JPPT | Single Center Retrospective Study

Mycophenolate Metabolite Trough Concentrations Are Not Well Correlated With Dosing or Adverse Outcomes in Pediatric Heart Transplant Recipients

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OBJECTIVE Although mycophenolate metabolite trough concentrations in serum are routinely obtained for pediatric orthotopic heart transplant (OHT) recipients, limited data support this practice. We sought to investigate the relationship of mycophenolic acid (MPA) and MPA glucuronide (MPAG) serum concentrations to dosing and adverse outcomes among pediatric OHT patients.

METHODS This retrospective study included OHT recipients ages 0 to 21 years who received mycophenolate mofetil (MMF) with MPA and MPAG serum trough concentration monitoring. The primary outcome was the relationship between MPA and MPAG serum concentrations and dosing. Secondary outcomes included the relationship of adverse outcomes to either MPA and MPAG concentrations or dosing.

RESULTS A total of 98 patients with 1287 MPA and MPAG trough serum concentrations (each) were included. The median initial MMF dose was 40.3 mg/kg/day (IQR, 35.12–51.83) and 1164.4 mg/m^2/day (IQR, 1080.77–1206.86). There was no correlation between either MPA or MPAG serum concentrations and mg/kg dosing, or mg/m^2 dosing. When comparing the adverse effect of bone marrow suppression with no adverse effect, the median MPA serum trough concentration was 2 (IQR, 1.1–3.2) versus 1.6 (IQR, 0.8–2.5), p = 0.003. When comparing the adverse effect of infection with no adverse effect, median MPA serum trough concentration was 0.9 (IQR, 0.49–1.7) versus 1.6 (IQR, 0.8–2.5), p < 0.001. The clinical utility of this finding is of uncertain benefit. There was no association between MPAG serum concentrations and any adverse outcome (p = 0.053).

CONCLUSIONS We did not identify a correlation between mycophenolate serum trough concentrations and either adverse outcomes or dosing. Based on these results, we discourage routine monitoring of mycophenolate trough concentrations.

ABREVIATIONS AUC, area under the concentration time curve; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MPAG, mycophenolic acid glucuronide; OHT, orthotropic heart transplant; PJP, *Pneumocystis jirovecii* pneumonia; rATG, rabbit anti-thymocyte globulin; SMX-TMP, sulfamethoxazole-trimethoprim; WBC, white blood cell

KEYWORDS adverse outcomes; drug monitoring; heart transplant; mycophenolate; pediatric; pharmacokinetic

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Introduction

Mycophenolate mofetil (MMF) is a commonly used immunosuppressant in children after orthotopic heart transplant (OHT).[1] Mycophenolate mofetil is a prodrug that is rapidly hydrolyzed by the liver to its active metabolite mycophenolic acid (MPA), which subsequently undergoes glucuronidation to its inactive metabolite, MPA glucuronide (MPAG). This undergoes elimination via urinary and biliary routes, although a portion of the latter route undergoes enterohepatic recirculation back into the active MPA metabolite.[2] Present literature evaluating the use of MMF therapeutic drug monitoring in routine clinical practice does not widely support this practice, secondary to conflicting results regarding associations to adverse outcomes.[3,4]

Despite no statement recommending serum trough concentration monitoring in the US Food and Drug Administration labeling and the lack of literature, serum trough MPA and MPAG concentrations are often obtained to guide dosing to minimize adverse effects at many transplant centers.[5,6] No large pediatric study exists that investigates the relationship of serum mycophenolate trough concentrations to dosing and adverse outcomes among pediatric heart transplant recipients. Therefore, we sought to evaluate the relationship between MMF dosing and therapeutic drug monitoring, along with its correlation to the prevalence of adverse effects.

