1) Cyclosporine:

It is a cyclic polypeptide with immune suppressant properties.

oUses:

- For the prevention of graft-versus host disease in hematopoietic stem cell transplantation patients, for the prevention of graft rejection in solid organ transplant patients.
- For the treatment of psoriasis, rheumatoid arthritis.
- The major adverse effects is dose related nephrotoxicity
- The greatest concern associated with long-term use of cyclosporine is the development of lymph proliferation disorder.
- Therapeutic range depends on type of organ transplant.

Why cyclosporine needs to be monitored:

- It has a narrow therapeutic index.
- It exhibits the desirable pharmacological effect only within narrow ranges of concentration in the blood, too much drug leads to nephrotoxicity and too little to graft rejection.
- The major adverse effect of the drug is hard to distinguish clinically from a lack of therapeutic effect. The drug is give prophylactically and graft rejection may be first indication of therapeutic ineffectiveness.

- **Therapeutic concentration:** Depends on the biologic fluid and assay procedure used.
  - Starting dose 5-10 mg/kg/day for transplantation.
  - Psoriasis, RA: 2-5 mg/kg/day in divided dose.
- **Bioavailability:** 30% range 8-60%. Intra and interindividually variable

Distribution: 4-5 L/kg

It is distributed in multiple compartment toxicity is not known to be associated with drug concentration at distribution phase.

$t_{1/2}$: 6-12 hrs

Clearance : 5-10 ml/kg/min

Hepatic metabolism

□ Effects of disease states and conditions on cyclosporine pharmacokinetics and dosing:

- The overall mean for all transplant group is a clearance of 6 ml/min/kg, a volume of distribution equal to 5 L/kg, and half-life of 10 hours for adults
- Average clearance is higher (10 ml/min/kg) and mean half-life is shorter (6 hrs) in children (≤ 16 yrs old).
- Because the drug is primarily eliminated by hepatic metabolism, clearance is lower (3 ml/min/kg)

and half-life prolonged (20 hrs) in point with liver failure.

- Immediately after liver transplantation, cyclosporine metabolism is decreased until the graft begins functioning in a stable manner.
- Renal failure does not change cyclosporine pharmacokinetics and the drug is not significantly removed by haemodialysis or peritoneal dialysis.

□ Drug interaction.

- The first are agents known to cause nephrotoxicity when administered with cyclosporine will increase the incidence of renal damage over that observed when cyclosporine or the other agent is given separately.
- Drugs in this category of drug interactions

include aminoglycoside antibiotics, vancomycin, cotrimoxazole, amphotericin B, NSAIDs.

- Drugs which inhibits cytochrome P450 and P-glycoprotein increases cyclosporine concentration.

→ Calcium channel blockers:

- Diltiazem
- Verapamil

→ Antibiotics:

- Clarithromycin
- Erythromycin

→ HIV protease inhibitors:

- Indinavir
- Ritonavir

- Drugs which induce cytochrome P-450 and P-glycoprotein and decrease cyclosporine concentration:

- Antibiotics : Rifampicin
- Anticonvulsants: Carbamazepine, phenytoin

Time to Sample:

- There are many ways of monitoring cyclosporine therapy
- The most common method is to sample the trough (just before the dose) concentration.
- AUC (0-12) is done by withdrawing multiple blood samples over the 12 hr dosing interval.
- AUC (0-4) is a very sensitive predicator for acute rejection.
- The cyclosporine concentration at 2 hr after administration of Neoral is the most accurate single sample marker for AUC (0-4).
- Although not the most sensitive predictor for outcomes, the trough concentration is still the most commonly used method to monitor cyclosporine therapy.

Specimens, collection methods and assays of cyclosporines:

- Blood concentration of cyclosporine are 2-5 times the concentration in serum because of extensive partitioning into red blood cells.
- Whole blood is the preferred specimen and should be collected in tubes with EDTA.
- Samples are stable for 7 days in plastic tubes at 4°C.
- While the popular monoclonal immunoassays offer improved specificity over the older polyclonal versions, they continue to measure varying amount of cross-reactive metabolites.
- The reference method of HPLC offers optimal specificity but takes longer.
- It might be considered in selected cases where significant interferences from meta-

bolites are suspected.

□ Protein binding, active metabolites, other considerations:

- Cyclosporine is 90% bound to albumin and lipoproteins in blood.
- Unbound fractions in blood vary widely among patients and are weekly correlated to lipoprotein concentrations in blood.

For example: Lower unbound fractions of cyclosporine have been reported in patients with hypercholesterolemia.

- Sampling for TDM:

Cyclosporine pharmacokinetic exhibit diurnal variation, therefore blood samples should be obtained at approximately the same time of day.

- After the drug has reached steady state, trough concentration yield the most useful information for routine TDM.
- Several blood samples between two or six hours after oral dosing can be obtained to minimize inter and intrapatient variability due to bioavailability.
- Cyclosporine levels should be monitored two to three times a week during the first few weeks to months of therapy, and less often later in the post-transplant period.
- More frequent monitoring is required if the patient has clinical problems that can change cyclosporine pharmacokinetics (liver dysfunction, diarrhea, drugs, etc).

- **Elimination:** Mainly through the bile to the faeces. Renal elimination <1%

Factors Affecting Plasma Levels :

Factor	Effect(s)
Food	- High fat meals may increase plasma level while low fat meal may decrease plasma concentrations. - Grapefruit increases Cyclosporine levels due to inhibition of the presystemic metabolism in the intestinal mucosa leading to increased bioavailiability after oral administration by 20 – 200%
Age	- Plasma level in children below 10 years may be decreased because they have a larger volume of distribution and faster body clearance.

Drugs	
a) Anticonvulsants Carbamazepiene Phenobarbital Phenytoin Nafcillin Octerotide Ticlopidine Rifampin Sulphonamides and trimethoprim	Decrease Cyclosporine level
b) Physiologic Disorders Fever Diabetes mellitus	Increase Fraction of unbound drug