The risk of infection is higher in the first few months after organ transplant (SOT) is infections with a large number of bacteria, fungi, viruses, and parasites. Immunosuppressants are given in high doses in initial posttransplant period to prevent acute rejection. The recipient is more susceptible to get infections during this period and hence antimicrobial prophylaxis is given. While diagnosing and treating the infectious complications of immunosuppression, the clinician must consider the following:

- The risk of infection is higher in the first few months after transplant but it may increase anytime when the patient’s cumulative immunosuppression increases, e.g., during the treatment of a rejection episode.

The most common complication of immunosuppression in solid organ transplant (SOT) is infections with a large number of bacteria, fungi, viruses, and parasites. Immunosuppressants are given in high doses in initial posttransplant period to prevent acute rejection. The recipient is more susceptible to get infections during this period and hence antimicrobial prophylaxis is given. While diagnosing and treating the infectious complications of immunosuppression, the clinician must consider the following:

- The risk of infection is higher in the first few months after transplant but it may increase anytime when the patient’s cumulative immunosuppression increases, e.g., during the treatment of a rejection episode.

Due to decreased innate and adaptive immune response, the classical signs and symptoms of infections are not usually seen, making it difficult to diagnose an infectious disease. A high index of suspicion is warranted.

Noninfectious complications can mimic infection, e.g., graft-vs-host-disease (GVHD) flare, transplant rejection, and drug toxicity (e.g., sirolimus-induced pneumonitis).

One of the most important concerns while treating infectious diseases in SOT is significant interactions between antimicrobial and immunosuppressive agents. Knowledge of these interactions is essential for successful management of solid organ transplant patients. We therefore decided to review the literature and present the interactions that commonly occur between these two life-saving groups of drugs.

Keywords: Antimicrobials, Calcineurin inhibitors, Corticosteroids, Drug–drug interaction, Immunosuppressants, Intravenous immunoglobulin, Monoclonal antibodies, mTOR inhibitors, Solid organ transplant.
immunosuppressants and antimicrobials. Appropriate dosing and delivery of antimicrobials in immunosuppressed patients with organ dysfunctions is a major therapeutic challenge.

Depending on the timeline, the nature of infections and microbes causing the infections changes. Depending on the timeline, patients are given antimicrobial prophylaxis; these drugs will then have interactions with the immunosuppressants the patient may be receiving as per duration after the solid organ transplant.

**Drug Interactions between Antimicrobials and Immunosuppressants**

Drug–drug interactions can be classified in a various ways: pharmacological interactions; pharmacokinetic interactions, which involve absorption, distribution (with protein and tissue binding, tissue binding), hepatic or nonhepatic metabolism, and renal or nonrenal excretion; and finally direct and indirect pharmacodynamic interactions. However, for the purpose of this review we will consider the two main types, i.e., pharmacodynamic and pharmacokinetic interactions between antimicrobials and immunosuppressants.

**Pharmacodynamic Interactions**

This refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects. Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action. So the drugs may increase or decrease each other’s efficacy or toxicity, thus it can be beneficial or harmful, both. Several examples of pharmacodynamic interactions among medications used in transplant recipients have been identified. For example, an increase in renal toxicity is observed with the coadministration of naproxen and cyclosporin A. Administration of tacrolimus with antimicrobials in renal toxicity is observed with the coadministration of naproxen with the immunosuppressants the patient may be receiving as per duration after the solid organ transplant.

**Pharmacokinetic Interactions**

Pharmacokinetics deals with the handling of the drug by the body and can be very complex, as several processes (such as absorption, distribution, metabolism, and elimination) work to alter drug concentrations in tissues and fluids. Pharmacokinetic interactions are defined as drug–drug interactions that alter the plasma concentration of one or both drugs. These interactions affect drug metabolism and disposition at each of the stages described above. There are several mechanisms by which drug interactions can occur. Many interactions occur secondary to effects on drug-metabolizing enzymes or drug transporters. Drug-metabolizing enzymes are known to alter drug absorption and metabolism. Drug transporters are likely to affect drug absorption, distribution, and elimination. The following enzymes metabolize most frequently used immunosuppressants (Table 1).

