

UNIT - 4

Chemotherapy of urinary tract infection -

→ UTI is an infection in any part of the urinary system i.e. kidney, ureters, bladder & urethra

→ UTIs are of the following types.

1) Complicated UTI -

pyelonephritis, women, men
obstruction, immunosuppression, renal failure

2) Uncomplicated UTI -

Healthy non pregnant women

3) CA-UTI (Catheter Associated UTI) -

urinary catheters are indwelling
in a person's body with signs

4) Asymptomatic Bacteriuria -

① men - voided urine
② women - Two repeated empirical

③ A single catheterised

pre-disposing factor -

Patient population

premenopausal
women of any age

Risk factors

use of diaphragm particularly those
having spermicide

• Diabetes

• UTI during childhood or previous
history of UTI

• Sexual intercourse

mother or female relative having previous history of UTIs

Postmenopausal s
older adult women

previous history of UTI before commencement
of menopause

- Deficiency of estrogen
- mental or functional impairment
- urinary catheterization
- urinary incontinence

Signs & Symptoms -

- 1) Upper UTI
 - i) Nausea
 - ii) Vomiting
 - iii) High temp.
- iv) Diarrhoea
- v) moderate to severe pain in back
- 2) Lower UTI -
 - i) Pelvic area pain
 - ii) urethral syndrome
 - iii) Fever
 - iv) pressure in lower abdomen

Treatment of urinary tract infection -

1) Empiric Therapy -

- i) The most common microorganisms isolated from urine cultures of UTI infected patients include E. coli
- ii) Before commencement of the empiric treatment patient prior urine culture results must be considered

Severely ill patients (symptoms high fever, shaking chill, & hypotension) -

1 st line	Ceftriaxone	can be used safely in patients with mild penicillin allergy & cross react
2 nd line	Gentamicin	i) only in patients who need parenteral therapy & have severe IgE mediated ii) significant nephrotoxicity/ototoxicity (warning)

Cystitis* / lower UTI (Complicated or Uncomplicated)

1 st line	Nitrofurantoin	i) most effective agent against E. coli ii) CrCl < 30 ml/min (avoid) iii) + systemic signs of infection of pyelonephritis or prostatitis (avoid) iv) Does not cover Proteus
2 nd line	Cephalexin	Active against Proteus E. coli & Klebsiella
3 rd line	Fosfomycin	Active against Enterococcus E. coli & ESBL positive E. coli Recommended for fosfomycin susceptibility test

2) Targeted Therapy -

→ most narrow agent.

→ Fluoroquinolones Should be avoided for uncomplicated cystitis unless there are no other options.

Drugs	Doses	Renal Adjustment
Amoxicillin	• 500mg PO TID	• CrCl 10-50ml/min So 500mg BID • CrCl < 10 ml/min So 500mg once daily.
Ceftriaxone	• 1g IM/IV q24h	• None
Cefuroxime	• 100mg PO BID (cystitis) • 200mg PO BID (Pyelonephritis)	• CrCl < 30ml/min Administer once daily

Chemotherapy of Sexually Transmitted Diseases -

Introduction - Sexually Transmitted Diseases (STDs) are characterised by a variety of clinical syndromes and infections caused by pathogens that can be transmitted & acquired by sexual activities.

→ STDs can be caused by viruses, bacteria or even protozoans.

→ These organisms spread from one person to another through blood, semen, vaginal fluids or other bodily fluids.

Many sexually transmitted infection like syphilis, hepatitis B, HIV, chlamydia, gonorrhoea, herpes & HPV can also be transmitted non-sexually like from pregnant mother.

