Calcineurin Inhibitors (CNI): Drug Interactions, Side Effects

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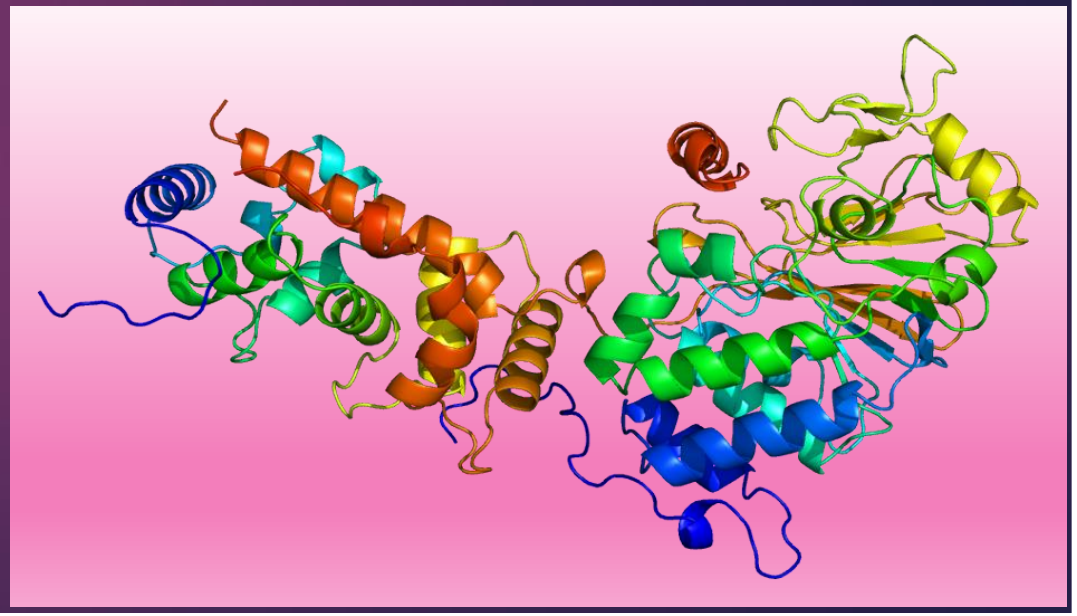

Food interactions

- Chemical compounds in grapefruit, known as the furanocoumarins, are potent inhibitors of cytochrome P-450 3A4 enzyme. Grapefruit or grapefruit juice can result in an increase in systemic exposure to cyclosporine or tacrolimus.
- Patients should be counseled to completely avoid grapefruit and grapefruit juice when being treated with cyclosporine or tacrolimus. In patients who refuse to avoid grapefruit and grapefruit juice, more frequent monitoring of blood cyclosporine or tacrolimus concentrations is required.

Drug interactions

- Cyclosporine and tacrolimus are substrates for cytochrome P-450 3A4/5 (CYP3A4/5) enzymes, any drug that is metabolized by these enzymes or that affects metabolism by these enzymes can potentially interact with calcineurin inhibitors.

Drug interactions

- Drugs that affect gastrointestinal motility or emptying (eg, prokinetic agents) may adversely affect absorption of calcineurin inhibitors.
- Laxatives can reduce oral cyclosporine and tacrolimus absorption by accelerating their passage through the intestine.
- By contrast, narcotics may prolong transit time in the intestine, increasing the time for absorption.

Drug interactions

- Divalent cations may influence the absorption of tacrolimus.
- To minimize these potential interactions, magnesium- and aluminum-containing products should not be administered within two hours of tacrolimus products, and tacrolimus drug concentrations should be closely monitored.
- carvedilol inhibits P-glycoprotein and may increase the blood concentrations of cyclosporine

Common types of drug interactions	Examples of interacting drugs	Approach to management in the absence of appropriate noninteracting alternatives
Drugs that inhibit CYP3A metabolism or P-gp efflux can **Increase immunosuppressant serum concentrations**,	• **Amiodarone** • ART (eg, **ritonavir**, cobicistat) • Azole antifungals (eg, **fluconazole**, **posaconazole**, **voriconazole**) • HIV protease inhibitors (eg, **atazanavir**, **nelfinavir**, **saquinavir**) • Macrolide antibiotics • Non-dihydropyridine CCB • HCV antiviral regimen: Ombitasvir-paritaprevir-ritonavir • Grapefruit juice	Closely monitor immunosuppressant concentrations and signs of toxicity (eg, tremors and headaches). Preemptive, dose reduction of immunosuppressant (eg, on average, only 25% of the standard dose of cyclosporine is required if administered concomitantly with HIV protease inhibitors).

