Enferm Infecc Microbiol Clin. 2012;**30(Supl 2)**:86-92

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Antimicrobial and immunosuppressive drug interactions in solid organ transplant recipients

Soledad Berdaguer[a], Javier Bautista[b], Mercè Brunet[c] and José Miguel Cisneros[d,*]

[a]*Department of Pharmacology, Hospital Universitario Virgen del Rocío-IBIS, Seville, Spain*
[b]*Clinical Pharmacy Unit, Hospital Universitario Virgen del Rocío-IBIS, Seville, Spain*
[c]*Department of Pharmacology, Hospital Clínic-IDIBAPS, Barcelona, Spain*
[d]*Infectious Diseases, Microbiology and Preventive Medicine Unit, Hospital Universitario Virgen del Rocío-IBIS, Seville, Spain*

Keywords:
Antibacterials
Antifungals
Antimicrobials
Antiretrovirals
Antivirals
Drug interaction
Immunosuppressants
Transplantation

A B S T R A C T

Infections are frequent and can be severe in recipients of solid organ transplantation. Prevention and treatment are priority objectives of multidisciplinary transplant teams. Interactions between antimicrobials (indicated for prevention and therapy) and immunosuppressants (for preventing rejection) make treatment more complex than in the general population. Co-administration of immunosuppressants and antibiotics can cause harmful interactions, modifying the pharmacokinetic and pharmacodynamic characteristics of both groups of drugs. The loss of the transplanted organ due to reduced levels of immunosuppressants is a unique consequence of the often lethal interactions in this group of patients. By contrast, elevated levels of these drugs cause toxicity, and reduced concentrations of antimicrobial treatment fail to contain the infection. Azoles, rifabutin, protease inhibitors, non-nucleoside reverse transcriptase inhibitors and antimicrobial macrolides all interact with immunosuppressants. In this article, we review interactions between antibiotics and immunosuppressants in order to adopt the most appropriate clinical approach (dosage adjustments, close monitoring of plasma levels and organ function) and determine whether they can be used together with any measure of safety.

Interacciones entre antimicrobianos y fármacos inmunosupresores en receptores de trasplante de órgano sólido

Palabras clave:
Antibacterianos
Antimicrobianos
Antifúngicos
Antivirales
Inmunosupresores
Interacción farmacológica
Trasplante

R E S U M E N

Las infecciones son frecuentes y más graves en receptores de trasplante de órgano sólido. La prevención y tratamiento es una prioridad objetiva de los equipos multidisciplinarios de trasplante. Las interacciones entre el antimicrobiano indicado para prevención y tratamiento y los inmunosupresores para prevenir el rechazo, hacen más complejo al tratamiento que en la población general. La coadministración de inmunosupresores y antibióticos puede causar interacciones perjudiciales, modificando las características farmacocinéticas y farmacodinámicas de ambos grupos de fármacos. La pérdida del órgano trasplantado por los niveles reducidos del inmunosupresor es una consecuencia excepcional de las interacciones en este grupo de pacientes, a menudo letal. Por el contrario, los niveles elevados de estos fármacos causan toxicidad y las concentraciones reducidas de antimicrobianos, fallo del tratamiento de la infección. Los azoles, la rifabutina, los inhibidores de la proteasa, los inhibidores no nucleósidos de la transcriptasa reversa y los antibióticos macrólidos son los fármacos que presentan más interacciones con los inmunosupresores. En este capítulo revisamos las interacciones entre los antibióticos y los inmunosupresores para, en consecuencia, adoptar la decisión clínica más conveniente: ajustar las dosis de los fármacos, realizar un control exhaustivo de los niveles plasmáticos o del funcionamiento del órgano o, por el contrario, si pueden ser utilizados con seguridad.

*Corresponding author.
E-mail: jmcisnerosh@gmail.com (J.M. Cisneros).

0213-005X/$ - see front matter

Antibacterial and immunosuppressive drug interactions in solid organ transplant recipients

The following interactions have been observed between immunosuppressive drugs used for solid organ transplant (SOT) patients and antibacterial drugs. The text shows the most relevant interactions; for additional information, please refer to Tables 1 to 7.