STDs/STIs	Causative organisms	Signs & Symptoms
Gonorrhoea	Neisseria gonorrhoea	Women - purulent vaginal discharge • pain or burning on passing urine • inflamed urethral opening Men - pain on passing urine • purulent urethral discharge • infection of the epididymis from the testis to the the vas deferens • urethral abscess or narrowing
Trichomoniasis	Trichomonas vaginalis	may produce few symptom in either sex Women often will have a frothy foul smelling greenish vaginal discharge Men - may have a urethral discharge

Chlamydia	Chlamydia trachomatis	women -	<ul style="list-style-type: none"> • produces few symptoms even with upper genital tract infection • purulent cervical discharge, frequently a beefy red cervix which is friable
Bacterial vaginosis	overgrowth of anaerobes	men -	most frequent cause of non-gonococcal urethritis
Candidiasis	Candida albicans		<ul style="list-style-type: none"> • not necessarily sexually transmitted • vaginal discharge with fishy odor
		women -	grayish in color curd like vaginal discharge which is color
Syphilis	Treponema pallidum		moderate to intense vaginal or vulval itching.
Genital herpes	Herpes simplex virus	men -	Itchy penile irritation
			occurs in 3 stages - primary & secondary & latent
			Primary Syphilis - Initially, painless ulcer occurs in women on the external genitalia (labia) in men on the penis in both sexes and ulcers & enlarged rubbery lymph
			<ul style="list-style-type: none"> • multiple painful vesicles later forming shallow ulcer which clear in 2 to 4 weeks & may be accompanied by watery vaginal discharge in women • Recurrent more than 50% of the time.

Syphilis

Syphilis is a sexually transmitted systemic

bacterial infection caused by *Treponema Pallidum*
This worm like spiral shaped organism called
spirochete

These spirochetes form ulcer known as a
chancre in the area they reside.

Etiology — spread disease through direct contact.

Signs & Symptoms —

- ① primary infection — ulcer inside —
- ② secondary infection —

After onset of the chancre the symptoms
start occur typically from 6 week. to 6 month
mucous patches in vagina or oral cavity
Alopecia

Generalised Lymphadenopathy

③ Tertiary infection — it can be defined as
symptomatic late Syphilis & Cardiovascular
syphilis.

④ Neurosyphilis —

- i) cognitive dysfunction
- ii) ophthalmic or auditory symptoms
- iii) cranial nerve palsies
- iv) meningitis

Treatment —

- i) Early Syphilis — primary, secondary, latent
Syphilis of duration < 1 year
i) Benzathine Pen. S — 2.4 million units IM once
- ii) Pen Allergy — patients allergic to pen should take
doxycycline 100mg b.i.d. for 10 days

2) Syphilis of duration > 1 year - ~~USA~~, late benign
i) Benzathine pen 6 - 2.4 million
ii) Pen allergy -

③ pregnant women - prior switching to alternative
medicine immediately
contraindication in pregnancy - Tetracycline, doxycycline

Gonorrhoea! —

- It is a sexual transmitted disease.

• First Neisser in 1879 discovered the bacterium
Neisseria gonorrhoeae gram negative diplococcal bacteria

- The word gonorrhoea has been derived from Greek
word flow of seed.

Etiology - It can also be accidentally transmitted
in children by other means like somite
The gonococcal bacterium has great affinity for the
columnar epithelium of the mucous membranes

In males It affects urethra Little's row penis
Tyson's perineal

Sign & Symptoms —

- i) males - redness & soreness
in genitals throat
- ii) Renal discharge iii) Bleeding from rectum
i) Painfull bowel movement
- iv) Burning with urination

Female - i)涩ed urination ii) Burning urination
 iii) A yellow green vaginal discharge
 iv) painfull sexual intercourse v) pain in sexual coldomine
 vi) Heavy bleeding with periods
 vii) painfull bowel movement (viii) bleeding from rectum

Treatment -

The CDC recommendations for treatment of gonorrhoea are summarised as under.

