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METHODOLOGICAL DEVELOPMENT OF TOPIC №7

practical lesson **" Immunosuppressive therapy of posttransplant patients"** (2 hours) in the discipline "Clinical Immunology and Allergology" for 6-th year students of specialty "Medicine"

Theme №7: Immunosuppressive therapy of posttransplant patients.

1. *Relevance of the topic:* At present time it is especially important to understand by the students of the importance of participating immune mechanisms of immunosuppressive therapy of posttransplant patients, which will determine the choice of modern treatment.
2. *The goals of the class:*
   - educational: students must study basic immunogical factors that determine the correct course of the immunosuppressive therapy of posttransplant patients
   - professionally oriented: students should be based on clinical and laboratory data to diagnose the risk of posttransplantant complications, to establish impressions for immunotropic treatment such conditions
   - educational: to form a sense of responsibility for the timeliness and correctness of professional actions.

3. *Equipment* for conducting classes: Presentation for multimedia demonstration, schemes, tables, immunograms, tests, situational tasks, histological and cytological preparations, non-typical situational tasks

5. *Integrative Relations of the theme:*

5.1.Internal Integration: The topic of this practical lesson is associated with the following topics of the cycle "Clinical Immunology and Allergology" classes for students of the 5th year as "Structure and Principles of Functioning of the Immune System" and "Assessment of the Immune System", Fragment "Immunology of infertility" in the topic " Autoimmune diseases: immunopathogenesis, immuniagnostic and treatment ».

5.2. Interdisciplinary integration:

Subjects	To know	To be able to
1	2	3
Histology and embryology	The structure of eggs and sperm. Meiosis.	Be able to determine the state of maturity and functional activity of gametes
Therapy	Diagnostic criteria for allergic diseases	Differentiate IgE-dependent and IgE-independent allergic diseases by clinical and laboratory features
Endocrinology	The main organs of the endocrine system: hypothalamus, pituitary gland, pineal gland	Diagnose fertility disorders associated with their function
Pediatrics	Approaches to anti-infective vaccination in adolescence in boys	To establish the probability of cross-reaction of anti-infective post-vaccine antibodies with antigens on sperm
1	2	3
Urology	Relationship of chronic inflammatory diseases of the genitourinary system in men, varicocele, with the formation of antisperm antibodies	Establish indications for therapeutic treatment of patients with antisperm antibodies and infertility.
Oncology	Types of tumors, diagnosis of tumor antigens	Establish indications for the treatment of cancer patients with antitumor vaccines
Virology	Features of hepatitis B viruses and papillomavirus groups	Be able to appoint a laboratory test for hepatitis B virus infection and the main pathogenic strains

		of papillomavirus, know the indications for antiviral prophylactic

5. Study questions:

1. Positive and negative immunological memory.
2. Prophylactic and therapeutic effect of vaccines
3. Allergic IgE-dependent diseases: modern approaches to their treatment
4. Immune system and carcinogenesis. Basic antitumor immune mechanisms
5. Basic principles of laboratory diagnosis of allergy and cancer patients before and after vaccine treatment

Main part

Immunosuppressive therapy of posttransplant patients

Transplantation is the process of transferring an organ or part of an organ (known as a graft) from one donor to either him/herself (autologous transplantation)

or another recipient (allogenous transplantation) or their genetically identical recipient (isograft transplantation). In addition to being subject to strict legal requirements, the donor and recipient must be histocompatible in allogenous transplantations to minimize the risk of transplant rejection. Because the MHC is only perfectly matched in isotransplantation (involving the transfer of genetically identical tissue, e.g., between identical twins, allogenous transplantation subsequently requires immunosuppressive therapy.

Transplant immunology

Major histocompatibility complex (MHC) and human leukocyte antigen (HLA)

- **HLA**: a gene cluster on chromosome 6 that codes for **MHC** molecules
- **MHC**: proteins present on the surface of all cells that display antigenic peptides as a normal physiological function so that they can be recognized by T lymphocytes as either self or non-self antigens
- **Types of MHC**
  - The **HLA I** cluster codes for **class I MHC** molecules and consists of three loci: **HLA-A**, **HLA-B**, and **HLA-C**.
  - The **HLA II** cluster codes for **class II MHC** molecules and also consists of three loci: **HLA-DR**, **HLA-DP**, and **HLA-DQ**.
- See "Major histocompatibility complex" for more details.

Allorecognition

- **Definition**: recognition of a foreign antigen as a non-self antigen by a host
- **Types of allorecognition**
  - Indirect allorecognition
    - HLA molecules on an allograft are extremely different from those of the recipient and are thus treated as foreign antigens by the antigen-presenting cells of the recipient.
    - The antigens are then broken down and presented by the antigen-presenting cells.
  - Direct allorecognition: HLA molecules on the allograft are exceptionally strong antigens and can directly stimulate the T cellswithout being broken down and presented by the antigen-presenting cells of the recipient.
- **Clinical importance**: Activation of a particular T cell by a foreign HLA peptide results in **clonal proliferation** of that type of T lymphocyte, a process that is mediated by **IL-2** and leads to **acute rejection**.
  - Activated cytotoxic (CD_8) T cells recognize other HLA class I molecules on all cells in the donor graft and cause target cell death by releasing molecules such as perforin and granulozyme.
  - Activated helper (CD_4) T cells recognize HLA class II molecules on dendritic cells within the transplanted organ.
    - The activated helper T cells recruit recipient macrophages to the graft.
    - The activated helper T cells help the plasma cells produce alloantibodies → damage the target cell directly or induce antibody-dependent cell-mediated cytotoxicity

Prerequisites for organ matching

Cross-matching (transplantation)

- Recipient serum is examined for preformed antibodies (donor-specific antibodies) against donor T and B lymphocytes
  - A negative cross-match against T and B cells indicates a lower risk of rejection reactions; therefore, transplantation may be performed.
  - A negative cross-match against T cells but a positive cross-match against B cells indicates a higher risk of acute rejection, but transplantation may still be performed with a high level of caution.
  - A positive cross-match against donor T and B lymphocytes indicates a high risk of hyperacute rejection; therefore, the transplantation must not be performed.

