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SPECIAL ARTICLE

Consensus recommendations for use of maintenance immunosuppression in solid organ transplantation: Endorsed by the American College of Clinical Pharmacy, American Society of Transplantation, and the International Society for Heart and Lung Transplantation

Joelle Nelson[1,2,3] | Nicole Alvey[4,5] | Lyndsey Bowman[6] | Jamie Schulte[7] | Maria Cristina Segovia[8] | Jennifer McDermott[9,10] | Helen S. Te[11] | Nikhil Kapila[8] | Deborah Jo Levine[12] | Robert L. Gottlieb[13] | Jose Oberholzer[14] | Maya Campara[15,16]

[1]Department of Pharmacotherapy and Pharmacy Services, University Health, San Antonio, Texas, USA

[2]Pharmacotherapy Education and Research Center, University of Texas Health San Antonio, San Antonio, Texas, USA

[3]Department of Pharmacy, Pharmacotherapy Division, College of Pharmacy, The University of Texas at Austin, Austin, Texas, USA

[4]Department of Pharmacy, Rush University Medical Center, Chicago, Illinois, USA

[5]Science and Pharmacy, Roosevelt University College of Health, Schaumburg, Illinois, USA

[6]Department of Pharmacy, Tampa General Hospital, Tampa, Florida, USA

[7]Department of Pharmacy Services, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA

[8]Department of Transplant Hepatology, Duke University Hospital, Durham, North Carolina, USA

[9]Richard DeVos Heart and Lung Transplant Program, Spectrum Health, Grand Rapids, Michigan, USA

[10]Department of Medicine, Michigan State University, College of Human Medicine, Grand Rapids, Michigan, USA

[11]Liver Transplantation, Center for Liver Diseases, Department of Medicine, University of Chicago Medical Center, Chicago, Illinois, USA

[12]Division of Critical Care Medicine, Department of Medicine, The University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

[13]Baylor University Medical Center and Baylor Scott and White Research Institute, Dallas, Texas, USA

[14]Department of Surgery/Division of Transplantation, University of Virginia, Charlottesville, Virginia, USA

[15]Department of Pharmacy Practice, University of Illinois Chicago, Chicago, Illinois, USA

[16]Department of Surgery, University of Illinois Chicago, Chicago, Illinois, USA

Correspondence
Joelle Nelson, Department of Pharmacotherapy and Pharmacy Services, University Health, San Antonio, TX, USA.
Email: joelle.nelson@uhs-sa.com

Abstract

Advances in maintenance immunosuppression over the past three decades have improved solid organ transplantation outcomes dramatically. Uninterrupted access to immunosuppression is paramount to minimize rejection and maintain allograft and patient survival. There is no standardized approach to maintenance immunosuppression management. Agents used vary based on transplanted organ, center-specific protocol, provider expertise, insurance formularies, ability to cover co-pays, recipient characteristics and tolerability. Published data reflects this heterogeneity. Despite this limitation, maintenance immunosuppression usage cross pollinates between organ groups with standard of care agents often being used off-label, making medication access a challenge for many transplant recipients. A multidisciplinary panel of American transplant clinicians was formed to review published literature on maintenance

immunosuppression with the goal to formulate consensus recommendations for their use in specific organ groups. These consensus recommendations are intended to provide transplant clinicians with a summary of literature on maintenance immunosuppression in the modern era and to support transplant team members working to secure medication access for patients.

KEYWORDS
drug approval, immunosuppression therapy, immunosuppressive agents, organ transplantation

1 | BACKGROUND

Organ transplantation is a lifesaving procedure for many individuals with end-stage organ disease.[1–7] The need for lifelong maintenance immunosuppression (M-IMS) is nearly universal as risk of rejection is omnipresent. Nonadherence to M-IMS is a contributing cause of poor post-transplant outcomes, with barriers to medication access a leading risk factor for nonadherence.[8] Consequently, ensuring patients have consistent access to M-IMS is an essential task of every transplant program.

The modern era of M-IMS began in the 1990s with the emergence of modified cyclosporine, tacrolimus, and mycophenolic acid (MPA) which has led to significant improvements in one-year allograft survival among all organ recipients by decreasing the rate of rejection.[1–7] Since that time, additional M-IMS agents have been introduced with novel mechanisms of action. (Figure 1) Current M-IMS practices involve a multi-drug regimen tailored to the individual based on rejection risk, organ characteristics, comorbidities, and side effects with modifications made as these factors change. As modifications to M-IMS occur, the ability to transition from one M-IMS regimen to another expeditiously and without interruption is essential for preventing allograft rejection, maintaining allograft and patient survival, and ensuring adherence.

The 2019 Organ Procurement and Transplantation Network Annual Data Report shows the most common M-IMS regimen prescribed at discharge was tacrolimus, mycophenolate meofetil (MMF), and corticosteroids for kidney (65%), pancreas (67%), liver (65%), heart (86%), and lung (80%) transplant recipients.[2–6] Tacrolimus and corticosteroids are the most common regimen for intestinal transplant recipients (44%).[7] (Table 1) However, these three agents are not universally accessible to all organ groups for rejection prophylaxis due to lack of sponsor-conducted registration phase 3 licensure trials to achieve organ-specific US Food and Drug Administration (FDA) approval or due to national formulary restrictions in select countries. For example, none of the above M-IMS agents are FDA-approved for use in pancreas or intestinal transplant (Table 2). Centers for Medicare and Medicaid Services (CMS) rely on US Pharmacopeia compendia, such as Micromedex and the American Hospital Formulary Service-Drug Information (AHFS-DI), to decide if off-label medication use is appropriate based on available evidence.[9,10] These resources include literature that support off-label use of M-IMS, but are neither comprehensive nor reflective of modern clinical practice. Consequently, off-label, off-compendia use is common in solid organ transplantation (SOT) as described in a 2018 study, where 67% of lung, 34% of intestine, 33% of pancreas, 22% of heart, and 17% of liver recipients were prescribed off-label, off-compendia M-IMS regimens.[11] Only recently was immediate-release tacrolimus (IR-TAC) FDA-approved for use in lung transplant based on real-world evidence of effectiveness.[12]

Although M-IMS is a protected class for Medicare-covered transplant recipients recent Medicare modernization efforts have introduced further barriers to access such as requirements for recurrent prior authorizations, step-therapy prerequisite, and formulary restrictions.[13,14] For patients that do not have Medicare at the time of transplant, challenges with medication access are also common and can lead to significant costs to patient, program, and health system.[11,15]

While comprehensive reviews of M-IMS have previously been published, these have been limited in scope and do not include newer agents or product formulations. To date, consensus recommendations do not exist on this topic. These consensus recommendations will adequately review the depth and breadth of available literature on modern, organ-specific immunosuppressive regimens for providers and provide recommendations, including

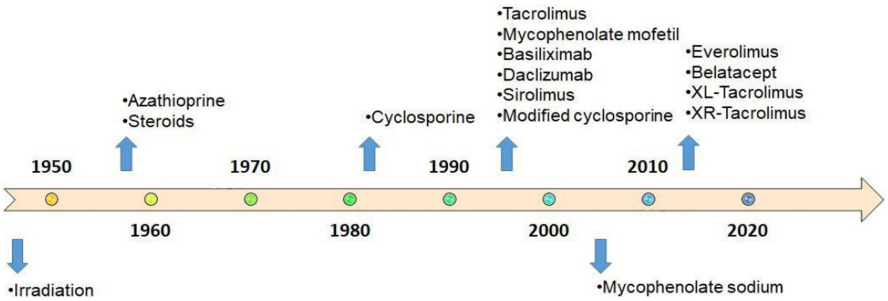

FIGURE 1 Timeline of maintenance immunosuppression

TABLE 1 Most common maintenance immunosuppressant regimens at discharge[2–7]

Organ Transplanted	Regimen
Kidney	Tacrolimus + MMF + Corticosteroids (66%) Tacrolimus + MMF (27%)
Pancreas	Tacrolimus + MMF + Corticosteroids (68%) Tacrolimus + MMF (26%)
Liver	Tacrolimus + MMF + Corticosteroids (65%) Tacrolimus + MMF (17%) Tacrolimus + Corticosteroids(6%)
Intestine	Tacrolimus + Corticosteroids (37%) Tacrolimus + MMF + Corticosteroids (30%) OTHER (18%) Tacrolimus + MMF (7%)
Heart	Tacrolimus + MMF + Corticosteroids (86%) Tacrolimus + MMF (7%)
Lung	Tacrolimus + MMF + Corticosteroids (82%) OTHER (11%)

expert opinion, to support medication access in the vulnerable SOT population.

2 | METHODS

2.1 | Consensus panel composition

The Consensus Panel was composed of multidisciplinary experts in abdominal and thoracic transplantation from different institutions across the United States. Panel included transplant physicians (abdominal surgeon, hepatologists, gastroenterologist, cardiologist, and pulmonologist) and transplant pharmacists. Authors were invited for their capacity as clinical experts based on executive committee members' recommendations, their scholarly activity, length of clinical experience, and active membership in the endorsing organizations (American College of Clinical Pharmacy, American Society of Transplantation, and International Society of Heart and Lung Transplantation).

2.2 | Consensus development based on evidence

Consensus Panel members were divided according to their expertise into kidney (2), pancreas (2), liver (4), intestine (2), heart (3), and lung (3) author workgroups with an identified lead in each group. Each workgroup was tasked with developing organ-specific key clinical questions that contribute to the current knowledge on use of modern M-IMS in SOT. Key clinical questions from each workgroup were distributed among the entire Panel of authors. The Panel finalized a list of key clinical questions to be addressed in preparation for literature review. Following completion of literature review, the Consensus Panel met over a series of three teleconferences to present findings and develop final recommendations. A draft of the document was reviewed, edited, and approved by all Panel members. Finally, the document was reviewed by endorsing societies and revised by the Consensus Panel for final approval.

2.3 | Literature review and analysis

Each workgroup performed literature review and analysis specific for their organ. Division of labor between the workgroups varied depending on workgroup size and the anticipated volume of literature to be reviewed. (Figure 2) However, to improve data consistency across workgroups, a literature evaluation tool was shared between Panel members indicating minimum necessary data collection point for every paper reviewed and included in final analysis (i.e., allograft survival at 12 months, patient survival at 12 months, and rejection incidence at 12 months). After completing literature review, each organ-specific workgroup developed their own recommendations to the previously identified key clinical questions and provided supporting literature evidence summaries. This information was shared with all Panel members. Subsequently, the Panel met over a series of three teleconferences to review organ-specific recommendations and supporting literature. Any group discrepancies were addressed until a consensus was achieved.

The Panel reviewed all available human studies published in English that were identified through PubMed database searches using Medical Subject Headings. Studies before January 1, 1995, were not considered for inclusion unless they were represented in larger systematic reviews or no other high-quality evidence existed. Studies describing pediatric transplantation were excluded. Keywords used to conduct literature searches were *immunosuppressants*, *immunosuppressive agents*, *cyclosporine*, *azathioprine*, *prednisone*, *corticosteroids*, *tacrolimus*, *basiliximab*, *daclizumab*, *mycophenolate*, *sirolimus*, *everolimus*, *belatacept*, *kidney transplantation*, *renal transplantation*, *pancreas transplantation*, *liver transplantation*, *hepatic transplantation*, *small bowel transplantation*, *intestinal transplantation*, *heart transplantation*, *cardiac transplantation*, *lung transplantation*, and *pulmonary transplantation*. Priority was given to evidence from randomized controlled

TABLE 2 Maintenance immunosuppressants with on- or off-label indications (endorsed by Micromedex and/or AHFS-DI)[9,10,15]

	CNI				Corticosteroids	Antimetabolites		mTORi		Co-stimulation inhibitors
		Tacrolimus				MPA				
	CyA-ME	IR-TAC	ER-TAC	LCPT	Prednisone	MMF	MPS	Azathioprine	Sirolimus	Everolimus	Belatacept
Kidney	FDA	FDA	FDA	FDA	FDA[b]	FDA	FDA	FDA	FDA	FDA	FDA
Pancreas	OFF LABEL	OFF LABEL	[a]	[a]	[a]	OFF LABEL	[a]	OFF LABEL	[a]	[a]	[a]
Liver	FDA	FDA	[a]	[a]	OFF LABEL	FDA	OFF LABEL	OFF LABEL	[a]	FDA	[a]
Intestine	[a]	OFF LABEL	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]
Heart	FDA	FDA	[a]	[a]	FDA[b]	FDA	OFF LABEL	OFF LABEL	OFF LABEL	OFF LABEL	[a]
Lung	OFF LABEL	FDA	[a]	[a]	[a]	OFF LABEL	OFF LABEL	[a]	[a]	[a]	[a]

Abbreviations: CNI, calcineurin inhibitors; CyA-ME, cyclosporine, microemulsion; ER-TAC, extended-release tacrolimus; FDA, FDA-approved indication; IR-TAC, immediate release tacrolimus; LCPT, LCP-tacrolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MPS, mycophenolate sodium; mTORi, mammalian target of rapamycin inhibitors; OFF LABEL, Endorsed by CMS-approved compendia Micromedex and/or AHFS. *CMS-recognized compendia accessed March 2022.*

[a]Neither FDA-approved nor endorsed by Micromedex and/or AHFS-DI.

[b]Delayed-release formulation only.

trials (RCTs) or meta-analyses. However, lower-level evidence, including abstracts, was reviewed in absence of higher quality data or full publications (Figure 2). The authors also searched clinicaltrials.gov for any ongoing appropriate clinical trials.

2.3.1 | Evidence grading

To evaluate evidence, the Panel followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to evaluate the quality of evidence and determine strength of recommendations in the healthcare setting (Table 3).[16–19] In cases where well-designed evidence was lacking, recommendations were provided as best practice and expert opinion after reviewing available lower grade evidence. The Consensus Panel reviewed all organ-specific recommendations, including the assigned strength of the recommendations and quality of evidence. Any discrepancies were discussed until a consensus was made.

3 | CLINICAL QUESTIONS AND RECOMMENDATIONS

3.1 | Calcineurin inhibitors

Calcineurin inhibitors (CNI) exert their activity on T cells by assorted interactions with calcineurin, directly or indirectly, via adaptor proteins ultimately preventing translocation of nuclear factor of activated T-lymphocyte to the nucleus and thus preventing the transcription of proliferative and pro-inflammatory cytokines such as interleukin (IL)-2, 4, 5, 6, 17. The overall effect is the inhibition of adaptive immune response through inhibition of T-cell activation and proliferation.