**CYP3A Modulation**

Immunosuppressive drug interactions can be caused by an anti-infective agent directly inhibiting cytochrome P450 3A4 (here abbreviated to CYP3A4) or via drug competition for CYP3A4 substrate sites. Both mechanisms may result in increased immunosuppressive concentrations. In contrast, CYP3A4 induction via increased synthesis or decreased breakdown of CYP isoenzymes may result in decreased concentrations of immunosuppressants (Table 2).

Phenytoin is a known inducer of CYP3A and CsA is a substrate of CYP3A. The ligand (phenytoin) binds to the pregnane X receptor (PXR) [also called steroid and xenobiotic-sensing nuclear receptor (SXR)]. This activated PXR complex forms a heterodimer with retinoid X receptor (RXR), which binds to the xenobioc-reactive

### Table 1: Common enzymes involved in metabolism of immunosuppressants

| Metabolizing enzyme | Drugs          | Nature and process |
|---------------------|----------------|--------------------|
| Cytochrome P450s    | Cyclosporine (CSA) | Substrate, inhibitor |
| (e.g., CYP 3A/5)    | Sirolimus (SIR)  | Substrate, inhibitor |
| Tacrolimus (TAC)    | MMF             | Substrate          |
| UDP-glucoronyl trans-ferase | | |
| Xanthine oxidase    | Azathioprine (AZA) | Substrate |

### Table 2: CYP3A substrates, inhibitors, inducers, and activators

| Drug category | Effect on CYP3A |
|---------------|----------------|
| Anticancer drugs |                 |
| Busulfan (S)  | Tamoxifen (S)   |
| Docetaxel (S) | Vinblastine (S, I) |
| Doxorubicin (S) | Vincristine (S, I) |
| Etoposide (S) | Vindesine (S)  |
| Paclitaxel (S) |               |
| Immunosuppressants |              |
| Cyclosporine (S, I) |                   |
| Methylprednisolone (I) |               |
| Sirolimus (S, I) |                  |
| Tacrolimus (S) |                     |
| Antibiotics/antifungal agents |               |
| Clarithromycin (S) |                      |
| Clotrimazole (I) |                       |
| Erythromycin (S, I) |                    |
| Itraconazole (S, I) |                   |
| Ketoconazole (S, I) |                |
| Antiretroviral agents |                |
| Amprenavir (S, I) |                         |
| Indinavir (S, I) |                           |
| Nelfinavir (S, I) |                            |
| Ritonavir (S, I) |                             |
| Saquinavir (S, I) |                              |
| Other cytotoxic drugs |                |
| Colchicine (S) |                                |
| Hormonal agents |                |
| Cortisol (S) | Hydrocortisone (S) |
| Dexamethasone (S, I) | Progesterone (S, I) |
| Estradiol (S, I) | Testosterone (S, A) |
| Cardiac agents |                |
| Amiodarone (S) | Nicardipine (S, I) |
| Atorvastatin (S) | Nifedipine (S, I) |
| Digiotoxin (PS) | Nitrendipine (S, I) |
| Diltiazem (S, I) | Pravastatin (S) |
| Felodipine (S) | Quinidine (S, I) |
| Fluvastatin (S) | Simvastatin (S) |
| Lidocaine (S) | Verapamil (S, I) |
| Lovastatin (S) |                         |

S, substrates; I, inhibitors; In, inducers; A, activators
enhancer module (XREM) region of the CYP3A4 gene. This leads to genetic transcription, with increased production of CYP3A4, increasing its ability to metabolize various molecules, such as cyclosporin A (see Fig. 1). Therefore, in patients who are given phenytoin, CsA levels are reduced as the rate of CsA metabolism is increased.\(^{11}\) In transplant recipients, a reduction in CsA levels increases the risk of graft rejection. Erythromycin, on the other hand, is a known inhibitor of CYP3A. Thus, when erythromycin and CsA are coadministered, CsA metabolism is reduced and plasma concentrations of CsA increase.\(^{12}\) This can result in toxicity from increased exposure to high CsA blood levels.

