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Report from the 2018 consensus conference on immunomodulating agents in thoracic transplantation: Access, formulations, generics, therapeutic drug monitoring, and special populations

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In 2009, the International Society for Heart and Lung Transplantation recognized the importance and challenges surrounding generic drug immunosuppression. As experience with generics has expanded and comfort has increased, substantial issues have arisen since that time with other aspects of immunomodulation that have not been addressed, such as access to medicines, alternative immunosuppression formulations, additional generics, implications on therapeutic drug monitoring, and implications for special populations such as pediatrics and older adults. The aim of this consensus document is to address critically each of these concerns, expand on the challenges and barriers, and provide therapeutic considerations for practitioners who manage patients who need to undergo or have undergone cardiothoracic transplantation.
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In 2009, the International Society for Heart and Lung Transplantation published an educational advisory regarding generic immunosuppression medications in thoracic transplantation.[1] At that time, the transplant community was faced with many of the maintenance immunosuppression drugs losing their patent protection and becoming available as generic formulations. The purpose of the advisory was to inform transplant providers about the generic approval process and recommend a strategy for monitoring patients if faced with having to switch to a generic formulation. Currently, the majority of drugs prescribed in thoracic transplantation have exhausted their patent protection and are available as generic formulations.

There are several barriers to the development of newer immunosuppressants in transplantation. One barrier is the process of drug discovery that is not only prolonged but often unsuccessful with <20% of drugs in Phase 1 testing completing Phase 3, and those drugs that actually make it to the market carry a hefty price tag. In addition, the approval requirements include the specification for a new drug to prove superiority or non-inferiority to currently available medications that would require costly long-term studies. Because event rates for rejection are low, proving superiority or non-inferiority would involve trials with large numbers of patients and uncertain outcomes.[2,3] If new drug studies were to be conducted in solid organ transplantation, it is reasonable to assume that renal transplantation would be the most likely indication owing to a variety of factors, including the non-lethal nature of kidney graft failure, ease of monitoring renal allograft function (serum creatinine), and lower trial expenditure, with the larger number of renal allograft recipients providing a larger potential market for the development of a chronic immunosuppressive drug. In the absence of a change in the way drugs are approved in the US and Europe, it is highly likely that clinicians will not have additional labeled drugs for thoracic transplantation in the next decade.

This consensus statement briefly reviews the generic approval process but moves beyond to examine what barriers exist for patients and providers for accessing immunosuppressants and whether the interference is due to the healthcare delivery system, insurance or payer, pharmaceutical industry and drug availability, or a combination of factors. This consensus statement will also address available formulations and important considerations with non-oral administration of immunosuppressants; data regarding generic products and outcomes associated with their use; recommendations for appropriate therapeutic drug monitoring of immunosuppression; and finally special populations such as infants and children, aging transplant recipients, and pregnant and nursing patients, especially those who are not commonly covered in most clinical trials or consensus documents.

Access

Paramount to successful outcomes in graft survival and ultimately patient survival is patient adherence, and adherence is contingent on having access to prescribed medications. Potential barriers to drug accessibility include availability and affordability, both of which may be greatly influenced by where the patient resides. Factors that govern accessibility are the type of medical and drug coverage that is obtainable by the patient, the drug approval process and labeling indication that may or may not limit the prescriptive use of medications, and drugs that are licensed but not marketed in certain countries owing to small market size.

The well-established immunosuppressants prescribed in thoracic transplantation are almost all available as generic drugs, and whereas branded drugs remain available, including newer formulations such as extended-release tacrolimus (TAC), the willingness of many third-party payers to authorize non-generic medications has declined. TAC is off label in lung transplants, whereas mycophenolate mofetil (MMF), mycophenolate sodium, and mTOR have varying approval for heart transplant globally. Whereas there are a growing number of medications approved to treat immunologic disorders and cancer, there have not been newer immunosuppressant agents approved for use in thoracic transplantation. Therefore, transplant providers are left with employing off-label use of newer compounds such as biologics licensed and labeled for rheumatoid arthritis or chemotherapeutic agents or continue prescribing the current immunosuppressants available.

Another barrier to access that has been a recent concern for solid organ transplantation has been the relabeling and restriction of available medications. If an existing drug undergoes approval for a new indication, it may no longer be available for transplantation. Therefore, access to transplant teams may be limited to only those

programs that have current protocols. Alemtuzumab, Campath, is a prime example because it is no longer commercially available in the US and EU. However, alemtuzumab, marketed as Lemtrada, is approved for multiple sclerosis with a stringent post-marketing surveillance program involving a certified prescriber and patient enrollment.[4] Transplant programs with existing protocols are still able to obtain alemtuzumab for a transplant indication. Any newer use involves applying for an off-label use through the company.

US experience

Drug access can be affected not only by the health insurance provider but also by the Food and Drug Administration (FDA) approved indication of the drug prescribed (Table 1).[5–11] Despite the standards of using a combination of corticosteroids and/or calcineurin inhibitors and/or antimetabolites in all organ recipients, access to these drugs continues to be plagued with increasing intensity of scrutiny on payer approval. Such variations in payer approval can be further complicated by payer source (such as government-funded insurance or private insurance), age of the patient at transplantation, subsequent ability to work, and marital status. Each of these life circumstances can impact drug accessibility. Most of the maintenance immunosuppressants carry approval for adult heart transplantation, but there are no drugs with the indication for lung transplantation or for pediatric transplantation in the US. Approval for insurance to pay for coverage is often dependent upon the type of coverage a patient holds and the agent requested. Despite guidelines, consensus documents, and newer single-center data supporting the use of some agents, payers may still deny access to patients owing to a lack of FDA labeling.

Drugs beyond maintenance immunosuppression, such as those used for induction therapy, including anti-thymocyte globulin and monoclonal antibodies (basiliximab and alemtuzumab);[12–15] or agents for antibody-mediated rejection and desensitization, such as rituximab, intravenous (IV) immunoglobulin, bortezomib, carfilzomib,[16–18] are not approved for use in thoracic transplantation. These agents are utilized during a hospitalization, and their fee is added to the overall cost of the in-patient stay; therefore, coverage is not an issue from a payer's perspective. These therapies lack approved indications and even randomized controlled data and often take specialized authorization in order for the treatment to occur in this setting. There is a growing concern among healthcare systems owing to increasing hospital formulary expenditures adding to the overall cost of transplantation. Transplant teams are faced with formulary restrictions, strict protocol development for the use of newer agents, or blanket denials owing to lack of strong data for use and prohibitive cost. If an agent is approved either by the healthcare system formulary or by the payer, outpatient infusion areas are often used to finish treatment for an antibody-mediated rejection or for desensitization therapy to minimize the hospital bill that would be associated with the therapy.

Non-US experience

Worldwide approved indications of transplant medications vary from country to country and between different areas in the EU (Table 1)[5–11] and are often limited in heart and lung transplants. Healthcare delivery is also diverse in areas that perform transplantation around the world; whereas some countries have universal healthcare or socialized healthcare systems, others have private payers and government insurers as well. Despite a lack of licensing, these agents are often prescribed and supplied off label through various agreement processes with the commissioners or payers for reimbursement. In the United Kingdom and Australia, prescriptions are written for innovator brands or a branded generic to ensure continuity and prevent switching to or between generic products. Other European countries allow the dispensing pharmacist to perform generic substitution at the time of dispensing.