Aminoglycosides (Table 1)

Since the nephrotoxicity of these drugs can be potentiated, renal function monitoring is recommended if there is concurrent use with cyclosporine and tacrolimus.[1,2] If renal impairment develops, dose adjustment for aminoglycosides or alternative antibiotic use should be considered.[3]

Beta lactams (Table 2)

Nafcillin may potentiate nephrotoxicity caused by cyclosporine; therefore, alternative antibiotic use is recommended.[4] Amoxicillin-clavulanate alters intestinal flora, affecting mycophenolate absorption by enterohepatic recirculation. Close clinical monitoring is advisable during concurrent use, until shortly after antibiotic treatment is finished.[5]

Macrolides (Table 3)

Clarithromycin may cause clinically relevant increases in cyclosporine levels by inhibition of cytochrome CYP3A4 enzyme. Monitoring of cyclosporine levels and reducing dosages is recommended. Remember to adjust the cyclosporine dose when the

Table 1
Interactions between aminoglycosides and immunosuppressants*

Immunosuppressants	AMK	GEN	ETM	EPT	KAN	TOB
Cyclosporine	**B**	**B**	**B**	**B**	**B**	**B**
Tacrolimus	**B**	b	b	b	b	b
Mycophenolate	c	c	c	c	c	b
Sirolimus	b	b	b	b	b	b
Everolimus	b	b	b	b	b	b
Azathioprine	c	c	c	c	c	c
Prednisone	c	c	c	c	c	c
Methylprednisolone	c	c	c	c	c	c
Dexamethasone	c	c	c	c	c	c
Polyclonal ab (ATG)	c	c	c	c	c	c
Basiliximab	c	c	c	c	c	c
Muromonab	c	c	c	c	c	c

[a]AMK: amikacin; ETM: streptomycin; EPT: spectinomycin; GEN: gentamicin; KAN: kanamycin; TOB: tobramycin.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Table 3
Interactions between macrolides and immunosuppressants*

Immunosuppressants	AZY	CLA	ERY	JOS	ROX	TEL	TRO
Cyclosporine	c	**B**	**B**	A	b	a	A
Tacrolimus	nd	**B**	**B**	B	nd	b	b
Mycophenolate	c	c	c	C	c	c	c
Sirolimus	b	**A**	**B**	B	b	**A**	a
Everolimus	c	a	**B**	B	b	a	a
Azathioprine	c	c	c	C	c	c	c
Prednisone	b	b	b	B	b	b	b
Methylprednisolone	c	**B**	**B**	B	b	b	**B**
Dexamethasone	b	b	b	B	b	b	b
Polyclonal ab (ATG)	c	c	c	C	c	c	c
Basiliximab	c	c	c	C	c	c	c
Muromonab	c	c	c	C	c	c	c

*AZY: azithromycin; CLA: clarithromycin; ERY: erythromycin; JOS: josamycin; ROX: roxithromycin; TEL: telithromycin; TRO: troleandomycin.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; nd: Data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Table 2
Interactions between beta lactams and immunosuppressants*

Immunosuppressants	AMP	AMC	CLO	NAF	CFU	CFZ	CFX	AZT	IMI	TIC
Cyclosporine	c	c	B	**B**	c	b	b	c	b	c
Tacrolimus	c	b	C	c	c	c	c	c	c	c
Mycophenolate	c	**B**	C	c	b	c	c	c	c	c
Sirolimus	c	c	C	c	c	c	c	c	c	c
Everolimus	c	c	C	c	c	c	c	c	c	c
Azathioprine	c	c	C	c	c	c	c	c	c	c
Prednisone	c	c	C	c	c	c	c	c	c	c
Methylprednisolone	c	c	C	c	c	c	c	c	c	c
Dexamethasone	c	c	C	c	c	c	c	c	c	c
Polyclonal ab (ATG)	c	c	C	c	c	c	c	c	c	c
Basiliximab	c	c	C	c	c	c	c	c	c	c
Muromonab	c	c	C	c	c	c	c	c	c	c

AMP: ampicillin; AMC: amoxicillin-clavulanate; AZT: aztreonam; CFU: cefuroxime; CFX: ceftriaxone; CFZ: ceftazidime; CLO: flucloxacillin; IMI: imipenem; NAF: nafcillin; TIC: ticarcillin.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

antibiotic cycle is finished.[6] Clarithromycin also increase tacrolimus levels due to inhibition of cytochrome CYP 3A4 metabolism. Monitoring of tacrolimus levels and appropriate dose adjustment is recommended to maintain stable tacrolimus exposure.[8]

Erythromycin has the same mechanism as clarithromycin, but to a greater extent, and cyclosporine dose adjustment is once again recommended. Additionally, the effect of oral erythromycin over cyclosporine levels may be greater when given intravenously.[7] A low tacrolimus dose should be used and blood levels should be monitored.[9] Due to the strong inhibition of cytochrome CYP 3A4 and P-glycoprotein by clarithromycin, sirolimus (rapamycin) levels may increase, and therefore this combination is not recommended.[10] Coadministration of sirolimus and erythromycin show increases in plasma levels of both drugs. Sirolimus levels should be monitored, and dose adjustment for both drugs is recommended.[11] Telithromycin may also increase sirolimus levels, and therefore this combination is not recommended.[12] Erythromycin increases levels of everolimus due to erythromycin inhibition of cytochrome enzyme CYP3A4. Dose adjustment of everolimus is recommended and, if possible, the combination should be avoided.[13] Clarithromycin, erythromycin and troleandomycin decrease clearance of methylprednisolone when used concomitantly. Empirical dose adjustment for methylprednisolone is recommended.[14-16]

Quinolones (Table 4)

Ciprofloxacin and the combination of norfloxacin and metronidazole appears to decrease mycophenolate levels by interfering with enterohepatic circulation in the bowel, decreasing absorption of mycophenolate mofetil.[5,17] Close clinical monitoring is advisable.