**Drug Transporters with Immunosuppressants**

Drug transporters play a significant role in the absorption, distribution, and elimination of immunosuppressants. Thus, modulation of transporter activity represents another mechanism by which these drugs can interact with one another as well as with other classes of agents. Recent studies have identified a number of drug transporters, the most prominent being P-glycoprotein (P-gp), the protein product of the multidrug resistance 1 gene (MDR1). CsA and TAC are P-gp substrates. In addition, depending upon the duration of exposure, CsA, TAC, and SIR have been shown to inhibit and induce P-gp. Other transporters, such as the multidrug resistance gene 2/3, the organic anion transporter proteins, the multidrug resistance-related proteins, and the sister of P-glycoprotein may modulate immunosuppressant action; however, further investigation is required. P-gp transports drugs from the intracellular portion of the cell to the extracellular portion. It is thought to provide a barrier function and help to excrete toxins from the body. P-gp is expressed on a variety of normal tissues, primarily in those with secretory or barrier functions: liver, intestine, kidney, the blood-brain barrier, and lymphocytes.\(^{10,13}\) In these tissues, P-gp transports drugs out of the organ or cell and is therefore thought to provide a protective function for the organism. P-gp acts as an export pump that extrudes drugs from the intracellular compartment to the extracellular compartment. When P-gp activity is inhibited, more drug is available to distribute to the systemic circulation. In other words, the bioavailability of a given drug is increased in the presence of a P-gp inhibitor. St. John's wort has been shown to induce P-gp.\(^{14}\) Since CsA is a P-gp substrate, the coadministration of St. John's wort and CsA results in a reduction in the systemic concentration of CsA. Coadministration of quercetin, an inhibitor of CYP3A4 and a modulator of P-gp, and oral CsA was shown to reduce the bioavailability in animal studies.\(^{15}\) Verapamil, on the other hand, is an inhibitor of CYP3A and P-gp. The coadministration of verapamil and everolimus resulted in increased bioavailability of everolimus (Table 3).\(^{16}\)

**Interactions between Antibacterial Agents and Immunosuppressants**

The major interactions between antibacterial and immunosuppressants are discussed below. Minor interactions are summarized in Table 4.

**Table 3: P-glycoprotein (P-gp) substrates, inhibitors, inducers, and activators**

| Drug category   | Effect on P-gp          |
|----------------|-------------------------|
| Anticancer drugs | Actinomycin D (S) |
|                | Methotrexate (S, In)   |
|                | Cisplatin (S, In)       |
|                | Mitomycin (S)           |
|                | Cytarabine (S)          |
|                | Paclitaxel (S)          |
|                | Daunorubicin (S, In)    |
|                | Taxol (S)               |
|                | Docetaxel (S)           |
|                | Tamoxifen (I, In)       |
|                | Doxorubicin (S, In)     |
|                | Vinblastine (S, I, In)  |
|                | Etoposide (S, In)       |
|                | Vinycristine (S, In)    |
|                | Fluorouracil (S, I, In) |
|                | Vindesine (S)           |
| Immunosuppressants | Cyclosporine (S, I, In) |
|                | Methyprednisolone (S)   |
|                | Prednisolone (S, I, In) |
|                | Sirolimus (S, I, In)    |
|                | Tacrolimus (S, I, In)   |
| Antibiotics and antifungal agents | Clarithromycin (I) |
|                | Clotrimazole (In)       |
|                | Erythromycin (S, I, In) |
|                | Itraconazole (S, I)     |
|                | Ketoconazole (I)        |
|                | Sparfloxacin (S)        |
| Antiretroviral agents | Amprenavir (S, In) |
|                | Indinavir (S)           |
|                | Nelfinavir (S, I, In)   |
|                | Ritonavir (S, I, In)    |
|                | Saquinavir (S, I)       |
| Other cytotoxic drugs | Colchicine (S, In) |
|                | Mitoxantrone (S, In)    |
| Hormonal agents | Aldosterone (S)         |
|                | Hydrocortisone (S, I)   |
|                | Cortisol (I)            |
|                | Insulin (In)            |
|                | Dexamethasone (S, In)   |
|                | Progesterone (I)        |
| Cardiac agents | Estradiol (In, MS)      |
|                | Testosterone (I)        |
|                | Amiodarone (I, In)      |
|                | Nicardipine (I, In)     |
|                | Atorvastatin (I)        |
|                | Nifedipine (I)          |
|                | Celprolol (S, I)        |
|                | Nitrendipine (I)        |
|                | Digoxin (S)             |
|                | Quinidine (S, I)        |
|                | Diltiazem (S, I, In)    |
|                | Talinolol (S)           |
|                | Felodipine (I)          |
|                | Terfenadine (I)         |
|                | Lidocaine (I)           |
|                | Verapamil (S, I, In)    |

