

CARDIAC TRANSPLANTATION

Immunobiology of Allograft Rejection, Endomyocardial Biopsy Surveillance, C4d & Allograft Vasculopathy

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Learning Objectives: Cardiac Transplantation

Clinical Scope & Physiology

Identify primary indications for orthotopic heart transplantation (DCM, severe ischemic cardiomyopathy).

Understand the three pillars of modern survival: Immunosuppression, donor matching, and EMB.

Analyze autonomic allograft denervation and its clinical consequences (absence of angina).

Allograft Rejection Pathology

Contrast acute cellular rejection (ACR) vs acute antibody-mediated rejection (AMR).

Examine histopathology of interstitial lymphocytic infiltration and myocyte necrosis (ISHLT grading).

Understand humoral rejection mechanics: Donor-specific anti-HLA antibodies, microvascular injury, and C4d deposition.

Long-Term Complications

Analyze cardiac allograft vasculopathy (CAV) as the primary long-term limitation to graft survival.

Examine the pathogenesis of diffuse, concentric coronary intimal fibrocellular hyperplasia.

Recognize opportunistic infections, post-transplant lymphoproliferative disorder (PTLD), and pharmacotoxicity.

Indications & Surgical Overview of Heart Transplantation

Primary Indications

Reserved for severe, intractable end-stage heart failure refractory to maximum medical therapy and resynchronization.

Dilated Cardiomyopathy (DCM, 54%): Idiopathic, genetic (titin mutations), viral/post-myocarditis, toxic.

Ischemic Heart Disease (IHD, 38%): Extensive prior infarctions with severe left ventricular remodeling.

Other indications: Congenital heart disease, hypertrophic/restrictive cardiomyopathy, intractable arrhythmias.

Global Volume & Evolution

>5,000 heart transplantations performed worldwide annually.

First performed by Christiaan Barnard in Cape Town in 1967; 1-year survival was initially dismal (<20%).

Modern outcomes: 1-year survival reaches 90%; 5-year survival exceeds 70–75%.

The Three Pillars of Success

1. Effective immunosuppressive regimens (calcineurin inhibitors, mTOR inhibitors, antimetabolites, steroids).
2. Rigorous candidate selection, HLA matching, and donor preservation techniques.
3. Protocol-driven surveillance with routine endomyocardial biopsy (EMB).

The Denervated Allograft: Clinical & Pathophysiologic Hallmarks

Autonomic Disconnection

Orthotopic transplantation severs all sympathetic and parasympathetic (vagal) cardiac nerve fibers.

Re-innervation is absent, incomplete, or functionally minimal in the majority of long-term recipients.

Loss of tonic vagal parasympathetic inhibition results in a resting tachycardia (typically 90–110 bpm).

Exercise Physiology

Heart rate response to exercise is delayed and blunted; Relies on circulating adrenal catecholamines.

Peak exercise heart rate is reached gradually; Recovery following exertion is similarly delayed.

Frank-Starling mechanism (preload-dependent stroke volume elevation) compensates for delayed chronotropy.

Silent Myocardial Ischemia

Afferent sensory C-fibers mediating cardiac pain are completely severed.

Patients with allograft ischemia or severe myocardial infarction experience NO classic angina pectoris.

Ischemia manifests insidiously as progressive congestive heart failure, fatigue, or sudden cardiac death.

Taxonomy of Cardiac Allograft Rejection

Rejection Classification	Underlying Mechanism / Drivers	Timeframe of Onset	Typical Histopathologic Feature
Hyperacute Rejection	Preformed donor-specific anti-ABO or anti-HLA antibodies; complement activation	Minutes to hours in operating room	Cyanotic, flaccid graft; widespread microvascular thrombosis and neutrophilic arteritis
Acute Cellular Rejection (ACR)	T-cell mediated (CD4+ helper, CD8+ cytotoxic T lymphocytes reacting against donor MHC)	Weeks to months (peaks 1–6 months)	Interstitial mononuclear/lymphocytic infiltrates with cardiac myocyte necrosis
Acute Antibody-Mediated (AMR)	De novo or memory donor-specific antibodies (DSA) targeting donor HLA or non-HLA antigens	Weeks to months; can occur late	Endothelial swelling, intravascular macrophage accumulation, capillary C4d deposition
Chronic Rejection / CAV	Immune-mediated endothelial injury leading to diffuse concentric coronary intimal thickening	Late onset (years after transplant)	Concentric fibrocellular intimal hyperplasia of coronary tree, pan-arterial stenosis

Endomyocardial Biopsy (EMB): The Diagnostic Gold Standard

Surveillance Protocol

Routine surveillance EMB is the only reliable modality for diagnosing acute rejection before irreversible damage occurs.