Cyclosporine, a cyclic, nonribosomal undecapeptide, was FDA approved in 1983. Its addition to the standard regimen of azathioprine and corticosteroids halved kidney rejection rates and increased 1-year allograft survival from 50–60% to 80%.[20–22] Cyclosporine is available in two, twice-daily formulations: modified (Neoral® or Gengraf®) and nonmodified (Sandimmune®). Formulations are not interchangeable as the original nonmodified formulation exhibits poor oral bioavailability and high intra-patient variability in absorption due to its dependence on bile acid salts.[23] These recommendations focus on modified, cyclosporine microemulsion (CyA-ME) given the infrequent use of nonmodified formulation in modern M-IMS regimens. Tacrolimus, a cyclic macrolactone hybrid product of polyketide and non-ribosomal peptide synthesis, appeared on the market in 1994 and is generally considered a more potent CNI due to its ability to reduce 1 year rejection rates to <10% across nearly all organs. Three formulations of tacrolimus exist, IR-TAC, or Prograf®, and extended-release formulations including extended-release tacrolimus (ER-TAC), Astagraf® (US brand) or Advagraf® (European brand), and LCP- tacrolimus (LCPT), Envarsus®. Dosage forms are not interchangeable as they have different pharmacokinetic profiles.[24]

FIGURE 2 Literature search and review summary

TABLE 3 GRADE criteria[19]

Level of evidence	Quality certainty	Meaning
A	High	The true effect is close to estimated effect
B	Moderate	The true effect is probably close to estimated effect
C	Low	The true effect may be markedly different from estimated effect
D	Very low	The true effect is probably markedly different from estimated effect
Recommendation level	**Strength of recommendation**	**Meaning**
1	Strong	Panel confident recommendation benefit outweighs risk
2	Weak	Panel uncertain, consider individual patient factors

As CNI have a narrow therapeutic index with wide inter- and intra-patient pharmacokinetic variability, therapeutic drug monitoring (TDM) is mandatory. Cyclosporine can be monitored with a 12-h trough or 2-h peak level. Peaks highly correlate with overall drug exposure and decreased acute rejection incidence but are less practical given the narrow window of time when peaks drawn are considered interpretable.[25–28] Tacrolimus requires 12- or 24-h trough monitoring depending on formulation used. Goal therapeutic drug levels vary based on factors such as time since transplant, organ(s) transplanted, concomitant immunosuppression, and past medical history including infections, risk of rejection, and malignancy. CNI have a variety of side effects, most significantly nephro- and neurotoxicity. Nephrotoxicity can be acute or chronic, with attendant hyperkalemia. Similarly, neurotoxicity has been associated with concentration peaks and can manifest as mild symptoms such as headaches or tremors, to more serious effects such as seizures or progressive reversible encephalopathy syndrome (PRES). Also common are metabolic side effects including hyperglycemia and hypertension.[29] Moreover, as CNI are predominantly metabolized through CYP3A4 and absorption is influenced by p-glycoprotein, numerous drug interactions exist. In patients who cannot take solid dosage forms, suspension formulations are used. Alternatively, IR-TAC can be administered sublingually. Intravenous formulations are less common due to heightened risk of nephrotoxicity.

1. *Is tacrolimus the most efficacious CNI for prevention of allograft rejection and loss at 12 months or longer?*
   1.1. *Recommendation (1A kidney, pancreas, liver; 1D intestine; 2B heart, lung).* Tacrolimus is superior to CyA-ME for the prevention of allograft rejection. Additionally, it is superior for reducing the severity of rejection in kidney and pancreas transplants.
   1.2. *Recommendation (1A kidney, pancreas; 1B liver)* . Tacrolimus is associated with improved allograft survival compared to CyA-ME.

1.3. *Recommendation (2B lung).* Tacrolimus may also provide an advantage for prevention of bronchiolitis obliterans syndrome (BOS) compared to cyclosporine.

Recommendation 1 Evidence Summary: Tacrolimus Efficacy

In **kidney transplant** numerous meta analyses and open-label RCTs have evaluated tacrolimus compared to CyA-ME.[30–37] Kramer and colleagues showed a composite endpoint of allograft loss, patient death and biopsy-proven acute rejection (BPAR) at 24 months occurred more frequently in CyA-ME treated patients (42.8% vs. 25.9%; $p < 0.001$).[38] Other RCTs have also shown less steroid-resistant rejection (4.2% in tacrolimus/MMF vs. 10.7% in CyA-ME/MMF) and less moderate to severe (Banff II–III) rejection with tacrolimus/MMF.[31,32] The 3-year analysis showed that while overall allograft survival was not different between groups, patients with DGF in the tacrolimus group experienced significantly better 3-year allograft survival compared to the CyA-ME arm (84.1% vs. 49.9%; $p = 0.02$). The landmark Symphony study compared four immunosuppression regimens: standard dose cyclosporine, low dose cyclosporine, low dose tacrolimus, and low dose sirolimus in 1645 low immunologic risk kidney transplant patients.[33] Low dose tacrolimus was significantly better than all other treatment arms in terms of BPAR (12.3% low dose tacrolimus vs. 25.8% standard cyclosporine, 24% low dose cyclosporine, and 37.2% low dose sirolimus, $p < 0.001$), mean calculated glomerular filtration rate (GFR), and 12-month allograft survival. Finally, two meta-analyses have been conducted evaluating the efficacy of tacrolimus compared to cyclosporine post-kidney transplantation.[36,37] The meta-analysis by Webster and colleagues identified that the allograft survival benefit of tacrolimus diminished with higher targeted tacrolimus troughs and when different cyclosporine formulations were accounted for.[36] The second meta-analysis concluded tacrolimus was superior to cyclosporine in terms of allograft loss (RR 0.089, 95% CI 0.057–0.122, $p < 0.001$) and acute rejection (RR 0.638, 95% CI 0.571–0.713, $p < 0.001$).[37]

Several randomized, prospective head-to-head studies investigated tacrolimus against CyA-ME based regimen in **pancreas transplant** recipients.[39–44] The EUROSPK study group conducted a multicenter trial of 205 simultaneous pancreas-kidney transplants receiving rabbit antithymocyte globulin (rATG), MMF, and short-term corticosteroids. The study demonstrated reduced 1-year incidence of BPAR with tacrolimus vs. CyA-ME (27.2% vs. 38.2%, $p = 0.09$) and improved allograft survival (91.3% vs. 74.5%, $p < 0.0005$).[40] This benefit was sustained at 3 years of follow up with rejection severity worse in patients receiving CyA-ME.[42,43] More initial episodes of BPAR were moderate or severe in CyA-ME (28% vs. 3%, $p = 0.009$). Single-center studies showed similar benefit with significant reduction in acute rejection rates and recurrence in the tacrolimus groups.[39,44] Also, significantly less allograft loss due to rejection was observed ($p = 0.026$) in tacrolimus-treated patients.[44] The interpretation of the impact of CNI choice in pancreas transplantation can be confounded by the distinct effects on glucose metabolism and insulin secretory capacity.[45]

Numerous randomized, prospective trials compared efficacy and safety of tacrolimus against CyA-ME in **liver transplantation**. Notably, a multicenter, open-label, randomized trial compared CyA-ME with tacrolimus in 606 liver transplants and showed 21% of tacrolimus patients and 32% of CyA-ME patients achieved the primary composite outcome of death, re-transplantation, or treatment failure for immunologic reasons at 12 months (RR 0.63, 95% CI 0.48–0.84, $p = 0.001$).[46] A 3-year follow up confirmed tacrolimus patients were still less likely to meet the composite endpoint (RR 0.75, 95% CI 0.60–0.95; $p = 0.016$).[47] Significantly more patients randomized to tacrolimus were alive at 3 years with their original allograft on the allocated study medication compared to CyA-ME (62.1% vs. 41.6, $p < 0.001$). Long-term outcomes of patients treated with tacrolimus versus CyA-ME were evaluated in other smaller prospective randomized clinical trials, where allograft and patient survival rates were similar between those receiving tacrolimus or CyA-ME, either in combination with corticosteroids with or without antimetabolites.[48–50] Adverse effects were also found to be significantly less in the tacrolimus group. Specifically, one study found more patients on CyA-ME (29.4%) were switched to tacrolimus, mostly due to lack of efficacy (acute or chronic rejection). In comparison 8% of tacrolimus patients were converted to CyA-ME, all due to adverse drug reactions, not lack of efficacy.[48]

The modern era of **intestinal transplantation** begins with the advent of tacrolimus and various antibody induction strategies. For this reason, in intestinal transplantation, there are no head-to-head comparative studies of tacrolimus vs. CyA-ME. Nonetheless, tacrolimus is the standard of care in all modern-day literature, including two case control studies as well as multiple large case series.[51–56]

Multiple RCTs outline both short- and long-term outcomes with tacrolimus compared to CyA-ME in **heart transplant**. A randomized, open-label, single-center study of 67 heart transplant patients compared the use of CyA-ME to tacrolimus with concomitant azathioprine and corticosteroids.[57] One- and five-year graft survival, freedom from rejection grade ≥ 3A and chronic allograft vasculopathy (CAV) was similar between groups. A single-center, RCT of 106 heart transplant patients receiving MPA, corticosteroids, and daclizumab induction compared tacrolimus with CyA-ME.[58] There was a longer rejection-free time period in the CyA-ME group (93 ± 100 days vs. 55 ± 81 days, $p = 0.1$), but a higher percentage of patients remained rejection-free in the tacrolimus group (28% vs. 39.2% cyclosporine, $p = 0.233$) with a trend toward less rejections per patient in the first year (0.94 ± 0.12 vs. 1.22 ± 0.14, $p = 0.138$). Longer-term randomized, open-label data comparing tacrolimus and CyA-ME found significantly higher freedom from rejection in the tacrolimus arm at 1 (65.5% vs. 30%, $p = 0.013$), 5 (65.5% vs. 23.3%, $p = 0.004$) and 10 years (65.5% vs. 21.7%, $p = 0.004$) in an intention to treat (ITT) analysis of 60 heart transplant patients.[59] Authors also evaluated freedom from cardiac allograft vasculopathy (CAV) in both groups at 1 year (96.4% tacrolimus vs. 88.5% cyclosporine, $p = 0.281$), 5 years (64% tacrolimus vs. 36% cyclosporine, $p = 0.085$), and 10 years (45.8% tacrolimus vs. 8% cyclosporine, $p = 0.003$). No difference in survival was found at 10 years. While many of the trials

comparing tacrolimus and cyclosporine do not necessarily find a survival difference, the cardiovascular side effect profiles are noticeably distinct. One prospective, randomized, concealed-allocation, open-label study with parallel arms of 129 stable heart transplant patients found tacrolimus-treated patients had significantly larger decreases in total and LDL cholesterol at 1, 3, and 6 months.[60] Additionally, coronary heart disease risk significantly decreased at 6 months in tacrolimus patients (9.3 to 7.9 vs. 9.2 to 9.5, $p = 0.0007$).

When used in combination with corticosteroids and an antimetabolite, tacrolimus was shown to have a decreased incidence in acute cellular rejection in **lung transplant** recipients relative to cyclosporine by multiple RCTs and meta-analyses. Tacrolimus-treated patients were significantly less likely to develop acute rejection, BOS, or lymphocytic bronchitis at 24 months (84.7% vs. 54.5%, $p = 0.002$) when used in combination with azathioprine, corticosteroids, and basiliximab induction, compared to cyclosporine.[61] Similar results were seen when evaluating the agents in combination with MMF, corticosteroids, and rATG in a randomized open-label study of 50 lung transplants. Treated rejection episodes per 100 patient days were lower with tacrolimus compared to CyA-ME (0.225 vs. 0.456, $p < 0.05$), with similar patient survival at 6 and 12 months.[62] Finally, a meta-analysis of three trials with 297 lung transplant recipients found fewer incidences of acute rejection per 100 patient days (mean difference −0.14, 95% CI, −0.28 to −0.01, $p = 0.04$) with tacrolimus-treated patients. No difference in patient survival was seen, but a trend toward decreased BOS was observed with tacrolimus.[63] Considering conversion in the setting of BPAR, a cohort of 20 lung transplant recipients with refractory BPAR transitioned from cyclosporine to tacrolimus had a reduced incidence and severity of rejection at the median follow-up of 25 months and BPAR was reversed in 55% of patients.[64] Considering BOS, in a randomized open-label trial of 274 lung transplant recipients who received tacrolimus vs. cyclosporine in combination with MMF and corticosteroids, the cumulative incidence of BOS was reduced with tacrolimus at 3 years (11.6% vs. 21.3%, $p = 0.037$) with similar rates of acute rejection and patient survival.[65] In a Cochrane Review of 413 lung transplant recipients, a decrease in the incidence of BOS at 24 months was seen with tacrolimus (RR 0.46, 95% CI 0.29–0.74) with similar rates of acute rejection and patient survival.[66] Lastly, in a prospective study of 79 patients with BOS on cyclosporine and an antimetabolite, conversion to tacrolimus at a mean of 30.4 months post-transplant resulted in less of a drop in forced expiratory volume (FEV1) time curve post-conversion at month 12.[67]

1. *Are extended-release formulations of tacrolimus as effective as immediate release formulation?*
   - 2.1. *Recommendation (1A kidney; 1B liver; 1C heart).* Once daily, extended-release formulations of tacrolimus are equally efficacious as IR-TAC for the prevention of acute rejection and patient and allograft survival.
   - 2.2. *Recommendation (1B kidney, pancreas, liver; 1C heart; 2D lung).* Kidney, liver, heart, and lung transplant recipients on LCPT have comparable tacrolimus exposure as those receiving IR-TAC with a reduced mean total daily dose (TDD). Pancreas and lung transplant recipients on ER-TAC had comparable tacrolimus exposure compared to those on IR-TAC.
   - 2.3. *Recommendation (2C pancreas).* Despite similar exposure, at 12 months, LCPT treated patients experienced less BPAR without affecting patient or allograft survival.
   - 2.4. *Recommendation (2D intestine).* There are limited data for ER-TAC use in intestine transplantation. However, there is no evidence of harm when used in this population.

Recommendation 2 Evidence Summary: Efficacy of Extended-Release Formulations of Tacrolimus

Use of de novo ER-TAC in **kidney transplant** was described in a randomized, open-label trial of 667 patients.[68] ER-TAC was compared to IR-TAC in combination with MMF and corticosteroids. BPAR rates at 24 weeks were similar (20.4% ER-TAC vs. 15.8% R-TAC, $p = 0.182$) as was 12-month patient and allograft survival. A similar study of 638 patients compared ER-TAC to IR-TAC to CyA-ME in combination with MMF, corticosteroids, and basiliximab induction.[69] At 12 months, efficacy failure (defined as death, allograft loss, BPAR, or lost to follow-up), was no different among the three groups. Considering LCPT, a randomized, open-label study of 543 kidney transplant recipients compared de novo LCPT to IR-TAC and found target tacrolimus trough levels were more rapidly achieved following the initial dose of LCPT (36.6% vs. 18.5%).[70] Overall, rates of treatment failure were noninferior to IR-TAC. Lastly, one randomized open-label trial of 326 stable kidney transplant patients assessed conversion from IR-TAC to LCPT.[71] LCPT was noninferior to IR-TAC for the primary efficacy endpoint, proportion of patients with efficacy failures (death, allograft failure, locally read BPAR, or loss to follow-up) at 12 months. Mean daily dose of LCPT was significantly ($p < 0.0001$) lower than pre-conversion IR-TAC dose at each visit while mean troughs were similar.