S, substrates; I, inhibitors; In, inducers; A, activators

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**Fig. 1:** Phenytoin induction of CYP3A4. P: Phenytoin molecule, PXR: Pregnanne S receptor
Macrolides
Commonly used macrolides are azithromycin and clarithromycin; erythromycin, being an old agent, is used rarely. These agents are commonly used for treatment of atypical pneumonia caused by Legionella spp., *Chlamydia pneumonia*, or *Mycoplasma pneumonia* and enteritis due to Campylobacter spp. Erythromycin is sometimes used as a prokinetic agent in gut motility disorder.

Erythromycin and clarithromycin are moderate to strong inhibitors of CYP3A4, while azithromycin has minimal effect on CYP3A4; thus, erythromycin and clarithromycin decrease the metabolism of calcineurin inhibitors (CsA, TAC) and mTOR inhibitors (SRL, EVR). There is thus 3- to 10-fold rise in the immunosuppressant levels, when these drugs are given concomitantly. The effect of erythromycin or clarithromycin is less when given orally. Erythromycin and clarithromycin also increase the absorption of CsA, by inhibiting its intestinal wall metabolism. If the combination is used, then at least 35–50% dose reduction of the immunosuppressant should be done; and daily drug level monitoring for calcineurin inhibitors and 72-hourly drug levels monitoring for mTOR inhibitors should be done.

Quinolones
Commonly used quinolones are ciprofloxacin, levofloxacin, and moxifloxacin. Ciprofloxacin decreases levels of MMF by interfering with enterohepatic circulation and absorption. Though levofloxacin does not increase the level of CSA, drug level monitoring is indicated. Moxifloxacin has no interaction with calcineurin and mTOR inhibitors. 18

Table 4: Minor interactions between antibacterials and immunosuppressants

| Antimicrobial | Immunosuppressant | Severity of interaction | Interaction | Suggested action |
|---------------|-------------------|-------------------------|-------------|------------------|
| Fluoroquinolones |                   |                         |             |                  |
| Ofloxacin     | CsA, TAC          | ++                      | ↑ Imm level | Choose alternative |
| Ciprofloxacin | CsA, TAC          | ±                       | May ↑ Imm level | No adjustment/consider monitoring Imm levels |
| Levofloxacin  | CsA               | ±                       | May ↑ CsA level | No adjustment/consider monitoring Imm levels |
| Moxifloxacin  | CsA, TAC, SRL, EVR | –                      | None        | No adjustment    |
| Macrolides    |                   |                         |             |                  |
| Erythromycin  | CsA, TAC, SRL, EVR | +++                    | ↑ Imm level | Avoid            |
| Clarithromycin| CsA, TAC, SRL, EVR | +++                    | ↑ Imm level | Avoid/↓ Imm by ½ |
| Telithromycin | CsA, TAC, SRL, EVR | +++                    | ↑ Imm level | Avoid            |
| Aminoglycosides|                   |                         |             |                  |
| Gentamicin, Tobramycin, Amikacin, Streptomycin | CsA, TAC | +++                    | Enhanced nephrotoxicity | Avoid/monitor Imm levels and renal function |
| Rifamycins    |                   |                         |             |                  |
| Rifabutin     | CsA, TAC, SRL, EVR | ++                      | ↓ Imm levels| Monitor Imm levels |
| Rifapentine   | CsA, TAC, SRL, EVR, Prednisone | ++ | ↓ Imm levels | Monitor Imm levels |
| Rifampin      | CsA, TAC, SRL, EVR, MMF, ECMS | +++ | ↓ Imm levels | Avoid/monitor Imm levels |
| Other antibacterials |               |                         |             |                  |
| Nafcillin     | CsA, TAC, SRL, EVR | ++                      | ↑ Imm levels| Monitor Imm levels |
| Quinupristin/dalfopristin | CsA | +++                    | ↑ CsA | Monitor Imm levels |
| Linezolid     | MMF, ECMS, AZA    | ++                      | Myelosuppression | Monitor WBC and platelets |
| Sulfonamides  | MMF, ECMS, AZA    | ++                      | Myelosuppression | Monitor WBC, hematocrit, platelets, and renal function |
| Tetracycline  | CsA, TAC, SRL, EVR | +                       | ↑ Imm levels | Monitor Imm levels |
| Tigecycline   | CsA               | +                       | ↑ Imm levels | Monitor Imm levels |
| Metronidazole | CsA, TAC, SRL, EVR | ±                       | May ↑ Imm levels | No adjustment/consider monitor levels |
| Chloramphenicol (intravenous) | CsA, TAC, SRL, EVR | ++ | ↑ Imm levels | ↓ CsA or TAC by 25% |
| Clindamycin   | CsA, TAC, SRL, EVR | ±                       | May ↓ Imm levels | No adjustment/consider monitoring levels |