Infection	Treatment of choice	Therapeutic Alternatives to ceftriazone
1) Uncomplicated i) urethritis ii) cervicitis iii) proctitis iv) pharyngitis patient ≥ 8 years exclude pregnancy	250mg of ceftriazone i.m. single dose followed by 100mg of doxycycline twice a day for 7 days	2gm of spectinomycin i.m. single dose. for pharyngitis g tube of Sulphamethoxazole- trimethoprim SMZ/TMP for 5 days Follow-up the treatment with doxycycline erythromycin
2) For patient < 8 years & pregnant women	250mg of ceftriazone i.m. single dose followed by 500mg of erythromycin base twice times a day for 7 days	

Alternative Treatment -

- 1) Azithromycin :- Azithromycin single dose + cefixime 400mg orally as a single dose.
Used in intramuscular injection.
gt single dose + spectinomycin 2gm intramuscularly as a single dose
- 2) Ampicillin (Eskayillin, Ampicillin) -
- gt is a synthetic derivative of penicillin.
- gt is effective pen. - gt is help blood level high
- 3) Cotrimoxazole - gt is another addition to the treatment of gonorrhoea.
- The drug available form of tablet.
- 4) Amoxycillin - gt is a bactericidal drug.
- 5) First Tetracyclines - Effective against the organism
- 6) Erythromycin
- 7) Gentamicin

Herpes infection

- Herpes simplex is a viral infection caused by the Herpes simplex virus.
- gt is caused by 2 major antigenic types HSV-1 & HSV-2
- HSV-1 - primarily oral infection
- HSV-2 - causes genital infection.

Herpes virus	common name	clinical syndrome
HHV-1	Herpes simplex virus type-1 (HSV-1)	Fever blisters
HHV-2	Herpes simplex virus type-2 (HSV-2)	Genital herpes
HHV-3	Variella zoster virus	chickenpox, shingles
HHV-4	Epstein-Barr virus	mononucleosis lymphoma
HHV-5	Cytomegalovirus	Neonatal birth defect
HHV-6	Human herpes virus 6	Rosola infantum
HHV-	H, , , -7	Rosola infantum

Etiology -

Herpes simplex virus 1 (HSV-1) - causes oral herpes
 Herpes simplex virus (HSV-2) - causes genital herpes & oral herpes

Signs & Symptoms -

- i) Blisters of herpes, generally on lips, mouth, gums or genital
- ii) Fever iii) Fever blisters iv) Genital lesions starting
- v) Enlarged lymph nodes in the neck
- vi) HSV can also spread to the eye

Treatment -

It includes following drug -

- i) primary infection -

(a) Herpetic gingivostomatitis - Acyclovir 5-10 mg/kg body weight s.h.o.w.s
 for 7-10 days

b) Herpetic whitlow & kerato-conjunctivitis -
Treated with oral acyclovir 200 mg five
times a day for 7 to 10 days.

-!- Chemotherapy of malignancy -!-

Introduction -

Cancer is a disease characterised by abnormal & uncontrolled cell division attacking the surrounding tissues & organs & also the distant body parts by circulating with blood & lymph.