Three studies examined use of ER-TAC formulations in de novo setting following **pancreas transplantation**.[72–74] A randomized, prospective, crossover pharmacokinetic study of 22 simultaneous pancreas-kidney (SPK) recipients demonstrated comparable tacrolimus exposure, serum creatinine, blood glucose, and lipase at 6 months between ER-TAC and IR-TAC.[72] In another prospective, single arm study of 14 SPK recipients on ER-TAC, 38% experienced rejection at 11 months while patient and kidney graft survival were 100%. Pancreas graft survival was 93%.[73] Lastly, in an observational LCPT study of 39 SPK recipients, although similar exposure was reported, LCPT-treated patients experienced significantly less BPAR (0% vs. 29%, $p = 0.01$) at 12 months.[74] This was accompanied by better glycosylated hemoglobin values (4.9% vs. 5.6% $p = 0.01$) at 6 months compared to IR-TAC.

De novo use and conversion to LCPT have been studied in **liver transplant**. In a randomized open-label study of 58 de novo liver transplant patients, freedom from acute rejection at day 180 and 360 was similar with LCPT versus IR-TAC (79% vs. 87% and 74% vs. 82%, respectively).[75] When used as conversion therapy in a

retrospective study of 25 patients recieving basiliximab induction with or without MMF, no rejection had occurred within 3 months of conversion.[76] Considering pharmacokinetics, LCPT demonstrated a more consistent profile with lower C_{max} and peak-trough fluctuation when converted from IR-TAC. Overall AUC was similar to IR-TAC at a 30% lower TDD with no new safety concerns occurred within 1 year of follow-up.[77] An additional retrospective, observational study of 150 patients converted from IR-TAC to LCPT at a ratio of 1:0.7 found maintained target tacrolimus trough levels with a reduced median TDD.[78] No episodes of rejection were seen at 24 months. ER-TAC has also been studied in both the de novo and conversion settings. A large, randomized, two-arm, parallel-group study of 475 liver transplant patients found ER-TAC to be non-inferior to IR-TAC at 24 and 52 weeks (BPAR 36.3% and a 37.9% vs. 33.7% and 35.4, respectively).[79] Severity of rejection and patient and allograft survival at 52 weeks were similar. A second multicenter, randomized, open-label, parallel group study of 615 liver transplant patients on de novo ER-TAC, MMF, single-dose methylprednisolone with or without basiliximab sought to determine whether a decreased initial dose of ER-TAC versus delaying therapy initiation to 5 days post-transplantation improved kidney function at 24 weeks.[80] GFR significantly improved in the decreased dose and delayed initiation arm compared to standard therapy. The lower dose arm also showed a lower incidence of BPAR compared to the standard dose arms. ER-TAC was also studied as conversion therapy in a two-arm, parallel-group, open-label trial of 91 liver transplant patients randomized to convert to ER-TAC versus continuing IR-TAC.[81] No patients reached the primary composite endpoint of this study, efficacy failure defined as BPAR, allograft loss, or death within 6 months post-conversion, leading authors to conclude that conversion of stable liver transplant recipients to ER-TAC is safe and effective.

LCPT use in **intestinal transplant** is limited to a case report of a 37-year-old male who received an abdominal wall vascularized composite allograft and small bowel transplant.[82] The patient was transitioned to LCPT in combination with MMF and prednisone. No adverse outcomes were noted.

LCPT was recently studied in **heart transplant** in a phase 2, single-center, open-label, non-inferior matched control study of 25 recipients who were matched 1:2 with a historical IR-TAC control.[83] Patients were maintained on MPA and corticosteroids that tapered off by 6 months. LCPT was noninferior to IR-TAC for the composite endpoint of death, acute cellular rejection and/or new allograft dysfunction within 1 year (20% vs. 40%, CI -40% to −0.5%). One year death was not observed with LCPT group compared to 14% of control group. Rejection incidence, mortality rates and Kaplan–Meier survival curves were not significantly different between the two groups. The rate of cardiovascular-related readmissions was higher in the IR-TAC group (50%) compared to LCPT group (20%) ($p = 0.046$). Trough levels were consistently higher with lower TDD in the LCPT group. De novo use of ER-TAC has also been studied. A small, prospective, randomized trial of 19 heart transplant patients who received basiliximab induction, MPA, and corticosteroids showed low incidence of acute rejection in both groups at 1 and 6 months.[84] Another study in 82 heart transplant recipients examining de novo ER-TAC revealed that trough levels are lower during the first week post-transplant compared to IR-TAC regimen.[85] In addition, patients in the IR-TAC group had a stronger inclination to develop stage 2 rejection, but this did not affect 1-year mortality (15% vs. 20%, respectively).

Conversion from IR-TAC to extended-release formulations has been evaluated in stable **lung transplant** recipients. Converting between once-daily formulations, a prospective pharmacokinetic evaluation of stable lung transplant patients switched from ER-TAC to LCPT in a 1:0.7 ratio found similar drug exposure between formulations.[86] Mean TDD was significantly less in LCPT at 6 months. No difference in adverse effects or spirometry were noted, and no BPAR occurred. In a single-arm, non-randomized study of 19 stable lung transplant recipients more than 6 months post-transplant, patients were switched from IR-TAC to ER-TAC with similar area under the curve (AUC) at 2 weeks pre- and post-conversion. There was no difference in adverse effects per patient month nor acute cellular rejection at 6 months after conversion.[87] In lung transplant recipients with cystic fibrosis, to achieve target C_{min} and similar AUC, an increase in dose may be required when converting from IR-TAC to ER-TAC.[88]

1. *What is the role of extended-release formulations of tacrolimus in modern M-IMS?*
   - 3.1. *Recommendation (1B kidney; 1C liver, heart)* . Complex medication regimens involving multiple daily doses have shown to decrease patient medication adherence. Decreased medication adherence is associated with worse outcomes. Once daily tacrolimus products may improve the rate of adherence compared to twice daily tacrolimus.
   - 3.2. *Recommendation (1B kidney; 1D pancreas).* Due to pharmacokinetic differences, LCPT abrogates peak-related side effects of tacrolimus, such as tremors, in transplant recipients.
   - 3.3. *Recommendation (1C kidney).* LCPT may be advantageous in recipients who are African American, elderly (≥65) and presumed or proven rapid metabolizers.
   - 3.4. *Recommendation (2C pancreas). De novo* LCPT use in the setting of MPA and corticosteroids may improve metabolic outcomes in the early (3–6 month) post-pancreas transplant period.

Recommendation 3 Evidence Summary: Role of Extended-Release Formulations of Tacrolimus

Two studies assessed ER-TAC's effect on adherence in **kidney transplant**. The first, a RCT of 219 stable kidney recipients converted from IR-TAC to ER-TAC at 3 months found of those who remained engaged with the regimen at 6 months, significantly more ER-TAC patients took the prescribed number of doses (88.2% vs. 78.8%, $p = 0.0009$).[89] Patients on IR-TAC missed more evening doses than morning (14.2% vs. 11.7%, $p = 0.0035$). Additionally, an observational prospective study of 1106 kidney and liver

transplant recipients on ER-TAC were assessed for adherence and acceptance at 3 and 6 months.[90] At 3 months, adherence was improved in 21%, unchanged in 69%, and worsened in 10% of patients. General acceptance score was improved in 28% and unchanged in 39% of patients. Results were similar at 6 months. Available data for LCPT conversion focus on its unique pharmacokinetic profile including lower C_{max}, percent fluctuation, swing, and C_{max}/C_{min} ratio with consistent drug exposure.[24,91] The STRATO study was an open-label, multicenter, prospective study of 30 kidney transplant recipients with clinically significant tremor that aimed to see if LCPT's lower C_{max} would impact tacrolimus's neurotoxic side effect profile. A statistically and clinically significant improvement in tremor (via FTM score, accelerometry device, and quality of life in essential tremor score) was observed 7 days post-conversion.[92] ASERTAA, a prospective randomized crossover study of 50 African American kidney transplants, found no significant difference in tacrolimus exposure or C_{max} in hypermetabolic (CYP 3A5 expressers) compared to nonexpressers.[93] However, IR-TAC C_{max} was significantly higher in hypermetabolic patients (33%, $p = 0.04$) compared to those on LCPT (11%, $p = 0.4$). Lastly, a pooled analysis of 861 kidney transplants from two RCTs found LCPT to have lower efficacy failure rates in African American and elderly (≥65 years old) patients.[94]

De novo use of LCPT in **pancreas transplant** recipients demonstrated possible benefit in lower BPAR (0% vs. 29%, $p = 0.01$) and HgA1c values (mean HgA1c 4.9% vs. 5.6% $p = 0.01$) compared to IR-TAC in an observational study of 39 SPK recipients.[74] A single report of converting 8 IR-TAC treated pancreas transplant recipients to LCPT found 100% of patients converted for neurotoxicity had documented improvement following conversion.[95]

A prospective, single-center, observational study of 125 **liver transplant** patients that were switched from IR-TAC to ER-TAC revealed a 12-month allograft survival rate of 96% with no episodes of acute rejection in patients switched to ER-TAC.[96] A self-reported improvement in 12-month medication adherence was observed (nonadherence rate 66.4% at baseline to 30.9%).

In **heart transplant**, improved medication adherence with ER-TAC was demonstrated in a pre-experimental study of 76 stable heart transplant patients.[97] Baseline self-reported non-adherence was 75% and significantly improved at 8 months (40.3%, $p < 0.0001$). Specifically, adherence improved in 56.9% of patients, was unchanged in 37.5% and was impaired in 5.6%.

1. *What is the role of cyclosporine in modern M-IMS?*
   4.1. *Recommendation (2C kidney, liver, heart, lung; 1D pancreas; expert opinion intestine).* While appropriately balancing risk vs. benefit, cyclosporine may be used as an alternative to tacrolimus in transplant recipients with tacrolimus intolerance.

Recommendation 4 Evidence Summary: Cyclosporine Role

In the modern era of SOT cyclosporine is not the agent of choice for M-IMS. However, its use in the setting of tacrolimus-associated side effects should be considered when conversion to other agents is not feasible.

One study conducted in **kidney and liver transplant** recipients (31% kidney, 48% liver) cited neurotoxicity as the most common reason for switching from tacrolimus to CyA-ME (55%).[98] Other reasons for switching to cyclosporine included diabetes and gastrointestinal intolerance in 24% of patients for each. The switch from tacrolimus to cyclosporine resulted in acute rejection within the first year after conversion in 18% of kidney and 31% of liver transplant patients.

A multicenter analysis of CNI use in **pancreas transplant** recipients illustrates the importance of converting tacrolimus treated patients to CyA-ME in case of adverse events in this transplant population. At 1 year, 20% of recipients had converted safely from tacrolimus to cyclosporine for diabetogenicity, nephrotoxicity, or rejection.[99] Although larger head-to-head studies in pancreas demonstrate tacrolimus is superior to CyA-ME in acute settings, long-term data from single-center reports demonstrate equivalent allograft and patient outcomes when used with MPA and corticosteroids.[100]

Available data comparing the two agents in **lung transplant** have found similar rates of patient and allograft survival.[61,63,65,66,101,102] Importantly, some studies found rates of side effects were significantly higher in tacrolimus-treated patients compared to those on CyA-ME.[62,63,65,101,103]

1. *Can tacrolimus monotherapy be safely used as M-IMS to prevent allograft rejection and loss at 12 months?*
   5.1. *Recommendation (2A kidney).* Tacrolimus monotherapy in the setting of alemtuzumab induction immunosuppression is as effective at preventing BPAR and achieves similar 1-year patient and allograft survival as IL2-receptor antagonist induction followed by tacrolimus and MPA in low immunologic risk transplant recipients. No recommendation can be made for tacrolimus monotherapy in recipients of high immunologic risk.
   5.2. *Recommendation (2C pancreas).* Tacrolimus monotherapy following alemtuzumab induction is comparably safe and effective at 12 months to a more conventional induction and maintenance regimen.
   5.3. *Recommendation (2B liver).* Tacrolimus monotherapy is a viable M-IMS to prevent allograft rejection or loss.
   5.4. *Recommendation (2C intestine).* Along with antilymphocyte antibody (ALA) induction, tacrolimus monotherapy can be safely used.
   5.5. *Recommendation (2C heart).* Tacrolimus monotherapy, after corticosteroids are weaned off by 2 months post-transplant, appears to be safe and efficacious.

Recommendation 5 Evidence Summary: Tacrolimus Monotherapy

The use of tacrolimus monotherapy has been most extensively studied in low immunologic risk **kidney transplant** recipients in the setting of alemtuzumab induction. In 2008, a prospective RCT of

131 deceased donor kidney transplant recipients compared tacrolimus monotherapy after alemtuzumab induction to tacrolimus-based triple drug therapy after basiliximab induction.[104] Patients with a PRA >25% were excluded. Rates of BPAR at 12 months were 20% in the alemtuzumab/tacrolimus monotherapy group compared to 32% with basiliximab/triple immunosuppression ($p = 0.09$). Allograft function and patient and allograft survival were no different; however, there was more cytomegalovirus (CMV) in the alemtuzumab/tacrolimus monotherapy arm. Two similarly-designed studies comparing alemtuzumab induction with tacrolimus monotherapy to IL-2 induction with tacrolimus/MPA showed similar 1-year patient and allograft outcomes in 116 low immunologic risk, predominantly living donor, kidney transplant recipients.[105,106] No data are available comparing tacrolimus monotherapy to triple therapy in the setting of ALA induction for both arms.

Reports of tacrolimus monotherapy in **pancreas transplantation** stem from a single-center, observational study where following alemtuzumab induction, 60 patients were maintained on tacrolimus (initial trough level of 10–12 ng/ml) monotherapy. With a mean follow-up period of 22 months patient, pancreas, and kidney allograft survival rates were 94%, 89%, and 87%, respectively. The incidences of acute rejection, corticosteroid-resistant rejection, and CMV infection were 30%, 7%, and 12%, respectively.[107] The lack of other available evidence evaluating tacrolimus monotherapy suggest that at present it cannot be highly considered to maintain pancreas transplant patients on monotherapy.