Imm, immunosuppressants; CsA, cyclosporine; TAC, tacrolimus; SRL, sirolimus; EVR, everolimus; MMF, mycophenolate mofetil; ECMS, enteric-coated mycophenolate sodium; AZA, azathioprine (data on EVR not always present, but included in table on basis of the similar route of metabolism to other immunosuppressants involved in drug–drug interactions)
**Aminoglycosides**

Aminoglycosides are nephrotoxic, and the nephrotoxicity is potentiated in presence of nephrotoxic immunosuppressants like CsA and TAC.\(^{23,24}\) Renal function monitoring is indicated when they are used concurrently. If renal dysfunction develops, aminoglycosides are better avoided, or the dose should be adjusted according to the GFR or creatinine clearance. One important consideration while dosing the antimalarials, which are renally excreted, is to continually adjust the doses to maximize efficacy and prevent toxicity.\(^{25}\)

**Antitubercular Drugs**

In most of the antitubercular regimes, rifamycins are the mainstay. All the rifamycins are strong inducers of CYP3A4. Rifampicin stimulates metabolism of cyclosporine by the CYP3A4 isozyme, resulting in an increase in cyclosporine clearance. Rifampicin also decreases the absorption of cyclosporine by inducing its metabolism by gut wall. Both rifampicin and rifabutin decrease the plasma levels of calcineurin and mTOR inhibitors, leading to acute graft rejection.\(^{26-29}\) This effect has been reported even with the concurrent use of multiple CYP3A4 inhibitors.\(^{30}\) In presence of these agents, maintaining therapeutic levels of calcineurin and mTOR inhibitors is extremely difficult; hence, these combinations should be avoided. In cases where rifamycins can’t be avoided for the treatment of tuberculosis, doses of immunosuppressive agents should be increased. Initially, the dose of calcineurin or mTOR inhibitors should be doubled. This should rapidly be increased with daily drug level monitoring till a stable dose has been achieved. Up to 10-fold increase in dose has been reported. Dose should be decreased with drug level monitoring, once rifamycins are discontinued. Rifapentine is a strong inducer of CYP3A4, but not much is known about this drug with regards to interaction with immunosuppressants.

Mycophenolate is metabolized into mycophenolic acid, which undergoes glucuronidation by uridine diphosphate glucuronosyltransferases (UGTs) in the liver, kidney, and intestine to its inactive metabolite (7-O-gluconoride). Rifampicin induces intestinal, kidney, and liver glucuronidation of mycophenolic acid by UGTs and reduces enterohepatic recirculation and absorption of mycophenolic acid. Also one metabolite of MMF, acyl-glucuronide, gets accumulated and attains higher blood level in presence of rifampicin, which may increase the toxicity or adverse effects. Hence in presence of rifampicin, its plasma level should be monitored, and the dose should be adjusted accordingly.\(^{31}\) Rifampicin is a potent liver enzyme inducer, which increases the metabolism of the steroids, thereby reducing the effect of steroids by blood levels. Steroid dose should be increased initially, and should be gradually decreased, once rifampicin is discontinued.\(^{32,33}\) Isoniazid and ethambutol do not seem to interact with immunosuppressive agents.