Schedule: Weekly for month 1, biweekly for months 2–3, monthly for months 4–6, then quarterly up to 1–2 years.

Can detect subclinical rejection episodes that are completely asymptomatic and easily reversible.

Biopsy Technique

A flexible biptome is introduced percutaneously via right internal jugular vein under fluoroscopic/echo guidance.

Crosses tricuspid valve into right ventricle; Engages interventricular septum (safe thick muscular wall).

Obtains 4–6 small fragments (1–2 mm each) of right ventricular subendocardial myocardium.

Specimen Processing

Pieces evaluated by routine H&E light microscopy, frozen section, and paraffin immunohistochemistry.

Must be examined by experienced cardiac pathologists to distinguish true rejection from biopsy artifacts.

Immunohistochemistry for complement C4d and CD68 macrophages is routine for AMR surveillance.

Acute Cellular Rejection (ACR): Immunopathology

Pathology Features

Initiated when recipient T cells recognize foreign donor Major Histocompatibility Complex (MHC/HLA) molecules.

Direct Pathway: Recipient CD4+ and CD8+ T cells directly engage intact donor allogeneic dendritic cells.

Indirect Pathway: Recipient antigen-presenting cells process shed donor HLA peptides and present them on self-MHC.

CD4+ Th1 cells release IFN-gamma and IL-2, activating macrophages and recruiting CD8+ cytotoxic T lymphocytes (CTLs).

CTLs release perforin and granzymes, inducing pore formation and caspase-mediated apoptosis of donor cardiac myocytes.

Cytokine elaboration (TNF-alpha, IL-1beta) locally depresses myocardial contractility even before overt myocyte death occurs.

Diagnostic Takeaway

Immunology Pearl: Direct allorecognition drives acute early rejection; Indirect allorecognition drives chronic vascular rejection.

ISHLT Histopathologic Grading of Acute Cellular Rejection

ISHLT 2004 Grade	Histopathologic Criteria	Clinical Significance & Management
Grade 0R (No Rejection)	No lymphocytic infiltrates; preserved, healthy cardiac myocytes with distinct striations	Normal baseline allograft histology; maintain baseline immunosuppression
Grade 1R (Mild Rejection)	Interstitial and/or perivascular infiltrates with up to ONE focus of myocyte damage	Common early post-transplant; usually resolves spontaneously; monitor closely without bolus steroids
Grade 2R (Moderate Rejection)	TWO or more distinct foci of lymphocytic infiltrates WITH associated myocyte damage	Clinically significant; requires augmented immunosuppression (high-dose intravenous pulse steroids)
Grade 3R (Severe Rejection)	Diffuse polymorphous infiltrates (lymphocytes, histiocytes, eosinophils) with widespread myocyte damage +/- edema/hemorrhage	Medical emergency; hemodynamic compromise; high-dose steroids, anti-thymocyte globulin (ATG)

Histopathologic Artifacts & Mimickers on EMB

The 'Quilty' Effect

Dense, well-circumscribed endocardial lymphoid aggregates (Quilty lesions).

Quilty A: Confined strictly to endocardium without invading underlying myocardium.

Quilty B: Extends into underlying subendocardial myocardium, mimicking cellular rejection.

Distinguished by absence of genuine myocyte necrosis and circumscribed nodular architecture; Benign.

Previous Biopsy Sites

Areas of prior bioptome bites show granulation tissue, abundant hemosiderin-laden macrophages, and fibrin thrombi.

Disorganized immature fibroblasts and proliferating capillaries must not be mistaken for rejection necrosis.

Healed scars show dense, paucicellular interstitial collagen.

Technical & Crush Artifacts

Mechanical bioptome shear causes dark, hyperchromatic squeezed nuclei ('crush artifact').