Therefore, access to medications for patients will once again vary depending on the regulations of the country and healthcare system where the patient resides, but medication may often be covered without the need for special approval under the care of transplantation. In some instances, rulings may be created to allow drugs that are approved for a similar indication to be dispensed for another, such is the case in Italy where mycophenolate is not approved for lung transplantation but can be applied for and covered owing to a law allowing drug reimbursement.

Formulations and administration

Immunosuppressants in current use are available in several different dosage forms, both commercially available and available as other formulations such as compounded oral suspensions. This section addresses the different drugs and dosage forms as well as approaches to administration, including enteric administration of immunosuppressants. Table 2[6–11,19–29] summarizes the formulations of immunosuppressants currently used.

TAC

TAC has become the cornerstone of immunosuppressive therapy for cardiothoracic transplant recipients.[30] TAC is commercially available as oral capsules, sachets, and IV formulations.[7] Alternative administration strategies have also been reported, with TAC given sublingually as sachets or as a compounded oral suspension.

The IV form of TAC contains a castor oil derivative, which has caused anaphylactic reactions.[7] IV TAC may be given as an intermittent infusion (over 4 hours) or as a continuous infusion at 10% to 33% of the daily oral dose; the use of a continuous infusion may decrease the risk of neurotoxicity and nephrotoxicity.[31] Owing to the possibility of adherence to polyvinyl chloride (PVC), IV TAC should be dispensed in non-PVC containers and administered with non-PVC tubing.[32]

Table 1 Approved Indications for Immunosuppressants[5–11]

Transplanted organ	Ciclosporin Neoral[5]/ Sandimmune[6]	Ciclosporin Sandimmune[6]	TAC IR capsules[7]	TACSR capsules[7]	TACsachets[7]	MMF[9]	MPA[8]	Azathioprine	Sirolimus[10]	RAD[11]
Heart	US AP Europe AP Australia AP C/S America	EU AP Australia AP	US AP Europe AP Australia AP	Europe Adult only Australia AP	Europe AP	US A Europe A[a] Australia A	Europe NO Australia NO	Europe AP Australia AP	Europe NO Australia NO	EU A[a] Australia A C/S America
Lung	Europe AP Australia NO C/S America	Europe AP Australia NO	Europe[b] AP Australia AP	Europe[b] A Australia AP	Europe[c]	Europe NO Australia Adult	Europe NO Australia NO	Europe AP Australia AP	EU NO Australia NO	EU NO
Kidney	US AP Europe AP Australia AP	Europe AP Australia AP	US AP Europe AP Australia AP	US AP Europe A Australia AP	Europe AP	US A Europe A[a] Australia AP	US A, peds > 5 years Europe A[a] Australia A	US A Europe AP Australia AP	US A Europe A[a] Australia AP	EU A[a] US A only Australia A
Liver	US AP Europe AP Australia AP	Europe AP Australia AP	US AP Europe AP Australia AP	Europe A Australia AP	Europe AP	US A Europe A[a] Australia A only	Europe NO Australia NO	Europe AP Australia AP	Europe NO Australia NO	EU A[d] Australia A

Abbreviations: A, adult; AP, adult and pediatric; C/S, Central and South America; IR, immediate release; MMF, mycophenolate mofetil; MPA, mycophenolic acid; NO, none; ped, pediatric; RAD, everolimus; SR, sustained release; TAC, tacrolimus.

[a]Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products in A patients.

[b]Treatment of allograft rejection resistant to treatment with other agents in ped and A patients.

[c]Licensed in combination with ciclosporin and steroids.

[d]For liver transplant, it should be used in combination with TAC and corticosteroids.

Table 2 Immunosuppressant Formulations[6–11,19–29]

Class	Drug	Dosage forms	Usual-dosing frequency	Administration considerations
Calcineurin inhibitors	CSA	Non-modified formulations (oil based)[6] Oral capsules: 10 mg, 25 mg, 100 mg. Oral solution: 100 mg/ml. Injectable solution: 50 mg/ml. Modified formulations (microemulsion)[5,19] Oral liquid-filled capsules: 10 mg (EU and Oz), 25 mg, 50 mg, 100 mg. Oral solution: 100 mg/ml.	Oral: 12 hours IV: continuous or intermittent infusion over 2—6 hours every 12 hours[6]	Avoid PVC-containing bags and tubing with parenteral formulation owing to leaching of DEHP[6] No known interactions with enteral feeds[20]
	TAC	Oral capsules (IR)[7]: 0.5 mg, 1 mg, 5 mg. Oral capsules (ER)[21]: 0.5 mg, 1 mg, 3 mg, 5 mg. Oral tablets (ER)[23]: 0.75 mg, 1 mg, 4 mg. Injectable solution[5]: 5 mg/ml Oral suspension (0.5 mg/ml) may be compounded from IR capsules with a 56-day stability[8] Sachets of 0.2 mg and 1 mg are available in the EU	Oral (IR): 12 hours Oral (ER): 24 hours IV: continuous or intermittent infusion over 4—6 hours every 12 hours[25]	Contents of IR capsules may be administered sublingually using 50%—70% of the oral dose[22] No significant interaction with continuous enteral feeds[20,24] ER capsules and tablets are not interchangeable Do not crush or open oral ER products owing to loss of sustained-release mechanism[35,36] Avoid PVC-containing bags and tubing with parenteral formulation owing to drug adsorption[7] Phthalate stripping
Anti-proliferatives	MMF	Oral capsule[9]: 250 mg. Oral tablet[9]: 500 mg. Powder for oral suspension[9]: 200 mg/ml. Powder for injection[9]: 500 mg.	12 hours	Suspension may be given through NGT (size 8 French or larger)[9] Do not crush tablets or open capsules owing to teratogenicity[9] No significant interaction with continuous enteral feeds[20] Requires acidic gastric pH for adequate absorption; do not coadminister with antacids (Mg, Al) and use proton pump inhibitors with caution[9]
	Mycophenolate sodium	Oral tablets (DR)[8]: 180 mg, 360 mg.	12 hours	Do not split or crush tablets owing to teratogenicity and loss of enteric coating[8] Do not coadminister with antacids (Mg, Al)[8] PK studies indicate no significant interaction with pantoprazole[26,27]
	Azathioprine	Oral tablets[28]: 25 mg, 50 mg, 75 mg, 100 mg. Powder for injection[28]: 100 mg Oral suspension (50 mg/ml) may be compounded from tablets with a 60-day stability[28,29]	24 hours	Do not split or crush tablets (follow local procedures to avoid exposure to crushed tablets)

(*continued on next page*)

Table 2 (*Continued*)