Common types of drug interactions	Examples of interacting drugs	Approach to management
Drugs that induce CYP3A metabolism or P-gp efflux **Decrease immunosuppressant serum concentrations**	• Antiseizure drugs: **Carbamazepine**, **Fosphenytoin**, **phenobarbital**, **phenytoin**, primidone) • **Enzalutamide** • Nafcillin, • **Rifampin**, • St. John's wort	• Closely monitor serum concentrations and signs of organ rejection. • **Immunosuppressant** dose **increases** • Enzyme induction can require **up to two weeks** to achieve **maximum effect** and **persists** for up to **two weeks after discontinuation** of the interacting medication. • Clinically **significant effects** can occur **within hours to days** of starting a CYP inducer.

calcineurin inhibitors drug interactions

Common types of drug interactions	Examples of interacting drugs	Approach to management in the absence of appropriate noninteracting alternatives
Coadministration of nephrotoxic drugs can cause **additive or synergistic kidney injury**.	•Aminoglycosides •Amphotericin B •Colchicine •Nonsteroidal antiinflammatory drugs (NSAIDs)	•Concomitant administration of cyclosporine and tacrolimus with other potentially nephrotoxic drugs should be avoided. •Suggested dose adjustments for use with colchicine are available in the Lexicomp monograph included within UpToDate.

Common types of drug interactions	Examples of interacting drugs	Approach to management in the absence of appropriate noninteracting alternatives
Coadministration of drugs that cause **severe hyperkalemia**.	•ACE inhibitors/ARBs •Amiloride •Spironolactone •Triamterene •Trimethoprim, trimethoprim-sulfamethoxazole (cotrimoxazole)	•Closely monitor serum potassium levels.

Common types of drug interactions	Examples of interacting drugs	Approach to management in the absence of appropriate noninteracting alternatives
Coadministration of cyclosporine with sirolimus can **increase sirolimus concentrations**.	•Cyclosporine	•Separate administration of sirolimus from cyclosporine by four hours; give sirolimus at a consistent time with respect to cyclosporine. •Closely monitor immunosuppressant serum concentrations.

Common types of drug interactions	Examples of interacting drugs	Approach to management in the absence of appropriate noninteracting alternatives
Coadministration of statin drugs with cyclosporine can **increase statin levels and risk of myotoxicity**.	•Atorvastatin •Lovastatin •Pitavastatin •Rosuvastatin •Simvastatin	•Pravastatin and fluvastatin are preferred due to decreased interactions. •Tacrolimus may be preferred over cyclosporine in patients receiving statin therapy. •Cyclosporine and simvastatin should not be used together. •Some combinations are considered contraindicated or statin daily dose limits are recommended in the product labeling.