Studies that evaluated tacrolimus monotherapy M-IMS in **liver transplant** recipients are heterogenous as different immunosuppression regimens were utilized in comparison groups, and the timing of monotherapy initiation were variable. Some studies left patients on tacrolimus monotherapy after induction or 2 weeks after liver transplant, while others start weaning adjunct M-IMS 3–6 month post-transplant.[108–117] Furthermore, two studies weaned adjunct M-IMS off in the comparative arm, rendering these arms on tacrolimus monotherapy as well.[108,109] Within the constraints of these limitations, most studies demonstrate a comparable allograft rejection rate and allograft survival rates at 12 months in patients on tacrolimus monotherapy.[108–112] However, some studies notably had relatively high overall rejection rates overall that would be unacceptable in the current era.[109–111]

Tacrolimus monotherapy is frequently used along with ALA induction in **intestinal transplantation** with favorable outcomes in terms of allograft survival and post-transplant complications.[51–53]

In **heart transplantation**, the most notable evidence available on tacrolimus monotherapy is the TICTAC trial.[118] This was a prospective, open-label, randomized study of 150 de novo isolated first heart transplant patients who received either tacrolimus monotherapy or tacrolimus/MPA. All patients were weaned off corticosteroids by 8–9 week post-transplant. There was no difference seen in the primary outcome of mean composite biopsy score at 6 months (tacrolimus 0.70 ± 0.44, 95% CI 0.6 to 0.8 vs. tacrolimus/MPA 0.65 ± 0.40, 95% CI 0.55 to 0.74, $p = 0.44$) or 12 months (tacrolimus 0.67 ± 0.39, 95% CI 0.59 to 0.76 vs. tacrolimus/MPA 0.62 ± 0.39, 95% CI 0.53 to 0.71, $p = 0.38$). Also, 3-year survival was similar between groups (92.4% tacrolimus vs. 97% tacrolimus/MPA, $p = 0.58$). There was no difference in the development of allograft vasculopathy nor freedom from treated rejection at 6 and 12 months. Nine of the 79 patients on tacrolimus monotherapy were started on MPA because of rejection. However, 26 of the 71 tacrolimus/MPA patients had MPA withdrawn due to leukopenia, 2 of which correlated with rejection. At 10 years, patient survival and freedom from CAV were similar between groups (68% vs. 80.9%, $p = 0.15$; and 75.6% vs. 84.6%, $p = 0.11$ in tacrolimus vs. tacrolimus/MPA, respectively) although crossover was common.[119]

3.2 | Antimetabolites

This class of drugs includes azathioprine and MPA. Azathioprine incorporates its metabolite, 6-thioguanine into DNA subsequently blocking synthesis. It has been proposed that CD28-dependent activation of the RAC1 G-protein mediates this immunosuppressive effect.[120] Nevertheless, its metabolite 6-methyl-MP also inhibits de novo synthesis of purines. The disruption of both the de novo and salvage pathways of nucleic acid synthesis convey a more extensive and severe side effect profile including alopecia, pancreatitis, and hepatotoxicity.[121] MPA inhibits de novo purine synthesis in activated lymphocytes; thus, disproportionately preventing active lymphocyte proliferation as they cannot use the salvage pathway to create guanosine.[122] Two formulations of MPA exist, the pro-drug (MMF, CellCept®) and the enteric coated formulation [mycophenolate sodium (MPS), Myfortic®]. Of note, these formulations are not bioequivalent.

Since these agents affect cells with rapid turnover, MPA is associated with myelosuppression and gastrointestinal side effects such as nausea, vomiting, and diarrhea. These are dose-related and often prompt MPA dose manipulations that have been associated with increased rejection in some populations.[123–128] Lastly, MPA is teratogenic and should be avoided 6 weeks prior to and during pregnancy. The FDA-required MPA Risk Evaluation Mitigation Strategy program was developed to educate healthcare providers and female patients of childbearing potential regarding these risks, importance of pregnancy prevention and planning, as well as need to report pregnancies to the Mycophenolate Pregnancy Registry.[129]

Plasma concentrations of MPA can be measured and have been correlated with clinical efficacy and toxicity; MPA AUCs <30 μg/ml/h correlate with increased rates of rejection whereas AUCs >60 μg/ml/h have been linked to increased leukopenia.[130,131] However, MPA undergoes enterohepatic recirculation and thus has a complex pharmacokinetic profile. MPA single time point concentrations do not correlate well with total drug exposure making AUC monitoring a challenge. Interestingly, since cyclosporine inhibits enterohepatic recirculation, MPA exposure is reduced by 30% in its

presence. Thiopurine *S*-methyltransferase (TPMT) activity can affect azathioprine drug exposure and subsequent myelosuppression. Approximately 10% of the population has a polymorphism in TPMT leading to low-level activity and increased risk of myelosuppression. Routine monitoring for the TPMT polymorphism prior to azathioprine initiation is recommended in the non-transplant setting.[132] While there are limited data in transplant population due to low usage rate, routine screening for TPMT is also recommended in all transplant patients before starting azathioprine.[133-136]

1. *Is MPA the superior antimetabolite in preventing allograft rejection and/or loss at 12 months?*
   - 6.1. *Recommendation (2B kidney).* There may be benefit to the use of MPA over azathioprine for the prevention of acute rejection.
   - 6.2. *Recommendation (1C pancreas, 1B liver).* MPA is more effective than azathioprine in reducing acute rejection rates at 12 months.
   - 6.3. *Recommendation (2D intestine).* Despite an absence of studies directly comparing MPA to azathioprine, MPA has been adopted as a standard component of early M-IMS in this population in lieu of azathioprine.
   - 6.4. *Recommendation (1B heart).* MPA has demonstrated better patient and allograft survival over azathioprine with a decreased incidence and severity of acute rejection.
   - 6.5. *Recommendation (2C lung).* Comparative data have variable results although there are some observational and cohort data demonstrating less acute rejection with MPA as compared to azathioprine and potential benefit in switching to MPA in the setting of BOS.

Recommendation 6 Evidence Summary: MMF Efficacy

In **kidney transplant**, two RCTs compare MMF to azathioprine in combination with CyA-ME and corticosteroids.[137,138] The first, a prospective, open-label, multicenter, randomized study of 477 kidney recipients compared three groups: those on 3 months of MMF followed by 9 months of azathioprine, 12 months of MMF, and 12 months of azathioprine. Investigators found significantly lower acute rejection and treatment failure rates with MMF-containing groups (43.7% and 43.2% vs. 58.6%, $p < 0.01$; 23.4% and 21% vs. 32%, $p < 0.04$, respectively).[137] The other study of 336 kidney transplants randomly assigned to either MMF or azathioprine found similar rate of clinical rejection at 6 and 21 months.[138] Of note, steroids were tapered at 6 months in stable patients. Two RCTs also compared both antimetabolites in the setting of tacrolimus. The first, a prospective open-label randomized study of 223 first-time kidney transplants compared three groups: tacrolimus/MMF, CyA-ME/MMF, and tacrolimus/azathioprine.[31] There was no difference in 12-month BPAR or patient and allograft survival, but corticosteroid-resistant rejection (4.2% in tacrolimus/MMF vs. 10.7% in CyA-ME/MMF and 11.8% in the tacrolimus/azathioprine) and moderate to severe (Banff II–III) rejection was lowest in the tacrolimus/MMF group. The 3-year analysis also showed BPAR requiring ALA therapy was lower in the tacrolimus/MMF group compared to tacrolimus/azathioprine (33% vs. 75%, $p = 0.03$).[32] The other RCT assessed corticosteroids and tacrolimus in combination with either azathioprine, MMF 1 gm/day, or MMF 2 gm/day.[139] BPAR at 1 year was 32.2%, 32.2%, and 8.6% in the azathioprine, MMF 1 gm/day, and MMF 2 gm/day groups, respectively ($p < 0.01$). ALA treatment of BPAR was the same. The mean dose of MMF in the 2 gm/day group decreased to 1.5 gm/day by 6 months, primarily due to GI-related side effects. Lastly, two meta-analyses and one systematic review confirmed MMF when used with a CNI reduced the risk of rejection when compared to azathioprine. Rates of allograft and patient survival did not differ between those on MMF and azathioprine.

Pancreas transplant recipients treated with MMF/CNI experienced significantly reduced acute rejection rates in the first post-transplant year compared to those on azathioprine/CNI according to several observational studies.[140–145] Additionally, an open-label, randomized, multicenter study showed numerically lower rates of rejection at 6 and 12-months, though not statistically significant.[146] However, time to rejection or treatment failure was significantly longer in MMF group ($p = 0.049$).

Two RCTs have compared azathioprine with MMF in **liver transplant** recipients. The largest study of 565 patients on CNI and corticosteroids randomized to receive either azathioprine or MMF found significantly more rejection at 6 months in those on azathioprine (47.7% vs. 38.5%, $p = 0.025$).[147] Additionally, patients on azathioprine were more likely to have multiple episodes of rejection and require ALA treatment. Both groups had similar patient and allograft survival. The second RCT of 57 patients compared azathioprine to MMF in combination with cyclosporine, corticosteroids, and antithymocyte globulin (ATG) induction.[148] While patients receiving azathioprine were more likely to develop rejection compared to those on MMF (44.8% vs. 21.4%; $p = 0.06$), patient survival was similar between the two groups. A 12-month follow-up of 63 patients again demonstrated that rejection was less likely to develop in patients receiving MMF (19.4% vs. 40.6%; $p = 0.06$).[149] The study population was small and follow-up limited to 12 months. Additionally, none of the studies performed protocol biopsies and the largest study used MMF 3 gm/day which is 50% more than the dose that is commonly used.

There are no head to head comparative studies for MPA versus azathiprine. Additionally, there are limited data for mycophenolate use in **intestinal transplantation** due to gastrointestinal toxicities associated with this medication.[150] However, it continues to remain a standard component in many early M-IMS regimens with tacrolimus, before transition to alternative therapy or tacrolimus monotherapy as illustrated in case reports and case series.[82,151–153]

Several well-designed clinical trials have compared the MMF and azathioprine in **heart transplant**. Notably, a prospective, multicenter study of 109 patients randomized to MMF or azathioprine found an overall low incidence of rejection (3 reversible subclinical rejections).[154] Considering long-term outcomes, a double-blind, randomized, active-controlled trial in 650 heart transplant patients (327 MMF and 323 azathioprine) in combination with CyA-ME and

prednisone found significantly lower rates of rejection requiring treatment (65.7% vs. 73.7%, $p = 0.026$)[155] Importantly, the overall mortality rate at 12 months was 6.2% in the MMF group compared to 11.4% in the azathioprine group ($p = 0.031$). At 36 months, the incidence of death or re-transplant was 11.8% in those on MMF compared to 18.3% on azathioprine ($p < 0.01$), and the time to death or re-transplant was also significantly shortened with azathioprine therapy.[156] Finally, a large ISHLT/UNOS registry study analyzed MMF compared to azathioprine on a cyclosporine-based M-IMS protocol in 5599 heart transplant recipients (657 in MMF group and 4942 in azathioprine group).[157] They found an actuarial survival benefit with MMF at 1 and 3 years compared to azathioprine (96% vs. 93% and 91% vs. 86%, respectively), and a relative risk (RR) of 3 year mortality of 0.62 in favor of MMF compared to azathioprine ($p = 0.011$). The Kaplan–Meier survival curve show a statistically significant improvement in the MMF group ($p = 0.0012$) with survival rates of 94.5%, 92.3%, and 87.1% at 1-, 2-, and 3-year post-transplant, respectively. MMF therapy at the time of discharge reduced the 3-year mortality risk by approximately 50% after controlling for other known risk factors for mortality in this population.

Multiple RCTs evaluated MMF versus azathioprine in **lung transplant** recipients. A prospective, randomized, open-label, multicenter study of lung transplant patients who received MMF or azathioprine in combination with ATG induction, cyclosporine, and corticosteroids found no difference in biopsy grade > A2, or grade unknown acute rejection, within first year (54.1% vs. 53.8%). There was no significant difference in the primary endpoint BOS, with 73% in the MMF group versus 75% in the azathioprine group free from BOS at 3 years; $p = 0.70$. While there was a trend towards improved survival with MMF at 1 year (88% vs. 80%, $p = 0.07$), there was no significant difference at 3 years between groups (75% vs. 69%). However, more patients discontinued azathioprine (59.6% vs. 46.5%, $p = 0.02$).[158] Secondly, in a randomized, prospective, dual center trial of 81 recipients on cyclosporine, corticosteroids, and either MMF or azathioprine, the incidence of BPAR grade 2 or greater (MMF 63% vs. azathioprine 58%, $p = 0.82$) and patient survival (MMF 86% vs. azathioprine 82%, $p = 0.57$) did not differ at 6 months.[159] In a small non-randomized cohort study ($n = 22$), of patients treated with ATG induction, cyclosporine, prednisone, and MMF or azathioprine, significantly fewer episodes of acute rejection were seen in those on MMF compared to azathioprine (0.26 ± 0.34 vs. 0.72 ± 0.43 episodes/100 patient-days, $p < 0.01$).[160] However, there was no statistically significant difference in BOS at 12 months (MMF 18% vs. azathioprine 36%, $p =$ NS). In a non-randomized, single-center experience of 156 lung transplant patients undergoing monthly surveillance bronchoscopies for at least 6 months post-transplant, patients treated with MMF had significantly fewer acute rejection episodes per patient (0.5 ± 1.0 vs. 1.5 ± 1.9, $p < 0.001$), recurrent rejection incidence (14% vs. 42%, $p < 0.001$), and less severe (grade 3) rejection (0.93% vs. 10.4%, $p = 0.01$). A significant decrease in allograft loss due to either death or re-transplantation ($p = 0.049$) and a trend toward improved survival at 5 years were also observed (MMF 79% vs. azathioprine 64%, $p = 0.062$).[161] Lastly, switching from azathioprine to MMF in the setting of BOS may offer benefit. In a single arm study of 13 lung transplant patients with BOS, MMF 3 gm/day (duration: 1 week to 24 months, mean 11.4 months) replacing azathioprine resulted with stabilization of pulmonary function tests in majority of patients after MMF initiation.[162]

1. *Where can MPS be advantageous over MMF?*
   - 7.1. *Recommendation (1A kidney; 1B pancreas, heart; 2C liver)* . MMF dose reductions are associated with increased rejection rates. Transplant recipients with gastrointestinal side effects may benefit from conversion to enteric-coated MPS. It is a safe and effective alternative to MMF.
   - 7.2. *Recommendation (2B lung)* . Available data for MPS describe that it can be utilized in combination with corticosteroids and a CNI. However, there are no data directly comparing MPS to MMF.

Recommendation 7 Evidence Summary: Role of Mycophenolate Sodium

In **kidney transplant**, two RCTs and one retrospective case control assessed MPS versus MMF. The first study, a double blind RCT of 322 stable kidney transplant patients found similar rates of neutropenia and GI side effects at 3 months and 12 months in those on MPS versus MMF.[163] Rates of BPAR and efficacy failure were similar. Overall incidence of infections was similar, but the number of serious infections was significantly lower with MPS (8.8% vs. 16.0%; $p < 0.05$). A larger retrospective case control of 1704 patients found significantly higher BPAR with MMF vs. MPS (30% vs. 22%, $p = 0.0004$) with a significantly higher risk of drug discontinuation and dose reduction (hazard ratio = 1.507, $p = 0.0002$ and 1.703, $p < 0.0001$, respectively).[164] The fewer dose reductions and discontinuations may have translated to lower BPAR, although data are correlational. Most recently, a multicenter, double-blind, RCT of 396 kidney transplant patients with self-reported GI symptoms found that those on MPS were more likely to have a change in baseline total Gastrointestinal Symptom Rating Scale (GSRS) score ≥ 0.3 (62% vs. 55%, $p = 0.15$).[160,165] A subgroup analysis found patients with indigestion, diabetes, on steroids, or converted between 6- and 12-month post-transplant had a significant improvement in GSRS.