Class	Drug	Dosage forms	Usual-dosing frequency	Administration considerations
mTOR inhibitors	Sirolimus	Oral tablets[10]: 0.5 mg, 1 mg, 2 mg. Oral solution[10]: 1 mg/ml.	24 hours	No known interactions with enteral feeds[20] Do not split or crush tablets[10] Administer 4 hours after ciclosporin to avoid increased sirolimus exposure/toxicity[10] The 0.5 mg tablet is not fully bioequivalent to the 1 mg, 2 mg, and 5 mg tablets when comparing C_{max}. Multiples of the 0.5 mg tablets should therefore not be used as a substitute for other tablet strengths.
	RAD	Oral tablets[11]: 0.25 mg, 0.5 mg, 0.75 mg, 1 mg. Tablet for oral suspension[11]: 2 mg, 3 mg, 5 mg.	12 hours	Do not split or crush tablets[11] Administer concurrently with ciclosporin or TAC[11]
Corticosteroids	Prednisone	Oral tablets: 1 mg, 2.5 mg, 10 mg, 20 mg, 25 mg, 50 mg. Oral solution: 1 mg/ml, 5 mg/ml.	24 hours	
	Prednisolone	Orally disintegrating tablet: 10 mg, 15 mg, 30 mg. Oral solution: 1 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml. Solution for injection: 50 mg/ml.	24 hours	
Methylprednisolone	Solu-Medrol		24 hours	

Abbreviations: Al, aluminum; $C_{max,}$ peak of drug concentration; CSA, ciclosporin A; DEHP, Di(2-ethylhexyl)phthalate; DR, delayed release; ER, extended release; IV, intravenous; IR, immediate release; Mg, magnesium; MMF, mycophenolate mofetil; NGT, nasogastric tube; Oz, official abbreviation for Australia; PK, Pharmacokinetic; PVC, Polyvinyl Chloride; RAD, everolimus; TAC, tacrolimus.

A TAC suspension may be useful for pediatric patients and patients with a nasogastric or orogastric tube. It is compounded as a 0.5 mg/ml suspension (stable for 56 days) or as a 1 mg/ml suspension with 4-month stability.[22,33] The exact conversion rate from a different dosage form to suspension cannot be determined because some of the TAC in the suspension may adhere to the feeding tube and enteral feedings can also alter gastrointestinal absorption of TAC. TAC sachets are available, which may be preferable for administration through nasogastric tubes, which prevents compounding and the stability of a compounded suspension.

Sublingual TAC may be useful for patients who cannot take capsules by mouth or with poor enteral absorption.[34] No consensus exists on the appropriate administration technique or the optimal dose conversion from oral to sublingual; however, most transplant centers utilize a 50% dose reduction and advise opening of the immediate-release capsule with contents deposited under the tongue.[22,25] Because TAC is a hazardous drug, those handling any form of TAC other than intact capsules are recommended to wear gloves as well as a non-permeable gown.[35]

A total of 2 extended-release formulations of TAC are available: capsules (Astagraf XL [US] and Advagraf [EU], Astellas)[36] and tablets (Envarsus XR, Veloxis Pharmaceuticals).[21] Data with these dosage forms are limited in heart and lung transplant recipients. Extended-release products are neither interchangeable with each other nor with immediate-release TAC. Studies have shown that a conversion dose of 1:1 has yielded appropriate levels after conversion from twice-daily TAC to daily TAC XL capsules, with <33% of patients studied needing dose changes in the follow-up period. It is necessary to use a 1:1 dose conversion and employ therapeutic dose monitoring in the period after conversion to ensure that goal levels are retained.[23, 37] There is no specific dose equivalence published in thoracic transplant during conversion from twice-daily TAC to TAC XR tablets. Patients and clinicians need to be aware of the different agents so that there is no inadvertent substitution of TAC XR tablets for XL capsules.

Ciclosporin

The introduction of ciclosporin (international non-proprietary name, with variations in spelling in some countries) in 1983 revolutionized transplant immunosuppression. A highly lipophilic compound, oral ciclosporin (Sandimmune, Novartis) has poor and highly intra- and interindividual variability in absorption that is heavily dependent on bile.[38] Sandimmune is commercially available as capsules, oral solution, and IV solution.[6] An oral microemulsion formulation of ciclosporin, available as capsules and an oral solution, was introduced in 1996 (Neoral, Novartis) with improvements in the intrasubject area under the curve (AUC) variability.[5,39]

The bioequivalence of the microemulsion and unmodified products has been compared in several small pharmacokinetic (PK) studies of adult and pediatric transplant recipients ($n \leq 50$).[40–54] The relative bioavailability of oral ciclosporin compared with microemulsion ciclosporin is consistently <80%, with an overall relative bioavailability of 76.3% (90% CI: 73.4%−79.3%) seen in a meta-analysis of available PK analyses,[55] below the threshold of bioequivalence of 80% to 125%[56] and far below the more stringent threshold of 90% to 110% often recommended for narrow therapeutic index medications.[57] On the basis of these data, ciclosporin and microemulsion ciclosporin should not be interchanged, and when converting between products, exposure differences should be considered, with empirical dose adjustments made to avoid sub- or supratherapeutic drug exposure.

IV ciclosporin has been associated with an anaphylactic-type reaction thought to be caused by the polyoxyethylated castor oil vehicle. Thus, close observation during initial infusion is recommended.[6] In addition, the polyoxyethylated castor oil vehicle can lead to phthalate stripping from PVC tubing and IV bags; only non-PVC bags and tubing should be utilized to minimize di(2-ethylhexyl)phthalate leeching.[6] If an oral dose is converted to an IV dose, the dose must be reduced to 25% to 33% of the oral dose, given twice daily as 2 to 6 hours infusions.[6] Given these considerations, IV ciclosporin should only be utilized when patients are unable to take or tolerate oral ciclosporin.

Anti-metabolites

The most commonly utilized anti-metabolites for maintenance immunosuppression are azathioprine and mycophenolate; the latter being utilized to a significantly higher degree in both heart and lung transplants.[58] Mycophenolate is available as 2 formulations: mycophenolic acid (MPA) enteric-coated tablets (Myfortic, Novartis)[8] and MMF (CellCept, Genentech). MMF is commercially available as capsules, tablets, powder for oral suspension, and lyophilized powder for IV administration.[9] Whereas they are not interchangeable, the bioequivalent dosing of MPA to MMF has been established at 360 mg MPA to 500 mg MMF.[59]

One consideration in the choice of mycophenolate formulation is the interaction between MMF and proton pump inhibitors. In multiple PK studies, transplant recipients have demonstrated a decrease in mycophenolate exposure while on a proton pump inhibitor[60–66]; mycophenolate AUC appears to be decreased by approximately 30% when MMF is coadministered with proton pump inhibitors. This interaction is not present with enteric-coated mycophenolate.[67,68] However, there are no reports demonstrating a clinical difference in rates of rejection,[69–71] although a trend to worse outcomes has been suggested.[66] Given the relative infrequency of mycophenolate therapeutic drug monitoring in clinical practice, careful consideration should be given to coadministration of proton pump inhibitors with, specifically, the MMF formulation.

It is imperative to use commercially available powder for suspension when enteral tubes are used. Mycophenolate is teratogenic; therefore, both MMF and MPA tablets should not be crushed, and capsules should not be opened

to make a solution for enteral tubes. Owing to the teratogenic properties of mycophenolate, the waste after the IV has been infused should be handled as cytotoxic and must be handled accordingly as directed by each hospital.