CNI inhibitors: side effects

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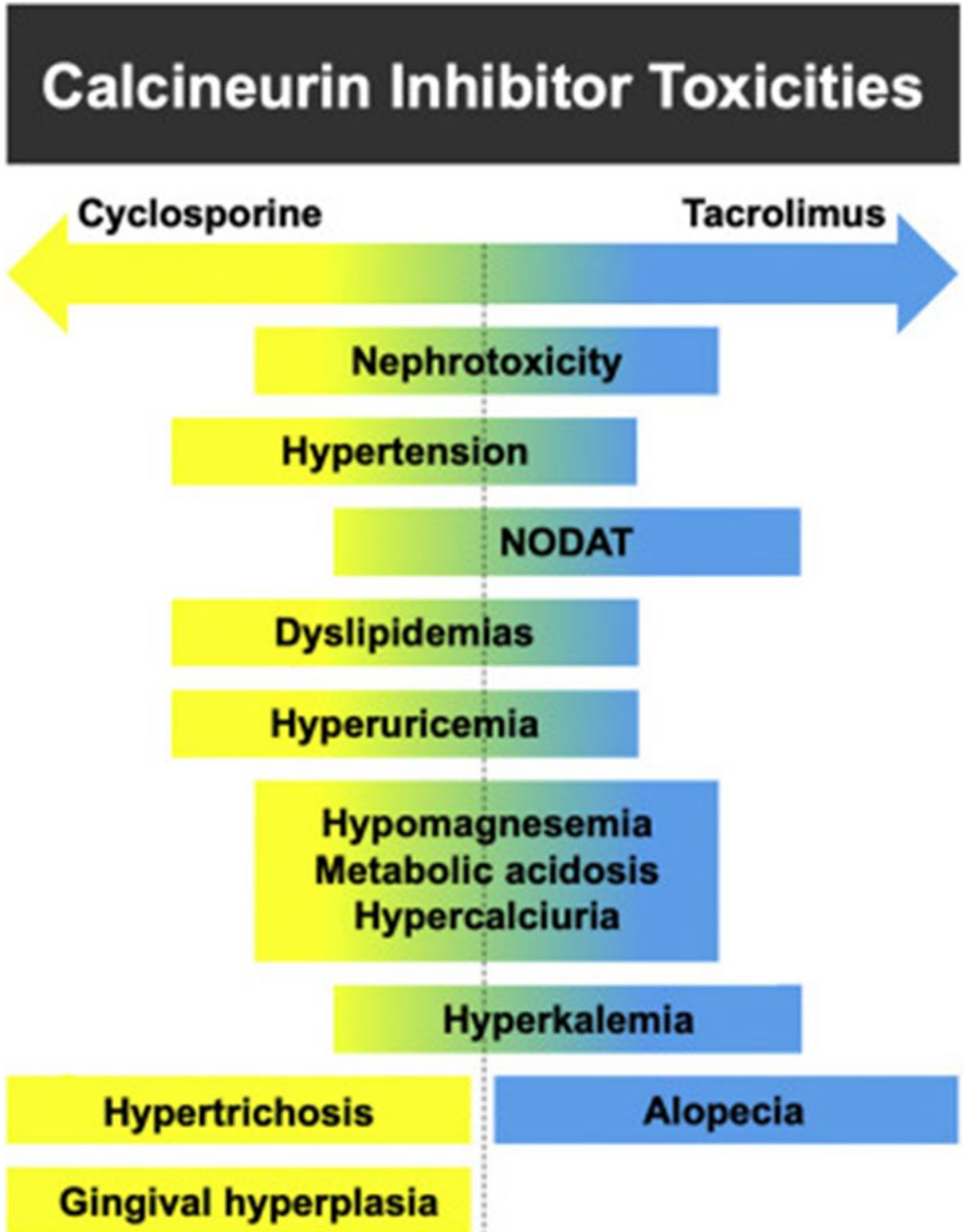
The Many Faces of Calcineurin Inhibitor Toxicity—What the FK?

Samira S. Farouk and Joshua L. Rein

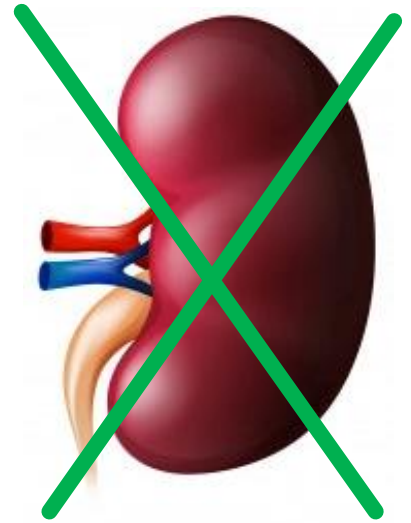
Calcineurin inhibitors (CNIs) are both the savior and Achilles' heel of kidney transplantation. Although CNIs have significantly reduced rates of acute rejection, their numerous toxicities can plague kidney transplant recipients. By 10 years, virtually all allografts will have evidence of CNI nephrotoxicity. CNIs have been strongly associated with hypertension, dyslipidemia, and new onset of diabetes after transplantation—significantly contributing to cardiovascular risk in the kidney transplant recipient. Multiple electrolyte derangements including hyperkalemia, hypomagnesemia, hypercalciuria, metabolic acidosis, and hyperuricemia may be challenging to manage for the clinician. Finally, CNI-associated tremor, gingival hyperplasia, and defects in hair growth can have a significant impact on the transplant recipient's quality of life. In this review, the authors briefly discuss the pharmacokinetics of CNI and discuss the numerous clinically relevant toxicities of commonly used CNIs, cyclosporine and tacrolimus.

