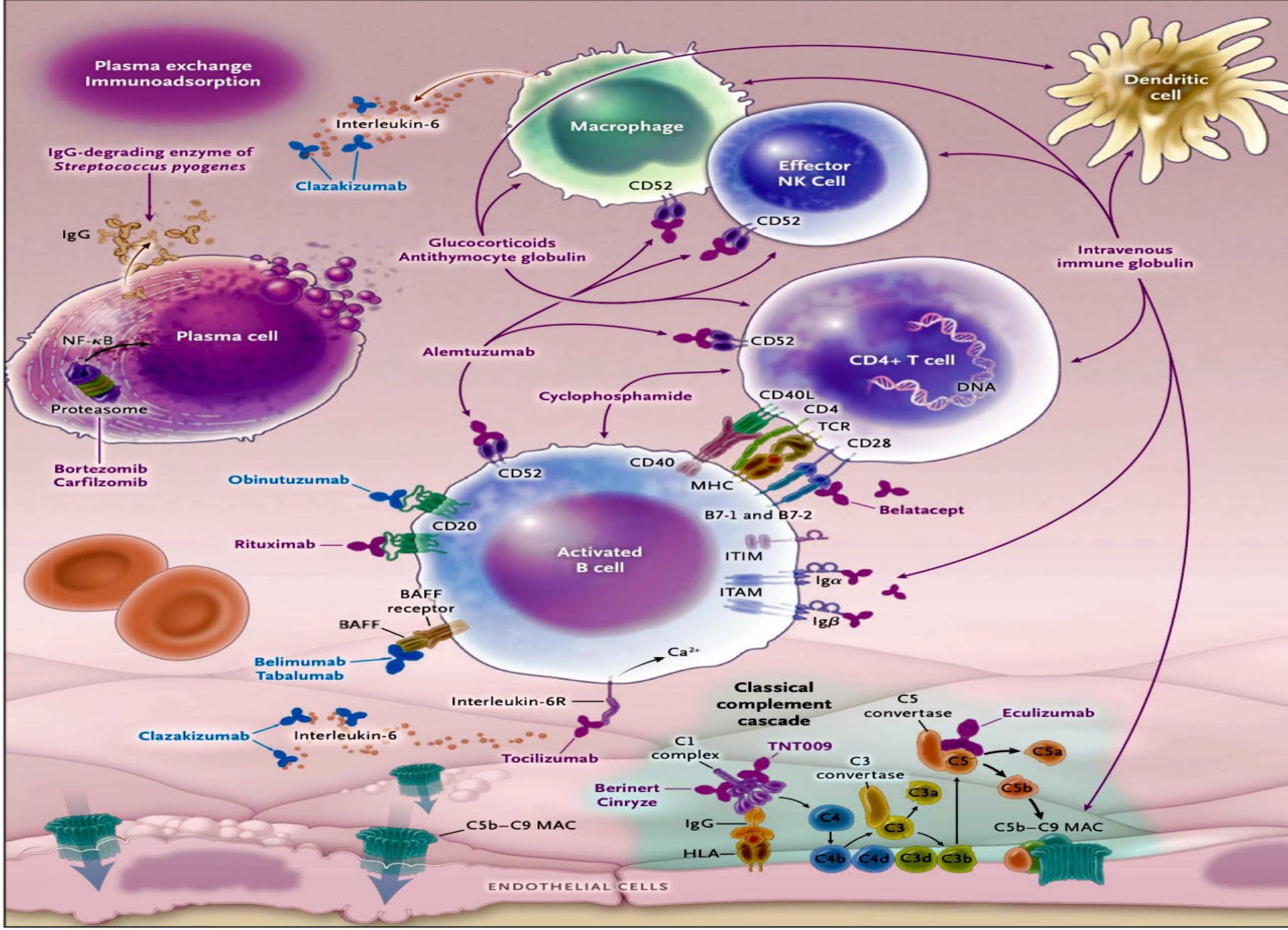

Antibody-Mediated Rejection of Solid-Organ Allografts nejm.org


Thank you
For your
Attention