Non-oral enteral administration

Non-oral enteral tubes are commonly utilized in pediatrics, those with dysphagia or gut dysfunction, and critically ill patients, among others. Enteral tubes can be classified by their termination point (gastric, duodenal, jejunal) as well as the type of placement (nasal vs percutaneous). Continuation of immunosuppression through periods of poor or limited oral intake is critical; therefore, administration through enteral tubes is often necessary or desired.

All available maintenance oral immunosuppressants apart from everolimus (RAD) are either commercially available as an oral solution or suspension (sirolimus, ciclosporin, glucocorticoids, MMF)[5,9,10,72] or have well-established compounded formulas (TAC, azathioprine) and should be used instead of crushing tablets or opening capsules to avoid mechanical clogging of the tube.[25,73] Given that ciclosporin[74] and sirolimus[75] are predominantly absorbed in the duodenum and jejunum, administration through a gastric tube is preferred over jejunal administration. MMF is absorbed in the small intestine after the prodrug is cleaved to active MPA.[76] Corticosteroids,[77] TAC,[78] and azathioprine[79] are absorbed throughout the entire gastrointestinal tract and therefore site of tube placement is less critical. MPA is enteric coated and should not be crushed.

Generics

The US Patent Office awards drug patents in the US for a period of 20 years. In addition, pharmaceutical companies may be granted a term of market exclusivity by the FDA at the time of approval that can run concurrently with the patent or extend beyond its expiration. The European Medicines Agency grants a 10-year market protection, which prohibits the marketing of generic, hybrid, or biosimilar agents even if they have been granted market authorization. This term of exclusivity will limit generic availability of a medication once a patent expires as well as factors in the differences in costs between the original, proprietary medication and a generic formulation.[80] Once exclusivity expires, more than 1 generic formulation may become available. Generic formulations must meet a bioequivalence standard. However, this testing is conducted either in vitro or in healthy volunteers, not patients.

Many oral preparations currently used for maintenance immunosuppression are available as generic formulations (depending on country approval of generic). The choice of the proprietary medication vs generic formulation is determined by several factors, most notably, cost and availability. Either the insurance carrier or the dispensing pharmacy makes the choice, and this choice may lead to different formulations being substituted for the brand medication. Internationally, regulations concerning this substitution vary from country to country and state to state, therefore, prescribers need to be aware of the possibility or legal requirement for generic substitution.

Transplant professionals have long been concerned about generic substitutions. Despite this, few clinical trials have been conducted to determine bioequivalence in transplant patients and/or outcome.[81]

Published studies comparing efficacy outcomes associated with generic immunosuppression agents with those associated with the brand (innovator) products lack robust study design and are often retrospective reports of small cohorts.[82–104] These reports are generally of a short duration of follow-up, are generally not performed in patients with thoracic transplants, and may be associated with variable practices of therapeutic drug monitoring, and many are non-randomized in their design. Most reports are limited to kidney and liver transplants; there are a small number of studies reporting outcomes among heart transplant recipients.[99,102–104] Whereas there are not high-quality data available, analysis of existing experiences in all organ types does not collectively demonstrate an increased risk of rejection or allograft dysfunction with the use of generic immunosuppressive agents, including calcineurin inhibitors or generically available anti-proliferative agents, compared with their respective innovator products. Isolated reports describing higher rejection rates with generic calcineurin inhibitors are limited to those also reporting variations in monitored drug concentrations between groups or non-bioequivalent formulations.[86,90] Specifically, with calcineurin inhibitors, clinical outcomes should be expected to be similar only with the achievement of similar PK targets guided by the appropriate level of therapeutic drug monitoring because some reports do indicate changes in concentration and dosing when transitioning between products.

When a brand substitution occurs, close laboratory follow-up of therapeutic monitoring and graft function should take place to ensure that a drug therapeutic level is maintained and outcomes are unaffected, although generic substitution or interchanging between generic manufacturers does not require informing the prescriber. Patients should be taught how to identify pills and educated about generic immunosuppressants and be included in the decision to switch. If their immunosuppressants have been switched, they should alert the transplant care provider to initiate more intensive monitoring. Patients should be monitored for immunosuppressive drug levels, evidence of transplant rejection, new-onset adverse effects of medications, and adequacy of immunosuppression until a new steady state has been established.

Because there can be dose adjustments when switching brand to generic or between generic products, consecutive substitutions between different generic formulations of the same drug should be avoided. Prescribers are often unaware of such substitutions, and changes in exposure can be more pronounced than for the change from branded product to generic product. Furthermore, the repeated switching between generic formulations can prove confusing for patients and may lead to mistakes with dosing. Pharmacists play an active role in both informing the patient about the

newly prescribed formulation when generic substitution is initiated by the prescribing physician and protecting patients from adverse outcomes from repeated subsequent brand substitution.

Analytic methodology for therapeutic drug monitoring

Immunosuppressant drug therapies have narrow therapeutic windows and high inter- and intraindividual variability, exhibiting therapeutic efficacy with an acceptable adverse effect profile within a narrow range of blood concentrations. Thus, therapeutic drug monitoring has become an integral part of immunosuppression management. Table 3[105–120] summarizes the various assays that are used worldwide for therapeutic drug monitoring of immunosuppression.

The concentrations of immunosuppressants can be determined using chromatographic or automated immunoassays methods. The 2 methods are not interchangeable, and interpretation will usually depend on the type of assay utilized. High-performance liquid chromatography (HPLC) is considered the gold standard because it provides both specificity and sensitivity for immunosuppressant measurements. Several techniques developed include isotopic immunoassay, non-isotopic immunoassay, HPLC with an ultraviolet detector, or liquid chromatography with mass spectrometry (LC-MS/MS). HPLC is the only assay that measures the parent compound without the interference of metabolites and gives a more accurate picture of blood concentration. HPLC can be laborious and expensive and requires specialized equipment and expertise for interpretation. Hence, the majority of centers use immunoassays.[115]

Immunoassays are prone to non-specific antibody cross-reactivity of metabolites of the parent drug, resulting in variable overestimation in drug concentration (positive bias). Examples of immunoassays available include microparticles coated with anti-sirolimus antibodies (MEIA) for TAC and sirolimus, chemiluminescence immunoassay for calcineurin inhibitors, and particle-enhanced turbidimetric inhibition immunoassay for mycophenolate. These techniques can also be high in cost, and multiple drugs cannot be analyzed simultaneously.[116,117]

The variability in results when switching from a chromatographic method to an immunoassay can result in inappropriate dosage adjustments of immunosuppression levels. In changing from an immunoassay to a chromatographic method, the reported level is likely to be lower owing to the specificity of the test and non-measurement of metabolites. Switching between immunoassays can also result in a degree of variability. For example, chemiluminescent microparticle immunoassay (CMIA) values in the measurement of sirolimus were more than 25% higher than those in MEIA measurements. Individual laboratory calibrations and reagent lot variation may also contribute to result variation.