**Other Antibacterials**

- Renal toxicity of cyclosporine is increased by nafcillin, vancomycin, and alternative antibiotic should be used. Higher doses of trimethoprim-sulfamethoxazole potentiate the nephrotoxicity of calcineurin inhibitors (CNI).\(^{34}\)
- Co-amoxiclav changes the intestinal flora and may affect MMF absorption by enterohepatic circulation. Close vigilance is required when used with MMF.\(^{20}\)
- Combination of norfloxacin with metronidazole (commonly used to treat dysentery on OPD basis) decreases MMF levels by affecting the enterohepatic circulation. Drug level monitoring of MMF is suggested.\(^{35}\)
- Dalfopristin/quinupristin are inhibitors of CYP3A4 and increase the blood levels of calcineurin inhibitors. Drug level monitoring is therefore advised. Calcineurin inhibitors and MMF increase the arthralgia and myalgia caused by dalfopristin/quinupristin inhibitors, through pharmacodynamic interaction.\(^{36}\)

**Interactions between Antifungal Agents and Immunosuppressants**

Azoles, echinocandins, and polyenes are all used in transplant recipients. These are summarized in (Table 5).

**Azoles**

All azoles are inhibitors of CYP3A4 with differing potency. In order of decreasing potency, they are ketoconazole (most potent), itraconazole and posaconazole (more potent than), fluconazole, voriconazole, and isavuconazole.\(^{37}\) They all decrease the metabolism of calcineurin and mTOR inhibitors. Ketoconazole has often been used along with calcineurin or mTOR inhibitors to decrease the dose of immunosuppressant and to decrease the cost for transplant.\(^{38-40}\) Voriconazole increases CsA and TAC levels (increase in AUC levels by 70 and 221%, respectively), and it is recommended to decrease the doses of CSA and TAC by 50 (half) and 33% (one-third), respectively.\(^{37,41}\) Voriconazole increases the level of sirolimus up to 10-fold (increase in AUC by 1014%) and thus, they can be safely administered together provided a specific protocol is used.\(^{42}\) Similarly, everolimus should be used with caution with voriconazole.\(^{43}\)

Posaconazole, like voriconazole, too increases the levels of calcineurin and mTOR inhibitors and requires empiric dose reduction of CsA to three-fourth of the normal dose and TAC to one-third of the normal dose.\(^{44,45}\) Posaconazole should not be administered with sirolimus as it increases its blood level by ninefold.\(^{46,47}\) Not much of data are available on posaconazole administered with everolimus, though one case report found 3.8-fold increase in everolimus levels. Still, posaconazole in contraindicated with everolimus.\(^{44,45}\) Posaconazole increases MMF levels due to inhibition of P-glycoprotein. The MMF levels should be monitored when used with posaconazole.\(^{47}\) Even after dose adjustment, drug levels of immunosuppressants should be monitored frequently when used with voriconazole or posaconazole.\(^{48}\)

The interaction of fluconazole with immunosuppressants is both drug-dependent and dose-dependent. At lower doses (100–200 mg/day), CsA levels are not altered but there is moderate to significant increase in TAC levels. As higher doses as used in systemic candidiasis (400 mg/day), significant dose reduction for CsA and TAC is needed, guided by drug level monitoring.\(^{49}\) Fluconazole also increases trough levels of sirolimus and everolimus; dose reduction and drug level monitoring are required.\(^{49,50}\) Isavuconazolium sulfate, a prodrug of the broad-spectrum azole isavuconazole, was approved by the U.S. FDA, in 2015, for the treatment of invasive aspergillosis and mucormycosis. Isavuconazole is a moderate inhibitor of CYP3A4 and a mild inhibitor of UGTs. It has been shown to increase the drug level of CsA, tacrolimus, and sirolimus. Thus, its effects are less than other azoles and it can be used in patients on immunosuppressants, with drug level monitoring.\(^{51}\)

Oral clotrimazole lozenges (for prophylaxis of oral mucocutaneous candidiasis) has been shown to increase the
levels of TAC up to twofold through CYP3A4 inhibition. The CNI or mTOR inhibitor levels should be monitored when used with oral clotrimazole.52,53