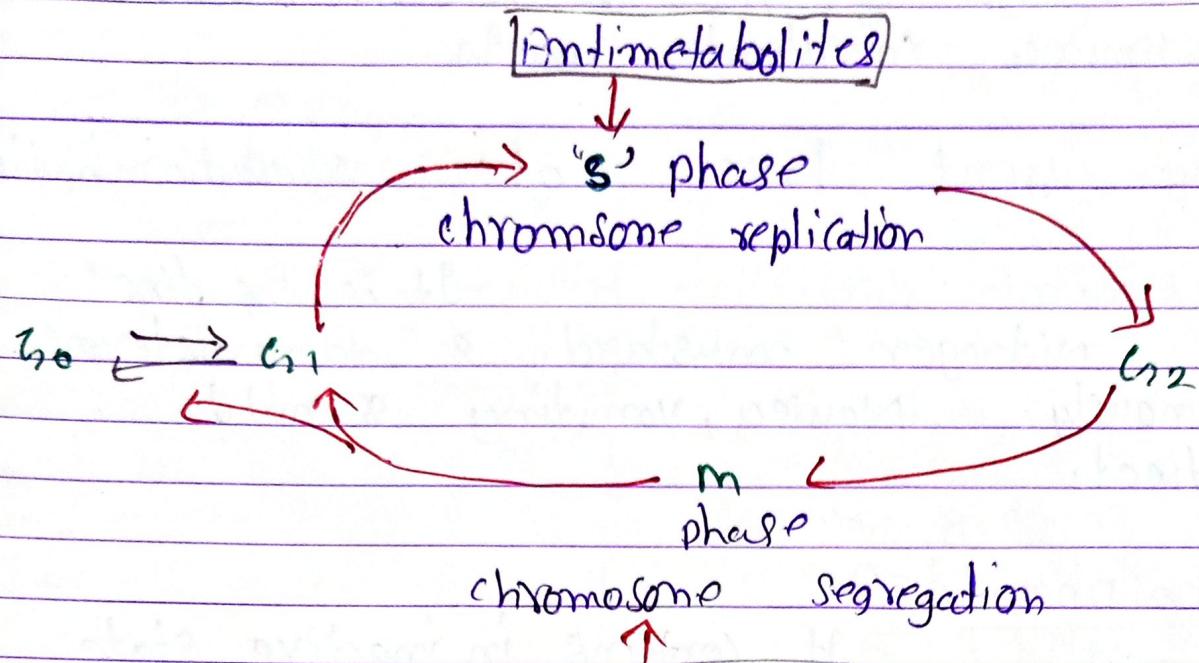
The main categories of cancer includes

- 1) Carcinoma - Cancer that begins in the skin or in tissues that line or cover including adenocarcinoma.
- 2) Sarcoma - Cancer that begins in bone, cartilage fat muscle, blood vessels
- 3) Leukaemia - Cancer that starts in blood forming tissue such as the bone marrow & causes large no. of abnormal blood cells.
- 4) Lymphoma & myeloma - Start cell of immune system.
- 5) Central Nervous System cancers - Start tissue of brain & spinal cord.

- Normal cell differs from the cancer cell in the following 4 characteristics -

- i) Uncontrolled
- ii) Metastasis
- iii) Loss of function

Cancer cell cycle & Different phases



Cell cycle & sites of Action Drugs

In the cancer cell the cell cycle control is disrupted by -

- 1) Abnormal growth factor function
- Abnormal growth CDK function
- Abnormal DNA synthesis

Anti cancer drug may be -

- 1) phase specific cell cycle active e.g. antimetabolites bleomycin, taxane & Vinca alkaloids.
- 2) Hormones & anti hormones
- 3) miscellaneous e.g. mab

Classification - M.C.

Alkylating Agents -

Alkylating agent produce highly

reactive carbonium ion intermediates which transfer alkyl groups to cellular macromolecules by forming covalent bonds.

- Alkylating agents have cytotoxic & radiomimetic

i) Mechlorethamine (Mustine HCl) - It is the first nitrogen mustard. & administered intravenously. Nausea, vomiting & mild side effect.

Cyclophosphamide -

- It contains in inactive state but after getting metabolised in the liver it get transformed into its active metabolite.

→ It has the immuno suppressant property.

Ilosamide - It is a derivative of cyclophosphamide having a longer & half life.

chlorambucil - It acts particularly on lymphoid tissue.

Antimetabolites -

It have structural similarity with the normal compound present in cell.

methotrexate -

It is structurally related to folic acid

Salvarsan - medicinal chemist.

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Principle of toxicology

MOT →

2 - Deoxyuridine monophosphate

Thymidylate
Synthesis
MTX

Folate dihydrofolate
reductase

MS 10-10 methylene
FH₄ (lethohydrofolate)

polyglutamate

MS 10-formyl FH₄ ← MS 10-formyl
FH₄

dUMP

Thymidylate

DNA RNA

Synthesis

Acute lymphocytic leukaemia

choriocarcinoma

Breast cancer

Head & neck carcinoma

Inflammatory diseases

ADR - i) common ADR ii) Renal damage
 iii) Hepatic function -
 Neuropathy toxicities

2) 6 - mercaptopurine (6-MP) -

It is the thiol analogue

of hypoxanthine 6-MP & 6-thioguanine (6-TG) were
 the first purine analogues to prove beneficial for
 treating neoplastic disease. 6-MP is used principally
 in acute lymphoblastic leukaemia.