Contraction band necrosis at specimen margins from mechanical trauma during forceps closure.

Subendocardial smooth muscle bundles and Purkinje fibers can mimic damaged cardiomyocytes.

Acute Antibody-Mediated Rejection (AMR): Pathogenesis

Humoral Mechanism

Mediated by donor-specific antibodies (DSA) directed against donor HLA class I, class II, or non-HLA antigens.

DSAs bind allogeneic endothelial cell antigens lining myocardial microvasculature (capillaries, arterioles).

Triggers classical complement cascade activation (C1q → C4 → C3 → C5b-9 membrane attack complex).

Microvascular Endothelial Injury

Endothelial cells become swollen, plump, and activated with loss of normal anticoagulant surface properties.

Promotes microvascular thrombosis, capillary plugging by inflammatory cells, and focal myocardial ischemia.

Recruits Fc-receptor bearing natural killer (NK) cells, monocytes, and neutrophils (antibody-dependent cytotoxicity).

Clinical Impact

Associated with severe hemodynamic graft dysfunction (graft failure), cardiogenic shock, and ventricular arrhythmias.

Strongly correlates with early development of accelerated cardiac allograft vasculopathy and reduced long-term survival.

Complement C4d: The Diagnostic Biomarker of AMR

Pathology Features

C4d is a stable split-product fragment generated during activation of the classical and lectin complement pathways.

Upon cleavage of C4, reactive thioester group forms covalent bonds with adjacent endothelial cell surfaces and basement membranes.

Unlike other complement components that clear rapidly, C4d remains covalently tethered to tissue for days to weeks.

Acts as a durable 'immunologic footprint' or biomarker of recent antibody-mediated complement activation.

Immunohistochemistry or immunofluorescence on EMB sections demonstrates strong, linear brown/fluorescent staining along myocardial capillary endothelial linings.

Routine C4d staining on all allograft biopsies has dramatically improved detection of subclinical AMR.

Diagnostic Takeaway

Pathology Pearl: C4d is a covalent footprint of complement activation; Capillary endothelial staining confirms humoral AMR even when cellular infiltrates are sparse.

ISHLT Pathologic Classification of AMR (pAMR)

pAMR Grade	Histologic Criteria (H&E)	Immunopathologic Criteria (C4d / CD68)
pAMR 0 (Negative)	No histologic features of AMR (normal microvasculature)	Negative immunopathology (no capillary C4d staining; no CD68 intravascular accumulation)
pAMR 1 (Suspicious / Mild)	Histologic features present (swollen endothelium, intravascular macrophages) OR	Positive immunopathology (capillary C4d staining), but not both simultaneously
pAMR 2 (Definite Moderate)	Both histologic features (microvascular inflammation/injury) AND	Positive immunopathology (strong, diffuse capillary C4d deposition in >50% of capillaries)
pAMR 3 (Definite Severe)	Severe histologic features (interstitial hemorrhage, capillary thrombosis, extensive myocyte necrosis) AND	Strong positive immunopathology (diffuse C4d staining); severe clinical graft failure

Cardiac Allograft Vasculopathy (CAV): The Ultimate Barrier

Clinical Significance

Single most important limitation to long-term survival beyond the first post-transplant year.

Affects ~30% of patients at 1 year, ~50% at 5 years, and >90% of survivors at 10 years.

Accelerated, diffuse form of arteriosclerosis uniquely restricted to the allograft organ.

Immune-Mediated Pathogenesis

Chronic, low-grade immune reaction directed against allogeneic donor vascular endothelial cells.

Endothelial injury stimulates chronic production of growth factors (PDGF, FGF, TGF-beta, VEGF).

Induces massive migration of vascular smooth muscle cells from media into intima, with extensive collagen synthesis.

Unique Coronary Anatomy

Distinct from conventional atherosclerosis: Concentric, uniform intimal hyperplasia rather than eccentric calcified plaques.

Diffusely affects entire coronary tree from epicardial trunks down into intramyocardial penetrating arterioles ('distal pruning').

Internal elastic lamina and media typically remain remarkably intact and preserved.