Key Words: Calcineurin inhibitors, Tacrolimus, Cyclosporine, Drug toxicity, Kidney transplantation


Calcineurin Inhibitor Toxicities
Cyclosporine
Tacrolimus
Nephrotoxicity
Hypertension
NODAT
Dyslipidemias
Hyperuricemia
Hypomagnesemia
Metabolic acidosis
Hypercalciuria
Hyperkalemia
Hypertrichosis
Alopecia
Gingival hyperplasia

Nonrenal Calcineurin Inhibitor Toxicity

1. *Gastrointestinal*
2. *Cosmetic*
3. *Hyperlipidemia.*
4. *Glucose Intolerance*
5. *Neurotoxicity*
6. *Infection and Malignancy*
7. *Thromboembolism*

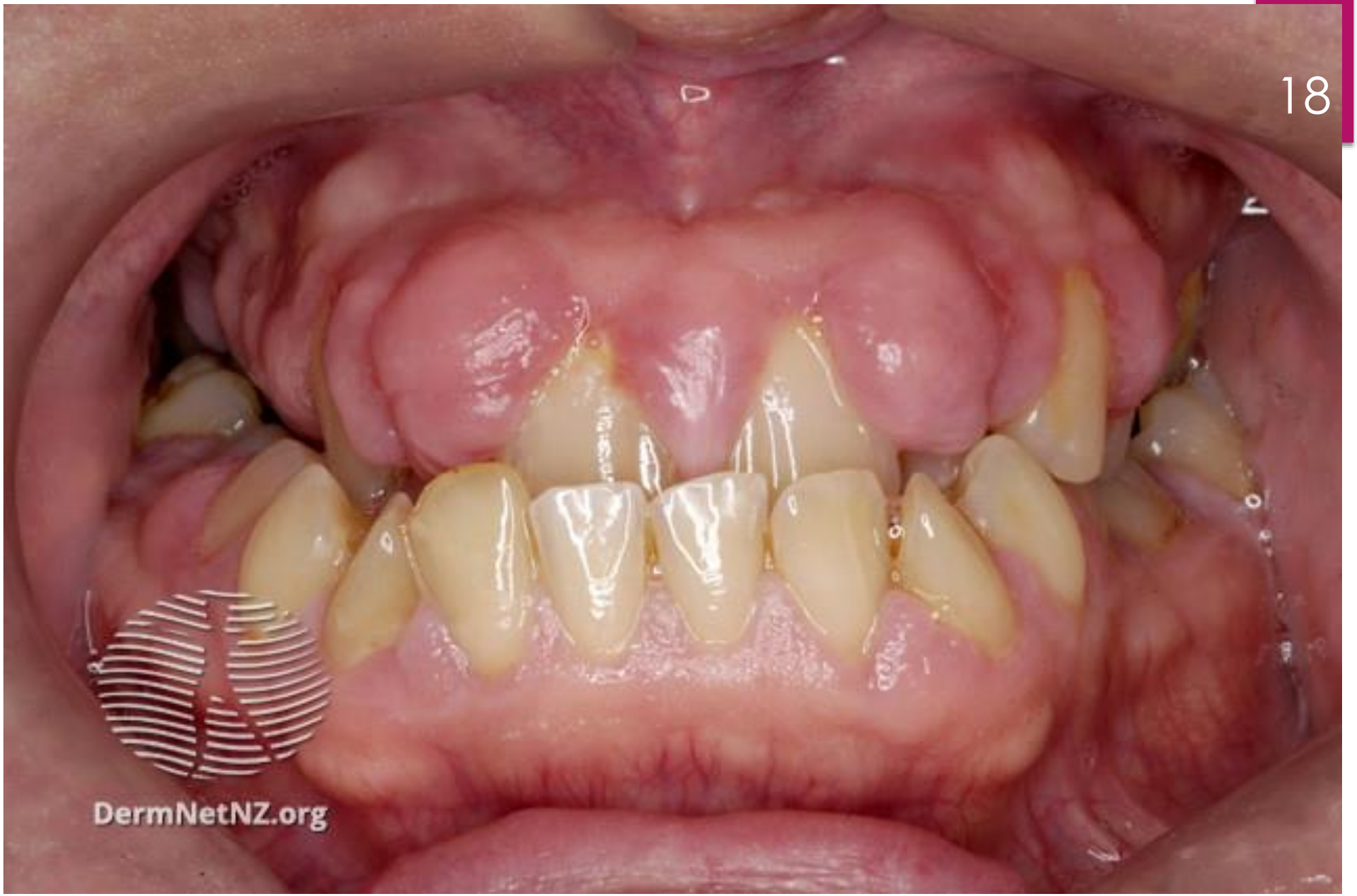


Gastrointestinal

- Anorexia, nausea, vomiting, diarrhea, and abdominal discomfort up to 75% (**tacrolimus**), and less frequently in ***cyclosporine***.
- Hepatic dysfunction, mild, self-limited, dose-dependent
- Elevations of serum aminotransferase, mild hyperbilirubinemia up to 50% (**cyclosporine**) and less frequently in tacrolimus.
- Cholelithiasis (**cyclosporine**)

Cosmetic

- **Gingival hyperplasia** and **hirsutism** occur **with cyclosporine** therapy but not with ***tacrolimus (hair loss, alopecia***).
- Principal risks: poor dental hygiene, higher doses of cyclosporine, and concomitant use of nifedipine .
- **Treatment**:
  - **Metronidazole** (750 mg three times daily) 2 weeks, while cyclosporine is continued.
  - **Azithromycin** (500 mg/day for three consecutive days), in mild or early disease.
- **Gynecomastia** in men and breast enlargement in women (**cyclosporine** prolactin)


DermNetNZ.org

Hyperlipidemia

- **More with cyclosporine**, Less with tacrolimus
- Mechanisms:
  - Abnormal low-density lipoprotein feedback control by the liver,
  - Altered bile acid synthesis,
  - Occupation of the low-density lipoprotein receptor by cyclosporine.