MOPA -

6- mercaptopurine

Hypoxanthine guanine

phosphoribosyl transferase

6 - Thioinosinic acid (thio-IMP)

⑤ Feedback inhibition

of Phosphoribosylamine Imp synthesis

Amp

Xmp

Thio-6mp

RNA

i) Nucleotide formation

ii) Inhibition of purine synthesis

iii) Incorporation into nucleic acids -

3) 5 - Fluorouracil (5-FU).

If it is pyrimidine

analogue which has a stable fluorine atom at 5th position of the uracil ring.

MOPA -

Target cell

5 - Fluorouracil (5-FU)

↓ Cytosol

uridine
phosphorylase

S FU

S-FURA

↓ phosphoribosyl transferase

SUMP

S-FUTP

↓ uridine kinase

RNA

S UDP

↓ Ribonucleotide reductase

S DUMP

DUMP

⑥

dTMP

Thymidylate
synthase

N⁵, N¹⁰ methylene FH₄

FH₂

Need for DNA
synthesis & cell growth

Vinca alkaloids — Vinca alkaloids are obtained from plant *Vinca Rosea*.

It acts by interfering with its assembly of microtubules in the metaphase caused due to its arrest.

1) Vincristine (oncovin) —

It is a spindle poison

& acts by causing arrest of the mitotic cycle

2) Vinblastine (velban) —

It acts by binding or crystallising the microtubule proteins of the mitotic spindle thereby leading to metaphase arrest.

Taxanes

1) Paclitaxel (Taxol) — It is an alkaloid ester obtained from *Taxus brevifolia* & *Taxus baccata* (European Yew).

Mot — It acts as a mitotic spindle poison through enhancement of tubulin polymerisation.

use — It is used for primary & secondary treatment of advanced ovarian cancer.

Etoposide

It is obtained from the roots of American may apple plant *Podophyllum peltatum*.

Some epipodophyllotoxin derivatives e.g- etoposide & teniposide are used for cancer treatment. They act by inhibiting the topoisomerase.

Camptothecin Analogue-

Camptothecin analogues are cytotoxic quinolone alkaloids which inhibit the DNA enzyme topoisomerase I.

Ex.- Topotecan

It is semi-synthetically derived from Camptothecin (a plant alkaloid obtained from the tree *Camptotheca acuminata*).

It has topoisomerase I inhibitory activity & produces its cytotoxic action during the S-phase of DNA synthesis.

Common side effects -

Antibiotics -

most antibiotics act by binding with the DNA or getting embedded in to the helical lattice b/w specific bases thereby blocking the transcription of new RNA, DNA & cell replication

i) Dactinomycin (Actinomycin D) -

i) It is obtained from *streptomyces parvillus* & has a high molecular weight.

ii) It acts by binding to DNA to inhibit the synthesis of mRNA & other forms of DNA depend RNA synthesis.

2) Anthracycline Antibiotics -

- i) The anthracycline glucoside antibiotics like doxorubicin daunorubicin are obtain from streptomyces peucetius var.
- ii) The anthracyclines are phase non-specific agent

(a) Doxorubicin - Treatment of lymphoma many solid tumors & acute Leukemia

(b) Daunorubicin - primarily used acute myeloid

Enzymes

They are certain enzyme used for the treatment of cancer. The common simple include

Asparaginase.

Enzyme derived from E. coli or *Exiguicoccus* cultures

MOA - Asparaginase inhibits asparagine synthetase enzyme & hydrolysis of asparagine to aspartic acid & ammonia

Radioactive Isotopes -

There are 3 radioactive isotopes, sodium phosphate (P^{32}), sodium iodide (I^{131}), radiogold (Au^{198}) used in the treatment of different types of cancer.