ABO compatibility

- **Hematopoietic stem cell transplantation**
  - ABO compatibility is **preferred** but incompatibility can be tolerated.
  - ~ 40% of allogenous stem cell transplantations are performed despite ABO incompatibility.
- **Solid organ transplantation**: ABO compatibility is **required**.

Rh compatibility is not required for solid organ transplantation. Both Rh compatibility and ABO compatibility are not essential for hematopoietic stem cell transplantation.

Histocompatibility

- **Principle**
  - MHC matching at the **HLA-DR**, **HLA-A**, and **HLA-B** loci
  - Matching of HLA-C, HLA-DP, and HLA-DQ is preferred but not always required.
- **Coding of mismatch degree** (**HLA-DR**, **HLA-A**, and **HLA-B**)
  - 0: no mismatch
  - 1: mismatch on either the paternal or maternal chromosome
  - 2: mismatch on both the paternal and maternal chromosome
  - 000: a complete match
  - 222: a complete mismatch
- **Odds of histocompatibility**
  - For a sibling, the probability that the patient has an HLA compatible sibling is $1 - (0.75)^n$ (where n is the number of siblings).
  - Between two randomly chosen, nonrelated individuals: 1 in 10,000

Types of graft based on histocompatibility between donor and recipient

Type	Definition	Examples
Autograft	Graft originates from the recipient.	Skin graft (split-skin graft or full-thickness) for skin transplantation Saphenous vein graft for vascular bypass surgery Bone graft from the iliac crest for bone reconstruction Semitendinosus graft for cruciate ligament reconstruction Autotransfusion of blood Hair transplantation
Isograft	Graft originates from a genetically identical person (identical twin).	Various organ transplantations (e.g., kidney, liver, or cornea)
Allograft	Graft originates from a genetically	

Types of graft based on histocompatibility between donor and recipient

Type	Definition	Examples
	different person.	
Xenograft	Graft originates from a different species (e.g., pig).	Porcine or bovine heart valves

Immunosuppressive therapy is not required for autograft transplantation.

Solid organ transplantation

Organ procurement

- **Overview**
  - The organ is harvested from a brain-dead donor (BDD) or donor after cardiac death (DCD).
  - The United Network for Organ Sharing (UNOS) is responsible for organ matching and the allocation of organs to candidates on a waiting list.
- **Waiting time**: time period from the entry of a potential transplant candidate on the UNOS list to the allocation of an organ
  - Kidney: 5 years
  - Liver: 11 months
  - Heart: 4 months
  - Lung: 4 months
  - Pancreas: 2 years
  - Kidney/ pancreas: 1.5 years
- **Contraindications for organ donation**
  - Malignancy
    - Non-curable or metastatic
    - High risk of transmission (e.g., melanomas, choriocarcinomas)
  - Donor sepsis
  - Transmissible spongiform encephalopathies (prion diseases such as Creutzfeldt-Jakob disease)
  - Cardiac arrest occurring before brain death
- **NOT contraindications to organ donation**
  - Hepatitis B or C infection
  - Low-grade, localized tumors without evidence of metastasis at the time of death
  - History of malignancy with a disease-free duration > 5 years
  - HIV infection
  - Hypertension, diabetes
  - Advanced age

Living donors

- **Overview**
  - The organ is harvested from a living donor (usually a relative) at the time of the transplant surgery.
  - Only kidney transplantation and liver transplantation can be performed using grafts from living donors.
- **Advantages**
  - Donor is in good general condition
  - Preoperative and perioperative immunomodulation is possible in the recipient.
  - Short cold ischemia time

- Minimal waiting time
- High degree of HLA compatibility if the donor is related to the recipient

- **Disadvantages**: increased morbidity and mortality in the donor

Organ preservation

Hypothermic solutions

- Extracellular solutions (e.g., Bretschneider solution): ↑ Na^+, ↓ K^+
- Intracellular solutions (e.g., University of Wisconsin solution, St. Thomas cardioplegia solution): ↓ Na^+, ↑ K^+

Ischemic times

- Warm ischemia time: time from the withdrawal of life support in the donor to the initiation of cold organ preservation
- Cold ischemia time: time from the initiation of cold organ preservation to the warming of the organ within the recipient following the restoration of blood perfusion

A prolonged ischemic time increases the risk of organ dysfunction in the post-transplant period.

Transplantation sites

Overview of organ transplantation sites

	Description	Examples
Orthotopic	The graft is placed in the normal anatomical position. The diseased or nonfunctional organ being replaced is removed.	Heart transplantation Liver transplantation
Heterotopic	The graft is placed in a site other than the normal anatomical position. The nonfunctional organ is usually left in place.	Kidney transplantation Pancreas transplantation
Paratopic	The donor organ is placed close to the normal anatomical position.	Pancreas transplantation

Post-transplant immunosuppressive therapy

Overview

- Intense immunosuppression in the early postoperative period (3–6 months)
- To minimize drug toxicity, use low doses of multiple drugs rather than high doses of a few drugs.
- Avoid excessive immunosuppression that increases the risk of post-transplant infections and post-transplant malignancy.

Phases

1. Induction therapy using **anti-T-lymphocyte antibodies**
   - Nondepleting antibodies (monoclonal): **basiliximab**
   - Lymphocyte-depleting antibodies (polyclonal): **thymoglobulin**
2. Maintenance therapy: commonly via a triple-drug regimen
   - Corticosteroids
   - Calcineurin inhibitor (e.g., cyclosporine or tacrolimus)
   - Antiproliferative agents (e.g., azathioprine, mycophenolate mofetil, sirolimus)

Immunosuppressive therapy is a balancing act: Too much immunosuppression, and the risk of infection increases; too little, and the risk of rejection increases.