**Echinocandins**

Echinocandins are widely used now in immunosuppressed patients as an alternative to azoles. All echinocandins are available only in intravenous formulation. Echinocandins are not significantly metabolized by CYP3A4; and none is a major P-glycoprotein substance, hence they have minimum interaction with the immunosuppressant.54 The original studies that led to approval of caspofungin had shown increased hepatotoxicity with concurrent use of caspofungin and CsA. CsA also increases AUC for caspofungin by almost 35%. 55 One more study found that AUC for TAC is decreased by 20% in presence of caspofungin.56 Subsequent studies, however, didn’t find any significant increase in hepatotoxicity or in the drug levels of CsA and tacrolimus in the presence of caspofungin.57,58 Current recommendation is to follow the standard dose and drug level monitoring of both CsA and tacrolimus when used with caspofungin. 55 CNIs do not have any interaction with the metabolites of MMF too. Anidulafungin has minimal pharmacokinetic interaction with CsA and no interaction with tacrolimus; hence, no dose modification for either drug is needed, when used concurrently.59,60 No data are available on interaction between mTOR inhibitors and caspofungin or anidulafungin. Micafungin doesn’t have any pharmacokinetic interaction with calcineurin inhibitors, MMF, or prednisone, but in one study it caused decreased blood levels of CsA in healthy volunteers, by 16%, hence CsA level monitoring is suggested.61,62 Micafungin has been found to increase sirolimus AUC by 21% and hence dose adjustment and drug level monitoring are suggested61

**Polynes**

Amphotericin-B is the polyene used in invasive mycoses. The most important dose-limiting side effect of amphotericin-B is nephrotoxicity. Calcineurin inhibitors too have nephrotoxicity and their concurrent use with amphotericin-B increases renal toxicity. Vigilant monitoring of renal function is recommended. Lipid formulations of amphotericin-B are less nephrotoxic than amphotericin-B deoxycholate and are the preferred agents for patients on calcineurin inhibitors.

**Interactions between Antiviral Agents and Immunosuppressants**

Most severe interactions occur between the antiretroviral agents (protease inhibitors) and immunosuppressants.

**Interactions with Antiretroviral Agents**

Patients infected with HIV-1 virus are being increasingly transplanted for organ failures.63 Accordingly, more incidences of interactions with immunosuppressants and antiretroviral drugs had been coming up. Most of the antiretroviral drugs are inhibitors of CYP3A4 and p-glycoprotein and have to be cautiously used with CNIs and mTOR inhibitors.

**Protease Inhibitors (PI)**

Patients receiving PIs require significant dose reduction of both calcineurin and mTOR inhibitors, to maintain a safe trough level. Lopinavir and ritonavir combination has shown 10-fold increase
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in the half-life of TAC.\textsuperscript{63} Case reports in kidney transplant patients receiving saquinavir or darunavir showed an increase in the tacrolimus trough level, leading to 96.5% reduction in the dose of tacrolimus.\textsuperscript{64,65} Even with cyclosporine dose was reduced by almost 85% in patients receiving nefilnavir and indinavir.\textsuperscript{66,67} Same interactions have been seen between sirolimus and PIs. There is not much data on everolimus with protease inhibitors, though the product monograph suggests avoiding everolimus with PIs.\textsuperscript{68}

Nucleotide Analogues

Tenofovir has renal toxicity, which may increase when combined with tacrolimus. Though there is no pharmacokinetic interaction between tenofovir and calcineurin inhibitors. Mycophenolate mofetil is metabolized through uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT) pathway; similarly, abacavir and zidovudine are metabolized by the same pathway. Hence, MMF levels should be monitored when used with these two nucleotide analogs.\textsuperscript{69}