Therefore emit beta (β) particles or ionising radiations in that destroy living tissues in their immediate vicinity

Miscellaneous Agents -

Hormones & Hormone Antagonists -

→ There are some specific hormones used in the treatment of malignant disease like endocrine related tumors & certain non endocrine malignancies (leukemia lymphomas)

→ The most useful hormones & antagonists are as follow

- 1) Adrenocorticosteroids - prednisone, prednisolone
- 2) Androgens - Testosterone propionate & fluoxymesterone
- 3) Antiandrogens Flutamide
- 4) Oestrogens - Diethylstilboestrol & ethynodiol diacetate
- 5) Progestogens - megestrol acetate, medroxyprogesterone

MOT - The steroid hormones bind to receptors proteins in the cytoplasm of cancer cells to exert their anticancer effects

Adrenocorticosteroids

- i) They act by inhibiting RNA & protein synthesis & interfering with lymphoid proliferation to produce lympholytic effect
- ii) These steroids inhibit growth of mesenchymal tissue & have anti inflammatory & immuno suppressive

All drug class vieweram.

Immunopharmacology

Immunostimulants -

→ Immunostimulants are the agents which are used to boost the resistance of the body against infections.

They augment the basal levels of immune response in individuals having impaired immune. However, they stimulate the immune system to fight against immunodeficiencies (like AIDS), infections & cancers.

→ The treat cancer & HIV infection.

⇒ Interferon- α & interleukin-2 (proleukin) were the earliest medications to stimulate the production of B-cells & killer T-cells.

⇒ By testing the no. of killer T-cells, it is believed that immunostimulants provide the needed T cells to attack & destroy infections or cancers in the affected person.

Cytokines -

The activity of various cytotoxic cells in the immune system is increased by IFNs which are endogenous proteins.

IFN- α -2b is a direct suppressor of cancer cell growth.

→ It is administered intramuscularly.

→ IFN- α -2b is used to treat Kaposi sarcoma in patient with AIDS. & common ADR.

Aldeleukin - It is used to treat metastatic renal cell carcinoma, malignant melanoma & colorectal cancer.

- It produce a good response in 20% of patient with renal cell carcinoma.

→ In low dose aldesleukin is well tolerated & can be given as outpatient ~~per~~ therapy

- In higher dose it can produce toxic effect-

→ These toxic effect are reversible

Levamisole -

It is an anthelmintic drug with non specific immunostimulatory properties.

In deficient animals & humans it restores many different immunologic functions.

→ Levamisole has been used in the treatment of tumors & other disease which manifest immune dysfunction including rheumatoid arthritis & crohn's disease.

Thalidomide -

→ It was once banned because it may cause phocomelia & other defects.

→ It has been used off label to treat recurrent aphthous ulcer, tuberculosis, & AIDS associated wasting syndrome.

→ Thalidomide also exhibits immuno suppressant as well as immunostimulant effect.

BCG - BCG & some other microbial products like - picibanil, levamisole, pachymesin & under trial to be used.

Immuno suppressants

Introduction -

- Immuno suppression involves an act that reduces the activation or efficacy of the immune system.
- It can be either endogenous or exogenous e.g. testosterones. This therapy is employed for the treatment of autoimmune disease & for treating or preventing the chances of rejection for organ transplant.

Glucocorticoids & thiopurines such as Azathioprine are still widely used but newer potent drugs have become the cornerstone of many treatments.

Classification - M.C.

MOA - It ip act by selectively suppressing certain T lymphocyte cell line & thus preventing them to get involved in immune response

→ Each immuno suppressant has a different way of suppressing cell line involved in an immune response.
Corticosteroid, calcineurin inhibitors, antimetabolites.

