THE IMMUNE SYSTEM:

* + - * It’s designed to protect the host from harmful foreign molecules.
      * This system can result into serious problems.
      * Allograft introduction can elicit a damaging immune response.
      * The immune system includes two major arms:

1. Cell-mediated immunity
2. Humoral (antibody-mediated) immunity

CYTOKINES:

* + - They are soluble, antigen-nonspecific, signaling proteins that bind to cell surface receptors on a variety of cells.
    - They include interleukins, interferon (INF), tumor necrosis factor (TNF), colony stimulating factor (CSF), and transforming growth factors (TGFs).
    - They activate natural killer cells, macrophages, and cytotoxic T cells.

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| *IL-2 stimulates the proliferation of antigen-primed (helper) T cells that produce more IL-2, IFN, and TNF.* |

* CELL-MEDIATED IMMUNITY:
* Th1 cells produce more IL-2, TNF-, and INF-
* Cell-mediated immunity activates:
  + - 1. Natural killer cells (kill tumors and virus-infected cells)
      2. Cytotoxic T cells (kill tumors and virus-infected cells)
      3. Macrophages (kill bacteria)

HUMORAL IMMUNITY:

* + - Th2 cells produce IL-4 and IL-5, which in turn cause:

1. B cell proliferation
2. B cell differentiation into memory cells
3. B cell differentiation into antibody-secreting cells (plasma cells)

MUTUAL REGULATION OF T HELPER LYMPHOCYTES:

* + - Th2 cells produce IL-10 which inhibits Th1 cytokine production.
    - Th1 cells produce INF- which inhibits Th2 proliferation.

Immunosuppressant Drugs

INHIBITORS OF CYTOKINE (IL-2) PRODUCTION OR ACTION:

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| *Calcineurin Inhibitors* | *Sirolimus (Rapamycin)* |
| Cyclosporine |
| Tacrolimus (FK 506) |

INHIBITORS OF CYTOKINE GENE EXPRESSION:

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| *Corticosteroids* |

CYTOTOXIC DRUGS:

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| *Cyclophosphamide – Methotrexate* |

INHIBITORS OF PURINE OR PYRIMIDINE SYNTHESIS (ANTIMETABOLITES):

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| *Azathioprine – Myclophenolate Mofetil – Leflunomide* |

ANTIBODIES THAT BLOCK T CELL SURFACE MOLECULES INVOLVED IN SIGNALING IMMUNOGLOBULINS:

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| *Antilymphocyte Globulins (ALG) – Antithymoctye Globulins (ATG) – Rho (D) Immunoglobulin – Basiliximab – Daclizumab – Muromobab-CD3 (OKT 3)* |

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| *Interferons* |

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| *Thalidomide* |

Inhibitors of Cytokine (IL-2) Production

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| *Cyclosporine – Tacrolimus (FK 506)* |

CYCLOSPORINE:

* + It’s a fungal polypeptide composed of 11 amino acids.
* Mechanism of Action:
  + - 1. It decreases the proliferation and differentiation of T cells primarily by inhibiting IL-2.
      2. It binds to cyclophilin (immunophilin) intracellular protein receptor.
      3. Cyclosporine-immunophilin complex binds to and inhibits calcineurin, a phosphatase necessary for the dephosphorylation of transcription factor required for interleukin synthesis.
      4. The transcription factor, nuclear factor of activated T cells (NFATc), promotes the synthesis of interleukins (IL-2).
* Pharmacokinetics:
  + - 1. It can be given orally or as an intravenous infusion.
      2. It’s given orally (25 or 100 mg) as soft gelatin capsules, or as microemulsion which has higher bioavailability.
      3. When taken orally, it’s slowly and incompletely absorbed.
      4. Peak levels are reached after 1-4 hours.
      5. Elimination half-life is 24 hours.
      6. Oral absorption is delayed by fatty meals (gelatin capsule formulation NOT microemulsion formulation).
      7. It’s given as an intravenous (50 mg/ml) solution made up in an ethanol-polyxyethylated castor oil mixture.
      8. 50-60% of cyclosporine accumulates in blood (erythrocytes, lymphocytes).
      9. It’s metabolized by P450 system (CYP 3A4).
      10. It’s excreted mainly through bile into feces; 6% is excreted in urine.
* Therapeutic Uses:

1. Organ transplantation (kidney, liver, heart) either alone or in combination with other immunosuppressants, such corticosteroids.
2. Graft-versus-host disease in bone marrow transplantation (lymphocyte response in the graft to the host antigen)
3. Autoimmune disorders (endogenous uveitis, rheumatoid arthritis, active Crohn’s disease, psoriasis, nephrotic syndrome, severe corticosteroid-dependent asthma, and early type 1 diabetes (low dose..7.5 mg/kg/d).

* Adverse Effects:
  + - 1. Nephrotoxicity (75%), increased by NSAIDs and aminoglycosides.
      2. Liver dysfunction
      3. Hypertension, hyperkalemia (K-sparing diuretics shouldn’t be used)
      4. Viral infections (herpes, cytomegalovirus)
      5. Lymphoma (predisposes recipient to cancer)
      6. Hirsutism
      7. Neurotoxicity (tremors, seizures, hallucinations)
      8. Gum hyperplasia
      9. Teratogenicity
      10. Anaphylaxis after IV
* Drug Interactions:

1. Clearance of cyclosporine is enhanced by the co-administration of microsomal inducers (phenytoin, phenobarbitone, and rifampin), which may lead to the rejection of transplant.
2. Clearance of cyclosporine is decreased by the co-administration of microsomal inhibitors (gentamycin, amphotericin B, erythromycin, ketoconazole, or grape fruit juice), which may lead to cyclosporine toxicity.
3. Monitoring of therapeutic drug is essential during cyclosporine therapy.

TACROLIMUS (FK 506)

* + - It’s a fungal macrolide antibiotic.
    - It’s not related chemically to cyclosporine.
    - It’s more potent than cyclosporine.
    - Both drugs have the similar mechanisms of action.
    - The internal receptor for tacrolimus is immunophilin-FK binding protein (FKBP).
    - Tacrolimus-FKBP inhibits calcineurin.
* Pharmacokinetics:

1. It can be given orally, intravenously, or topically (ointment).
2. Oral absorption is variable and incomplete because it’s reduced by fat and carbohydrate meals.
3. Its half-life after IV infusion is 9-12 hours.
4. It highly binds to serum proteins; it’s highly concentrated in erythrocytes.
5. It’s metabolized by P450 in the liver.
6. It’s excreted mainly in bile and minimally in urine.

* Therapeutic Uses:

1. Similar to those of cyclosporine
2. Prevention of rejection of liver and kidney transplants (with glucocorticoids)
3. Atopic dermatitis and psoriasis (topically)

* Toxic Effects:

1. Nephrotoxicity (more than cyclosporine)
2. Neurotoxicity (more than cyclosporine)
3. GIT disturbances
4. Metabolic disturbances (hyperglycemia)
5. Hyperkalemia
6. Anaphylaxis

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| *It neither causes hisutism nor gum hyperplasia.* |

* Differences between Cyclosporine and Tacrolimus:

1. TAC is 10-100 times more potent than CsA in inhibiting immune responses.
2. TAC has decreased episodes of rejection.
3. TAC is combined with lower doses of glucocorticoids.
4. It has more potent nephrotoxic and neurotoxic effects than CsA.