Table 4
Interactions between quinolones and immunosuppressants*

Immunosuppressants	CIP	LEV	MOX	NAL	NOR	OFL
Cyclosporine	b	b	nd	nd	b	c
Tacrolimus	b	b	a	b	b	b
Mycophenolate	**B**	c	c	c	**B**	c
Sirolimus	c	c	c	c	c	c
Everolimus	c	c	c	c	c	c
Azathioprine	c	c	c	c	c	c
Prednisone	b	b	b	b	b	b
Methylprednisolone	b	b	b	b	b	b
Dexamethasone	b	b	b	b	b	b
Polyclonal ab (ATG)	c	c	c	c	c	c
Basiliximab	c	c	c	c	c	c
Muromonab	c	c	c	c	c	c

CIP: ciprofloxacin; LEV: levofloxacin; MOS: moxifloxacin; NAL: nalidixic acid; NOR: norfloxacin; OFL: ofloxacin.
*__A__/a: these drugs should not be coadministered; __B__/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; __C__/c: no clinically significant interaction expected; nd: Data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Tuberculostatics (Table 5)

Rifampin markedly reduces cyclosporine levels by the induction of its metabolism by the liver and the gut wall, and graft rejection can develop. Concomitant use of these drugs should be avoided.[18] Rifampin causes strong induction of cytochrome CYP 3A4 and decreases tacrolimus levels, and cases of acute rejection have been observed. Blood levels should be monitored and dosage increased to maintain therapeutic levels.[19] Concomitant use of mycophenolate and rifampin leads to higher blood levels of the acyl-glucuronide metabolite of mycophenolate. Although not demonstrated, this phenomenon may lead to an increase in adverse effects and toxicity. Blood levels should be monitored and the dose adjusted as required.[20] Concomitant use with rifampicin markedly decreases sirolimus levels (C_{max} 71% and AUC 82%), and therefore this combination is not recommended. Concomitant use of rifampicin and rifabutin markedly decreases sirolimus levels, and therefore this combination is not recommended. Rifapentine may act the same way, but to a lesser extent, making it an acceptable alternative.[12] With rifampin, everolimus clearance is increased up to 172% and AUC and blood levels decreased due to cytochrome CYP 3A4 and P-glycoprotein induction.[21] The manufacturer recommends increasing the dose from 10 mg to 20 mg by increasing the dose by 5 mg on day 4 and 8 following the start of rifampin, although there are no clinical data to support this adjustment.[22] Rifampin causes clinically significant decreases in the effects of steroids, to the point of adrenal insufficiency. Increasing the dose of steroids is recommended and the dose should be reduced progressively after discontinuation of rifampin.[23,24]

Table 5
Interactions between tuberculostatics and immunosuppressants*

Immunosuppressants	ISO	RIF	RFB	RFP	PYR	ETB	ETI
Cyclosporine	b	**A**	b	b	b	b	c
Tacrolimus	b	**A**	b	b	c	c	c
Mycophenolate	c	**A**	a	b	c	c	c
Sirolimus	c	**A**	**A**	b	c	c	c
Everolimus	b	**A**	a	b	c	c	c
Azathioprine	c	c	c	c	c	c	c
Prednisone	c	**B**	b	b	c	c	c
Methylprednisolone	c	**B**	b	b	c	c	c
Dexamethasone	c	**B**	b	b	c	c	c
Polyclonal ab (ATG)	c	c	c	c	c	c	c
Basiliximab	c	c	c	c	c	c	c
Muromonab	c	c	c	c	c	c	c

ETB: ethambutol; ETI: ethionamide; ISO: isoniazid; RIF: rifampin; RFB: rifabutin; RFP: rifapentine; PYR: pyrazinamide.
*__A__/a: these drugs should not be coadministered; __B__/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; __C__/c: no clinically significant interaction expected; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Other antibacterial drugs (Tables 6 and 7)