Renal transplantation

Overview

- **Number of procedures**: 23,401 in 2019 in the US
- **Indication**: patients with end-stage renal disease (CKD 5)
- **Contraindications**
  - Absolute
    - Unsuitable vascular anatomy
      - Aortobifemoral bypass or an aortoiliac stent graft that extends to both external iliac arteries
      - Circumferential calcification of the iliac vessels
      - Thrombosis of iliac vein and inferior vena cava
    - Active infection (e.g., tuberculosis, invasive fungal infections, osteomyelitis)
    - Malignancy in the past 2 years
    - BMI $\geq$ 50 kg/m^2
    - Active alcohol or substance use (except tobacco)
    - Lack of adequate social support (e.g., patient in a nursing home, homeless patient)
  - Relative
    - Age < 1 year or > 75 years
    - Diseases of the lower urinary tract
- **Specific contraindications for living donors**
  - Pregnancy
  - Psychiatric diseases or psychosocial problems
  - Diseases potentially leading to kidney damage
    - Proteinuria > 300 mg/day
    - Hypertension that does not respond to treatment
    - Diabetes mellitus
- **Technique**
  - The left kidney is preferred in living-donor kidney transplantations because it has a longer renal vein.
  - Kidney transplants are transplanted heterotopically in the **iliac fossa** since this position holds several advantages over orthotopic implantation.
    - The transplanted kidney can be more easily palpated, biopsied, and evaluated via ultrasound.
    - Vascular anastomosis with the inguinal arteries is easier.
    - Distance between the ureter and bladder is shorter.

Two healthy, fully functioning kidneys are an essential requirement for kidney donation by a living donor.

The left kidney is preferred for living-donor transplantation as it has a longer renal vein.

Complications

- Acute tubular necrosis
- Graft rejection
- Post-transplant infection
- Vascular
  - Early
    - **Renal vein thrombosis**
    - Renal artery thrombosis
  - Late: **renal artery stenosis**
- Urological
  - Urinary leakage
  - Urinary tract obstruction
- Lymphocele
- Calcineurin-induced nephrotoxicity

Post-transplant care

- Serial monitoring of renal function tests
- See "Post-transplant immunosuppressive therapy."
- See "Prevention of post-transplant infections."

Diagnostic algorithm for renal dysfunction following renal transplantation

1. Consider prerenal causes of acute renal failure.
   - In hypotensive or normotensive patients, measure the BUN:creatinine ratio to rule out dehydration.
   - In hypertensive patients, consider renal artery stenosis and perform Doppler ultrasonography.
2. Measure urine protein and order a dipstick urine test for hematuria.
   - Hematuria or proteinuria: renal biopsy
   - No hematuria or proteinuria
     - If the patient is not taking anticalcineurins: renal biopsy
     - If the patient is taking anticalcineurins: measure serum anticalcineurin levels
     - ↑ Anticalcineurin levels: Reduce anticalcineurin dose and remeasure creatinine.
     - Unchanged anticalcineurin levels (i.e., within the target range): Perform renal and bladderultrasound to rule out obstruction.
     - ↓ Anticalcineurin levels: Carry out a renal biopsy.

Prognosis

The graft functions stays functional for ~ 14 years, longer if received from a living donor.

Overview of survival rates after kidney transplantation

	1-year survival rate	2-year survival rate	5-year survival rate
Cadaveric graft	88%	81%	71%
Graft from living donor	94%	93%	84%

Renal transplantation has a better prognosis than dialysis in end-stage renal disease.

Liver transplantation

Overview

- **Indications**
  - **Hepatocellular carcinoma** without metastatic disease and with either one lesion measuring ≤ 5 cm or three lesions each measuring ≤ 3 cm
  - Fulminant hepatic failure
  - Decompensated cirrhosis with a MELD score ≥ 15
    - Hepatitis C
    - Alcoholic cirrhosis
    - Primary biliary cirrhosis
    - Primary sclerosing cholangitis
    - Biliary atresia
    - Hemochromatosis
    - α1-antitrypsin deficiency
    - Wilson disease
  - Severe metabolic dysfunction due to liver-related diseases with systemic manifestations (e.g., Crigler-Najjar syndrome type I, glycogen storage disorders types I, III, IV)
- **Contraindications**
  - MELD score < 15

- Alcohol or drug use disorder
- Hepatocellular carcinoma with metastatic spread
- Intrahepatic cholangiosarcoma
- Severe cardiac or pulmonary disease
- HIV/AIDS
- Extrahepatic malignancy
- Uncontrolled sepsis
- Fulminant hepatic failure with a sustained ICP > 50 mm Hg or CPP < 40 mm Hg
- Lack of adequate social support

- **Technique**: orthotopic transplantation
  - Transfer of the entire organ from a BDD
  - Split-liver transplantation from a living donor or BBD

Complications

- Graft rejection
- Post-transplant infections
- Post-transplant malignancy
- Vascular complications
  - **Hepatic artery thrombosis**
  - Portal vein thrombosis
  - Postoperative hemorrhage
- Biliary complications
  - **Biliary leakage**
  - Biliary stricture

Diagnostic algorithm in the case of clinical or laboratory features of hepatic dysfunction

- **< 6 months post-transplant**: duplex ultrasonography to identify biliary or vascular pathology
  - No evidence of biliary dilation or vascular pathology: liver biopsy
  - Evidence of biliary dilation: ERCP or percutaneous transhepatic cholangiography
- **> 6 months post-transplant**: liver biopsy

Post-transplant care

- Serial monitoring of liver function tests, including ALP
- See "Post-transplant immunosuppressive therapy."
- See "Prevention of post-transplant infections."