Table 6: Interactions between antivirals and immunosuppressants

| Antiviral agents—non-HIV | Immunosuppressant | Severity of interaction | Interaction | Suggested action |
|-------------------------|-------------------|-------------------------|-------------|------------------|
| Acyclovir               | MMF, ECMS         | ±                       | ↑ ACV, ↓ MPA| None             |
| I.V. Acyclovir          | CsA, TAC          | +++                     | Nephrotoxicity | Monitor renal function |
| Valacyclovir            | MMF, ECMS         | ±                       | ↓ MPA       | None             |
| Ganciclovir             | MMF, ECMS, AZA    | ++                      | Neutropenia  | Monitor WBC      |
| Valganciclovir          | MMF, ECMS, AZA    | ++                      | Neutropenia  | Monitor WBC      |
| Foscarnet               | CsA, TAC          | +++                     | Nephrotoxicity | Monitor renal function, Ca, Mg |
| Ciclofoxir              | CsA, TAC          | ±                       | Nephrotoxicity | Monitor renal function |
| Acalvocyvir             | MMF, ECMS         | ±                       | ↑ ACV, ↓ MPA| None             |
| I.V. Acalvocyvir        | CsA, TAC          | +++                     | Nephrotoxicity | Monitor renal function |
| Valacyclovir            | MMF, ECMS         | ±                       | ↓ MPA       | None             |
| Ganciclovir             | MMF, ECMS, AZA    | ++                      | Neutropenia  | Monitor WBC      |
| Oseltamivir             | CsA, TAC, MMF     | ±                       | 13% increase in TAC trough only | Monitor Imm levels |
|                         | SRL               | –                       | None        | None             |
| Zanamivir               | CsA, TAC, SRL, EVR|                        | None        | None             |
| MMF, ECMS               | –                 | None                    | Myelosuppression | Hold MMF, ECMS, AZA and monitor WBC, hematocrit, and platelets |
| Leflunomide             | MMF, ECMS, AZA, SRL, EVR | +++ | None | None             |
|                         |                   |                         |             |                  |
| Antiretroviral agents—NNRTIs | CsA, TAC, SRL, EVR | ++                     | ↓ CsA, ↓ TAC | Monitor Imm level |
| EFV                     |                   |                         |             |                  |
| NVP                     | CsA, TAC, SRL, EVR| ±                       | May ↓ Imm level | Monitor Imm level |
| ETR                     | CsA, TAC, SRL, EVR| ±                       | May ↓ Imm level | Monitor Imm level |
| DLV                     | CsA, TAC, SRL, EVR| ++                      | ↑ Imm level  | Monitor Imm level |
| Antiretroviral agents—PIs | CsA, TAC, SRL, EVR | ++                     | ↑ CS     | CsA 25–50 mg daily |
| ATV, DRV, FPV, IDV, LPV, NFV, RTV, SQV, TPVr | with RTV regimens | ++                     | ↑ TAC/SRL/EVR | TAC 1 mg once or twice a week |
|                         |                   |                         |             | SRL 1 mg once or twice a week |
|                         |                   |                         |             | When using RTV-PI boosted regimen |
|                         |                   |                         |             | TPVr interaction unpredictable |
| Antiretroviral agents—NRTIs | MMF/ECMS         | +                       | None        | None             |
| ZDV                     |                   |                         |             |                  |
| D4T                     | MMF/ECMS          | +                       | None        |                  |

Imm, immunosuppressant; CsA, cyclosporine; TAC, tacrolimus; SRL, sirolimus; EVR, everolimus; MMF, mycophenolate mofetil; ECMS, enteric-coated mycophenolate sodium; AZA, azathioarine (Data on EVR not always present, but included in table on basis of similar route of metabolism to other immunosuppressants involved in drug–drug interactions.); NNRTIs, nonnucleoside reverse transcriptase inhibitors: DLV, delavirdine; EFV, efavirenz; ETR, etravirine; NVP, nevirapine, NRTIs, nucleoside reverse transcriptase inhibitors: AZT, zidovudine; D4T, stavudine (none of the NRTIs are expected to interact with CsA, TAC, SRL, EVR); PIs, protease inhibitors: ATV, atazanavir; DRV, darunavir; FPV, fosamprenavir; IDV, indinavir; LPV, lopinavir + ritonavir; NFV, nelfinavir; RTV, ritonavir; SQV, saquinavir; TPV, tipranavir + ritonavir; ZDV, zidovudine; D4T, stavudine
Interactions between Antimalarial Drugs and Immunosuppressants

Artemether/lumefantrine is a new antimalarial drug. Artemether is an inducer of CYP3A4 and it has the potential to decrease the levels of CNIs and mTOR inhibitors. Drug levels should be monitored while patient is on artemether/lumefantrine. 

CONCLUSION

Immunosuppression plays a vital role in improving graft survival and has improved patient outcomes significantly over the 50 years. Infections with either bacteria, fungi, viruses, or parasites are the most common complication of immunosuppression. Significant interactions occur between immunosuppressants and antimicrobials. Therefore, appropriate dosing and delivery of antimicrobials in these patients is a major challenge. Modulation of cytochrome P450 3A4 and drugs transporters such as P-gp may alter the blood levels of both antimicrobials and immunosuppressants causing alteration in organ function, ineffective immunosuppression, etc. Careful choice of antimicrobials and therapeutic drug level monitoring are essential aspects to improve the outcomes in these patients.

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