Nephrotoxicity can be potentiated by the simultaneous administration of cyclosporine and vancomycin, while monitoring renal function.[3] Mycophenolate and metronidazole, given in combination with norfloxacin, can decrease mycophenolate concentration. Blood levels should be monitored.[17] Dalfopristin/quinupristin can increase cyclosporine concentration by inhibition of cytochrome CYP 3A4.[25] Cyclosporine levels should be monitored if both drugs are combined. Additionally, cyclosporine appears to increase the risk of myalgia and arthralgia caused by dalfopristin/quinupristin. Dalfopristin/quinupristin increases tacrolimus levels up to 15%, and therefore monitoring of tacrolimus blood levels is recommended. It also appears that tacrolimus potentiates arthralgia and myalgia caused by dalfopristin/quinupristin.[26]

Table 6
Interactions between other antimicrobials and immunosuppressants (I)*

Immunosuppressants	TIG	VAN	DAP	CLI	MET
Cyclosporine	b	**B**	b	b	b
Tacrolimus	b	b	nd	c	b
Mycophenolate	nd	c	nd	c	**B**
Sirolimus	nd	c	nd	c	c
Everolimus	nd	c	nd	c	c
Azathioprine	nd	c	nd	c	c
Prednisone	nd	c	b	c	c
Methylprednisolone	nd	c	b	c	c
Dexamethasone	nd	c	b	c	c
Polyclonal ab (ATG)	nd	c	nd	c	c
Basiliximab	nd	c	nd	c	c
Muromonab	Nd	c	nd	c	c

CLI: clindamycin; DAP: daptomycin; MET: metronidazole; TIG: tigecycline; VAN: vancomycin.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; nd: data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Table 7
Interactions between other antimicrobials and immunosuppressants (II)

Immunosuppressants	LIN	COT	DAL	DOX	TET
Cyclosporine	nd	b	**A**	c	c
Tacrolimus	nd	b	**B**	c	**B**
Mycophenolate	nd	**C**	nd	c	c
Sirolimus	nd	**C**	b	c	c
Everolimus	nd	c	b	c	c
Azathioprine	nd	c	nd	c	c
Prednisone	nd	c	b	c	c
Methylprednisolone	nd	c	b	c	c
Dexamethasone	nd	c	b	c	c
Polyclonal ab (ATG)	nd	c	c	c	c
Basiliximab	nd	c	c	c	c
Muromonab	nd	c	c	c	c

COT: cotrimoxazole; DAL: dalfopristin/quinupristin; DOX: doxycycline; LIN: linezolid; TET: tetracycline.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; nd: data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Antifungal and immunosuppressive drug interactions in solid organ transplant recipients

The following interactions have been observed between immunosuppressant and antifungal drugs used in SOT patients. The text shows the most relevant interactions, and more information is displayed on Tables 8-10.

Azoles (Table 8)

The most clinically significant drug interactions observed with azoles in SOT recipients occur with concomitantly administered immunosuppressive agents, specifically, with the calcineurin inhibitors (cyclosporine and tacrolimus) and the mammalian target of mTOR-inhibitor, sirolimus.[27]

Table 8
Interactions between azoles and immunosuppressants[a]

Immunosuppressants	KET	ITR	FLU	VOR	POS
Cyclosporine	**A**	**A**	**B**[b]	**B**[b]	**B**[c]
Tacrolimus	**A**	**A**	**B**[d]	**B**[d]	**B**[d]
Mycophenolate	nd	nd	**C**	**C**	c
Sirolimus	**A**	**A**	**B**[e]	**A**	a
Everolimus	**A**	a	b	a	a
Azathioprine	nd	nd	nd	nd	nd
Prednisone	nd	nd	nd	nd	nd
Methylprednisolone	nd	nd	nd	nd	nd
Dexamethasone	nd	nd	nd	nd	nd
Polyclonal ab (ATG)	nd	nd	nd	nd	nd
Basiliximab	nd	nd	nd	nd	nd
Muromonab	nd	nd	nd	nd	nd

FLU: fluconazole; ITR: itraconazole; KET: ketoconazole; POS: posaconazole; VOR: voriconazole.
[a]__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; nd: data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.
[b]Recommended percentage dose reductions of cyclosporine = 50%.
[c]Recommended percentage dose reductions of cyclosporine = 25%.
[d]Recommended percentage dose reductions of tacrolimus = 33%.
[e]Recommended percentage dose reductions of sirolimus = 50%.