In **pancreas transplant** recipients, a multivariate analysis revealed that MMF use and duration of diabetes are both risk factors for GI complications such as non-infectious diarrhea.[166] Moreover, following pancreas transplantation, MMF dose manipulation due to side effects, has been associated with increased rejection rates and should be avoided.[123,128] A retrospective evaluation of 15 pancreas transplant recipients with gastroparesis was performed a median 182 (69–1523) days post-transplant to determine MPA AUC while on MMF.[167] Subsequently, patients were converted to MPS with similar drug exposure (MPA peak, trough and AUC_{0-12}) as MMF. However, despite similar exposure, MPS-treated patients experienced significant reduction in upper and lower GI side effects (100% MMF vs. 20% MPS, $p < 0.001$). Similar findings were reported in an observational cohort study, where MPS was associated with lower incidence

of acute diarrhea and reduced diarrhea severity as compared to MMF.[166] Moreover, MPS use was associated with less adverse event driven dose manipulations in this population.[168] A multicenter, prospective, observational study showed comparable clinical efficacy when MPS was used in de novo setting or when introduced later, following pancreas transplantation.[169]

Several studies have assessed the role of MPS in patients who developed GI intolerance to MMF after undergoing **liver transplant**. Fifty-five percent of 36 patients who were converted to an equimolar dose of MPS at a median of 45 month post-transplant had resolution of their GI symptoms, 17% had improvement, and 28% had either no change or worsening.[170] Another study compared MMF and MPS in two parts. The first part was a prospective, double blinded RCT between de novo MMF and MPS.[171] GSRS in the 30 analyzed patients trended toward better tolerability with MPS versus MMF but was not statistically significant. The second part, a conversion study of 29 patients, found significant improvement in GI symptoms ($p < 0.001$) in patients transitioned to MPS. Additionally, in a prospective, open-label, longitudinal study of 31 patients, GI symptoms ($p = 0.002$) and quality of life ($p = 0.0009$) improved in those transitioned to MPS.[172] Similarly, three observational studies observed similar improvements in GI symptoms after conversion to MPS.[173–175] Though these studies were small, had limited follow up, and did not necessarily use equimolar dosing of MPS, they add to the body of evidence that MPS is a safe and efficacious alternative in patients experiencing GI intolerance while on MMF therapy.

In **heart transplant**, MMF has been associated with gastrointestinal side effects in many clinical trials and often prompt dose reductions in clinical practice. A retrospective review of 182 heart transplant recipients on MMF identified that 71% of patients required a dose decrease due to an intolerance or toxicity.[127] Also, rejection was significantly higher in patients with GI intolerance to MMF requiring a dose reduction compared to those on target study doses (65% vs. 35%, $p = 0.002$). Interestingly, this finding was not replicated in patients who had a dose reduction for leukopenia or infection. This finding was also substantiated in a single-blind, prospective, multicenter, 12-month study comparing MMF to equimolar MPS in combination with CyA-ME and corticosteroids. The original trial found the incidence of treatment failure (defined as a composite of biopsy-proven and treated acute rejection, allograft loss or death) was similar for both groups at 6 (52.6% MPS vs. 57.9% MMF) and 12 months (57.7% MPS vs. 60.5% MMF, p = NS).[176] However, the authors also noted significantly more patients on MMF had ≥2 dose reductions throughout the study compared to MPS (26.9% vs. 42.1%, $p = 0.048$). This prompted a post hoc analysis that revealed MMF patients who did not undergo dose reductions experienced a 38.5% treatment failure, 57.7% BPAR and 11.5% BPAR ≥3A rate compared to 60% treatment failure, 70% BPAR and 44% BPAR ≥ 3A rate in those that underwent ≥1 dose reduction.[177] When comparing all patients with ≥1 dose reduction, there was a decreased incidence of treatment failure (46.8% EC-MPS vs. 60% MMF, p = NS) and BPAR (55.3% EC-MPS vs. 70% MMF, p = NS) at 12 months. Of the rejections seen at 12 months in the dose reduction groups, those in the MMF group were more likely to have more severe rejection (grade ≥ 3A) compared to those in the EC-MPS group (44% MMF vs. 23.4% EC-MPS, $p = 0.032$). The average daily dose as a percentage of recommended protocol dose was significantly higher for MPS (88.4% vs. 79%, $p = 0.016$) and days below the protocol-required dose was significantly higher for MMF (39.4% vs. 24.8%, $p = 0.016$).

Although no head-to-head studies comparing MMF to MPS exist in **lung transplant,** data for MPS use exist. A prospective, randomized, multicenter, open-label study was conducted in 165 adult lung transplant recipients that received cyclosporine, corticosteroids, and de novo MPS 1080 mg twice daily that was either continued or switched to everolimus 4–12 weeks post-transplant.[178] There was no significant difference in the primary endpoint of BOS within 3 years post-transplant between groups based on intention to treat (ITT) (24 MPS vs. 24 everolimus, $p = 0.87$) or per protocol (PP) (10 MPS vs. 15 everolimus, $p = 0.16$). Three-year patient survival and one-year acute rejection was not significantly different between groups (MPS 84% vs. everolimus 76%, $p = 0.19$ and 46.3% vs. 38.1%, respectively). However, leukopenia (46% vs. 24%, $p < 0.01$), diarrhea (26% vs. 9%, $p < 0.01$), and CMV infection (12% vs. 4%, $p = 0.04$) were more frequent with MPS and venous thromboembolism (5% vs. 17%, $p = 0.02$) more frequent with everolimus.

1. *What is the Role of azathioprine in modern M-IMS?*
   - 8.1. *Recommendation (1C kidney, pancreas, liver, heart, lung)* . Azathioprine is the antimetabolite of choice for all transplant recipients that are, or desiring to become, pregnant.
   - 8.2. *Recommendation (1B kidney, heart, lung; 2C pancreas; 1D intestine)* . Azathioprine may be used in place of MPA in those intolerants to MPA products, such as gastrointestinal toxicity, that require an antimetabolite.

Recommendation 8 Evidence Summary: Role of Azathioprine

In 2007, the FDA changed the pregnancy rating of MMF from "C" to "D" meaning there is positive evidence of human fetal risk. This change was a result of pregnancy registries and published literature showing an increased risk of spontaneous abortion, congenital malformations, and other abnormalities. Specifically in **kidney transplant**, an analysis of 444 pregnancies found discontinuation of MPA before conception result in higher live birth and lower miscarriage rates (78% vs. 48% and 20% vs. 48%, respectively $p < 0.001$) than those on MPA early in pregnancy.[179] Based on this, current guidelines recommend discontinuing MPA and considering the risks and benefits of transitioning patients who are, or are planning on becoming pregnant, to azathioprine.[180,181] It is important to note that although azathioprine is also labeled pregnancy category D, that rating is based on animal studies showing fetal anomalies and embryonic resorption. However, clinical studies in SOT have not seen these results replicated.[182–186] Most notably, The National Pregnancy Transplant Registry evaluated 56 patients (46 **kidney**, 7 **pancreas–kidney**, 2 **heart**, and 1 **lung**) converted off MPA at least 6 weeks prior to 58 pregnancies and found 51 live births (88%), four spontaneous abortions (7%), two stillbirths (3%), and one therapeutic termination

(2%) with no above average birth defects observed.[187] Additional smaller studies in **kidney, pancreas-kidney, liver, heart**, and **lung** transplant found increased incidence of teratogenicity and spontaneous abortions.[188–191]

Available data show less GI side effects with azathioprine compared to MPA in kidney transplant. In a RCT comparing azathioprine, MMF 1 gm/day, or MMF 2 gm/day in combination with corticosteroids and tacrolimus, the mean dose of MMF in the 2 gm/day group decreased to 1.5 gm/day by 6 months, primarily due to GI-related side effects.[139] A meta-analysis of 3143 kidney recipients from 19 RCTs found a significantly greater risk of diarrhea in MMF-treated patients compared to azathioprine (RR 1.57, 95% CI 1.33 to 1.86, $p < 0.0001$).[192]

Although no conversion studies exist in the **pancreas** population, due to significant rejection risk reported with MPA dose manipulation in the setting of GI toxicity, the use of AZA as an alternative is recommended. While MPA reduced early acute rejection rates, short- and long-term efficacy data demonstrates no difference with azathioprine in terms of pancreas allograft and patient survival.[146,193]

In **intestinal transplantation**, in the setting of MPA-associated gastrointestinal toxicities, azathioprine use has been reported in a case series with documented amelioration of gastrointestinal symptoms.[150] Its use was also described in a case series where azathioprine was used along with belatacept and prednisone as a rescue therapy in setting of tacrolimus associated kidney dysfunction.[194]

Azathioprine has been associated with less GI side effects compared to MMF in **heart transplant**. Specifically, in a 3-year, randomized, double-blind trial comparing MMF or AZA in combination with cyclosporine and corticosteroids, MMF showed a higher incidence of diarrhea (52.4% vs. 39.4%) and esophagitis (9% vs. 3.8%).[156]

Less gastrointestinal side effects have been reported with azathioprine in comparison with MMF in **lung transplant**. Specifically, less nausea was reported with azathioprine 2 mg/kg/day (34%) vs. MMF 3 gm/day for first 3 months followed by 2 gm/day (43%) in a prospective, randomized, open-label, multicenter study.[158] In a randomized, prospective, open-label, dual center trial including 81 adult lung transplant patients 61.5% (8 of 13) of MMF patients who discontinued drug subsequently tolerated azathioprine. Dose reductions were most common due to leukopenia (similar between groups). GI complaints, necessitating drug discontinuation, were more common with MMF [5 of 43 (11.6%) vs. 0 with azathioprine].[159]

3.3 | Corticosteroids

Along with azathioprine, corticosteroids are the longest used immunosuppressants in SOT. Their mechanism of action is multifaceted and involves inhibition of cytokine synthesis, redirection of lymphocyte traffic, and anti-inflammatory effects. Intravenous methylprednisolone and oral prednisone are the most commonly used corticosteroids for prevention and treatment of rejection. A vast majority of transplant recipients are maintained on corticosteroids indefinitely. However, due to significant morbidity associated with chronic use, early corticosteroid withdrawal following transplantation has been attempted across all organs.

1. *Is corticosteroid withdrawal a safe and effective immunosuppression strategy in the era of modern M-IMS?*
   - 9.1. *Recommendation (1B kidney, liver, heart; 1C pancreas).* While corticosteroids remain the cornerstone of M-IMS for most patients, sustained effort to eliminate corticosteroids due to their metabolic complications has been successfully attempted.
   - 9.2. *Recommendation (1B intestine; 2D lung).* Corticosteroids are a standard component of M-IMS however, elimination efforts have been attempted in lung.

Recommendation 9 Evidence Summary: Corticosteroid Withdrawal

In **kidney transplantation** it is important to note that induction immunosuppression was used in the majority of studies assessing corticosteroid withdrawal. Net states of immunosuppression should be considered when deciding to withdrawal corticosteroids. Corticosteroid withdrawal has been successfully done in low and moderate risk kidney transplant recipients, but may result in higher incidence of BPAR with similar patient and allograft survival.[195–217] Long-term similar patient and allograft survival were confirmed in a follow-up analysis of a landmark study.[218] The adjusted hazard ratios of all-cause and death-censored allograft failure in those assigned to withdraw from steroids were 0.83, 95% CI 0.62–1.10, $p = 0.19$ and 0.78, 95% CI, 0.52–1.19, $p = 0.25$; and did not differ between groups. Corticosteroid withdrawal has also been associated with improvement in metabolic endpoints such as hyperlipidemia, serum triglycerides, need for insulin to treat diabetes, and changes in HgA1c.[211,212] Two-thirds of kidney transplants are maintained on corticosteroids long term.[2]

In **pancreas transplantation**, observational studies show similar death-censored allograft loss and patient survival between patients maintained on chronic corticosteroid therapy vs. rapid corticosteroid withdrawal.[219–227] Improvement in metabolic outcomes has also been reported. Nevertheless, vast majority of patients are maintained on corticosteroids for life. A meta-analysis of existing clinical trials on steroid avoidance in pancreas and pancreas-kidney transplantation concluded that too little evidence exists to favor the use or the avoidance of steroids.[228]

There are several RCTs that evaluated corticosteroid withdrawal in **liver transplant** recipients, but they are heterogenous, and majority of them have very small sample sizes.[109,110,229–242] Nonetheless, most demonstrate noninferiority of corticosteroids withdrawal in terms of BPAR, allograft and patient survival.[109,110,229–240] However, the small sample sizes may predispose to the lack of a statistical significance. Corticosteroid withdrawal was observed to decrease the prevalence of DM, hypertension, dyslipidemia, and bone disease in some studies, though this benefit was not seen in others.[109,231,234,235]

In **intestinal transplantation**, corticosteroids are a standard component of early- and long-term M-IMS regimens as illustrated

by observational studies that persistently include them as essential components of M-IMS in this population.[51,52,54–56,150–153,194,243–246]

In **heart transplantation**, most patients are either maintained on corticosteroids or withdrawal is attempted at 3–6 months or greater post-transplant.[247–252] At 1 and 5 years post-transplant, 89% and 52% of recipients, respectively, continued to be maintained on corticosteroids.[253] Predominantly low immunologic risk patients have successfully undergone early corticosteroid withdrawal (within 2 months post-transplant) or avoidance although time to withdrawal and concomitant immunosuppression varied in these trials.[118,254,255] In a retrospective cohort study, patients who successfully underwent early corticosteroid withdrawal within 2 months post-transplant had improved survival compared to those who failed early withdrawal attempts.[255] In a large cohort study of the ISHLT registry in adult primary heart transplant recipients, long-term corticosteroid use >5 years was associated with an increased risk of mortality through 10 years after transplant compared to corticosteroid withdrawal at ≤2 years (HR = 1.57, 95% CI 1.40 to 1.75, $p < 0.0001$).[256] Less post-transplant diabetes mellitus, bone loss, and improvement in muscle strength has been reported in recipients without corticosteroids as compared to those on corticosteroid maintenance.[254]

In **lung transplantation**, corticosteroids are a standard component of M-IMS regimens as illustrated by available studies that persistently include them as essential components of M-IMS in this population.[61,62,65,156,157,176,257] Nonetheless, corticosteroid withdrawal late post-lung transplantation in stable recipients has been retrospectively evaluated in two studies. The first, a non-comparative study of 34 patients whose steroids were withdrawn a median of 877 ± 233 days post-transplant found 80% successfully remained off.[258] Steroids were restarted in six patients due to functional deterioration. The second study attempted to withdraw steroids in 35 patients a median 70 ± 13 months post-transplant.[259] However, discontinuation of steroids did not occur in 27 patients due to unstable PFT's ($n = 21$) and BOS with associated poor lung function ($n = 6$). A decrease in mean cholesterol levels was seen in those with withdrawal, with no impact on blood pressure, weight, or FEV1.