CAV vs Native Atherosclerosis: Morphological Comparison

Pathologic Feature	Cardiac Allograft Vasculopathy (CAV)	Native Coronary Atherosclerosis (CAD)
Distribution Pattern	Diffuse, longitudinal pan-arterial narrowing along entire vessel length ('pruning')	Focal, patchy, eccentric segmental lesions concentrated at branch points and bifurcations
Geometry of Plaque	Concentric, uniform, symmetric circumference of thickened intima	Eccentric, asymmetrical plaque with residual compliant normal wall opposite lesion
Vessel Caliber Involved	Epicardial arteries AND small intramyocardial penetrating arterioles	Confined almost exclusively to major epicardial coronary arteries; spares small arterioles
Internal Elastic Lamina	Preserved and intact; media is uniformly thin and smooth	Fragmented, disrupted, and thinned beneath core of lipid/necrotic plaque
Calcification & Lipids	Minimal to absent calcification; predominantly fibrocellular smooth muscle and collagen	Prominent atheromatous lipid core (cholesterol clefts), necrosis, and heavy calcification
Clinical Presentation	Silent ischemia (denervated); presents as heart failure, arrhythmias, or sudden death	Classic angina pectoris (effort-induced retrosternal pressure relieved by nitroglycerin)
Revascularization Options	Poor candidates for PCI/CABG due to diffuse distal involvement; re-transplant is only definitive cure	Readily amenable to focal stent placement (PCI) or coronary bypass grafting (CABG)

Infectious Complications in Heart Transplant Recipients

First Month (0–30 Days)

Dominated by hospital-acquired bacterial and candidal infections.

Sternotomy wound infections, mediastinitis, nosocomial pneumonia, central line sepsis, *Clostridioides difficile*.

Similar to conventional non-transplant cardiac surgery complications.

Intermediate Period (1–6 Months)

Peak period of maximal immunosuppressive intensity.

Opportunistic viral pathogens:
Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes Simplex (HSV).

Pneumocystis jirovecii pneumonia (PCP);
Listeria monocytogenes meningitis; *Nocardia*;
Aspergillus.

Late Period (>6 Months)

Community-acquired respiratory infections (influenza, pneumococcus) in well-maintained patients.

Chronic opportunistic infections in patients requiring augmented rejection therapy.

CMV reactivation is particularly deleterious as it accelerates cardiac allograft vasculopathy.

Post-Transplant Lymphoproliferative Disorder (PTLD)

Pathology Features

Life-threatening malignancy occurring in 2–5% of heart transplant recipients under chronic immunosuppression.

Pathogenesis: Suppressed T-cell surveillance allows uncontrolled proliferation of Epstein-Barr virus (EBV)-infected B lymphocytes.

Greatest risk in EBV-seronegative recipients receiving an organ from an EBV-seropositive donor (D+/R-).

Spectrum ranges from benign polyclonal infectious mononucleosis-like plasmacytic hyperplasia to aggressive monomorphic diffuse large B-cell lymphoma (DLBCL).

Involvement: Frequently extranodal — gastrointestinal tract, central nervous system, allograft itself, liver, and lungs.

Management: Immediate reduction of baseline immunosuppression; Anti-CD20 monoclonal antibody (rituximab); Cytotoxic chemotherapy if monomorphic.

Diagnostic Takeaway

Oncology Pearl: EBV-driven PTLD can manifest directly within the cardiac allograft, masquerading clinically as severe refractory allograft rejection.

Immunosuppressive Drug Toxicities: The Non-Immune Toll

Calcineurin Inhibitors (CNIs)

Cyclosporine and Tacrolimus form the backbone of maintenance immunosuppression.

Mechanism: Inhibit calcineurin, blocking NFAT dephosphorylation and T-cell IL-2 synthesis.

Toxicity: Renal afferent arteriolar vasoconstriction causing progressive chronic nephrotoxicity; Systemic hypertension; Neurotoxicity (tremor, PRES); Post-transplant diabetes (tacrolimus).

Antimetabolites

Mycophenolate Mofetil (MMF) and Azathioprine.

Mechanism: Inhibit inosine monophosphate dehydrogenase (IMPDH), blocking de novo purine synthesis in lymphocytes.

Toxicity: Bone marrow suppression (leukopenia, anemia), severe gastrointestinal intolerance (diarrhea, colitis).

Corticosteroids & mTOR Inhibitors

Prednisone: Cushingoid habitus, osteopenia/osteoporosis, accelerated atherosclerosis, glucose intolerance.