Prognosis

- High mortality rate within first postoperative year due to the greatest immunosuppression and subsequent infections
- 5-year survival rate: ~ 80%
- Very good prognosis for pediatric liver transplantation

Heart transplantation

Overview

- **Number of procedures**: 3552 in 2019 in the US
- **Indications**
  - **End-stage heart failure** (NYHA class IV) and an ejection fraction < 20% with no other viable treatment option
  - Otherwiese untreatable, intractable, life-threatening ventricular arrhythmias
  - Hypoplastic left heart syndrome
  - Severe Ebstein anomaly
  - Pulmonary atresia
  - Heterotaxy lesions
- **Contraindications**

- Absolute contraindications
  - AIDS with recurrent opportunistic infections
  - Malignancy within the past 5 years
  - Obstructive lung disease with an FEV_1 < 1 L/min
  - Pulmonary hypertension
    - Pulmonary artery systolic pressure > 60 mm Hg
    - Mean transpulmonary gradient > 15 mm Hg,
    - Pulmonary vascular resistance > 6 Wood units
  - Active SLE, sarcoidosis, or amyloidosis with multisystem involvement
  - ESRD or irreversible hepatic failure if cardiac transplantation alone is being considered
- Relative contraindications
  - Any active infection (except device-related infection in individuals with ventricular assist devices)
  - Age > 72 years
  - FEV_1 < 40% of the normal value
  - Pulmonary infarction in the past 6–8 weeks
  - Heparin-induced thrombocytopenia in the last 100 days
  - Chronic renal failure (creatinine > 2.5 mg/dL)
  - Hepatic dysfunction (bilirubin > 2.5 mg/dL, serum transaminase more than 3 times the upper limit, or INR > 1.5 without warfarin)
  - Active peptic ulcer disease
  - Severe malnutrition (BMI < 18 kg/m^2)
  - Morbid obesity (BMI > 35 kg/m^2)
  - Severe diabetes mellitus
  - Uncontrolled hypertension
  - Severe peripheral vascular disease
  - Abdominal aortic aneurysm > 6 cm
  - Symptomatic carotid stenosis
  - Irreversible neurological disease
  - Mental illness
  - Drug, tobacco, or alcohol consumption in the past 6 months
- **Technique**: A graft from a deceased donor is transplanted orthotopically.
  - Midline sternotomy
  - Systemic anticoagulation and cardiopulmonary bypass with therapeutic hypothermia
  - The aorta is cross-clamped and the recipient heart is excised at the level of the mid-atrium, leaving the pulmonary veins and vena cava intact.
  - Creation of an atrial cuff in the donor heart
  - Anastomosis of the atrial cuff first with the remnant of the recipient's left atrium, then the right atrium.
  - Anastomosis of the pulmonary artery and aorta
  - Closure of the midline sternotomy, rewarming the patient, and weaning off of cardiopulmonary bypass

Complications

- Post-transplant infection
- Graft rejection
  - Hyperacute and accelerated rejection → cardiogenic shock
  - Acute rejection → arrhythmias, heart failure
  - Chronic rejection → acquired transplant vasculopathy → accelerated coronary artery disease→ angina, low stress tolerance
- Pulmonary hypertension → right heart failure

Post-transplant care

- Surveillance endomyocardial biopsies to identify rejection reactions
- See “Post-transplant immunosuppressive therapy.”

- See "Prevention of post-transplant infections."

Prognosis

Overview of survival rates after heart transplantation			
	1-year survival rate	3-year survival rate	5-year survival rate
Primary transplants	87%	79%	72%
Retransplants	82%	67%	58%

Lung transplantation

Overview

- **Indication**: patients with advanced lung disease refractory to maximal medical or surgical therapy, disabling symptoms during activities of daily living, and risk of death > 50% over the next 2 years
  - COPD
  - Idiopathic pulmonary fibrosis
  - Genetic disorders such as CF and α1-antitrypsin deficiency
  - Idiopathic pulmonary arterial hypertension (IPAH)
  - Sarcoidosis
  - Lymphangioleiomyomatosis
  - Pulmonary Langerhans cell histiocytosis
- **Contraindications**
  - Absolute
    - Malignancy in the past 2 years
    - Chronic advanced illnesses (e.g., heart, renal, or hepatic insufficiency)
    - Uncontrolled or untreatable pulmonary or extrapulmonary infection
    - Poor cardiac function
    - Acute medical conditions, such as sepsis, myocardial infarction, or liver failure
    - Uncorrectable bleeding diathesis
    - HIV infection, ongoing HBV, HCV, or TB infections
    - Significant chest wall or spinal deformity
    - BMI ≥ 35
    - History of nonadherence to medical therapy
    - Psychiatric conditions or psychosocial problems
    - Lack of adequate social support
    - Severely limited functional status with poor rehabilitation potential
    - Active alcohol, tobacco, or substance use disorder
  - Relative
    - Age > 75 years
    - BMI 30–35
    - Progressive or severe malnutrition
    - Severe, symptomatic osteoporosis
    - Prior chest surgery with lung resection
    - Infection with highly resistant or virulent bacteria, fungi, and/or certain strains of mycobacteria
- **Techniques**: A graft from a deceased donor is transplanted orthotopically.
  - Bilateral orthotopic lung transplantation (BOLT) is the preferred procedure.
  - In a single-lung transplant, the right lung or the lung with the worse pulmonary function is chosen for replacement.
- **Types of lung transplant**
  - Lobe [11]

- Single-lung
- Double-lung
- Heart-lung

Complications

- Pneumonia
- Primary graft dysfunction due to ischemia-reperfusion injury
- Airway anastomotic complications
  - Bronchial necrosis and dehiscence
  - Tracheobronchomalacia
  - Excess granulation tissue
  - Focal infection
  - Stenosis
  - Fistula
- Chronic graft dysfunction → bronchiolitis obliterans syndrome and restrictive allograft syndrome
- Malignancy
  - Nonmelanoma skin cancer
  - Post-transplant lymphoproliferative disease
  - Kaposi sarcoma, malignancy of the colon, breast, or bladder)

Post-transplant care

- Pulmonary rehabilitation
- Serial monitoring of lung function tests (e.g., PFT, CT scan of the chest, bronchoscopy)
- See "Post-transplant immunosuppressive therapy."
- See "Prevention of post-transplant infections."