3.4 | Mammalian target of rapamycin inhibitors

mTOR inhibitors (mTORi) block interleukin 2- and 15-driven proliferation of hematopoietic and nonhematopoietic (vascular smooth muscle) cells by inhibiting the activation of p70S6 kinase. This inhibition prevents the cell cycle from progressing from G1 to S phase, inhibiting proliferation of T and a wide range of other cells.[260] Two oral formulations exist, once daily sirolimus (Rapamune®) and twice daily everolimus (Zortress®). Everolimus was derived from sirolimus by substituting a hydroxyethyl chain at position-40 of the sirolimus molecule, making it more hydrophilic and bioavailable but also reducing its half-life. Additionally, mTORi are not commonly used first line as M-IMS (Table 2) but rather second line in place of or in combination with other first-line agents for various indications. Like CNI, mTORi have numerous drug interactions due to CYP 3A4 and p-glycoprotein. TDM is required due to their narrow therapeutic index.

The most common side effects include myelotoxicity, dyslipidemia, delayed wound healing, lung toxicity, and aphthous ulcers. These frequently lead to discontinuation in patients on mTORi. Both agents are linked to enhanced nephrotoxicity if co-administered with standard dose CNI.[261] Additionally, everolimus has been associated with peripheral edema, constipation, and urinary tract infections.[262] However, mTORi side effect profile does differ from antimetabolites including less observed diarrhea and leukopenia representing an alternative to antimetabolites.[178,263] Due to side effects associated with wound healing, dehiscence and allograft thrombosis, use is in the early post-transplant period (<30–90 days) is generally avoided across all organ types.[123,243,260,262,264,265]

1. *What is the role of mTORi in the context of kidney function?*
   - 10.1. *Recommendation (1A kidney; 1B liver, lung; 2B heart)* . mTORi may be considered in combination with low-dose CNI, MPA, with or without corticosteroids to minimize CNI-associated kidney dysfunction.
   - 10.2. *Recommendation (1A kidney; 2B pancreas; 1B liver; 2B heart)* mTORi may also be considered as a replacement to CNI to minimize CNI-associated kidney dysfunction.
   - 10.3. *Recommendation (2C kidney).* Antimetabolites can be replaced by a mTORi when used in combination with low-dose CNI as a kidney-sparing strategy.

Recommendation 10 Evidence Summary: Role of mTORi in Kidney Function

Everolimus and sirolimus are FDA approved for rejection prophylaxis in **kidney transplant** in combination with cyclosporine and corticosteroids.[260,262] A meta-analysis found lower SCr (WMD −18.31 μmol/L, 95% CI −30.96 to −5.67) in eight trials that replaced a CNI with mTORi with no difference in acute rejection rates.[266] Notably, rejection rates and GFR were decreased when low-dose mTORi was used in combination with standard-dose CNI compared to high-dose mTORi and reduced-dose CNI. mTORi use in place of or in combination with CNI to minimize associated kidney dysfunction needs to balance its side effects and BPAR risk with this potential benefit. Five large RCTs comparing de novo mTORi usage to CNI found mixed impact on kidney function.[33,267–270] Often patients had higher rates of 6- and 12-month BPAR and mTORi-associated complications including delayed wound healing, mouth ulcerations, and hyperlipidemia. However, two of these RCTs that included rATG induction saw similar 12 month BPAR rates in those on sirolimus triple therapy compared to CNI triple therapy, but were likely underpowered for assessment of rejection outcomes.[267,268] Five large RCTs investigating conversion of CNI to mTORi 1–6 months post-transplant found significant improvement in kidney function with similar BPAR, patient and graft survival 12–24 months post-transplant.[271–275] One large RCT converted patients >6 months posttransplant from CNI to sirolimus found significantly higher GFRs at 12 and 24 months in those on assigned therapy but no

statistically significant difference in ITT analysis.[271] Post-hoc analysis identified patients with GFR > 40 ml/min had more favorable risk–benefit profile. When mTORi are used in combination with CNI to replace antimetabolites, the CNI dose should be reduced given available literature finding significantly worse kidney function in patients on mTORi and standard dose CNI compared to those on MMF-triple therapy.[276–278] Effects on worse kidney function were not replicated when mTORi were used in combination with reduced dose CNI.[270,279–281]

Replacing a CNI with an mTORi in **pancreas transplant** along with MPA with or without corticosteroids also resulted in improvement of CNI-associated nephrotoxicity with minimal impact on allograft and patient survival.[282–285] A large, open-label, RCT examined outcomes of sirolimus vs. tacrolimus-based M-IMS in simultaneous pancreas kidney transplant patients on concomitant MMF, steroids, and ATG induction.[264] Due to risk of wound healing issues, sirolimus therapy was introduced at 3 months. Mean 12-month CrCl was significantly higher in the sirolimus group (78.25 ± 24.89 vs. 65.49 ± 17.83 ml/min/1.73 m^2 respectively, $p = 0.009$). There was no difference between the two groups in terms of rejection and allograft survival. However, more patients in sirolimus group developed de novo donor specific antibodies (dnDSA) and had significantly higher rates of drug discontinuation. There was a significant conversion from sirolimus to tacrolimus-based immunosuppression leading the authors to not recommend sirolimus as primary choice.

Most high-quality literature in **liver transplant** examines mTORi in combination with, or in place of, CNI to minimize kidney dysfunction. Available literature shows regimens containing mTORi have similar efficacy compared to those without. Everolimus is FDA approved for rejection prophylaxis in liver transplant in combination with reduced-dose tacrolimus and corticosteroids.[262] Additionally, multiple RCTs saw improvement in patients' kidney function when everolimus was used in place of, or in combination with low dose CNI.[286–293] Notably, many of these RCTs rely on per-protocol analyses for these findings due to high rates of dose alterations, drug discontinuation, or patient compliance affecting intent-to-treat analyses. Similarly, three RCTs examined replacing or reducing CNI with sirolimus addition 4–36 week post-transplant and found significant improvements in kidney function.[294–296] Although two of the studies saw no change in rejection rates, one of the RCTs found higher rates of BPAR (12.2% vs. 4.14%, $p = 0.02$), but decreased allograft loss (3.4% vs. 8.3%, $p = 0.04$) with sirolimus/MMF compared to CNI/MMF.[295] Specifically, one additional randomized study found patients converted to sirolimus 4–6 weeks post-transplant with half-dose CNI had preserved kidney function at 3 months [eGFR 74 (57–95) vs. 67 (55–85) ml/min/1.73 m^2, $p = 0.004$]; but the effect was temporary.[286-294,296,297] A meta-analysis of sirolimus compared to CNI in 543 patients from 11 studies confirmed these findings however with a nonsignificant improvement in GFR of 3.38 ml/min, 95% CI −2.93 to 9.69, observed in those on sirolimus.[298] Its use in those with a baseline GFR > 50 ml/min was associated with a significant improvement of 10.35 ml/min (95% CI 3.98–16.77). Sirolimus had no significant association with death (RR 1.12, 95% CI 0.66–1.88) or allograft failure (RR 0.80, 95% CI 0.45–1.41), but it was significantly associated with infection (RR 2.47, 95% CI 1.14–5.36), rash (RR 7.57, 95% CI 1.75–32.7), ulcers (RR 7.44, 95% CI 2.03–27.28), and discontinuation of therapy (RR 3.61, 95% CI 1.32–9.89). Lastly, de novo use of sirolimus to replace or reduce CNI should be avoided as it has not been shown to impact kidney function and has been correlated to increased adverse events, BPAR, allograft loss, sepsis, and death.[299–301]

mTORi may offer benefit by stabilizing or modestly improving kidney function in **heart transplant** patients with reduced or withdrawn CNI. The NOCTET study randomized 282 patients ≥1 year after heart or lung transplantation to everolimus with reduced CNI and found GFR significantly decreased in 58% of heart transplant controls compared to the everolimus group with similar allograft function, rates of rejection, death, and major cardiac events between groups ≥1 year after transplant ($n = 176$ patients with ≥5 years of follow-up, 125 which were heart transplant).[257] Similarly, three other randomized studies in heart transplantation found significant improvements in eGFR or CrCl at 12 months in those converted to mTORi 1.5 to ≥12 months post-transplant compared to reduced- or standard-dose CNI.[302–304] However, associated renal benefit needs to be balanced with rejection risk when removing or decreasing CNI exposure. In the open-label, multicenter, randomized SCHEDULE trial, 115 de novo heart transplant recipients receiving rATG induction, MMF and corticosteroids were randomized to either cyclosporine or everolimus with reduced-exposure cyclosporine followed by cyclosporine withdrawal 7–11 weeks post-transplant.[303] Treated BPAR was significantly higher in the everolimus arm (50% vs. 23%, $p < 0.01$). It is important to note that mTORi side effects and treatment discontinuations are common. Specifically, there were more treatment discontinuations in those on sirolimus compared to a CNI (42.1% vs. 15.8%, $p = 0.003$) with diarrhea, anemia, rash, mouth ulcers, stomatitis, acne, and infection occurring significantly more with sirolimus. Proteinuria assessment prior to and during mTORi therapy is important as proteinuria altered the response of renal function to everolimus in a randomized, prospective study comparing everolimus and MMF in combination with reduced cyclosporine. If baseline proteinuria was ≥150 mg per day, CrCl was significantly worse from baseline to year 3 as compared to no proteinuria.[305]

In **lung transplant**, mTORi can be used > 3 months post-transplant in combination with reduced CNI, MPA, and corticosteroids to minimize the nephrotoxicity of the CNI. Of the four RCTs and one single arm study examining this combination, all (three examining everolimus and two sirolimus) found improvement in kidney function.[178,257,306–308] Rates of rejection, chronic lung allograft dysfunction (CLAD), and death were similar although many of these studies were not powered to detect a difference. Increased rates of mTORi side effects and pneumonia did occur in mTORi arms.

1. *What is the role of mTORi in the setting of MPA replacement?*
   11.1. *Recommendation (2B kidney). De novo* use of mTORi in place of an antimetabolite has shown comparable or lower rates of rejection when used with a CNI.

11.2. *Recommendation (1C kidney; 1B pancreas).* Use of mTORi in the setting of MPA intolerance can be recommended with low dose CNI with or without corticosteroids.

11.3. *Recommendation (1B pancreas).* Considering that MPA dose discontinuation or manipulation due to GI toxicity has been associated with rejection, the use of mTORi in place of MPA dose reduction has been linked with lower rejection rates if used in combination with tacrolimus, with or without corticosteroids.

Recommendation 11 Evidence Summary: Role of mTORi in MPA replacement

Of published **kidney transplant** RCTs examining de novo mTOR use in place of an antimetabolite, two found lower rates of acute rejection with mTORi compared to antimetabolites, whereas two found no difference.[276,277,309,310] Additionally, one found a significantly reduced risk of antibody-mediated rejection (AMR) with everolimus in combination with CyA-ME and prednisone compared to MMF.[276] In the setting of MPA intolerance, use of mTORi has been reported as an effective alternative following kidney transplantation.[311,312]

Care of **pancreas transplant** recipients is often complicated by gastroparesis that may be exacerbated by MPA-based M-IMS regimen. Consequently, use of mTORi as a rescue therapy in setting of MPA-associated GI intolerance has been extensively explored. Based on findings from several observational studies, early conversion to sirolimus in setting of MPA intolerance should be considered an important strategy that does not affect overall patient and allograft survival.[283,284,313,314] Late conversion to mTORi due to MPA intolerance is also safe and effective approach, but clinical complications are frequent warranting close monitoring.[313] As increased rejection has been observed with MPA dose manipulations or discontinuation, comparative use of mTORi in this setting has also been explored.[123,128,315–318] De novo use of mTORi along with low dose tacrolimus/steroids yielded lower rejection rates than MPA-treated patients whose MPA was stopped due to intolerance. Overall, mTORi use had comparable short-and long-term allograft outcomes to MPA treated patients.

1. *What is the role of mTORi in the setting of malignancy?*

12.1. *Recommendation (2C kidney; 1B liver, 1C heart)* . mTORi have been associated with a reduction in *de novo* and recurrent malignancies following transplant and may be of value in the setting of cancer.

Recommendation 12 Evidence Summary: Role of mTORi in Malignancy

A registry study of malignancies in 33,249 deceased donor **kidney transplant** recipients found mTORi use was associated with a significantly reduced risk of post-transplant de novo malignancy (RR 0.39, 95% CI 0.24-0.64, $p = 0.0002$) and non-skin solid malignancy (RR 0.44, 95% CI 0.24-0.82, $p = 0.0092$).[319] A systematic review of 13 studies analyzing mTORi use within 3 months post-kidney transplant demonstrated a reduced risk of post-transplant malignancy compared to the use of CNI-based regimens (RR 0.67, 95% CI 0.51–0.86, $p = 0.002$).[320]

In **liver transplant**, the SiLVER study was an international, multicenter, randomized, open-label study of 528 recipients with HCC at the time of transplant who were randomized at 4–6 weeks to sirolimus-containing therapy or standard therapy.[321] Investigators found higher recurrence-free survival rates in those on sirolimus at 1 and 3 years post-transplant; however, this significance was lost by the end of the 8-year study period. Also, overall survival was better in those on sirolimus 5 years post-transplant (HR, 0.7, 95% CI 0.49–1.00). Interestingly, subgroup analyses revealed that low risk (within Milan criteria) patients benefited most. Lastly, one randomized, multicenter, open-label study evaluated HCC recurrence rates in 118 living donor liver transplants with HCC (most within Milan criteria) at the time of transplant on everolimus/reduced tacrolimus compared to standard tacrolimus.[322] Rate of HCC recurrence at 12 months was lower in the everolimus/reduced tacrolimus group ($n = 0$) compared to standard tacrolimus ($n = 5$).

In a retrospective cohort study of 454 **heart transplant** patients malignancy occurred significantly less with everolimus ($n = 4$) versus MMF ($n = 23$), ($p < 0.001$), at a median follow-up of 69 months.[323] A small observational study of 10 recipients with multiple and/or recurrent skin cancer were switched to everolimus with a significant decrease in the mean number of tumors per patient as compared to same time period prior to everolimus (3.7 vs. 1.5, $p = 0.03$).[324] Lastly, in a retrospective cohort study of 523 patients, de novo malignancy (HR 0.34, 95% CI 0.18 to 0.62, $p < 0.001$) and post-transplant lymphoproliferative disorder (PTLD) risk (HR 0.13, 95% CI 0.03 to 0.59, $p = 0.009$) were significantly less in sirolimus-treated patients compared to CNI.[325]

1. *What is mTORi's impact on graft rejection or chronic graft dysfunction?*

13.1. *Recommendation (2C intestine)* . Use of mTORi is associated with less rejection compared to a CNI, corticosteroid-containing regimen, as well as improved allograft survival at 12 months.

13.2. *Recommendation (2B lung)* . Substitution of antimetabolites with mTORi may decrease rates of BOS. Comparative data have found similar and lower rates of rejection with mTORi.