Corticosteroids inhibit all stages of T-cell activation
Acute rejection calcineurin inhibitors inhibit the phosphate required for the production of interleukin
Sirolimus is an mTOR inhibitor

Antimetabolites Azathioprine, mycophenolate inhibit cell proliferation

Biologics inhibit functioning of cytotoxic T killer cell

use - DLT is used to preventing organ rejection

- ② 3 immunosuppressant e.g mizoromab (D₂, mycophenolate, & tacrolimus are treatment of organ rejection.
- ③ Reducing the frequency of relapses

contraindications -

- 1) In case of drug allergy
- 2) Depending patient condition include renal or hepatic failure, hypertension
- 3) pregnant women only in clinically urgent situation.
- 4) Patient taking immunosuppressant should avoid live vaccines

Adverse effects -

It has many significant adverse effect. They may increase the risk for certain types of cancers especially skin cancers. & lymphoma.

Drug interactions -

- 1) Drug that increase the therapeutic levels of immunosuppressant can cause toxicity.
- 2) Grapefruit juice should be avoided as it can increase the bioavailability of cyclosporine by 20-200%.
- 3) Food rich in potassium can increase cyclosporine nephrotoxicity.
- 4) Meals having a high salt content can increase sirolimus level.

→ Cytostatics -

Cytostatics act by inhibiting cell division.
Smaller doses of cytostatics are used in immunotherapy while malignant disease require large dose treatment.

→ proliferation of both T cells & B cells are also affected by these compound.

- This class include following category of drug
- 1) Alkylating agent - Drug viewerian
 - 2) Antimetabolites - Drug viewerian
 - 3) Cytotoxic antibiotics - Drug

corticosteroids

→ It is the first pharmacologic agent used transplantation & also in various autoimmune disorders. They are still being used for attenuating rejection episodes.

→ Steroids suppress acute rejection of solid organ allografts & are also used chronic graft versus host disease

→ The exact mechanism responsible for the immunosuppressive action of corticosteroids is not yet clear. They mainly affect the T-lymphocytes.

Antibodies (Target Drug to Antigen) -

Rejection reaction

can be prevented by employing potent immunosuppressive methods by the help of various antibodies.

2 types — 1) polyclonal antibodies

2) monoclonal antibodies

Polyclonal Antibodies -

Antibodies inhibit the cell mediated immune reactions e.g. graft-versus-host disease (GVHD).

It also inhibits T lymphocytes to cause their breakdown.

Antithymocyte Globulins -

Thymocytes are cells that develop in the thymus & serve as T cell precursors.
→ Antibodies developed against them are prepared by immunising large rabbits horse with human lymphoid cells, & thus they are polyclonal.

Monoclonal Antibodies -

These antibodies are action specific & act directly towards exactly defined antigens.

use - Same

T-cell Receptor Directed Antibodies - muramomab- CD₃ (OKT3)

Muramomab CD₃ is a murine monoclonal antibody synthesised by hybridoma technology & directed against the glycoprotein CD₃ antigen of human T cells.

MOR = Muramomab-CD₃ bind to CD₃ protein & disrupts T lymphocyte.

Kinetic, w/e, PDR - Same

Drug Acting on Immunophilins -

Cytokines are soluble antigen non specific signalling proteins that bind to cell surface receptors on various cells.

They include the ILs interleukins (IFNs), Tumor necrosis factors, transforming growth factors & colony stimulating factor.

Calcineurin Inhibitors -

It is an enzyme that activates T-cells of immune system.

I) Cyclosporine - (CsA) -

It is one of the most widely used calcineurin inhibitor immuno suppressant used since 1983.

Chemically it is a cyclic fungal peptide having 11 amino acid

Mech - Cyclosporine acts by binding to cyclophilin a cytosolic protein / immune competent lymphocytes to form a cyclosporine-cyclophilin complex.

Inhibit the phosphatase calcineurin enzymes

Kinetic, w/o, ATP - Some -

m-TOP inhibitor (protein Drugs)

The m-TOP inhibitors act to inhibit the mammalian Target of Rapamycin -

Rapamycin is a serine/threonine specific protein kinase belonging to phosphatidylinositol-3 kinase family.