- Up to two-thirds of patients develop *de novo* hyperlipidemia in the first post-transplantation year.
- Lipid levels may decrease by switching from cyclosporine to tacrolimus

Glucose Intolerance, new-onset diabetes mellitus after transplantation

- **More with tacroliomus-**
- toxic to pancreatic islets, increased concentrations of FKBP in islet cells. The effect is dose related and may be exaggerated by concomitant corticosteroid use.
- Obesity, African-American or Hispanic ethnicity, family history of diabetes, and hepatitis C infection may predispose to NODAT.

Neurotoxicity

- Mild tremor with both cyclosporine and tacrolimus, severe headache,
- A calcineurin-inhibitor pain syndrome: symmetrical pain in the lower limbs, usually involving the bones of the feet, ankles, and knees. Magnetic resonance imaging (MRI) may show marrow edema.
- improve with cessation of the drug and/or use of calcium channel blockers.
- The neurologic side effects are usually reversible
- more common with tacrolimus than with cyclosporine
- Less with prolonged-release formulations

Risk of malignancy

- Both cyclosporine and tacrolimus are associated with an increased risk of squamous cell skin cancer and benign or malignant lymphoproliferative disorders. Spontaneous regression of lymphoma may occur if the drug is discontinued early.
- The level of immunosuppression the principal factor on the risk of posttransplant malignancy.
- Suggests that cyclosporine itself may promote cancer progression, principally via the production of transforming growth factor (TGF)-beta.
- Both the in vitro and in vivo changes were prevented by the administration of anti-TGF-beta antibodies.

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