All azole antifungals inhibit the metabolism of cyclosporine, tacrolimus, sirolimus and everolimus, which are significantly metabolised by CYP3A4 and P-glycoprotein. Ketoconazole, itraconazole, voriconazole and posaconazole are strong inhibitors and fluconazole is a weak inhibitor of CYP3A4.[27]

Ketoconazole and itraconazole increase cyclosporine, tacrolimus, sirolimus and everolimus levels. Coadministration with these drugs is not recommended. Itraconazole increases mycophenolate levels due to inhibition of P-glycoprotein. Close monitoring of levels is recommended.[12,22,27]

Fluconazole increases cyclosporine, tacrolimus, sirolimus and everolimus levels. Fluconazole oral therapy takes one week for the full magnitude of the interaction to be appreciated. Coadministration of oral fluconazole with cyclosporine or tacrolimus requires a dose reduction of immunosuppressants and monitoring levels. No dosage adjustments are recommended for cyclosporine or tacrolimus during concomitant administration of intravenous fluconazole. Fluconazole increases trough concentrations of sirolimus and probably increases that of everolimus. Dosage adjustments and close monitoring of mTOR inhibitors drugs are therefore recommended.[12,22,27,28]

Voriconazole increases cyclosporine levels (C_{max} and AUC 13% and 70%, respectively). It is recommended that the dose of cyclosporine be reduced 50%. Voriconazole also increases tacrolimus levels (C_{max} 117% and AUC 221%, respectively), and therefore it is recommended that the dose of tacrolimus be reduced 33%. Voriconazole also increases sirolimus levels (C_{max} 556% and AUC 1014%, respectively), and therefore coadministration of voriconazole with this drug is contraindicated. For the same reason, voriconazole is contraindicated in combination with everolimus.[12,22,27-29]

Posaconazole increases tacrolimus levels due to the inhibition of its metabolism by cytochrome CYP 3A4. Close monitoring of levels is recommended. Posaconazole increases mycophenolate levels due to

inhibition of P-glycoprotein, and therefore close monitoring of mycophenolate levels is recommended. The effect of posaconazole on sirolimus remains unknown, and is not predictable, due to the variable exposure of posaconazole. Concomitant administration of both drugs is not recommended and should be avoided if possible. For the same reasons, concomitant use of posaconazole with everolimus is not recommended.[12,22,28,30]

Echinocandins (Table 9)

Echinocandins have very few drug interactions. Cyclosporine increases caspofungin AUC by 35% and causes transient elevation of transaminases. Close monitoring of levels is recommended. Caspofungin decreases tacrolimus levels by 26%. Blood levels should be monitored and the dose increased. Micafungin increases sirolimus AUC by 21%, and therefore it is recommended that sirolimus levels be monitored.[12,31]

Table 9
Interactions between echinocandins and immunosuppressants*

Immunosuppressants	CAS	MIC	ANI
Cyclosporine	**B**	**B**	c
Tacrolimus	**B**	c	c
Mycophenolate	**c**	nd	nd
Sirolimus	nd	B	nd
Everolimus	nd	nd	nd
Azathioprine	nd	nd	nd
Prednisone	c	c	c
Methylprednisolone	c	c	c
Dexamethasone	c	c	c
Polyclonal ab (ATG)	nd	nd	nd
Basiliximab	nd	nd	nd
Muromonab	nd	nd	nd

CAS: caspofungin; MIC: micafungin; ANI: anidulafungin.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; nd: data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Polyene and pyrimidines (Table 10)

Since nephrotoxicity of polyene drugs can be potentiated with the concurrent use of cyclosporine or tacrolimus, caution and close monitoring of renal function is recommended. Lipid amphotericin B formulations, especially liposomal amphotericin B, are less nephrotoxic than amphotericin B deoxycholate. If renal impairment develops, alternative antifungal drugs should be considered.

Table 10
Interactions of pyrimidines and polyenes with immunosuppressants

Immunosuppressants	FUC	ABD	ABL	ABC
Cyclosporine	b	**B**	**B**	**B**
Tacrolimus	b	**B**	**B**	**B**
Mycophenolate	nd	c	nd	nd
Sirolimus	nd	**B**	b	b
Everolimus	nd	**B**	**B**	**B**
Azathioprine	nd	nd	nd	nd
Prednisone	nd	**B**	b	b
Methylprednisolone	nd	**B**	b	b
Dexamethasone	nd	nd	nd	nd
Polyclonal ab (ATG)	nd	nd	nd	nd
Basiliximab	nd	nd	nd	nd
Muromonab	nd	nd	nd	nd

ABL: liposomal amphotericin B; ABC: amphotericin B lipid complex; ABD: amphotericin B deoxycholate; FUC: flucytosine.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; nd: data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Table 11
Interactions between antivirals and immunosuppressants*

Immunosuppressants	ACV	GCV	RBV	FSC	CFV
Cyclosporine	nd	**B**	Nd	**b**	nd
Tacrolimus	nd	**B**	Nd	**b**	nd
Mycophenolate	**C**	**B**	Nd	nd	nd
Sirolimus	nd	**B**	**B**	nd	nd
Everolimus	nd	**B**	**B**	nd	nd
Mizoribine	nd	**B**	nd	nd	nd
Azathioprine	nd	nd	nd	nd	nd
Prednisone	nd	nd	nd	nd	nd
Methylprednisolone	nd	nd	nd	nd	nd
Dexamethasone	nd	nd	nd	nd	nd
Polyclonal (ATG)	nd	nd	nd	nd	nd
Basiliximab	nd	nd	nd	nd	nd
Muromonab	nd	nd	nd	nd	nd

ACV: acyclovir; CFV: cidofovir; GCV: ganciclovir; FSC: foscarnet; RBV: ribavirin.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; nd: Data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Antiviral and immunosuppressive drug interactions in solid transplant recipients

The following interactions have been observed between immunosuppressive drugs used for SOT patients and antivirals. The text shows the most relevant interactions (see Table 11 for more information).