In general, whole blood is required for immunosuppressant testing. Measurement of ciclosporin levels with HPLC is the only assay that is completely specific for the parent compound, with other assays measuring metabolites to varying degrees. However, the CMIA ciclosporin immunoassay has a relatively good correlation with LC-MS/MS and has minimal cross-reactivity with metabolites.[115] CMIA testing of TAC is also free from error owing to low hematocrit. Antibody-conjugated magnetic immunoassay testing of TAC and ciclosporin are subject to interference from various proteins, including endogenous antibodies. Unexplained drug concentrations obtained through this method, including false positives, should be validated using an alternate assay method. Hematocrit impacts TAC and sirolimus results through the MEIA assay, with low hematocrit levels resulting in higher immunosuppressant levels.[115]

The immunoassays available for RAD show a high cross-reactivity to RAD metabolites, including 40-O-desmethyl RAD or sirolimus. As a result of this cross-reactivity, some centers have reported the use of the sirolimus CMIA to determine RAD concentrations. CMIA cross-reactivity between sirolimus and RAD is higher at lower concentrations (100% at 1 ng/ml and 78% at 25 ng/ml), and indirect measurement poses a significant calculation error risk.[119]

Therapeutic drug monitoring of MMF involves the measurement of MPA—the active metabolite. MPA can be measured in plasma or serum, unlike the other immunosuppressants, which require whole blood testing. The enzyme-multiplied immunoassay technique and cloned enzyme donor immunoassay overestimate MPA concentrations compared with HPLC with an ultraviolet detector owing to significant cross-reactivity with the MPA acyl glucuronide metabolite. The new Roche total MPA assay has been shown to have <5% cross-reactivity with MPA acyl glucuronide metabolite and may prove to be a good alternative to LC-MS/MS.[120–122]

Recommendations for specific immunosuppressants

Calcineurin inhibitors

$AUC_{0–12}$, a measure of overall calcineurin inhibitor exposure, correlates well with clinical outcomes in transplant recipients. However, even the condensed version ($AUC_{0–4}$), which focuses on the greatest period of variability for these agents, requires at least 3 blood draws for calculation. This method is therefore not feasible in routine clinical practice. Ciclosporin trough concentration (C0) correlates poorly with AUC; hence, there has been an interest in measuring 2-hour levels (concentration at 2 hours [C2]), approximating peak levels, to guide immunosuppression. Ciclosporin C2 levels correlate better with $AUC_{0–4}$ than ciclosporin C0 levels, and limited evidence has suggested that ciclosporin C2 monitoring may reduce ciclosporin dose requirements in patients with heart transplant and may be associated with lower rates of cellular rejection in patients with lung transplants.[123,124] However, the overall body of evidence to support ciclosporin C2 to guide therapy is weak, and the timing of C2 levels in the clinic is often impractical. Therefore, C0 remains the preferred method for routine monitoring of ciclosporin.[125]

TAC C0 correlates well with $AUC_{0–4}$ in heart transplant recipients ($r^2 = 0.74$), and data in kidney transplant patients

Table 3 Immunosuppressant Immunoassays[105–120]

Immunosuppressant	Immunoassay	Analytic range, ng/ml	Average mean of positive bias, % (vs LC-MS/MS)	Specific metabolite cross reactivity, %	Notes
Ciclosporin[107,120]	ACMIA CSA flex; extended range flex	25—500; 350—2,000	12	AM4N 4	Increased bias: low albumin and endogenous antibodies. Hence, unexplained elevations should be confirmed with other assay methods
	CEDIA CSA plus; plus high range	25—400; 450—2,000	17	AM1 8 AM4N 30 AM9 18	
	CMIA CSA	30—1,500	—	AM1 0.1	
	EMIT 2,000 CSA; CSA specific assay	25—500; 350—2,000	13	AM4N 8—13	
TAC[111,117]	ACMIA TAC-R flex	1.2—30	16.6	M-I 15 M-IV 18	No sample before treatment required Increased bias: low albumin and endogenous antibodies. Hence, unexplained elevations should be confirmed with other assay methods
	CEDIA FK	2.0—30	33	M-I 38	
	CMIA FK	<1.0—30	18—20	M-I 45 M-II 94	Free from HCT effects Low detection limit
	EMIT 2,000 FK	2.0—30	28—30	M-I 10 M-IV 21	
	MEIA FK	3.0—30	20	M-II 54 M-III 67 M-V 62	Increased bias with HCT <25
	QMS FK	0.7—30	17—30		
SIR[105,106,108,110,112,116,118,119]	ACMIA SIR	2.0—39	12.6 at 3 ng/ml <5 at 11–12 ng/ml		
	CEDIA SIR	5.0—30	20.4		Use not recommended
	CMIA SIR	2.0—30	21.9	F4 36.8 F5 20.3	Greater positive bias at a lower concentration Some have used SIR CMIA to test RAD concentration. Cross-reactivity higher at lower concentrations (100% at 1 ng/ml and 78% at 25 ng/ml). Note: indirect measures pose significant calculation error risk
	MEIA SIR	2.5—30	25	F4 37 F5 (major) 58 7-o-demethyl 63	Limit to detection: 1.1 ng/ml <10% bias when HCT is at 35%—45% for SIR '5—22 mg/l 20% positive bias when HCT <35% 20% negative bias when HCT >45%
RAD[119,119]	Innofluor Certican (FPIA)	2.0—40	23—30	45-OH 16.3 12-OH 33 11-OH 18.3 14-OH 15.3 39-O-desmethyl 43 27-o-desmethyl 142 40-O-desmethyl (SIR) 68	Higher interpatient variability Higher bias (2 ×) when concentration is <15 ng/ml
	QMS RAD	1.3—20	11	SIR 46	Linear between 1.5 ng/ml and 20 ng/ml
MPA[107,120]	CEDIA MPA	0.3—10	15—18 41.7 RTx 52.3 OLT	140—215 AcMPAG	
	EMIT 2,000 MPA	0.1—15	14.6 30 early post-op 45 with CSA	135—185 AcMPAG	
	PETINIA	0.2—30	8.3—22.4	52 AcMPAG (package insert)	Approximately 10% of samples with >20% bias
	Roche total MPA	0.4—15	1—17	<5 AcMPAG	

Abbreviations: ACMIA, antibody-conjugated magnetic immunoassay; AcMPAG, MPA acyl glucuronide; CEDIA, cloned enzyme donor immunoassay; CMIA, chemiluminescent microparticle immunoassay; CSA, ciclosporin A; EMIT, enzyme-multiplied immunoassay technique; FPIA, fluoresence polarization immunoassay; HCT, hematocrit; LC-MC/MC, liquid chromatography with mass spectrometry; MEIA, anti-SIR antibodies; MPA, mycophenolic acid; OH, hydroxide; OLT, liver transplantation; PETINIA, particle-enhanced turbidimetric inhibition immunoassay; RAD, everolimus; RTx, kidney transplant; SIR, sirolimus; post-op, post-operation; TAC, tacrolimus.