Prognosis

- Median survival for all adult recipients: 5.7 years
- 1-year survival rate: 78%
- 5-year survival rate: 51%

Hematopoietic stem cell transplantation

Hematopoietic stem cell

- A stem cell that can give rise to all lines of blood cells via hematopoiesis.
- Excellent regenerative capacity
- Ability of homing to the bone marrow following intravenous injections

Overview of hematopoietic stem cell grafts

	Bone marrow transplant	Peripheral blood stem cell transplant	Umbilical cord blood transplant
Source	Bone marrow aspiration from the posteriorsuperior iliac spine	Pheresis of peripheral blood after administering a myeloid growth factor (e.g., G-CSF, GM-CSF) or plerixafor (a CXRC4 antagonist) for 4–5 days	Umbilical cord blood that is collected at the time of delivery and stored in stem cell banks
Risk of graft-vs-host disease(GvHD)	Lowest	Highest	Low
Engraftment	By 3 weeks	By 2 weeks	By 4 weeks

Autologous vs. allogenous stem cell transplantation		
	Autologous stem cell transplantation	Allogenous stem cell transplantation
Definition	Removal and storage of a patient's own hematopoietic stem cells, which are retransfused back to the patient after high-dose myeloablativechemotherapy	Transfer of hematopoietic stem cells of a sibling or unrelated donor to a recipient
Indications	Germ cell tumors, soft tissuesarcoma: to allow the administration of higher doses of antineoplastictherapy Multiple myeloma Lymphoma	Leukemia (e.g., acute lymphoblastic leukemia) To replace abnormal but nonmalignant cells of the lymphohematopoietic system in conditions such as: Severe combined immunodeficiency Aplastic anemia Thalassemia Relapse of lymphoma or multiple myeloma following autologous stem cell transplantation
Preferred graft source	Bone marrow transplant	Peripheral blood stem cell transplant
Advantages	Low risk of GvHD and late-onsetpost-transplant infections Low risk of graft rejection	Graft-versus-tumor effect: Donor T lymphocytes attack malignant hematopoietic stem cells of the recipient that remain after high-dose chemotherapy. Low risk of early-onset post-transplant infections
Disadvantages	High-risk of early-onsetpost-transplant infections No graft-versus-tumor effect	Moderate to high risk of GvHD and late post-transplantinfection Increased risk of graft rejection Can cause chromosomal abnormalities on FISH analysis of peripheral blood or bone marrow after transplant, leading to discrepancy between genotype and phenotype (e.g., if the donated stem cells are from a sex-mismatched donor)

Procedure

1. Preparation of a hematopoietic stem cell graft from the donor using bone marrow aspirate, peripheral blood, or umbilical cord blood
2. Transplant preparative regimen: recipient preparation using high-dose chemotherapy and/or total body irradiation
   - Rationale
     - To eradicate the underlying disease
     - To prevent graft rejection in the setting of allogenous HSCT
   - Regimens
     - Severe combined immunodeficiency: No recipient preparation is required.
     - Aplastic anemia: antithymocyte globulin and high-dose cyclophosphamide
     - Thalassemia, sickle cell anemia: antithymocyte globulin, high-dose cyclophosphamide, and busulfan
     - Malignancies: various combinations of total body irradiation, antithymocyte globulin, cyclophosphamide, busulfan, melphalan, thiotepa, carmustine, and etoposide
3. Intravenous injection of the harvested hematopoietic stem cells
4. Stem cell engraftment
   - Definition: anatomical and functional incorporation of transfused hematopoietic stem cells in the recipient's bone marrow
   - Factors that affect the success rate of engraftment
     - Earlier engraftment
       - A myeloid growth factor (e.g., G-CSF, GM-CSF) may be used to accelerate stem cell engraftment by 3–5 days.
     - Peripheral blood stem cell transplant

- Delayed engraftment
- Methotrexate, which is used to prevent GvHD, delays stem cell engraftment by 3–5 days.
- Umbilical cord stem cell transplant

  - Confirmation
- Increase in granulocyte count beyond 500 cells/μL
- FISH or analysis of STNRs after PCR: evidence of chimerism in peripheral leukocytes

5. In allogenous stem cell transplantation: regimen to prevent GvHD

Complications

Hepatic venoocclusive disease (hepatic VOD)

- **Definition**: clinical syndrome characterized by obstruction of hepatic sinusoids with cellular detritus resulting from endothelial lesions in hepatic sinusoids and venules
- **Etiopathogenesis**: toxic injury to endothelium of sinusoids and venules (from, e.g., myeloablativehigh-dose chemotherapy, liver radiation, pyrrolizidine alkaloids) → initiation of coagulation cascade → embolism formation (fibrin, cellular debris) → progressive obstruction of sinusoids → intrahepatic post sinusoidal portal hypertension
- **Clinical features**
  - Painful hepatomegaly, right upper quadrant pain, jaundice
  - Signs of fluid retention: ascites, edema, weight gain
- **Diagnostics**
  - Clinical diagnosis
  - Blood tests: hyperbilirubinemia
  - Supportive diagnostics: hepatic Doppler ultrasonography, liver biopsy
- **Differential diagnoses**
  - Budd-Chiari syndrome, acute/chronic liver disease
  - GvHD
- **Treatment**: supportive (no specific treatment available)
  - Based on limited evidence from studies, defibrotide has been used successfully in the treatment of hepatic VOD.
  - Consider TIPS in severe cases of VOD in liver transplanted individuals.
- **Complications**: hepatic encephalopathy, multiorgan failure
- **Prognosis**: highly variable
- **Prevention**
  - Limiting hepatotoxicity by choosing less hepatotoxic treatment regimens, monitoring drug blood concentrations, and finding the least toxic route of administration.
  - Ursodeoxycholic acid and antioxidants may be beneficial.

Engraftment syndrome

- **Definition**: clinical syndrome characterized by fever, rash, diarrhea, and/or, in more severe cases, organ dysfunction
- **Etiopathogenesis**
  - Poorly understood; associated with HSCT
  - Thought to be mediated by the release of proinflammatory cytokines (e.g., IL-2, IL-6, TNF-α, interferon-γ), erythropoietin, and products of neutrophil degranulation and oxidative metabolism; involves systemic endothelial damage
- **Clinical features**
  - Fever, skin rash, diarrhea
  - Transient encephalopathy
  - Pulmonary edema, hypoxia, weight gain
- **Diagnostics**: clinical diagnosis
- **Differential diagnoses**
  - Acute and hyperacute GvHD, preengraftment syndrome, hematopoietic graft rejection
  - Drug/radiation-induced toxicity
  - Sepsis

- **Treatment**: depends on severity, but mainly involves corticosteroids (e.g., methylprednisolone, prednisolone), supportive measures (e.g., antipyretics, diuretics), and cardiovascular support (e.g., intubation and mechanical ventilation)
- **Complications**: hepatic and renal dysfunction
- **Prognosis**: highly variable, ranging from spontaneous resolution to fatal outcomes
- **Prevention**: limited data suggest that G-CSF avoidance and use of prophylactic corticosteroids can decrease ES incidence [15]

Other

- **Graft failure**
  - Primary graft failure: stem cell engraftment failure
  - Secondary graft failure: graft failure after stem cell engraftment
- **GvHD**
- **Immunosuppression-related complications**
  - Post-transplant infections
  - Post-transplant malignancy

The mortality rate of allogenous stem cell transplantation is declining but is still as high as 50%.