Use of acyclovir must be carefully considered when combined with potentially nephrotoxic agents. Ganciclovir plus mycophenolate mofetil slightly decreased renal clearance. Thus, this drug combination may have an impact on patients' kidney function, and renal function should therefore be monitored. Mizoribine and ganciclovir exert a strong synergism in anti-CMV activity.[32] Ribavirin-induced activation of mTOR and p53 enhances IFN-dependent signalling for the IFN-alpha/ribavirin combined treatment.[33] Nephrotoxicity is the most common adverse effect of both foscarnet and cidofovir. They have only been used as second-line antiviral drugs in transplant recipients, but considering the widespread use of calcineurin inhibitors as the backbone of immunosuppressive treatment, they would have a clear effect on the development of nephrotoxicity.

Antiretroviral and immunosuppressive drug interactions in solid organ transplant recipients

The most relevant interactions between immunosuppressive drugs used for SOT and antiretroviral drugs are shown below (more information in Tables 12-14).[14]

Nucleotide analogues (Table 12)

There were no clinically significant pharmacokinetic interactions when tenofovir disoproxil fumarate was coadministered with tacrolimus. Given that tacrolimus can affect renal function, close monitoring is recommended when coadministered with tenofovir disoproxil fumarate. Abacavir and zidovudine, which are also glucuronidated, could alter mycophenolate levels. Monitoring the concentration of mycophenolate is recommended. Chewable/dispersible didanosine tablets and powder for oral solution contain an antacid that may decrease the absorption of dexamethasone. They should be taken at least two hours apart from antacids.[34]

Table 12
Interactions between nucleotide analogues and immunosuppressants

Immunosuppressants	ABC	ddI	FTC	3TC	d4T	TEN	ZDV
Cyclosporine	c	c	c	c	c	b	c
Tacrolimus	c	c	b	b	b	**B**	c
Mycophenolate	**B**	c	c	c	c	b	**B**
Sirolimus	c	c	c	c	c	b	c
Everolimus	nd	nd	nd	nd	nd	nd	nd
Azathioprine	c	b	c	c	c	c	c
Prednisone	nd	nd	nd	nd	nd	nd	nd
Methylprednisolone	c	c	c	c	c	c	c
Dexamethasone	c	**B**	c	c	c	c	c
Polyclonals (ATG)	nd	nd	nd	nd	nd	nd	nd
Basiliximab	nd	nd	nd	nd	nd	nd	nd
Muromonab	nd	nd	nd	nd	nd	nd	nd

ABC: abacavir; ddI: didanosine; FTC: emtricitabine; 3TC: lamivudine; d4T: stavudine; TEN: tenofovir; ZDV: zidovudine.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; nd: data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Protease inhibitors (Table 13)

Concentrations of cyclosporine, tacrolimus and sirolimus may increase when coadministered with protease inhibitors (PIs) due to CYP3A4 inhibition. More frequent therapeutic concentration monitoring of these drugs is recommended until plasma levels have stabilised.

Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA). MPA undergoes glucuronidation; coadministration of inducers of glucuronidation, such as some PIs, could alter mycophenolate levels. Monitoring of mycophenolate concentration is therefore recommended.

Dexamethasone coadministration may decrease IPs concentrations due to CYP3A induction by dexamethasone. Clinical monitoring of antiviral efficacy is therefore recommended.[34]

Table 13
Interactions between protease inhibitors and immunosuppressants*

Immunosuppressants	ATZ	DAR	FOS	LOP	NEL	RIT	SAQ	TIP
Cyclosporine	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Tacrolimus	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Mycophenolate	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Sirolimus	**B**	**B**	**B**	**B**	**B**	**B**	**B**	**B**
Everolimus	a	a	a	a	a	a	a	a
Azathioprine	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**
Prednisolone	b	b	b	**B**	b	**B**	b	b
Dexamethasone	b	**B**	**B**	**B**	**B**	**B**	**B**	b
Polyclonals (ATG)	nd	nd	nd	nd	nd	nd	nd	nd
Basiliximab	nd	nd	nd	nd	nd	nd	nd	nd
Muromonab	nd	nd	nd	nd	nd	nd	nd	nd

ATZ: atazanavir; DAR: darunavir; FOS: fosamprenavir; LOP: lopinavir; NEL: nelfinavir; RIT: ritonavir; SAQ: saquinavir; TIP: tipranavir.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; nd: data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label; a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs), and entry and integrase inhibitors (Table 14)

Rilpivirine with dexamethasone is contraindicated as significant decreases in rilpivirine plasma concentrations may occur due to CYP3A enzyme induction, which may result in loss of virologic response and possible resistance to rilpivirine or to NNRTIs.