Inhibitors of Cytokine (IL-2) Action

SIROLIMUS (RAPAMYCIN):

* + It’s derived from a fungal origin.
  + It binds to FKBP, and the formed complex binds to mammalian target of rapamycin (mTOR).
  + mTOR is a serine-threonine kinase essential for cell cycle progression and DNA repair.
  + Sirolimus blocks the progression of T cells from G1 S phase of the cell cycle (antiproliferative action).
  + SRL does NOT block the IL-2 production, but rather it blocks the cellular response to IL-2.
  + SRL is a potent inhibitor of B cell proliferation and immunoglobulin production.
* Pharmacokinetics:

1. It’s given orally and topically; it’s reduced by fatty meals.
2. It highly binds to plasma proteins.
3. It’s metabolized by CYP3A4 in the liver.
4. It’s excreted in bile.

* Pharmacodynamics:

1. Immunosuppressive effects
2. Antiproliferative action
3. Equipotent to cyclosporine

* Uses:

1. Preservation of solid organ allografts alone or combined with CsA, TAC, or corticosteroids
2. Hematopoietic stem cell transplant recipients
3. Topically with cyclosporine in cases of uveoretinitis
4. Renal transplant alone or in combination with TAC, CsA, steroids, or mycophenolate.
5. Heart allografts
6. In halting graft vascular disease
7. Synergistic action with CsA

* Toxic Effects:

1. Hyperlipidemia (cholesterol, triglycerides)
2. Thromobocytopenia
3. Hepatotoxicity
4. Hypertension
5. GIT dysfunction
6. Leukopenia

Inhibitors of Cytokine Gene Expression

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| *Corticosteroids: Prednisone – Prednisolone – Methylprednisolone – Dexamethasone* |

* They have both anti-inflammatory and immunosuppressant effects.
* Mechanism of action:

1. They inhibit the synthesis and the release of inflammatory mediators by binding to glucocorticoid receptors, and the formed complex interacts with DNA to inhibit the gene transcription of inflammatory genes.
2. They decrease the production of cytokines (IL-1, IL-2, INF, TNF, and adhesion factors).
3. They decrease the production of prostanoids due to decreased expression of cyclo-oxygenase 2 (COX2).
4. They decrease the generation of immunoglobulins, nitric oxide, and histamine.
5. They inhibit antigen processing by macrophages.
6. They suppress T helper function.
7. They decrease T lymphocyte proliferation.
8. They stabilize lysosomal membranes.

* Pharmacokinetics:

1. They can be given orally or parenterally.
2. They enter cells by diffusion.
3. They are metabolized by the liver.

* Pharmacodynamics:

1. Suppression of response to infection
2. Suppression of endogenous glucocorticoid synthesis
3. Metabolic effects

* Indications:

1. First-line therapy Solid organ allografts (prednisone & methylprednisolone)
2. First-line therapy Hematopoietic stem cell transplantation
3. Autoimmune diseases, such as refractory rheumatoid arthritis, systemic lupus erythematosis, and asthma (prednisone, prednisolone)
4. Oral prednisone is employed for the prophylaxis of rejection
5. High doses of IV methylprednisone are used as first-line therapy for the treatment of rejection
6. Acute or chronic rejection of solid organ allograft

* Adverse Effect:

1. Osteoporosis
2. Hypercholesterolemia
3. Hyperglycemia
4. Hypertension
5. Cataract
6. Infection
7. Adrenal suppression

Cytotoxic Drugs

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| *Cyclophosphamide – Methotrexate* |

CYCLOPHOSPHAMIDE:

* It’s an alkylating agent. to DNA; it’s an anticancer drug as well
* It’s an inactive drug; it’s activated into. phosphamide
* It cab be given orally and intravenously.
* It destroys proliferating lymphoid cells.
* It has both anticancer and immunosuppressant actions.
* It’s effective in autoimmune diseases, such as SLE, RA, and autoimmune hemolytic anemia.
* Side Effects:

1. Hemorrhagic cystitis
2. Bone marrow suppression
3. Alopecia
4. GI upset
5. Sterility (testicular atrophy & amenorrhea)
6. Cardiac toxicity

METHOTREXATE:

* + - It’s a folic acid antagonist; it acts by inhibiting dihydrofolate reductase, and thus interfering with the de-novo synthesis of purines.
    - It can be given orally or parenterally. it’s excreted in urine
    - It inhibits DNA, RNA, and protein synthesis.
    - It interferes with T-cell replication.
    - It can be used in case of rheumatoid arthritis, psoriasis, Crohn’s disease and graft-versus-host disease.
* Adverse Effects:

1. Bone marrow suppression
2. Pulmonary fibrosis
3. Renal & hepatic disorders
4. Alopecia
5. Nausea, vomiting, diarrhea

Inhibitors of Pyrimidine or Purine Synthesis (Antimetabolites)

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| *Azathioprine – Mycophenolate Mofetil - Leflunomide* |

AZATHIOPRINE:

* + It’s a derivative of mercaptopurine.
  + It’s a prodrug.
  + It inhibits the de novo synthesis of purines required for lymphocyte proliferation.
  + It’s cleaved to 6-mercaptopurine then to 6-mercaptopurine nucleotide, and thioinosinic acid (nucleotide analogue).
  + It prevents clonal expansion of both B & T lymphocytes.
* Pharmacokinetics:

1. It can be given orally or intravenously.
2. It’s widely distributed, but it does NOT cross the blood brain barrier.
3. It’s metabolized in the liver to 6-mercaptopurine or to thiouric acid by the action of xanthine oxidase.
4. It’s excreted primarily in urine

* Drug Interactions:

1. Co-administration of allopurinol with azathioprine may lead to increased toxicity due to inhibition of xanthine oxidase by allopurinol.

* Clinical Uses:

1. Acute glomerulonephritis, SLE
2. Rheumatoid arthritis
3. Crohn’s disease

* Adverse Effects:

1. Bone marrow depression (leukopenia, thrombocytopenia)
2. Gastrointestinal toxicity
3. Hepatotoxicity
4. Increased risk of infections
5. Mutagenicity and possible carcinogenicity

MYCOPHENOLATE MOFETIL:

* + - It’s a semisynthetic derivative of mycophenolic acid from a fungal source.
* Mechanism of Action:

1. It inhibits the de novo synthesis of purines (guanosine phosphate).
2. Mycophenolate (prodrug) is hydrolysed to mycophenolic acid which is a potent inhibitor of inosine monophosphate dehydrogenase (IMP), crucial for purine synthesis. That would lead to the deprivation of proliferating B & T cells of their nucleic acids.

* Pharmacokinetics:

1. It can be given orally, intravenously, or intramuscularly.
2. It’s rapidly and completely absorbed after oral administration.
3. It undergoes first-pass metabolism to give the active moiety, mycophenolic acid (MPA).
4. MPA is extensively bound to plasma proteins.
5. It’s metabolized in the liver by glucuronidation.
6. It’s excreted in urine as glucuronide conjugate (cumulative effect).
7. Dose is 2-3 g/d

* Clinical Uses:

1. Alternative to CsA or TAC (combined with prednisone)
2. Solid organ transplants for refractory rejection
3. Steroid-refractory hematopoietic stem cell transplant patients
4. Lupus nephritis, rheumatoid arthritis, and dermatological disorders

* Adverse Effects:

1. GIT toxicity (nausea, vomiting, loss of appetite, GIT hemorrhage, pancreatitis)
2. CNS toxicity (muscle weakness, numbness of limbs and tongue)
3. Leukopenia, neutropenia
4. Mutagenic and carcinogenic effects
5. Lymphoma

* Drug Interactions:

1. Antacids with Al or Mg and cholestyramine decrease its intestinal absorption.
2. It’s contraindicated during pregnancy.

