

Immunosuppression Dosing in Obese Solid Organ Transplant Recipients



*B. Andrew Mardis, Caitlin R. Mardis, and
Nicole A. Pilch*

Outline

- Introduction
- Polyclonal and Monoclonal Antibodies
- Calcineurin Inhibitors
- Antiproliferative Agents
- Mammalian Target of Rapamycin Inhibitors
- Costimulatory Blockade
- Intravenous Immunoglobulin
- Summary Table: Immunosuppression Medication Dosing in Obese Patients

Introduction

As with the general population, the rates of obesity among transplant recipients continue to increase, and some patients continue to gain weight following transplantation.¹⁻¹¹ Across organ transplantation, the contraindicated body mass index (BMI) limits are being increased.¹²⁻¹⁵ Armstrong and colleagues describe a multifactorial etiology of obesity following kidney transplant due to a sedentary lifestyle during recovery from chronic renal failure and the transplant event, negative metabolic effects of high dose steroids, and baseline obesity prior to transplantation.¹⁶ In addition to the effects of obesity on the pharmacokinetics and dynamics of immunosuppressant medications, obesity has significant effects on the management and outcomes of this critical population.

The impact of obesity and its sequelae have been well documented in kidney transplantation. In 1999 and 2002, Meier-Kriesche and colleagues described the impact of increased BMI on the relative risk of death-censored graft loss and chronic allograft nephropathy.^{17,18} Post-transplant hypertension, dyslipidemia, insulin resistance, and diabetes are all prevalent among obese kidney transplant recipients, and these various components of the metabolic syndrome have made cardiovascular disease the primary cause of death with a functioning graft for this patient population.^{16,19} Obese kidney transplant patients are also at a risk for surgical site infections, wound

complications, delayed graft function, and decreased graft survival, while patients who are extremely obese may even be at risk for decreased overall survival.^{17,20-24}

With the increase in prevalence of transplantation for nonalcoholic fatty liver disease, liver transplant recipients may become, on average, the most obese of all transplant recipients. However, it should be noted that obesity as determined by standard measures such as BMI can complicate the study of the prevalence and risk of obesity in this patient population, as BMI may overestimate obesity given significant levels of ascites.^{11,25} The impact of obesity on graft and patient survival outcomes following liver transplantation remains unclear. An evaluation of over 18,000 liver transplant recipients in the United Network of Organ Sharing (UNOS) database in 2002 showed that morbidly obese patients had higher rates of primary graft nonfunction—30-day, 1-year, and 2-year mortality—while both severely and morbidly obese patients had significantly higher 5-year mortality.²⁶ Leonard and colleagues at the Mayo Clinic reported no differences in survival based on BMI if a corrected BMI was used following ascites removal.¹¹ More recently, a meta-analysis performed by Saab and colleagues demonstrated that there was no difference in mortality between control and increased weight patients even when stratified by BMI and accounting for ascites.²⁷ However, they did see worse survival in obese patients when pooling studies evaluating similar causes of liver disease. Both pre- and post-transplant obesity have been tied to increased cardiovascular risks for those receiving a liver transplant.^{25,26,28} Also, obesity in the liver transplant population has been associated with increased perioperative complications, increased wound infections, and increased hospital length of stay as well as costs at the time of transplantation.^{26,29}

The most recent listing criteria published by the International Society of Heart and Lung Transplantation (ISHLT) for heart transplant candidates recommend candidates achieve a BMI $<30 \text{ kg/m}^2$ or weigh $<140\%$ of their ideal body weight (IBW) before being listed for cardiac transplantation to limit the poor outcomes previously reported.³⁰⁻³² Subsequently, Russo and colleagues evaluated nearly 20,000 heart transplant recipients through the UNOS database. They found similar risk-adjusted median survival when comparing underweight, normal weight, overweight, obesity I, and obesity II/III patients; however, BMI in the underweight and obesity II/III groups was associated with decreased survival in multivariate Cox proportional hazard regression analysis, as was similarly seen by Grady and colleagues.^{33,34} These results potentially suggest that obese I patients are acceptable candidates for transplantation, although another UNOS database review in 2012 showed increased mortality for patients with a BMI 30 kg/m^2 or greater.³⁵ Nonetheless, obese patients wait for donor organs longer and are less likely to receive an organ as compared to nonobese patients waiting for heart transplantation.⁹ Following transplantation, obesity continues to be common and is linked to cardiovascular disease in the graft and possible chronic allograft vasculopathy, which can lead to both fatal and nonfatal cardiac events.^{36,37}

ISHLT recommends a BMI $>30 \text{ kg/m}^2$ as a relative contraindication for lung transplantation, although many transplant centers make this an absolute contraindication due to reports suggesting up to a three-fold increase in post-transplant mortality in obese patients.^{12,15,38} To assess the effect of obesity at the time of transplantation, Allen and colleagues performed an analysis of the UNOS database including over 11,000 patients who received a lung transplant between 1987 to 2008. Overweight and obese patients had lower survival than did normal-weight patients, and BMI strata continued to be predictive of mortality after risk adjustment in multivariate analysis. When first-year deaths were removed, this difference was no longer present suggesting that overweight and obese patients have a higher degree of early mortality.⁷ However, a similar analysis of lung trans-