M-I, M-II, M-IV are metabolites of tacrolimus: M-I (13-O-demethyltacrolimus); M-II (31-O-demethyltacrolimus); M-III (15-O-demethyltacrolimus); M-IV(12-hydroxytacrolimus).

suggest an equivalence between TAC C0−guided and TAC C2−guided therapy.[126,127] Whereas one study suggests that TAC C2 monitoring may have utility in patients with lung transplants, overall C0 is the preferred method for monitoring of TAC in everyday practice for cardiothoracic transplant recipients.[125,128]

C2 monitoring for calcineurin inhibitors can be considered in selected clinical scenarios. One such example is a patient with persistently low C0 levels despite escalating calcineurin inhibitor doses. A patient with normal C2 and low C0 levels may have an abnormally high drug clearance, and more frequent dosing (i.e., every 8 hours) could be implemented to reach therapeutic C0 concentrations. Conversely, simultaneously low C2 and C0 levels suggest poor drug absorption, and in this case, either further dose escalation or addition of an agent to intentionally cause a drug interaction would be prudent. Considering another scenario where repeated cellular rejection occurs in the setting of therapeutic C0 levels, if low C2 concentrations are detected, further dose titration to obtain a therapeutic C2 level could be considered. This notion is supported by the pharmacodynamic profile of the calcineurin inhibitors, which exhibit maximal IL-2 suppression approximately 2 hours after dosing.[124]

Finally, patients with cystic fibrosis (CF) have lower peak concentrations, smaller $AUC_{0-12,}$ and shorter elimination half-life.[129] Consequently, to achieve similar C0, patients with CF require a 39% higher dose of TAC. C0 monitoring may not always be the most accurate measure of AUC_{0-12}, and patients with CF also demonstrate high intra- and interindividual patient variability.

Anti-metabolites

Whereas MPA has a more predictable PK profile than the calcineurin inhibitors, numerous factors can alter drug exposure (Table 4).[126] In light of this variability, therapeutic drug monitoring has been explored as a means to optimize mycophenolate dosing. Unfortunately, determining the ideal timing for sampling MPA levels has proven difficult given the complicated PKs of this agent.

AUC_{0-12} monitoring of MPA has been evaluated primarily in kidney transplant recipients; the majority of these papers are retrospective and are of lower-quality methodology.[130] Some studies identified associations between AUC_{0-12} and either acute rejection or adverse events, whereas others did not.[130,131] C0 levels have also been evaluated in over 2-dozen studies, including 8 with heart transplant recipients.[131,132] Of these 8 papers, 5 found associations between low C0 levels and cellular rejection, whereas 3 found no relationship. Of note, 1 of these papers reported that low MPA C0 levels were only associated with rejection in the setting of therapeutic calcineurin inhibitor troughs.[133] None of the cardiothoracic studies were able to correlate C0 levels with adverse drug events.

Single-point monitoring of MPA at time points other than C0 is complicated by several factors. First, the background calcineurin inhibitors impact serum concentrations of MPA because ciclosporin interferes with MPA clearance, whereas TAC does not (Table 4).[126] One group of authors sought to determine the best single-time point for MPA monitoring in heart transplant recipients. These investigators found that when combined with ciclosporin, there is a poor correlation between AUC_{0-12} of MPA at all measured time points (C0, C2, C3, C4, and C6).[133] However, when combined with TAC, MPA levels at all other time points (C2, C4, C6, and C8) were better surrogates of the AUC_{0-12} than at C0.

Another factor impacting the timing of single-point monitoring is the dosage form. Enteric-coated mycophenolate has a delayed peak compared with MMF, which could influence the accuracy of single-point measurements taken early after administration.

In summary, the data are insufficient to recommend any form of routine drug monitoring for MPA in cardiothoracic transplant recipients. For patients with unexplained drug

Table 4 Clinical Factors Influencing Mycophenolate PKs[126]

Clinical consideration	Factor	Impact on MMF	Mechanism
Drug−drug interactions	Ciclosporin	Reduced exposure to MPA and increased levels of MPAG	Inhibition of MRP-2, which reduces enterohepatic recirculation and prevents second peak
	Steroids	Reduced exposure to MPA	Increased clearance due to induction of UDPGT
	Antibiotics	Reduced MPA exposure	Eradication of enteric flora, leading to reduced enterohepatic recycling
Disease-state considerations	Renal failure	Increased free MPA levels, increase in MPAG, and possible decrease in total MPA exposure	Elevated urea displaces MPA from albumin, leading to higher clearance
	Liver failure	Reduced MPA exposure and decreased MPAG levels	Decreased enterohepatic recycling
	Hypoalbuminemia	Increased free MPA exposure and lower total MPA levels	Increased MPA clearance because of higher free concentrations
Time after transplantation		Increased MPA exposure	Improvements in serum albumin and renal function, along with steroid weaning

Abbreviations: MMF, mycophenolate mofetil; MPA, mycophenolic acid; MPAG, 7-O-MPA-glucuronide; MRP-2, multidrug resistance–associated protein 2; PK, pharmacokinetic; UDPGT, UDP-glucuronosyltransferase.

Table 5 Therapeutic Monitoring Targets for mTOR Inhibitors[134-139]

mTOR regimen	RAD	SIR
In heart: combination with CNI (i.e., TAC + mTOR)	C_0 goal of 3–8 ng/ml[134]	C_0 goal of 4–12 ng/ml[135]
In Heart: CNI-sparing regimen (i.e., mTOR + MPA)	C_0 goal of 6–10 ng/ml[136]	C_0 goal of 10–15 ng/ml
In lung: combination with CNI	C_0 goal of 6–8 ng/ml[137]	C_0 goal of 4–8 ng/ml[138]

Abbreviations: C_0, trough concentration; CNI, calcineurin inhibitor; MPA, mycophenolic acid; RAD, everolimus; SIR, sirolimus; TAC, tacrolimus

side effects or cellular rejection, C0 monitoring can be considered (goal 1.5–4.0 μg/ml). The choice of C0 vs other time points is strictly related to logistical practicality. Given the limitations of the available literature on this topic, the strength of evidence behind this recommendation is weak.

mTOR inhibitors

C0 monitoring is the preferred method for mTOR inhibitors because trough levels correlate with clinical outcomes. The goal trough level is determined according to the concomitant immunosuppression therapy (Table 5).[134-139] Some studies in lung transplantation have demonstrated that calcineurin inhibitor–sparing regimens allow calcineurin inhibitor exposure to be reduced with improvement of renal function with no graft loss. No studies demonstrate a relationship between mTOR AUC_{0-12} monitoring and efficacy in the thoracic population.[139]

Induction agents

Induction agents used in cardiothoracic transplant recipients include rabbit anti-thymocyte globulin (rATG) and equine anti-thymocyte globulin (ATGAM) and basiliximab. Basiliximab is well tolerated, has a fixed dosing regimen, and does not have any routine monitoring parameters.

Table 6 Suggested Dose Adjustment for Hematologic Toxicities of rATG[142,143]

Laboratory parameter	Dose adjustment
WBC >3 × $10^3/\mu$l and ANC >1.5 × $10^3/\mu$l and Platelets >75 × $10^3/\mu$l	No change
WBC of 2–3 × $10^3/\mu$l or ANC of 1–1.4 × $10^3/\mu$l or Platelets of 50–70 × $10^3/\mu$l	Decrease next dose by 50%
WBC <2 × $10^3/\mu$l or ANC <1 × $10^3/\mu$l or Platelets <50 × $10^3/\mu$l	Hold next dose

Abbreviations: ANC, absolute neutrophil count; rATG, rabbit anti-thymocyte globulin; WBC, white blood cell count.