Decreased exposure of cyclosporine, tacrolimus and sirolimus with efavirenz coadministration may be expected due to CYP3A induction. Dose adjustments of the immunosuppressants may be

Table 14
Interactions between non-nucleoside reverse transcriptase inhibitors, entry and integrase inhibitors and immunosuppressants

Immunosuppressants	EFV	ETV	NEV	DEL	RIL	MRV	RAT
Cyclosporine	**B**	**B**	**B**	**B**	b	c	**C**
Tacrolimus	**B**	**B**	**B**	**B**	b	**c**	**C**
Mycophenolate	**B**	b	**B**	**B**	c	c	b
Sirolimus	**B**	**B**	**B**	**B**	c	c	**C**
Everolimus	a	a	a	a	a	nd	nd
Azathioprine	c	c	c	c	c	c	C
Prednisolone	B	b	b	b	c	c	**C**
Dexamethasone	b	**B**	b	**B**	**A**	c	**C**
Polyclonals (ATG)	nd	nd	nd	nd	nd	nd	nd
Basiliximab	nd	nd	nd	nd	nd	nd	nd
Muromonab	nd	nd	nd	nd	nd	nd	nd

DEL: delavirdine; EFV: efavirenz; ETV: etravirine; MRV: maraviroc; NEV: nevirapine; RAT: raltegravir; RIL: rilpivirine.
*__A__/a: these drugs should not be coadministered; **B**/b: potential interaction –may require close monitoring, alteration of drug dosage or timing of administration; **C**/c: no clinically significant interaction expected; nd: data not available; **A, B, C**: indicate that the interaction has been assessed by study or within the product label. a, b, c: indicate that the interaction has been predicted based on the metabolic profiles of the drugs.

required. Close monitoring of immunosuppressant concentrations for at least 2 weeks is recommended when starting of stopping treatment with efavirenz. The same recommendation is valid for nevirapine and etravirine.

Delavirdine, unlike other currently available NNRTI agents, is an inhibitor rather than an inducer of CYP isoenzymes, and has the potential to increase concentrations of cyclosporine, tacrolimus and sirolimus. Delavirdine may also alter mycophenolate levels. Therapeutic concentration monitoring is recommended for immunosuppressant agents when coadministered with delavirdine. Dexamethasone coadministration may decrease delavirdine concentrations. It should therefore be used with caution.[34]

Conflicts of Interest

SB, JB and MB declare that they have no conflicts of interest. JMC received grants in the last three years from Astellas, Pfizer and Novartis.

