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Diagnosis and treatment of acute rejection after heart transplantation

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Acute cardiac allograft rejection is a known complication in heart transplant recipients. It involves the recipient's immune system recognizing the transplanted heart as foreign and generating an immune response against it. Two types of acute rejection, acute cellular rejection(ACR) mediated by activated T cell and antibody mediated rejection(AMR) by preformed or late occurred donor-specific antibodies, are well recognized in heart transplantation. Diagnosis and treatment for ACR and AMR are somewhat different. Diagnosis and treatment strategies are vital for ensuring long-term graft survival. I. Diagnosis A. Acute cellular rejection The gold standard for diagnosis of ACR is Endomyocardial biopsy but it is invasive procedure having complication. The diagnosis can be achieved through noninvasive methods including various diagnostic tools and techniques aimed at assessing the status of the transplanted heart without invasive procedures like biopsies. These methods often involve monitoring cardiac function, immunological markers, and tissue characteristics. Various techniques and tests are employed to detect rejection without invasive procedures. These methods include:

1. Biomarker Analysis: Blood tests can identify specific biomarkers associated with rejection such as BNP(NT-proBNP) , providing early indications of rejection episodes.
2. Echocardiography: This imaging technique assesses heart function and can reveal abnormalities indicative of rejection. The graft function assessment using echocardiography especially helpful for diagnosis of acute rejection late(> 1 year) after transplantation.
3. Cardiac MRI: Magnetic resonance imaging can provide detailed images of the heart, aiding in the detection of rejection-related changes. T1 and extracellular volume fraction quantification, and T2 value can be helpful for acute rejection diagnosis and could potentially decrease the number of routine Endomyocardial biopsy.
4. Gene Expression Profiling: Gene expression profiling plays a crucial role in diagnosing acute rejection after heart transplantation. This advanced molecular technique involves analyzing the expression levels of specific genes within the transplanted heart tissue. Gene expression profiling enables the early detection of rejection

episodes by assessing the immune response and tissue damage within the transplanted heart. This allows for prompt treatment and minimizes the risk of graft failure. This technique provides a valuable tool for rejection surveillance, allowing physicians to detect rejection episodes promptly. This early detection enables timely intervention, such as adjusting immunosuppressive medications, to prevent severe rejection and maintain the graft's long-term viability. Gene expression profiling also aids in tailoring immunosuppressive therapy for individual patients, optimizing treatment outcomes. It also reduces the need for invasive heart biopsies, which are currently the gold standard for rejection diagnosis.

B. Antibody mediated rejection AMR occurs when the recipient's immune system produces antibodies that attack the transplanted heart, leading to potential graft dysfunction or failure. Diagnosis of AMR involves a combination of clinical assessments and laboratory tests. Various methods are employed to diagnose AMR:

1. Clinical Assessment: Physicians monitor the patient for clinical signs such as unexplained graft dysfunction, reduced cardiac output, or symptoms like shortness of breath and edema. Clinical suspicion is very important to detect AMR because the routine test including biopsy may miss the diagnosis of AMR.
2. Endomyocardial Biopsy: Endomyocardial biopsy remains a gold standard for diagnosing AMR. Microscopic examination of biopsy samples evaluates the extent of antibody-mediated damage in the graft tissue and the presence of antibodies in the graft using immunohistochemical stain.
3. Donor-Specific Antibodies (DSA): Detecting DSA in the recipient's blood is crucial. Elevated levels of DSA against donor-specific antigens support the diagnosis of AMR.
4. Cardiac Imaging: Non-invasive imaging methods like echocardiography and MRI can help assess cardiac function and identify signs of graft dysfunction.

II. Treatment A. Acute cellular rejection Acute cellular rejection occurs when the recipient's immune system recognizes the transplanted heart as foreign and generates an immune response against it. Immunosuppression therapy is the cornerstone of managing acute cellular rejection. Immunosuppression therapy is the cornerstone of managing acute cellular rejection. This includes medications such as corticosteroids, calcineurin inhibitors, antimetabolite, proliferation signal inhibitors and monoclonal antibodies. Treatment strategies are decided according to 2004 the ISHLT grading of Endomyocardial biopsy of heart allograft. Usually grade IR does not need any treatment and grade 2R or greater need augmentation of immunosuppression. In severe cases, when rejection is not controlled by medication alone, more aggressive interventions may be necessary, such as plasmapheresis or thymoglobulin treatment. B. Antibody-mediated rejection (AMR) Antibody-mediated rejection following heart transplantation is a critical concern. AMR occurs when the recipient's immune system produces antibodies against the transplanted heart, leading to graft dysfunction. Several strategies have been explored to manage this condition effectively. The basic principles are followings

1. Suppression of T cell response: Intravenous high dose steroid usually effective but sometimes antithymocyte globulin is needed.
2. Reducing the circulating antidonor antibodies (donor-specific antibody:DSA): Direct elimination of circulating antidonor Abs by plasmapheresis and inhibition of residual Abs by intravenous Ig are very effective. Suppression or depletion of B cell by anti-B cell monoclonal Ab such as rituximab (anti-CD20) and epartuzumab (anti-CD22) help to reducing circulating antidonor Abs and prevent the return of circulating antidonor Abs. In some patients, therapy targeting to B cell may not be effective because of long-lived plasma cells. In this case, prteosome inhibitor such as borterzomib and anti-CD 19 monoclonal Ab are effective to reduce plasma cells. This desensitization of patient antibodies has shown promise in reducing the risk of heart transplant rejection. This involves reducing the patient's immune response to donor antibodies, thereby minimizing the chances of rejection. Additionally, immunosuppression strategies play a crucial role in preventing AMR.
3. Supporting heart graft function; Inotropic support and sometimes mechanical circulatory support are needed to sustain graft function until when AMR is treated.
4. Monitoring: Regular monitoring of the recipient's antibody levels and cardiac function is essential for early detection and intervention in cases of recurrence of AMR.

In conclusion, the treatment of acute rejection after heart transplantation involves a combination of adequate immunosuppressive medications, close monitoring through biopsies and noninvasive methods, and timely adjustments to the treatment plan. This comprehensive approach aims to prevent rejection and support the long-term success of the transplant.