LEFLUNOMIDE:

* + - It’s a prodrug.
    - It’s a pyrimidine synthesis inhibitor (dihydro-orotate dehydrogenase)
    - Its active metabolite enters the enterohepatic circulation.
    - It’s orally active.
    - It has a long duration of action (weeks).
    - It’s approved only for rheumatoid arthritis.
* Toxic Effects:

1. Elevation of liver enzymes
2. Renal impairment
3. Teratogenicity
4. Cardiovascular effects (tachycardia)

Antibodies

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| *Antilymphocyte Globulin (ALG) – Antithymocyte Globulin (ATG) – Rho Immunoglobulin – Basiliximab – Daclizumab - Infliximab* |

ANTIBODY PREPARATION:

* Antibodies are prepared by immunization of either horses or rabbits with human lymphoid cells producing mixtures of polyclonal antibodies directed against a number of lymphocyte antigens (variable, less specific).
* By hybridoma technology producing antigen-specific, monoclonal antibodies (homogenous, specific)
* Hybridomas are produced by fusing mouse antibody-producing cells with immortal, malignant plasma cells.
* Recombinant DNA technology can be used to replace part of the mouse gene sequence with human genetic material.
* Humanized antibodies contain ZU or XI in their names.

ANTILYMPHOCYTE GLOBULIN (ALG) & ANTITHYMOCYTE GLOBULIN (ATG):

* + - They are polyclonal antibodies obtained from the plasma or serum of horses hyperimmunized with human lymphocytes.
    - They bind to the surface of circulating T lymphocytes. Then the antibody-bound cells are phagocytosed in the liver and spleen leading to lymphopenia and impaired T-cell response and cellular immunity.
* Pharmacokinetics:
  + - 1. They can be given intramuscularly or as slow IV infusion.
      2. Their half-life is 3-9 days.
* Clinical Uses:

1. Combined with cyclosporine for bone marrow transplantation
2. Treatment of initial allograft rejection
3. Steroid-resistant rejection

* Adverse Effects:

1. Antigenicity (antibodies are formed against ATG and ALG by B-cell mediated immunity)
2. Leukopenia & thrombocytopenia
3. Risk of viral infection and malignancy
4. Anaphylactic and serum sickness reactions (fever, chills, flu-like syndrome)

RHO (D) IMMUNOGLOBULIN:

* + - Rho (D) is a concentrated solution of human IgG to globulin containing higher titer antibodies against Rho (D) antigen of red cells.
    - It’s given to Rh-negative mothers within 72 hours after delivery of an Rh-positive baby (2 ml, IM) to prevent hemolytic diseases of the next Rh-positive babies.
* Adverse Effects:

1. Local pain
2. Fever

MUROMONAB-CD3 (OKT 3):

* + - It’s a murine monoclonal antibody.
    - It’s directed against glycoprotein CD3 antigen of human T cells.
    - It’s prepared by hybridoma technology.
    - It’s given intravenously.
    - It’s metabolized and excreted in bile.
    - It’s used for the treatment of acute rejection of renal allografts and steroid-resistant acute allografts.
    - It’s used to deplete T cells from the donor’s bone marrow before transplantation.
* Mechanism of Action:

The drug binds to CD3 proteins (antigen recognition sites) leading to transient activation and cytokine release followed by disruption of T-cell function, depletion, and decreased immune response.

* Adverse Effects:

1. Anaphylactic reactions
2. Fever
3. CNS effects(seizures)
4. Infection
5. Cytokine release syndrome (Flu-like illness to shock-like reaction)

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| *Prednisolone & diphenhydramine are given to reduce cytokine release syndrome.* |

MONOCLONAL ANTIBODIES: BASILIXIMAB & DACLIZUMAB (IL-2 ANTAGONISTS):

* + Basiliximab is a chimeric human-mouse IgG (25% murine, 75% human protein).
  + Daclizumab is humanized IgG (90% human protein).
  + Mechanism of Action:

1. They act by binding to CD25 (alpha-subunit chain of IL-2 receptor on activated lymphocytes and interfere with T cell proliferation.
2. They are IL-2 receptor antagonists.
3. They block IL-2-stimulated T cell replication and T cell response system.
4. Basiliximab is more potent that daclizumab.
   * They act by binding to CD25 (alpha-subunit chain of IL-2 receptor on activated lymphocytes and interfere with T cell proliferation.
   * They are obtained by replacing murine amino acid sequence with human ones.
   * They have less antigenicity and longer half lives than murine antibodies.
   * They are given intravenously.
   * The half-life of basiliximab is 9 days; the half-life of daclizumab is 20 days.
   * They are well tolerated.
   * They are given with CsA and corticosteroids for prophylaxis of acute rejection in renal transplantation.
     + INFLIXIMAB:
       - It’s a chimeric human-mouse IgG.
       - It’s directed against TNF-.
       - It’s approved for the treatment of ulcerative colitis, Crohn’s disease, and rheumatoid arthritis.
         * OMALIZUMAB:

It’s a humanized monoclonal IgE.

It’s directed against Fc receptors on mast cells and basophils.

It’s approved for the treatment of asthma in steroid-refractory patients.

Interferons

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| *Interferon  - Interferon  - Interferon * |

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| ***TYPE I IFNs (IFN-, )*** | ***TYPE II IFNs (IFN-)*** |
| Acid-stable proteins | Acid-labile |
| Act on some target cell receptors | Acts on separate target cell receptors |
| Induced by viral infections | Produced by activated T cells |
| Leukocytes produce IFN- |
| Fibroblasts & endothelial cells produce IFN- |

* They are harvested from leukocytes and prepared by recombinant DNA cloning technology.
* They have both antiproliferative and antiviral actions.
* They modulate the function of immune cells.

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| ***IFN-*** | ***IFN-, *** |
| Immune enhancing | Effective in inhibiting cellular proliferation |
| Increased antigen presentation with macrophages and natural killer cells | More effective than IFN- in this regard |
| Cytotoxic T cell activation |

* Clinical Uses:

1. Treatment of certain infections (hepatitis) as hepatitis C (IFN-)
2. Multiple sclerosis (IFN-) to reduce the rate of exacerbation
3. Treatment of autoimmune diseases (rheumatoid arthritis)
4. Treatment of certain forms of cancer (melanoma, renal cell carcinoma)
5. Fever, chills

Thalidomide

* + It’s a sedative, drug-teratogenic-X.
  + It has immunomodulatory actions.
  + Its mechanism of immunomodulation is unknown.
  + It’s used for the treatment of erythema nodosum leprosum.
  + It’s used for the management of skin manifestations of lupus erythematosus.
  + It can be given orally.
  + It inhibits TNF-
  + It reduces phagocytosis by neutrophils.
  + It increases IL-10 production.
  + Clinical Uses:

1. Myeloma
2. Rheumatoid arthritis
3. Graft versus host disease
4. Leprosy reactions
5. Treatment of skin manifestations of lupus erythematosis
   * It’s currently under trial as an anticancer drug (breast, ovary, prostate, and multiple myeloma). It may have an antiangiogenic action.

Clinical Uses of Immunosuppressive Agents

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| *Autoimmune Conditions* | |
| Acute Glomerulonephritis | Prednisone |
| Mercaptopurine |
| Cyclophosphamide |
| Autoimmune Hemolytic Anemia | Prednisone |
| Cyclophosphamide |
| Meracptopurine |
| Azathioprine, high dose of -globulin |
| *Organ Transplantation* | |
| Kidney & Heart Transplants | Cyclosporine |
| Azathioprine |
| Prednisone |
| ALG |
| Tacrolimus |
| Liver Transplant | Cyclosporine |
| Azathioprine |
| Tacrolimus |
| ALG |
| Prednisone |
| Bone Marrow Transplant | Cyclosporine |
| Cyclophosphamide |
| Prednisone |
| Methotrexate |
| ALG |
| Total Body Radiation |