References

1. Termeer A, Hoitsma AJ, Koene RA. Severe nephrotoxicity caused by the combined use of gentamicin and ciclosporine in renal allograft recipients. Transplantation. 1986;42:220-1.
2. Hows JM, Chipping PM, Fairhead S, Smith J, Baughan A, Gordon-Smith EC. Nephrotoxicity in bone marrow transplant recipients treated with ciclosporine A. Br J Haematol. 1983;54:69-78.
3. Novartis Spain. Sanndimmun neoral (ciclosporin microemulsion). Spanish summary of product characteristics. June 2011.
4. Jahansouz F, Kriett JM, Smith CM, Jamieson SW. Potentiation of ciclosporin nephrotoxicity by nafcillin in lung transplant recipients. Transplantation. 1993;55:1045-8.
5. Borrows R, Chusney G, Loucaidou M, James A, Van Tromp J, Cairns T, el al. The magnitude and time course of changes in mycophenolic acid 12-hour predose levels during antibiotic therapy in mycophenolate mofetil based renal transplantation. Ther Drug Monit. 2007;29:122-6.
6. Sádaba B, López de Ocáriz A, Azanza JR, Quiroga J, Cienfuegos JA. Concurrent clarithromycin and ciclosporin A treatment. J Antimicrob Chemother. 1998;42:393-5.
7. Harnett JD, Parfrey PS, Paul MD, Gault MH. Erythromycin-ciclosporine interaction in renal transplant patients. Transplantation. 1987;43:316–8.
8. Kunicki PW, Sobieszczanska-Malek M. Pharmacokinetic interaction between tacrolimus and clarithromycin in a heart transplant patient. Ther Drug Monit. 2005;27:107-8.
9. Jensen C, Jordan M, Shapiro R, Scantlebury V, Hakala T, Fung J, et al. Interaction between tacrolimus and erythromycin. Lancet. 1994;344:825.
10. Capone D, Palmiero G, Gentile A, Basile V, Federico S, Sabbatini M, et al. A pharmacokinetic interaction between clarithromycin and sirolimus in kidney transplant recipient. Curr Drug Metab. 2007;8:379-81.
11. Claesson K, Brattström C, Burke JT. Sirolimus and erythromycin interaction: two cases. Transplant Proc. 2001;33:2136.
12. Rapamune. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000273/WC500046437.pdf
13. Kovarik JM, Beyer D, Bizot MN, Jiang Q, Shenouda M, Schmouder RL. Effect of multiple-dose erythromycin on everolimus pharmacokinetics. Eur J Clin Pharmacol. 2005;61:35-8.
14. Fost DA, Leung DY, Martin RJ, Brown EE, Szefler SJ, Spahn JD. Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. J Allergy Clin Immunol. 1999;103:1031-5.
15. LaForce CF, Szefler SJ, Miller MF, Ebling W, Brenner M. Inhibition of methylprednisolone elimination in the presence of erythromycin therapy. J Allergy Clin Immunol. 1983;72:34-9.
16. Szefler SJ, Rose JQ, Ellis EF, Spector SL, Green AW, Jusko WJ. The effect of troleandomycin on methylprednisolone elimination. J Allergy Clin Immunol. 1980;66:447-51.
17. Naderer OJ, Dupuis RE, Heinzen EL, Wiwattanawongsa K, Johnson MW, Smith PC. The influence of norfloxacin and metronidazole on the disposition of mycophenolate mofetil. J Clin Pharmacol. 2005;45:219-26.
18. El-Agroudy AE, Refaie AF, Moussa OM, Ghoneim MA. Tuberculosis in Egyptian kidney transplant recipients: study of clinical course and outcome. J Nephrol. 2003;16:404-11.
19. Hebert MF, Fisher RM, Marsh CL, Dressler D, Bekersky I. Effects of rifampin on tacrolimus pharmacokinetics in healthy volunteers. J Clin Pharmacol. 1999;39:91-6.
20. Naesens M, Kuypers DR, Streit F, Armstrong VW, Oellerich M, Verbeke K, et al. Rifampin induces alterations in mycophenolic acid glucuronidation and elimination: implications for drug exposure in renal allograft recipients. Clin Pharmacol Ther. 2006;80:509-21.
21. Kovarik JM, Hartmann S, Figueiredo J, Rouilly M, Port A, Rordorf C. Effect of rifampicin on apparent clearance of everolimus. Ann Pharmacother. 2002;36:981-5.
22. Everolimus. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001038/WC500022814.pdf
23. Kyriazopoulou V, Parparousi O, Vagenakis AG. Rifampicin-induced adrenal crisis in addisonian patients receiving corticosteroid replacement therapy. J Clin Endocrinol Metab. 1984;59:1204-6.
24. McAllister WA, Thompson PJ, Al-Habet SM, Rogers HJ. Rifampicin reduces effectiveness and bioavailability of prednisolone. Br Med J (Clin Res Ed). 1983;286:923-5.
25. Monarch Pharmaceuticals Ireland Ltd. Synercid (Quinupristin/Dalfopristin). UK Summary of product characteristics, March 2005.
26. Raad I, Hachem R, Hanna H. Relationship between myalgias/arthralgias occurring in patients receiving quinupristin/dalfopristin and biliary dysfunction. J Antimicrob Chemother. 2004;53:1105-8.
27. Dodds-Ashley E. Management of drug and food interactions with azole antifungal agents in transplant recipients. Pharmacotherapy. 2010;30:842-54.
28. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. Pharmacotherapy. 2006;26:1730-44.
29. Voriconazole. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000387/WC500049756.pdf
30. Posaconazole. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000610/WC500037784.pdf
31. Eschenauer G, DePestel DD, Carver PL. Comparison of echinocandin antifungals. Ther Clin Risk Manag. 2007;3:71-97.
32. Kuramoto T, Daikoku T, Yoshida Y, Takemoto M, Oshima K, Eizuru Y, et al. Novel anticytomegalovirus activity of immunosuppressant mizoribine and its synergism with ganciclovir. J Pharmacol Exp Ther. 2010;333:816-21.
33. Su WC, Liu WL, Cheng CW, Chou YB, Hung KH, Huang WH, et al. Ribavirin enhances interferon signaling via stimulation of mTOR and p53 activities. FEBS Lett. 2009;583:2793-8.
34. Available at: http://www.hiv-druginteractions.org