13.3. *Recommendation (1A heart)* . mTORi have been used in combination with, or in place of, antimetabolites, as well as in combination with, or in place of, CNI with or without corticosteroids. They have been associated with both prevention and reduced progression of CAV.

Recommendation 13 Evidence Summary: Impact of mTORi on Graft Rejection or Chronic Graft Dysfunction

De novo sirolimus use significantly improved outcomes following **intestinal transplantation**. Sirolimus use alongside tacrolimus and corticosteroids dramatically reduced 30-day BPAR rates (73.7% vs. 16.7%, $p < 0.002$) and improved 12-month allograft survival (57.9%

vs. 91.7%, $p < 0.04$) compared to tacrolimus/corticosteroids alone in a case control of 31 patients.[243] However, a significantly higher rate of wound dehiscence and reoperation was reported in sirolimus treated group (33.3% vs. 5%, $p = 0.05$). Similar outcomes were reported in other observational studies with sirolimus and one case series with everolimus.[244–246] In another case series of 22 patients, addition of mTORi to standard therapy allowed for the reduction of immunosuppression in majority (68.2%) of patients.[326]

mTORi offer a unique benefit in **heart transplantation** by decreasing incidence and/or reducing progression of CAV. However, risks should be weighed, patient selection criteria considered, and strategies incorporated to mitigate risks as highlighted in literature below. Importantly, the timing of mTORi initiation is critical. The EVERHEART trial was a 6-month, open-label, multicenter randomized trial that compared safety (wound healing delays, pericardial or pleural effusion, and renal insufficiency) in heart transplants receiving everolimus immediately (≤144 h post-transplant) or after a 4–6-week delay (using MMF as a bridge) along with reduced-dose CyA.[327] The study found significantly higher rates of adverse events leading to discontinuation in those who had immediate everolimus initiation.

In the open-label, multicenter, randomized SCHEDULE trial described previously CAV incidence was significantly less in the everolimus group at 5–7 years post-transplant (53% vs. 74% $p = 0.037$), however, treated BPAR was significantly higher (50% vs. 23%, $p < 0.01$).[302,328] Additionally, CAV progression was significantly decreased in those on everolimus at 36 months (change in maximal intimal thickness 0.09 ± 0.05 vs. 0.15 ± 0.16 mm, $p = 0.03$). Comparing everolimus to antimetabolites, A2310 was a 24-month, open-label, multicenter, RCT comparing de novo everolimus 3 mg or 1.5 mg with corticosteroids/reduced-dose cyclosporine to MMF with corticosteroids/standard dose cyclosporine in 721 patients. There was a benefit in terms of CAV as mean increase in maximal intimal thickness at 12 months was significantly less with everolimus 1.5 mg compared to MMF [0.03 (±0.05) mm versus 0.07 (±0.11) mm, $p < 0.001$].[263] A pre-specified sub study conducted in 189 patients in A2310 also demonstrated significantly less CAV at 12 months with everolimus as compared to MMF (12.5% vs. 26.7%, $p = 0.018$).[329] Additionally, the RAD B253 study included 634 patients randomized to de novo everolimus 1.5 mg, 3 mg, or azathioprine with cyclosporine/corticosteroids found a significantly lower incidence of CAV at 24 months with everolimus 1.5 mg (33.3%) compared to azathioprine (58.3%), $p = 0.017$.[330] Sirolimus has also been shown to prevent and/or delay progression of CAV. A RCT of 136 heart transplant recipients on either de novo sirolimus or azathioprine in combination with CyA-ME and corticosteroids found all vasculopathy parameters significantly increased in those on azathioprine up to 2 years post-transplant. This was not observed in sirolimus-treated patients. Mean intima (0.35 ± 0.26 mm vs. 0.19 ± 0.12 mm, $p < 0.000$), media thickness (0.32 ± 0.19 mm vs. 0.22 ± 0.16 mm, $p = 0.0048$), and plaque burden (29.4 ± 19.1 vs. $16.2 \pm 9.6\%$, $p < 0.0001$; 28.7 ± 15.3 vs. $18.3 \pm 11.3\%$, $p = 0.0002$) at 6 and 24 months were significantly increased with azathioprine compared to sirolimus.[331] Lastly, a single-center, open-label, RCT of 78 de novo transplants patients found sirolimus/MMF had the highest freedom from CAV (93.3% vs. 80.8% tacrolimus/sirolimus vs. 73.5% tacrolimus/MMF, $p =$ NS).[332] Some RCTs found no statistically significant difference in rates of acute rejection, allograft loss, and death between mTORi/MPA and tacrolimus/MPA groups from 1–5 years post-transplant.[263,330–332] However, it is important to note, one RCT found increased mortality with higher everolimus exposure (3 mg arm, goal trough 6–12 ng/ml), thus this arm was terminated early. In addition, an increase in 3-month mortality was observed with everolimus 1.5 mg arm as compared to MMF if rATG induction was utilized, but not basiliximab or no induction. Mortality at 24 months was similar to MMF.[263] One RCT examined 46 heart transplant patients with graft atherosclerosis compared outcomes between a control group maintained on MMF or AZA to those randomized to sirolimus. Authors found that significantly more control patients met the primary composite endpoint of clinically significant events including death, acute myocardial infarction, need for angioplasty or bypass surgery, and/or a >25% increase in catheterization score as compared to those randomized to sirolimus (14 vs. 3 patients, $p < 0.001$).[333]

In the setting of **lung transplant**, two RCTs and one observational study saw significant decreases in incidence of BOS when mTORi were used in combination with CNI and corticosteroids, in place of an antiproliferative.[291,334,335] Although significant findings often came from per-protocol analyses given high withdrawal rate in mTORi arms. One study did find similar rates of rejection, CLAD, and allograft survival 1-year post-transplant in patients on sirolimus versus azathioprine containing regimens.[336] Additionally, rates of BPAR were significantly lower in two studies evaluating everolimus-containing regimens compared to MMF or azathioprine.[291,335] These potential benefits of mTORi in place of antimetabolites need to be balanced with the higher rates of withdrawal (up to 64%).[291,335,336]

1. *What is the role of mTORi in the setting of CMV infection or disease?*
   14.1. *Recommendation (1B kidney, lung; 2A heart).* Regimens that include mTORi may provide protection from CMV.

Recommendation 14 Evidence Summary: Role of mTORi in Setting of CMV

Six RCTs compared the impact of mTORi-, CNI-, or antimetabolite-containing regimens on CMV infection in **kidney transplant**. Three RCTs found significantly lower CMV infections when sirolimus replaced a CNI in combination with MMF with or without corticosteroids, although these were secondary findings.[33,268,274] When MMF was replaced by everolimus in three large RCTs, rates of CMV infection and/or disease were also significantly reduced 12–36 months post-transplant.[277,280,337] A meta-analysis of 4622 patients from 11 studies confirmed these findings showing a reduced risk of CMV infection in patients on mTORi compared to MMF (RR 0.43, 95% CI 0.29 to 0.63, $p < 0.0001$).[338] Larger studies are needed focusing on CMV as a primary endpoint to elucidate complete clinical implications.

Available literature for everolimus use in place of antimetabolites in **heart transplant** have found it to associated with less CMV. In a 12-month, multicenter, randomized, open-label study of de novo patients randomized to everolimus significantly less CMV was seen compared to those on MMF (8.8% vs. 32.5%, $p < 0.001$).[339] CMV data from three RCT that included 1009 de novo heart transplant patients comparing everolimus with either azathioprine or MMF demonstrated a reduction in odds of experiencing CMV infection with everolimus compared to azathioprine (OR 0.32, 95% CI 0.17–0.59, $p < 0.001$) and MMF (OR 0.20, 95% CI 0.08–0.47, $p < 0.001$).[340]

In **lung transplant** four studies, three multicenter RCTs and one case control, evaluated replacing MMF or azathioprine with either sirolimus or everolimus. Significantly lower rates of CMV, viral infections, and lower respiratory tract infections were observed, although these were secondary outcomes.[291,334–336] Rates of BPAR were significantly lower in two studies evaluating everolimus-containing regimens compared to MMF or azathioprine.[291,335] Whereas the other study saw similar rates of rejection and allograft survival 1-year post-transplant in patients on sirolimus versus azathioprine containing regimens.[336] These potential benefits of mTORi in place of antimetabolites need to be balanced high rates of withdrawal due to drug related adverse reactions, including venous thromboembolism, observed in available literature.[291,335,336]

3.5 | Co-stimulation Inhibitors

Belatacept is the only FDA-approved co-stimulation inhibitor for prophylaxis of rejection in SOT. It is also the only immunosuppressant medication that does not work directly on T cells. Designed as a CTLA-4 IgG, belatacept works primarily by binding to B7-1/B7-2 expressed by APCs, with a resulting effect of blocking T-cell costimulation via CD28, an integral step in their activation. Inhibition prevents T-lymphocyte proliferation, cytokine production and ultimately allograft rejection. Belatacept is approved for use in Epstein–Barr Virus (EBV) seropositive kidney transplant recipients only, in combination with MMF, corticosteroids, and basiliximab induction. It is a weight-based intravenous infusion that is eventually dosed on an every 4-week basis.[341] Given its long half-life of 8–9 days allowing for less frequent dosing and administration route, belatacept is an appealing option for transplant recipients who struggle with medication compliance. Moreover, belatacept has a favorable side effect profile with no nephrotoxic and minimal metabolic effects and no required TDM. Due to an increased risk of PTLD, belatacept should not be used in patients with an unknown or negative EBV serostatus.

1. *What is the role of de novo belatacept in modern M-IMS?*
   - 15.1. *Recommendation (1B kidney).* Belatacept can be used in EBV seropositive patients to improve kidney function and metabolic outcomes including hypertension, diabetes, and hyperlipidemia through the avoidance of CNI. Despite an increase in early rejection, belatacept decreased long-term death and allograft loss.
   - 15.2. *Recommendation (2C kidney).* When compared to tacrolimus-based M-IMS, belatacept improved kidney function, albeit with increased rates of rejection that were reduced with a transient concomitant course of tacrolimus.
   - 15.3. *Recommendation (2B liver).* De novo use of belatacept cannot be recommended given higher rates of death and allograft loss.

Recommendation 15 Evidence Summary: De novo Belatacept Efficacy

Large, RCTs compared de novo belatacept to cyclosporine-based triple immunosuppression with MMF and prednisone. The first was comprised of 666 **kidney transplants** and found a 43% reduction in the risk of death or allograft loss at 7 years in those treated with more-intensive (MI) or less-intensive (LI) belatacept compared to cyclosporine (HR 0.57, 95% CI 0.35 to 0.95, $p = 0.02$ and 0.57, 95% CI 0.35 to 0.94, $p = 0.02$ of MI and LI, respectively).[342] Mean eGFR was 70.4, 72.1, and 44.9 ml/min per 1.73 m^2 for belatacept MI, belatacept LI, and cyclosporine regimens ($p < 0.001$ for overall treatment effect). Of note, acute cellular rejection rates were higher in belatacept patients and usually occurred within the first 3 months.[343] Also, a high rate of PTLD was discovered in EBV seronegative recipients, leading to the medication's black box warning.

A similarly designed study in expanded criteria donors found improvements in mean eGFR (53.9, 54.2, and 35.3 ml/min per 1.73 m^2 $p < 0.001$ for overall treatment effect) for belatacept MI, belatacept LI compared to cyclosporine-treated patients at 7 years with similar rates of rejection, death, and allograft loss.[344] A Cochrane systematic review found belatacept to be associated with better allograft function, as well as diabetic, lipid, and hypertensive profiles, compared to CNI.[345] Three more recently published retrospective studies compared belatacept to tacrolimus M-IMS. The first study evaluated belatacept versus tacrolimus with MPAs in the setting of early corticosteroid withdrawal at post-operative day 5 in a low immunologic-risk population. This open label, randomized controlled, multicenter trial did not find superiority in the composite endpoint of death, allograft loss, or MDRD eGFR < 45 at 12 months (8.4%, 14.4%, and 13.3% of alemtuzumab/belatacept, rATG/belatacept, and rATG/tacrolimus, respectively), although longer term follow-up is ongoing. BPAR rates were significantly higher in belatacept arms. Rates of neurologic adverse events and electrolyte abnormalities were significantly reduced in both belatacept arms compared to tacrolimus. Outcomes were not compared to a corticosteroid-containing regimens.[346] The second study compared a historical tacrolimus cohort to belatacept in combination with basiliximab, MMF, and corticosteroids. Given a significantly higher rate of 1-year BPAR (50.5% vs. 20.5%, $p < 0.001$) a nine-month course of low-dose tacrolimus was added and found to have similar rates of BPAR (16% vs. 20.5%, $p = 0.9$) and superior eGFR at 4 years (63.8 vs. 46.2 ml/min) but no difference in death, allograft loss, or viral infections.[347] Another retrospective propensity matched cohort study found an increased rate of acute rejection (OR 3.12, 95% CI 2.13 to 4.57, $p < 0.001$) and no difference in risk of death or allograft loss at 1 year

with belatacept (HR 0.84, 95% CI 0.61 to 1.15, $p = 0.28$ and HR 0.83, 95% CI 0.62 to 1.11, $p = 0.20$).[348]

One large, partially blinded, RCT in 250 **liver transplant recipients** compared de novo high and low dose belatacept to tacrolimus in combination with MMF and corticosteroids. The high-dose regimen was also investigated with and without basiliximab induction. This study was terminated early, as rates of death and allograft loss were significantly higher in belatacept groups, leading to a black box warning on the medication.[349] Since then, very low-level data have been published including a single arm cohort of four patients converted off belatacept to MMF monotherapy with resulting worse allograft function. Patients were then started on triple therapy with the addition of a CNI and corticosteroids with resulting worsening in kidney function.[350]

1. *Can patients be safely converted to belatacept to eliminate or minimize CNI exposure?*
   - 16.1. *Recommendation (2B kidney).* It is safe to convert stable, living, or deceased donor, low immunologic risk transplant recipients from CNI to belatacept. While such a conversion has been shown to improve kidney allograft function, along with a modest decrease in the development of NODAT and hypertension, these benefits must be weighed with an increased risk of acute rejection and infection, particularly CMV.
   - 16.2. *Recommendation (2D pancreas, liver, intestine; 2C heart, lung).* Conversion to belatacept from a CNI can be considered in patients experiencing CNI-associated side effects, specifically nephrotoxicity. Optimal dosing strategy, as well as safety and efficacy outcomes, are still unclear with available evidence. Benefits must be weighed against increased risk of acute rejection and infection.