Materials and Methods

This retrospective study included patients ages ≤21 years with status after OHT from March 2016 to February 2021. Patients were eligible for enrollment if they were initiated on MMF after OHT and obtained at least 1 MPA and MPAG concentration. Patients were followed for a period of 6 months after OHT. The primary outcome was to evaluate the correlation between serum MPA and MPAG trough concentrations to dosing, evaluated in mg/kg and mg/m^2 equivalence. Secondary outcomes included association of dosing in (mg/kg equivalence) to adverse outcomes, including allograft rejection, bone marrow suppression, gastrointestinal intolerance, and infection. We also sought to investigate the association of serum MPA and MPAG trough concentrations to the adverse outcomes noted previously. Median serum trough concentrations of MPA and MPAG were compared to adverse outcomes, including rejection, gastrointestinal intolerance, bone marrow suppression, and infection occurring ± 7 days from serum MPA/MPAG trough concentration monitoring. A time frame of ± 7 days was chosen based on the half-life of MMF and the frequency of lab monitoring. Gastrointestinal intolerance was defined as the presence of ≥3 stools per day described as loose, watery, or more frequent by the provider. Bone marrow suppression was defined as leukopenia (white blood cell count, ≤3 × 10^3 cells/μL) or thrombocytopenia (platelets ≤50,000/μL). Infections were defined as any culture-positive viral, bacterial, or fungal infection. Biopsy-proven rejection also included 1R1A identified via biopsy, in patients who were subsequently treated for rejection. Clinical rejection was identified via the electronic chart on the basis of treatment in lieu of a biopsy.

Protocolized induction immunosuppression included 3 daily intravenous doses of rabbit anti-thymocyte globulin (rATG; 1.5 mg/kg/dose) along with methylprednisolone (20 mg/kg/dose during the course of 30 minutes; maximum of 1000 mg/dose), followed by a rapid 5-day intravenous corticosteroid taper. After the third dose of rATG, a remaining 2 doses of rATG are provided (for a total of 5 possible doses) if the patient demonstrated insufficient lymphocyte depletion (CD3 count >25 cells/mm^2). Maintenance immunosuppression included oral tacrolimus 0.05 mg/kg (maximum 3 mg) every 12 hours titrated to a serum trough concentration goal of 10 to 12 ng/mL for months 1 to 3, followed by goal serum trough concentration of 8 to 10 ng/mL until 12 months, along with enteral or intravenous MMF 1200 mg/m^2/day divided every 12 hours started on day 5 after transplantation. At our center we routinely draw blood for a serum trough MPA/MPAG concentration 1 week following initiation of MMF and then weekly thereafter. Trough concentrations are obtained 11.5 hours after the MPA dose. Serum MPA and MPAG trough concentrations were measured by quantitative liquid chromatography–tandem mass spectrometry and were determined in our hospital's clinical laboratory. Patients receiving mycophenolate sodium were converted to the equivalent dose of MMF using a conversion of 360:500 mg. Opportunistic infection prophylaxis was provided for 6 months, which included cytomegalovirus prophylaxis stratified by serologic risk (valganciclovir or acyclovir), oral candidiasis prophylaxis (nystatin), and *Pneumocystis jirovecii* prophylaxis (trimethoprim/sulfamethoxazole). A surveillance endomyocardial biopsy was performed after OHT at 1 to 2 weeks, 4 weeks, then every 1 to 2 months thereafter, and with suspicion of acute rejection. All samples were examined by a dedicated cardiac pathologist.

Pearson association was used to assess relationships between serum MPA and MPAG trough concentrations and dosing in mg/kg and mg/m^2 equivalence. Continuous variables are described using median (IQR) and analyzed using Kruskal-Wallis test for secondary end points. Any p values <0.05 were considered significant, unless otherwise specified. A Bonferroni correction to adjust for multiple comparisons was used to analyze the relationship between serum MPA and MPAG trough concentrations and the 5 adverse outcomes of interest; in this analysis only, $p < 0.01$ was used to assess statistical significance. Statistics were analyzed using Stata version 14.2 (Stata Corp, College Station, TX).