Sirolimus / Everolimus: Inhibit mTOR; Cause hyperlipidemia, impaired surgical wound healing, interstitial pneumonitis.

Clinical Case: Accelerated CAV Presenting as Silent Failure

Pathology Features

A 52-year-old male 6 years status-post orthotopic cardiac transplantation for ischemic cardiomyopathy presents for routine follow-up.

Reports progressive fatigue and mild exertional dyspnea over 2 months. Denies any chest pressure, palpitations, or diaphoresis.

Physical examination: Elevated jugular venous pressure (10 cm H₂O), bilateral lower extremity pitting edema, S3 gallop.

Echocardiogram: New anterior and lateral wall motion abnormalities; Left ventricular ejection fraction has dropped from 60% to 28%.

Coronary Angiography: Diffuse, smooth, concentric tapering across entire LAD and circumflex arteries with complete distal vessel pruning.

Pathology Correlate: Severe cardiac allograft vasculopathy causing silent, unperceived extensive myocardial ischemic injury in a denervated heart.

Diagnostic Takeaway

Board Pearl: Denervated heart transplant patients NEVER experience angina; New-onset heart failure or dyspnea must be evaluated immediately for CAV.

Master Summary: Cardiac Transplantation Pathology

Early Surveillance

EMB is the mandatory gold standard for early rejection detection.

Acute cellular rejection (ACR) characterized by lymphocytic infiltrates and cardiomyocyte necrosis (ISHLT 0R–3R).

Antibody-mediated rejection (AMR) diagnosed by microvascular inflammation and endothelial complement C4d capillary deposition.

Late Complications

Cardiac allograft vasculopathy (CAV) is the primary long-term killer: Concentric, diffuse intimal fibrocellular hyperplasia.

Opportunistic infections (CMV, PCP) peak months 1–6; EBV-associated PTLD requires vigilant monitoring.

Prognostic Milestones

1-year survival >90%; 5-year survival >70–75%.

Careful candidate selection, protocol EMB, and calibrated immunosuppression remain vital to long-term allograft survival.

Cardiac Transplantation: Advanced Pathology & SGD Module 19

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

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Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 20

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Cardiac Transplantation: Advanced Pathology & SGD Module 25

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Cardiac Transplantation: Advanced Pathology & SGD Module 26

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Cardiac Transplantation: Advanced Pathology & SGD Module 27

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Cardiac Transplantation: Advanced Pathology & SGD Module 30

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Cardiac Transplantation: Advanced Pathology & SGD Module 31

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Cardiac Transplantation: Advanced Pathology & SGD Module 32

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Cardiac Transplantation: Advanced Pathology & SGD Module 33

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Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 36

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

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Cardiac Transplantation: Advanced Pathology & SGD Module 37

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

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Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

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Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 38

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

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Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 39

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 40

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 41

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 42

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 43

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 44

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 45

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 46

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 47

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 48

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 49

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 50

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 51

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 52

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

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Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 53

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

Masson trichrome staining highlights progressive perivascular and interstitial allograft fibrosis.

Transmission electron microscopy demonstrates endothelial swelling and capillary basement membrane duplication in chronic AMR.

Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 54

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

Subendocardial ischemia in biopsies must be distinguished from immunologic allograft injury.

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Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 55

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

Pathology Criteria

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Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 56

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

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Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 57

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

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Translational Horizons

Donor-derived cell-free DNA (dd-cfDNA) in peripheral blood provides non-invasive molecular rejection surveillance.

Gene expression profiling (AlloMap) quantifies peripheral blood mononuclear cell rejection signatures.

Xenotransplantation using genetically edited porcine cardiac allografts represents the future frontier.

Cardiac Transplantation: Advanced Pathology & SGD Module 58

Transplant Immunology

Crossmatching techniques (complement-dependent cytotoxicity vs flow cytometry) minimize hyperacute risk.

Panel Reactive Antibody (PRA) score quantifies pre-transplant sensitization.

Non-HLA antibodies (anti-endothelial cell antibodies, anti-AT1R) are emerging drivers of refractory AMR.

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Translational Horizons

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Cardiac Transplantation: Advanced Pathology & SGD Module 59

Transplant Immunology

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