Recommendation 16 Evidence Summary: Safety of Belatacept Conversion

One RCT with long-term follow-up and three large observational studies have been published in **kidney transplant analyzing belatcapt conversion**. The RCT evaluated belatacept conversion at 6–36 months post-transplant. Belatacept 5 mg/kg on days 1, 15, 29, 43, and 57 with subsequent 28-day dosing thereafter was added to CNI, antimetabolite, and corticosteroids and compared to a CNI-continuation group (split between tacrolimus and cyclosporine-containing regimens). Patients were of low immunologic risk (predominantly white, first-time transplants, with PRAs < 20%, and without recent history of rejection). At 12 and 36 months, kidney function was improved in the belatacept group, but rejection rates were higher with the majority occurring early post-conversion. At 12 months, blood pressure tended to be lower in the belatacept group compared to the CNI group. At 36 months, more viral and fungal infections occurred in the belatacept group.[351,352] Two observational studies found similar results. A cohort of 219 patients converted to belatacept found an increase in mean eGFR (32 ± 16.4 at baseline to 38 ± 20 ml/min per 1.73 m^2 at follow-up, $p < 0.0001$), with conversion <3 months post-transplant being the largest predictive factor of an increase in GFR >10 ml/min per 1.73 m^2 at 12 months. Acute rejection rate was 8.2% post-conversion.[353] Similarly, another cohort of 280 patients found a significant improvement in eGFR in those converted <6 months post-transplant (12.7 ± 15.4 vs. 6.4 ± 11.9 ml/min per 1.73 m^2, $p = 0.009$). Considering infections, the same cohort found a 1-year opportunistic infection (OI) rate of 12.1% in belatacept-treated patients with the most common being CMV (18/42 OI; 42.9%) and *Pneumocystis* pneumonia (12/42 OI; 28.6%).[354] Similarly, among 181 belatacept-treated patients matched to 181 controls, 17.7% experienced CMV disease versus 2.8% of controls. CMV disease cumulative incidences were 6.33 and 0.91/100 person-years (p-y) in belatacept and control groups, respectively. CMV disease risk was highest in those >70 years and with eGFR <30 ml/min; cumulative incidences were 18.4 and 5.2/100 p-y, respectively.[355]

A phase II, multicenter, open-label randomized trial examined concomitant corticosteroid and CNI avoidance in **SPK transplant** population. Following a rapid, early corticosteroid taper, tacrolimus exposure was minimized over the first 24 weeks and eventually discontinued by week 40. The study was halted early due to significantly higher incidence of BPAR in pancreas allografts in the belatacept arm following CNI withdrawal. Moreover, compared to patients on tacrolimus and MPA, kidney function at 52 weeks and glycosylated hemoglobin were similar. There were no differences in metabolic outcomes, such as use of antihypertensives or lipid lowering agents.[356] However, a recent abstract demonstrated that in eight pancreas transplant recipients progression of kidney dysfunction was halted by converting patients from a corticosteroid-free, CNI-MPA-sirolimus based regimen to belatacept with 4–6 weeks of tacrolimus overlap. While no improvement in eGFR was achieved, no further decline was observed with no impact on pancreas allograft in terms of HgA1c, C-peptide, and glucose values. Authors noted that patients converted to belatacept did not experience any serious viral infections or donor-specific antibody (DSA).[357]

In **liver transplant**, data are limited to a case report of a gentleman, who converted 5 years post-transplant to belatacept as a last-line option after experiencing MMF-associated colitis, CNI-associated CKD, and mTORi-associated lung injury. Six months post-conversion, the patient's lung injury had recovered, and CKD stabilized (eGFR 20-30 ml/min/1.73 m^2).[358]

Intestine transplant data are limited to a single-center report presented as an abstract during the 2017 International Congress of the Intestinal Rehabilitation and Transplant Association.[194] In a small cohort of six intestine transplant recipients on tacrolimus monotherapy experiencing CNI nephrotoxicity, patients were switched to either belatacept with azathioprine and prednisolone ($n = 2$), low dose tacrolimus (levels < 3; $n = 2$), or no other maintenance therapy ($n = 2$). Majority of patients (83.3%) demonstrated an immediate improvement in eGFR; one patient demonstrated a decrease in proteinuria, without a significant improvement of the eGFR. Two patients discontinued belatacept due to intolerance. There were three bowel rejection episodes, two (66%) had development of dnDSA.

Similarly, data are limited to case reports and small case series in **heart transplant**.[359–361] The largest series published to date is a descriptive, retrospective review of 40 heart transplant patients receiving belatacept with reduced dose CNI or CNI withdrawal, corticosteroid maintenance, and MMF with or without everolimus in the majority of patients.[360] The most common reason for belatacept use was need for kidney recovery. Mean GFR was 35 ± 20 ml/min/m^2 at the time of conversion and had increased to 55 ± 43 ml/min/m^2 after 12 months. One case of PRES and two cases of thrombotic microangiopathy (TMA) resolved post-conversion. The improvement in kidney function was more pronounced in those converted ≤3 months post-transplantation. Rates of infection and rejection via protocol biopsy were similar pre versus post belatacept initiation. However, rates of grade 2R and 3R rejections were higher after belatacept initiation. Also, a case report of a young female heart transplant converted to belatacept found no issues of allograft rejection nor dysfunction.[362]

Lastly, in **lung transplant** data are limited to one prospective observational study, two small case series, and a case report, none of which have comparator groups. Of note, dosing regimens used were different, often higher, from FDA-approved dosing. In the largest study to date, 85 lung transplant recipients were prospectively evaluated after conversion to belatacept with reduced CNI exposure at a median of 293 days after transplant (IQR 148–611). Kidney function remained stable throughout conversion with no allograft function decline. Belatacept was discontinued in 33% of patients, mostly due to infectious complications.[363] In a single-center case series of eight lung transplant recipients with kidney dysfunction on their existing CNI-based regimen, belatacept was added at a median post-transplant day 585 (IQR 139–1414) to the maintenance regimen to allow for temporary discontinuation or withdrawal of CNI. One patient had mild ACR, which responded to treatment with IV methylprednisolone. FEV1 remained stable at 1, 3, and 6 months following conversion and decreased by a smaller amount compared a historical cohort (median −1.3% vs. −2.2%).[364] Additionally, a case series of nine lung transplant patients who underwent conversion from a CNI-based regimen to belatacept due to intolerance demonstrated an increase in mean eGFR (32.5 vs. 45.3 ml/min/m^2, $p = 0.03$), by median end of follow-up at 418 days. No difference in composite rejection standardized score was found pre- and post-belatacept conversion.[365] Lastly, a case report of a 56-year-old male bilateral lung transplant recipient with hemolytic uremic syndrome attributed to both tacrolimus and sirolimus, was converted to belatacept, MPA, and prednisone. No episodes of ACR were seen on biopsy at 3 and 6 months following conversion.[366]

1. *Does belatacept use impact the appearance of DSA after transplantation and reduce the rate of AMR?*
   17.1. *Recommendation (2C kidney*). Belatacept may have a potential favorable impact on DSA.

Recommendation 17 Evidence Summary: Belatacept Impact on DSA

Numerous small studies have found decreased DSA development with belatacept use in kidney transplant.[367,368] The post hoc Kaplan–Meier analysis of BENEFIT and BENEFIT-EXT found dnDSA incidence at 7 years was significantly lower in belatacept- vs. cyclosporine-treated **kidney transplant** patients ($p < 0.01$). In BENEFIT, dnDSA development was 1.4%, 3.5%, and 12.1% in belatacept MI, belatacept LI, and cyclosporine-treated patients, respectively. In BENEFIT-EXT dnDSA development was 3.8%, 1.1%, and 11.2% in belatacept MI, belatacept LI, and cyclosporine-treated patients, respectively.[369]

3.6 | Interleukin-2 receptor antagonists

Interleukin-2 receptor antagonists (IL2RA) competitively bind the alpha subunit of the high-affinity interleukin-2 receptor that is selectively expressed on activated T-lymphocytes. Inhibition prevents cytokine-mediated lymphocyte proliferation, a critical step in allograft rejection. There were two IL2RA, basiliximab (Simulect®) and daclizumab (Zenapax®), approved by the FDA for rejection prophylaxis in kidney transplantation along with cyclosporine and corticosteroids.[370,371] Despite limited FDA approval, IL2RA use was expanded over time across all organ transplant groups but is generally limited to induction therapy. Currently, basiliximab is the only IL2RA agent available for use. Administration of two doses of daclizumab in a 2-week interval in kidney transplant recipients achieved sustained blockade of the alpha receptor for over 10 weeks post-transplantation.[372] For many transplant clinicians, the long terminal half-life of IL2RA (basiliximab single dose is 7.2 days, daclizumab single dose is 20 days) and favorable adverse event profile made them attractive M-IMS options, particularly in cases where rapid CNI withdrawal or minimization is needed. To date, single-center studies where IL2RA were used as M-IMS have been published in all organ groups.

1. *Should IL2RA be used as M-IMS to prevent acute rejection safely and effectively?*
   18.1. *Recommendation (2C kidney, pancreas, liver, intestine, heart, lung).* Available data do not offer clear benefit for use in any one organ setting. Use as a M-IMS should be avoided and limited to only the most extreme clinical situations where there is no other alternative.

Recommendation 18 Evidence Summary: IL2RAs as M-IMS

A *Simulect CNI-Replacement Study Group* was formed to evaluate the risk of sensitization against the basiliximab. In 2008 the Group published their observational experience, in an abstract format, of seven patients who underwent **kidney transplantation** with MPA, corticosteroids and 40 mg basiliximab administered once monthly for 6 months. The CNI dose was reduced to 50% on day 1, 25% at week 2, and then discontinued at month 1. Median follow up was 7.2 years. One patient experienced allograft loss due to chronic rejection, following reduction of MMF dose due to GI side effects. There were no ACR episodes or infectious complications. Patients had stable eGFR at 6 months.[373] In 2004,

a case series of 21 kidney transplant recipients experiencing CNI-associated side effects (12 nephrotoxicity, four neurotoxicity, two TMA, two diabetes and one polyomavirus nephropathy [PVN]) were switched from CNI to sirolimus and two doses of daclizumab. No patients experienced ACR. Five patients experienced progressive allograft loss despite switch (causes included PVN, chronic allograft nephropathy, TMA, and nonadherence). Patients with neurotoxicity and PTDM experienced improvement or cessation in symptom progression. Patient survival was 100% at the end of observation period.[374] In 2002, a case series of 11 patients (seven heart, two liver, two heart/kidney) with CNI-associated nephrotoxicity were given a "CNI Holiday" for 48–72 h during which IL2RA were administered every 7–20 days for a mean period of 21 days. All patients' kidney function improved, then stabilized. No cases of ACR were reported. However, six patients died in the period ranging from 2 weeks to 7 months following "CNI Holiday." Causes of death included allograft failure, cancer/PTLD, cerebrovascular accident, pneumonia, and perforated diverticulitis.[375] A smaller case series demonstrated two kidney transplant patients experiencing CNI nephrotoxicity achieve stable eGFR after conversion to basiliximab every 2–4 weeks along with MPA and corticosteroids for 24–30 months. Stable allograft function was seen with no rejection or serious infectious complication.[376]

A case control study in 25 **pancreas transplant** recipients experiencing CNI-associated side effects (nephrotoxicity, neurotoxicity and PTDM) underwent conversion from CNI to monthly daclizumab infusions. Allograft survival at 1, 3, and 5 years was 88%, 79%, and 60% in the IL2RA group and 67%, 44%, and 44% in the control group (p values 0.06, 0.01, and 0.05). There was no difference in patient survival between groups.[377]

In 15 **liver transplant** recipients, kidney function stabilized after CNI was converted to IL2RA every 2 months for a median of 26 months (2–51 range). However, three patients experienced acute rejection following conversion, with one resulting in death due to allograft loss. Authors also describe infectious complications in the setting of IL2RA maintenance.[378]

The use of IL2RA for maintenance is most frequently described in the setting of **intestinal transplantation**. Multiple single-center reports describe use as standard of care.[379–381] Most frequently, the IL2RA induction is extended for up to 1-year post-transplant as an overall immunosuppressive "booster" strategy or if CNI minimization is warranted. Various dosing approaches have been described. In 2013, a case control study demonstrated a significant reduction in acute rejection with the use of IL2RA therapy in 7 intestinal transplant patients (39–22% $p = 0.02$). Allograft survival at 3 years was higher if IL2RA at any time point after transplantation (67% vs. 49% $p = 0.03$).[379] Benefit is often confounded by the descriptive nature of published data and absence of well-matched comparison or control group.

In 2009, a case-control study was published comparing 17 **heart transplant** recipients who were converted from CNI (10) and sirolimus (7) based regimens to IL2RA due to nephrotoxicity to 10 control patients on CNI with stable kidney function. IL2RA were administered in 2-month intervals for 2–32 months. Following conversion, four patients died due to pneumonia, perforated diverticulitis, severe BPAR, and complications of acute-on-chronic kidney failure. In the surviving cohort, kidney function improved after 1 month and remained stable for the remainder of the observation period. Left ventricular ejection fraction after conversion did not statistically differ between the groups (55 ± 15% in CNI patients, 54 ± 11% in sirolimus patients and 55 ± 9% in controls).[382]

There are three case series describing use of basiliximab maintenance in **lung transplantation**. One described extending traditional basiliximab induction regimen to include a third dose given 20 days postoperatively. This allowed investigators to lower CNI exposure in the early postoperative period that resulted in recovery of kidney function (eGFR).[383] The remaining two case series describe basiliximab use to minimize CNI-associated nephro- ($n = 9$) and neurotoxicity ($n = 3$) allowing for CNI minimization (nephrotoxicity) and avoidance (neurotoxicity). This ultimately resulted in recovery of organ function in 12 lung transplant recipients.[384,385]

TABLE 4 Summary of clinical trials investigating maintenance immunosuppressants in adult population

Organ	Number of trials
Kidney	46
Pancreas	1
Liver	20
Intestine	1
Heart	6
Lung	9

Note: Includes trials not yet recruiting, recruiting, enrolling by invitation, or active-not recruiting. Accessed on October 30, 2021.

4 | FUTURE RESEARCH NEEDS

A search of ClinicalTrials.gov resulted in a list of studies investigating M-IMS in the adult SOT population. (Table 4) The majority of these studies investigate novel dosage forms and certain organ groups are underrepresented. These patterns highlight the urgency of FDA to recognize the need for research of novel therapeutic M-IMS in SOT under the umbrella of "rare" or "ultra-rare" disease, and allow for use of accelerated drug approvals, as well as surrogate endpoints and biomarkers in SOT research. Some historical limits placed on transplantation research have recently been updated to now permit use of modern immunosuppression combinations as standard of care in clinical trials as it was a previously identified limitation which shows movement in the right direction.[386]

These consensus recommendations highlights the paucity of well-designed literature available in lung, pancreas and intestine transplantation and should serve as a call to action for the entire transplant community. In areas of practice such as SOT, where clinical trials are impractical due to small population size, every

consideration should be given for creation of a clinical trial network to allow for collaborative research practice using registry study research design.

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CONFLICT OF INTEREST

Author personal and financial relationships with industry and other entities are detailed in Appendix A.

ORCID

Joelle Nelson https://orcid.org/0000-0002-1162-6362
Maya Campara https://orcid.org/0000-0003-3402-4716

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SUPPORTING INFORMATION

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