When considering a regimen to prevent GvHD following allogenous HSCT for hematological malignancies, the risk of GvHD should always be weighed against the loss of a beneficial graft-vs-tumor effect and the risk of graft failure due to drug toxicity.

Complications

Complications after transplantation can be divided into graft-related (graft rejection, graft-versus-host disease) and immunosuppression-related complications (infection, malignancy).

We list the most important complications. The selection is not exhaustive.

Graft-related complications

Graft rejection

- **Definition**: graft failure as a result of damage to the graft by the host's immune response

Types of graft rejection			
	Hyperacute rejection	**Acute rejection**	**Chronic rejection**
Frequency	< 1% of post-transplant organ dysfunction	~ 50% of post-transplantorgan dysfunction	~ 50% of post-transplant organ dysfunction
Onset	**< 48 hours** after transplantation(usually within minutes to hours)	**< 6 months** after transplantation (usually within weeks to months)	**> 6 months** after transplantation (usually after a few years)
Risk factors	**ABO incompatibility** HLA incompatibility	**HLA incompatibility** Inadequate immunosuppression or noncompliance	**Previous episode of acute rejection** Poor HLA match Prolonged cold ischemia time Hyperlipidemia Inadequate immunosuppression or noncompliance

Types of graft rejection			
	Hyperacute rejection	**Acute rejection**	**Chronic rejection**
Pathophysiology	**Humoral rejection** (**type II hypersensitivity reaction**): preformed cytotoxic antibodies of the recipient against class I HLAmolecules or blood group antigensof the donor → activation of the **complement** system and adhesion to cells → **thrombosis** of vessels →graft **ischemia**	Allorecognition →T-lymphocyte induced cell-mediated and/or humoral immunity **Acute cellular rejection**(**type IV hypersensitivity reaction**) Donor MHC class IIantigens react with host CD4+ T cells, which then differentiate into Th1 helper T cells →cytokine (INF-γ) release →macrophagerecruitment →parenchymal and endothelialinflammation Donor MHC class Iantigens react with host CD8+ T cells →direct cytotoxic cell damage **Acute humoral rejection**(**type II hypersensitivity reaction**): host antibodies, formed**before** or **after** transplantation, react against donor HLAantigens	Involves cellular as well as humoral immune responses, making it a combination of hypersensitivity type II and IV reaction Donor MHC class IIantigens react with host CD4+ T cells →differentiation into Th1 helper T cells →cytokine (INF-γ) release → macrophagerecruitment →parenchymal and endothelial inflammation
Clinical findings	Intraoperative assessment: swelling of the organ as soon as perfusion is restored	Pain in the graft region Graft edema Fever and deterioration of general condition In kidney transplants ↑ Blood pressure and kidney function lab values ↓ Urine output	Slow, progressive loss of organ function
Diagnosis	Biopsy: small vessel **thrombosis**→ischemia → graft **necrosis**	Screening test: serial organ function tests to look for a decline in organ function Biopsy (confirmatory test) Dense interstitiallymphocytic infiltrate with vasculitis Heterogenous mononuclear aggregates with or without antibodydeposition Positive C4d staining indicates humoralgraft rejection. [17] Negative C4d staining indicates cellular rejection. Liver transplants: graft eosinophilia [18]	Biopsy: predominantaly arterio sclerosis, but also: Interstitial fibrosis Obstruction of vessels Vascular smooth muscle proliferation Graft atrophy [19] Organ-specificmanifestations Glomerular sclerosis(kidneys) Accelerated coronary artery disease (heart) Vanishing bile duct syndrome (liver) Bronchiolitis obliterans (lung)

Types of graft rejection			
	Hyperacute rejection	**Acute rejection**	**Chronic rejection**
Prevention	Preoperative cross-matching and ABO grouping	Preoperative cross-matching and ABO grouping Preoperative HLAmatching (see "Histocompatibility.") Post-transplant immunosuppressive therapy	Irreversible process with no known prevention
Treatment	Graft removal	Change or increase dosage of **immunosuppressive therapy** Acute cellular rejection First-line: high-doseglucocorticoids Second-linelymphocytedepleting antibodies or OKT3 (muromonab or anti-T-cellantibody) Acute humoral rejection First-line options: Plasmapheresis IVIG Anti-CD20antibodies Lymphocytedepleting antibody Corticosteroidsmay be used as an adjunct.	Graft removal

Graft rejection manifests as a failure of the transplanted organ and is very difficult to distinguish from other post-transplant complications. A biopsy is required to confirm the diagnosis

Graft-versus-host disease (GvHD)

- **Definition**: damage to the host as a result of a systemic inflammatory reaction induced by **T lymphocytes** present in the graft
- **Etiology**: GvHD is associated with transplantation of lymphocyte-rich organ transplants
  - Transfusion of nonirradiated blood products
  - Liver transplantation
  - Allogenous **hematopoietic stem cell transplantation**; the inflammatory reaction triggered by grafts can be used therapeutically to target tumor cells, e.g., in leukemia (graft-versus-tumor-effect).
  - Small bowel transplantation

Types of GvHD		
	Acute GvHD	**Chronic GvHD**
Epidemiology	Incidence Without prophylaxis: 70–100% With prophylaxis: 9–50%	Incidence: ~ 40% of patients following allogeneic stem cell transplantation
Onset	< 100 days after transplantation	> 100 days after transplantation