Table 7 Anti-thymocyte Globulin Dose According to T-Cell Count[144]

Absolute CD3 counts, cells/μl	ATGAM dose, mg/kg	rATG dose, mg/kg
>100	10	1.5
75–100	5	0.75
50–75	2.5	0.375
25–50	0.15	0.15
<25	Hold next dose	Hold next dose

Abbreviations: ATGAM, equine anti-thymocyte globulin; rATG, rabbit anti-thymocyte globulin.

Therefore, the remainder of this section will focus on rATG and ATGAM.

For cardiothoracic transplants, rATG is commonly prescribed in a fixed daily-dose regimen of 1 to1.5 mg/kg/day, aiming for a cumulative dose of 4.5 to 7.5 mg/kg.[140,141] Under this strategy, doses are only reduced or held if cytopenias or infusion-related reactions occur (Table 6).[142,143]

An alternative monitoring strategy has been described with ATGAM in heart and lung transplant recipients, where peripheral T-cell counts are used to guide dosing (Table 7).[144] In 1 small study of 34 patients, a T-cell–guided dosing strategy reduced overall rATG/ATGAM doses by 48% with acceptably low rates of infection and rejection.[144] In lieu of specific T-cell counts, other data have suggested that an absolute lymphocyte count (target level of <200 cells/μl) may also be a valid monitoring parameter for rATG induction.[145]

Special populations

Clinical trials are known to exclude certain populations from inclusion into the trial and often leave the clinician assuming that the therapy should be applied to all. In transplantation, where clinical trials are sparse, often, registry data or single-center data are relied on — the body of evidence in a special population that lacks robust data and long-term consensus information.

Infants and children

The overall goal of immunosuppression in children is the same as in adults: to prevent acute cellular rejection and graft vasculopathy while avoiding drug adverse effects. Physiologic differences and organ maturation and growth require a different approach to immunosuppression in

Table 8 Approach to Immunosuppression in Pediatric Recipients

Serial number	Considerations regarding immunosuppression
1.	Dosages of immunosuppression are based on mg/kg/day or mg/kg/m^2.
2.	Dosages must be re-evaluated, and dose adjusted for interval weight gain.
3.	Drug monitoring for CNI and mTOR includes standard trough levels as in adults.
4.	Drug monitoring for MPA is not routinely done. An AUC is likely more useful than a trough.
5.	Dose adjustment should take into account the metabolism and maturity of renal clearance.
6.	Certain populations, such as infant recipients, likely require relatively less Immunosuppression therapy.
7.	Careful consideration should be given to prolonged steroid use in children given the long-term effects on growth and development.
8.	It requires the use of commercially available oral liquid dosage forms for infants and children who cannot swallow whole tablets or capsules. Where no such products exist, using extemporaneously prepared liquids or manipulating the dosage form, that is, opening capsules and emptying powdered drug into a small volume of water and giving the correct proportion of compounded dose may be done.

Abbreviations: AUC, Area Under the Curve; CNI, calcineurin inhibitor; MPA, mycophenolic acid.

children compared with adults. Table 8 illustrates some of the differences in the approach to immunosuppression in infants and children compared with adults.

There are also stark differences in peri- and post-operative immunosuppression of this population. No randomized controlled trials exist in the pediatric population to inform an optimum induction protocol or long-term immunosuppressant drug combination, dose, or duration. Drug combinations of immunosuppressants used in children vary widely among transplant centers and countries. Therefore, immunosuppressant combinations and management are based on experience in adults, clinical experience, availability of palatable oral liquid dosage forms, side effects, and pill burden. Other important outcomes in children when considering life-long drug therapy that require attention are growth and development, cognitive function, and psychosocial adaptation. The optimum calcineurin inhibitor/anti-metabolite/steroid protocol has not been investigated in children in randomized controlled studies with long-term follow-up. These studies should include PKs of immunosuppressants in infants and children because this is poorly understood. Finally, the role of induction agents and mTOR inhibitors in improving short- and long-term outcomes in children should be investigated in randomized controlled studies.

Adherence to immunomodulating medications is critical to transplant recipient survival and quality of life. Unfortunately, studies show that young adults are at a higher risk of non-adherence than older adults.[146] Although biologic factors do play a role, non-adherence and limited ability to self-care have a significant impact on graft and patient survival and likely contribute to the survival difference between adolescents and younger age groups. There are very limited data systematically examining adherence among pediatric recipients, including individual, familial, psychologic, and psychosocial risk factors for predicting non-adherence. There are even fewer interventional studies targeting medication adherence among pediatric patients with transplants. Pre-transplant evaluation should include assessment of known and suspected contributors to predicting medication non-adherence. If there is documented non-adherence before transplantation, appropriate interventions should be taken before listing for transplantation.

Post-transplant longitudinal follow-up should include (1) anticipatory guidance regarding medication non-adherence, (2) consistent counseling and implementation of strategies for the promotion of transition to self-care as patients approach early adolescence, (3) team approach with the knowledge and skillset among transplant team members to recognize medication non-adherence, and (4) strategies to intervene once non-adherence is recognized.

Pregnant recipients

Many transplant recipients wish to attempt to become pregnant despite the risk of allograft rejection, graft loss, or high-risk fetal outcomes.[147,148] Registry data indicate that this is still a rare occurrence in the thoracic transplant cohort. Obstetric complications such as pre-eclampsia, hypertension, low birth-weight babies, cesarean sections, and pre-term deliveries occur more frequently in transplant recipients than in the general population. The rates of these complications appear to be higher in cardiothoracic transplants. Some transplant medications have well-recognized teratogenicity; however, adverse effects seen in the fetus can also be the result of the mother's underlying condition, time since transplantation, and the graft function. Stability of graft function is crucial to a successful pregnancy outcome, and this should be a primary consideration of immunosuppression management during pregnancy. Breastfeeding makes an important contribution to neonatal health and is possible with most of the usual immunosuppressant regimens. Conversations about immunosuppressive medication regimens should happen well in advance of conception. Immunosuppression must be continued through pregnancy, and all of the current drugs used cross the placenta into the fetal circulation.[149,150] Adjustment of medications to the safest combination of immunosuppressant drugs before a planned pregnancy is necessary. Table 9[5–11,19,28,151–156] lists the classically used agents in thoracic transplantation and the potential adverse effects in pregnancy as well as the recommendations for breastfeeding.[151]

Older adults

Consensus statements on the selection of heart and lung transplant recipients have consistently identified older age as a relative contraindication to transplantation.[157,158] In the

Table 9 Immunosuppressant Drugs in Pregnancy and Breastfeeding[5–11,19,28,151–156]