Types of GvHD		
	Acute GvHD	**Chronic GvHD**
Pathophysiology	Donor **T lymphocytes** trigger a **type IV hypersensitivityreaction** in the host organs, leading to severe organ damage.	Mostly unknown
Clinical presentation	Pruritic or painful maculopapular rash Gastrointestinal upset Nausea, vomiting, diarrhea Cramping abdominal pain Hepatic dysfunction Jaundice Hepatosplenomegaly In rare cases: lagophthalmos, hemorrhagic conjunctivitis, conjunctival pseudomembrane formation	Sicca syndrome Chronic enteritis Bloody diarrhea Abdominal pain Weight loss Hepatic dysfunction: jaundice Bronchiolitis obliterans Chronic cough Wheezing Dyspnea Myasthenic symptoms Polymyositis Scleroderma-like and lichenoid skinchanges
Diagnostics	Anemia, thrombocytopenia, leukopenia ↑ ALP Confirmatory test: **biopsy** of skin, rectum, or liver shows endothelial damage and lymphocytic infiltration Skin: damaged epidermis and hair follicles Liver: segmental disruption of small bile ducts Intestines: disruption of crypts, mucosal ulceration	Spirometry: obstructive lung disease Confirmatory test: biopsy of the skin, oral cavity, liver, or lung
Prevention	Irradiated blood products (for immunocompromised individuals) **Antithymocyte globulin** **Cyclosporine** PLUS one of the following: Methotrexate Mycophenolate mofetil	
Treatment	Optimize GvHD prophylaxis (e.g., cyclosporine levels) < 50% skin involvement: topical steroids Involvement of the GI tract, liver, or > 50% of skin: systemic steroids and/or topical steroids Octreotide to control severe diarrhea	First-line: **corticosteroids** Second-line : cyclosporine and increased corticosteroid dose

The skin, intestines, and liver are the most commonly affected organs in GvHD.

Immunosuppression-related complications

Infection

Overview of post-transplant infections		
Early onset (< 1 month after transplantation)		Surgical site infections Other hospital-acquired infections (e.g., nosocomial urinary tract infection) Candidiasis (caused by non-albicans species) C. difficile
Late onset	1–6 months	HHV-6, HHV-7 HSV Aspergillosis

Overview of post-transplant infections

	6–12 months	Viral infections CMV HSV VZV EBV Adenovirus BK polyomavirus Hepatitis B and hepatitis C viruses Pneumocystis carinii pneumonia Listeriosis Nocardiosis
	> 12 months	Viral infections CMV HSV VZV EBV leading to post-transplant lymphoproliferative disease JC polyomavirus HPV Tuberculosis Invasive fungal infections Aspergillosis Coccidioidomycosis Histoplasmosis Cryptococcal meningitis Blastomycosis

Post-transplant malignancy

- **Incidence**: 0.4% following organ transplantation
- **Common malignancies**
  - **Non-Hodgkin lymphoma**
  - Nonmelanoma skin cancer (especially squamous cell carcinoma)
  - Kaposi sarcoma
  - Hepatocellular carcinoma
  - Anal or vulval carcinoma

Prevention of post-transplant infections

Pretransplant measures

- Screen both the donor and the recipient for infections and treat any existing infections in the recipient.
  - All pretransplant patients
    - Serological screening for CMV, HSV, VZV, EBV, HIV, HBV, HC, *T. pallidum*
    - Tuberculin skin test or interferon-gamma release assay
    - Urinalysis and urine culture
    - Chest x-ray
    - Patients from endemic regions: serological tests for *S. stercoralis*, *Leishmania*, *Coccidioides immitis*, *T. cruzi*
  - Heart transplant recipients: *T. gondii* serology
  - Lung transplant recipients
    - Sputum stains and culture
    - Patients from endemic regions: *H. capsulatum* serology
  - In kidney transplant recipients from endemic regions: urine microscopy for *Schistosoma*
- Ensure that vaccinations are up-to-date.
- Perioperative antibiotic prophylaxis

Post-transplant measures [19]

- **Monitoring**
  - CMV viral loads in blood monthly for a minimum of 12 months

- EBV viral loads in blood monthly for a minimum of 12 months
- In kidney transplant recipients: BK virus viral loads monthly for 6 months, then at 9 and 12 months

- **Universal prophylaxis**
  - PCP prophylaxis with trimethoprim-sulfamethoxazole for a minimum of 6–12 months
  - CMV prophylaxis with ganciclovir or valganciclovir for 12–14 weeks
- **Specific situations**
  - Recipients seronegative for *T. gondii* who receive a heart transplant from a seropositive individual: pyrimethamine with folinic acid for 6 months
  - Hematopoietic stem cell transplantation
    - Acyclovir for prophylaxis against HSV and VZV
    - 12 months post-transplantation: tetanus, diphtheria, *H. influenzae*, polio, and pneumococcalpneumonia vaccination
    - 24 months post-transplantation: MMR, VZV, and possibly pertussis vaccination

Because the symptoms of CMV infections can appear similar to those of transplant rejection, differentiating between conditions can be difficult.

Acute and chronic graft-versus-host disease (GVHD) are multisystem disorders that are common complications of allogeneic hematopoietic cell transplant (HCT). GVHD occurs when immune cells transplanted from a non-identical donor (the graft) recognize the transplant recipient (the host) as foreign, thereby initiating an immune reaction that causes disease in the transplant recipient.

Clinical manifestations of acute GVHD include a classic maculopapular rash; persistent nausea and/or emesis; abdominal cramps with diarrhea; and a rising serum bilirubin concentration. In contrast, patients with chronic GVHD commonly demonstrate skin involvement resembling lichen planus or the cutaneous manifestations of scleroderma; dry oral mucosa with ulcerations and sclerosis of the gastrointestinal tract; and a rising serum bilirubin concentration.