Drugs	Use in pregnancy	Potential adverse effects	Special instruction	Breastfeeding[151]	Compatible with paternal exposure
Prednisone/ methylprednisolone[152,153]	Yes	A small risk of cleft palate with or without lip involvement cannot be excluded if high doses are used in the first trimester; the risk seems to be negligible at low doses, for example, 10–15 mg prednisolone daily.[154,155]	Treatment with corticoids should be continued during pregnancy whenever needed.[154,155]	No limitations on breast feeding[154,155]	Yes[155]
Ciclosporin [5,6,19]	Yes	Human data from registries has not revealed teratogenic risk. Adverse effects including intrauterine growth retardation, a higher rate of cesarean deliveries, and pre-maturity, and increased maternal complications, such as hypertension and pre-eclampsia have been described; however, causal link with ciclosporin has not been proven[154,155]	Monitor levels closely; increase dosage to achieve the desired levels— dosage levels increase owing to change in liver metabolism and increased V_d	Yes[155]	Yes[155]
TAC[7]	Yes	Until now, no teratogenic potential has been recognized for humans. The systemic use of TAC during pregnancy is acceptable. A detailed ultrasound examination should be offered to confirm normal fetal development. After TAC exposure in late pregnancy, the newborn's kidney function and potassium levels should be checked as a precaution.[154]	Monitor levels closely; increase the dose to achieve desired levels— increase due to change in liver metabolism and increase in V_d	Yes[154,155]	Yes on the basis of limited evidence[155]
Mycophenolate [8,9]	No	Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45%–49%) and congenital malformations (estimated rate of 23%–27%) have been reported after MMF exposure during pregnancy. A total of 2 complementary forms of contraception simultaneously are recommended by manufacturers to minimize the potential for contraceptive failure and unintended pregnancy (European label for CellCept).[156]	Discontinue 6–12 weeks before planned conception or immediately if unplanned[155,156]	Not recommended [155,156]	Manufacturers recommend that male patients or their female partners use reliable contraception during treatment of the male patient and for at least 90 days after cessation of MMF. Male patients of reproductive potential should be made aware of and discuss with a qualified healthcare professional the potential risks of fathering a child.[3] However, there are very limited data of compatibility with paternal exposure.[155]

(*continued on next page*)

Table 9 (*Continued*)

Drugs	Use in pregnancy	Potential adverse effects	Special instruction	Breastfeeding[151]	Compatible with paternal exposure
Azathioprine[28]	Yes	A teratogenic potential in humans has not been recognized. It may be prescribed during pregnancy. A detailed ultrasound examination may be offered to confirm normal fetal development.[154]	Preferred anti-proliferative in pregnancy at doses ≤2 mg/kg/day	Yes[155]	Yes[155]
SIR/RAD [10,11]	No	Animal studies reveal reduced fetal weight, structural malformations, fetal loss. No evidence of malformations from human case reports[154]; however, data are very limited, and use during pregnancy should only be in exceptional circumstances.	Discontinue 6–12 weeks before planned conception or immediately if unplanned	Not recommended	Sirolimus can lead to oligospermia, which was reversible in some patients

Abbreviations: MMF, mycophenolate mofetil; RAD, everolimus; SIR, sirolimus; TAC, tacrolimus; V_d, volume of distribution of a drug.

case of heart transplantation, the prevalence of older patients with heart failure continues to grow.[159] In addition, with the exception of CF and certain forms of pulmonary arterial hypertension, the incidence and prevalence of end-stage lung diseases also increase with age.[160] Nonetheless, several factors make drug therapy problematic in this population, such as comorbidity burden, the potential for drug–drug interactions due to concomitant medications, and adherence related to medication complexity and medication burden.[161] Unfortunately, older patients have thus far been largely excluded from clinical immunosuppressive trials. In general, older recipients have less frequent clinically significant acute rejections. Older organs transplanted into younger recipients have been linked to more potent immune responses and higher acute rejection rates.[161] Although adverse effects with conventional drug immunosuppression can also be seen in younger patients, tolerance to these agents seems to decrease with increasing age, and older patients seem to be more prone to medication-related adverse effects. In particular, diabetes mellitus, osteoporosis, and chronic renal insufficiency are associated with higher morbidity and mortality in older cardiothoracic transplant patients.[161]

In general, aging is associated with impaired organ function and impaired homeostasis affecting absorption, distribution, metabolism, and excretion of immunosuppressants (Table 10).[161,162] Immunosuppression and immune function in the elderly is in general characterized by less effective immune responses with lower acute rejection rates in addition to more frequent comorbidities.[161] Hypertension, hyperglycemia, and hyperlipidemia can influence the selection of TAC over ciclosporin, and weaning of corticosteroids might have a positive impact on osteoporosis and diabetes. Chronic renal insufficiency can be managed with alternate strategies, including calcineurin inhibitor minimization or calcineurin inhibitor free with immunosuppression consisting of MMF and proliferation signal inhibitors.[163]

Thus, an overall reduction of immunosuppression as well as age-specific immunosuppressive regimens may be beneficial for elderly transplant recipients. This approach should take into consideration the optimal protection of the graft with age-specific changes of metabolism as tied to the adverse effects such as infections, de novo malignancies, or nephrotoxicity.[161]

Consensus summary

The consensus conference did not discuss biosimilars, the biologic products that are highly similar to and have no clinically meaningful differences from reference medicine.

There was no discussion of PK in the consensus conference either. This topic is currently an active area of research, and the impact it may have on initial dosing of immunosuppressants, dealing with drug interactions, or individualizing immunosuppressants is not ready for a consensus conclusion.

Without a significant change in the drug approval processes, thoracic transplant is unlikely to have newer agents approved for this indication. Improvements in patient outcomes are therefore likely to depend on developing a deeper

Table 10 PK Changes in the Elderly[161]

PKs	Changes in the elderly	Impact on immunosuppression
Absorption	Reduced GI motility	Decreased C_{max} and Increased T_{max}, delayed drug activity
	Reduced splanchnic blood flow	Decreased dissolvent reducing absorption
	Reduced gastric emptying	
	Increased gastric pH	
	Decreased surface area of the small intestine	
Distribution	Decreased lean body mass	Lipophilic drugs have lower trough levels but longer half lives (e.g., CNI, mTOR inhibitors)
	Decreased body water	Hydrophilic drugs have a smaller distribution and higher troughs
	Increased body fat	Changes in absorption in the intestine
	Variability in P-gp expression/activity	
Metabolism	Decreased serum protein concentration	Changes in drug clearance and fraction of free drug
	Decreased liver volume	Reduced first-pass metabolism and hepatic clearance
	Decreased hepatic blood flow	
	Decreased expression of CYP450 enzymes	
Excretion	Decreased renal function	Impaired renal clearance
	Decreased biliary excretion	Impaired hepatic clearance

Abbreviations: C_{max}, peak of drug concentration; CNI, calcineurin inhibitors; GI, gastrointestinal; P-gp, P-glycoprotein; PK, pharmacokinetic; T_{max}, time of C_{max}.

understanding of factors to improve therapeutic drug monitoring and interpretation of drug levels, improving adherence and using these skills to optimize and individualize dosage of available immunosuppressants. These skills become even more essential for our special patient populations where dosing becomes more complex. Off-label drug use will also be an area of innovation; however, this will be limited by access to drugs. It appears that generic medications can be managed safely with appropriate monitoring, although this creates a burden of monitoring that may not be manageable in some centers.

Expert reviewers

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