Definition

GVHD has been classically divided into acute and chronic variants based on the time of onset using a cutoff of 100 days. However, this conventional division has been challenged by the recognition that signs of acute and chronic GVHD may occur outside of these designated periods. This observation has led to the increased use of clinical findings, rather than a set time period, to differentiate between acute and chronic GVHD. The widely accepted National Institutes of Health (NIH) consensus criteria used to diagnose GVHD classify manifestations of GVHD as "diagnostic" or "distinctive" of chronic GVHD or as common to both acute and chronic GVHD. Patients with GVHD are subclassified based on the timing of presentation and the features present:

- **Classic acute GVHD** – Cases present within 100 days of hematopoietic cell transplant (HCT) and display features of acute GVHD. Diagnostic and distinctive features of chronic GVHD are absent.
- **Persistent, recurrent, late onset acute GVHD** – Cases present greater than 100 days post-HCT with features of acute GVHD. Diagnostic and distinctive features of chronic GVHD are absent.
- **Classic chronic GVHD** – Cases may present at any time post-HCT. Diagnostic and distinctive features of chronic GVHD are present. There are no features of acute GVHD.
- **Overlap syndrome** – Cases may present at any time post-HCT with features of both chronic GVHD and acute GVHD. On occasion, this is colloquially referred to as "acute on chronic" GVHD.

Epidemiology

While risk factors for the development of acute GVHD have been identified, reliable estimates of GVHD incidence in various cohorts are not available due to variability in the identification, measurement, and documentation of acute GVHD.

Clinically significant acute GVHD occurs in patients who receive an allogeneic hematopoietic cell transplant (HCT) despite intensive prophylaxis with immunosuppressive agents. The exact incidence of acute GVHD after allogeneic HCT is unknown. Reported incidence rates range from 9 to 50 percent in

patients who receive an allogeneic HCT from a genotypically human leukocyte antigen (HLA)-identical sibling. Acute GVHD is also common in matched unrelated donors and in haploidentical related donors.

Risk factors

Numerous studies have identified the following risk factors for the development of acute GVHD:

- Degree of HLA disparity (HLA mismatch or unrelated donor)
- Donor and recipient sex disparity (female donor to male recipient)
- Intensity of the transplant conditioning regimen
- Acute GVHD prophylactic regimen used
- Source of graft (peripheral blood or bone marrow greater than umbilical cord blood)

Less well-established risk factors include increasing age of the host, the cytomegalovirus (CMV) status of the donor and host, donor Epstein-Barr virus (EBV) seropositivity, peripheral blood stem cell versus bone marrow transplantation, the presence of a sterile environment (including gut decontamination), and particular HLA haplotype. However, risk factors for acute GVHD differ by underlying disease, requiring distinct risk models for each condition.

What immunosuppressants do transplant patients take?

The most commonly used immunosuppressants include:

- Prednisone.
- Tacrolimus (Prograf)
- Cyclosporine (Neoral)
- Mycophenolate Mofetil (CellCept)
- Imuran (Azathioprine)
- Rapamune (Rapamycin, Sirolimus)

Immunosuppressive strategies in lung transplantation

Since the first human lung transplant in 1963, nearly 65,000 lung transplantations have been reported worldwide. Unfortunately, median survival remains the lowest of the solid organ transplants at 6.5 years. The main challenges to long-term survival are acute and chronic rejection, infectious complications, drug toxicities, and malignancies. Although conventional maintenance immunosuppression therapy consisting of a calcineurin inhibitor (CNI), anti-metabolite, and corticosteroids remains the dominant drug regimen for lung transplantation, immunosuppressive strategies continue to evolve to address these challenges. We will review the current available immunosuppressive medications, the data behind their use, and some of the adjunctive therapies and clinical tools that are being developed to improve long-term outcomes. In this review, the term chronic lung allograft dysfunction (CLAD) as described by a consensus definition from the pulmonary council of the International Society of Heart and Lung Transplantation (ISHLT) including its subtypes, bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS), has been used in place of the historical term BOS unless specified by the study.

Induction immunosuppression

nduction therapy utilizes intensive immunosuppression in the perioperative and/or the immediate post-operative period to reduce the risk of T-cell mediated early rejection. Induction agents primarily target T-cells and cause depletion and/or interruption of their activation and proliferation. According to the most recent International Society for Heart and Lung Transplantation (ISHLT) registry data, the proportion of patients receiving induction immunosuppression has increased over the last decade with 76% of adult lung transplant recipients receiving any induction agent in 2020. The three commonly used induction agents are basiliximab, anti-thymocyte globulin (ATG) and alemtuzumab. Two other

induction agents that had previously been used are now no longer available due to manufacturers voluntary withdrawal (daclizumab and muromonab-CD3).

Maintenance immunosuppression

The purpose of maintenance immunosuppression after lung transplantation is to prevent acute and chronic rejection. This is delicately balanced by the need to prevent adverse side effects, infectious complications, and the risk of malignancy from the immunosuppressives. Conventional maintenance immunosuppression has been triple drug therapy and most commonly includes a CNI (tacrolimus or cyclosporine), an antiproliferative agent (mycophenolate or azathioprine), and corticosteroids. According to the 2018 International Society for Heart and Lung Transplantation (ISHLT) registry database report, the most commonly used combination at 1-year follow-up is one including tacrolimus, mycophenolate, and corticosteroids. The use of cyclosporine and azathioprine has seen a steady decline in the last decade while the introduction of mammalian target of rapamycin (mTOR) inhibitors and a co-simulation blocker have emerged to aid in maintenance immunosuppression for those who do not tolerate a conventional regimen.

Induction therapy after kidney transplantation is intensive immunosuppression in the initial days after transplant when the immune system of the recipient has the first contact with donor antigens. Initial intensive immunosuppression may be required to prevent acute rejection and graft loss, and subsequent immunosuppression may be decreased to minimize adverse events associated with immunosuppressive drugs. Induction agents include lymphocyte-depleting antibodies such as rabbit antithymocyte globulin, alemtuzumab, muromonab-CD3, rituximab, and bortezomib; lymphocyte-nondepleting antibodies such as interleukin 2 receptor antibodies; and other discontinued or investigational agents such as efalizumab and alefacept. Induction therapy may be adjusted for special situations such as living-donor kidney transplant, pediatric transplant, hepatitis C virus-seropositive recipients, recipients who require desensitization, patients who are at risk for developing delayed graft function, and old donors.