Results

A total of 127 patients received a heart or combined heart kidney transplant. One patient >21 years was excluded, 8 patients excluded for not receiving MMF after transplantation, and 8 for not having a full 6 months of follow-up. A total of 110 patients were screened, 12 of whom were excluded because there was no therapeutic drug monitoring performed, leading to 98 OHT recipients with a combined total of 1287 MPA and MPAG serum concentrations (each) included for analysis. Three of these patients received a combined heart-kidney transplant.

The patient demographics (Table 1) comprised 56.2% male patients, 52.4% white patients, with a median age of 7.42 years (IQR, 1.75–14.3). For immunosuppression, 98.9% of patients received corticosteroids and rATG induction, and 97.9% of patients received tacrolimus and MMF maintenance therapy. Of the 32 patients with a diagnosis of rejection (either biopsy proven or clinical rejection), 88% were diagnosed via biopsy.

Median initial total daily MMF dose was 1000 mg/day (IQR, 600–1515), 40.35 mg/kg/day (IQR, 35.12–51.83), and 1164.4 mg/m^2/day (IQR, 1080.77–1206.86). There was no association identified between serum MPA trough concentration and dosing in mg/kg (r = 0.07) or mg/m^2 (r = 0.018), or between serum MPAG trough concentration and dosing in mg/kg (r = 0.07) or mg/m^2 (r = 0.203; Figure 1). No statistically significant association was identified between mycophenolate total daily dose (mg/kg/day) and any adverse outcome (p = 0.341; Figure 2).

Table 1. Baseline Characteristics

Demographic	Variable (n = 98)
Male, n (%)	53 (54)
Race, n (%)	
White	51 (52)
Black	18 (18.4)
Asian	1 (1)
Other	8 (8.2)
Unknown	20 (20.4)
Age, median (IQR), yr	7.17 (1.77–13.92)
Height, median (IQR), cm	129 (86–154.75)
Weight, median (IQR), kg	29.6 (12.18–47.93)
Induction, n (%)	
Corticosteroids + rATG	97 (98.9)
Corticosteroids + gasiliximab	1 (1)
Calcineurin inhibitor, n (%)	
None	1 (1)
Cyclosporine	1 (1)
Tacrolimus	96 (97.9)
Viral prophylaxis, n (%)	
None	3 (3.1)
Valganciclovir	85 (86.7)
Ganciclovir	4 (4.08)
Acyclovir	6 (6.1)
PJP prophylaxis, n (%)	
None	0
SMX-TMP	87 (88.8)
Dapsone	7 (7.1)
Atovaquone	3 (3.1)
Pentamidine	1 (1)
Fungal prophylaxis, n (%)	
None	0
Nystatin	87 (88.8)
Fluconazole	11 (11.2)
Initial MMF dose/day, median (IQR), mg	1000 (600–1515)
Initial MMF dose, median (IQR), mg/kg/day	40.35 (35.12–51.83)
Initial MMF dose, median (IQR), mg/m^2/day	1164.41 (1080.77–1206.86)

MMF, mycophenolate mofetil; PJP, Pneumocystis jirovecii pneumonia; rATG, rabbit anti-thymocyte globulin; SMX-TMP, sulfamethoxazole-trimethoprim

Median serum MPA trough concentrations varied by adverse effect (Figure 1 and Table 2). No differences in serum MPA trough values were identified in patients with rejection or gastrointestinal intolerances versus those without. When comparing the patients with bone marrow suppression to those with no adverse effect, the median serum MPA trough concentration was 2 (IQR, 1.1–3.2) versus 1.6 (IQR, 0.8–2.5), p = 0.003. When comparing patients with infection to those with no adverse effect, the median serum MPA trough concentration was 0.9 (IQR, 0.49–1.7) versus 1.6 (IQR, 0.8–2.5), p < 0.001. Median serum MPAG trough concentrations did not vary for adverse effects observed (p = 0.053; Figure 3).

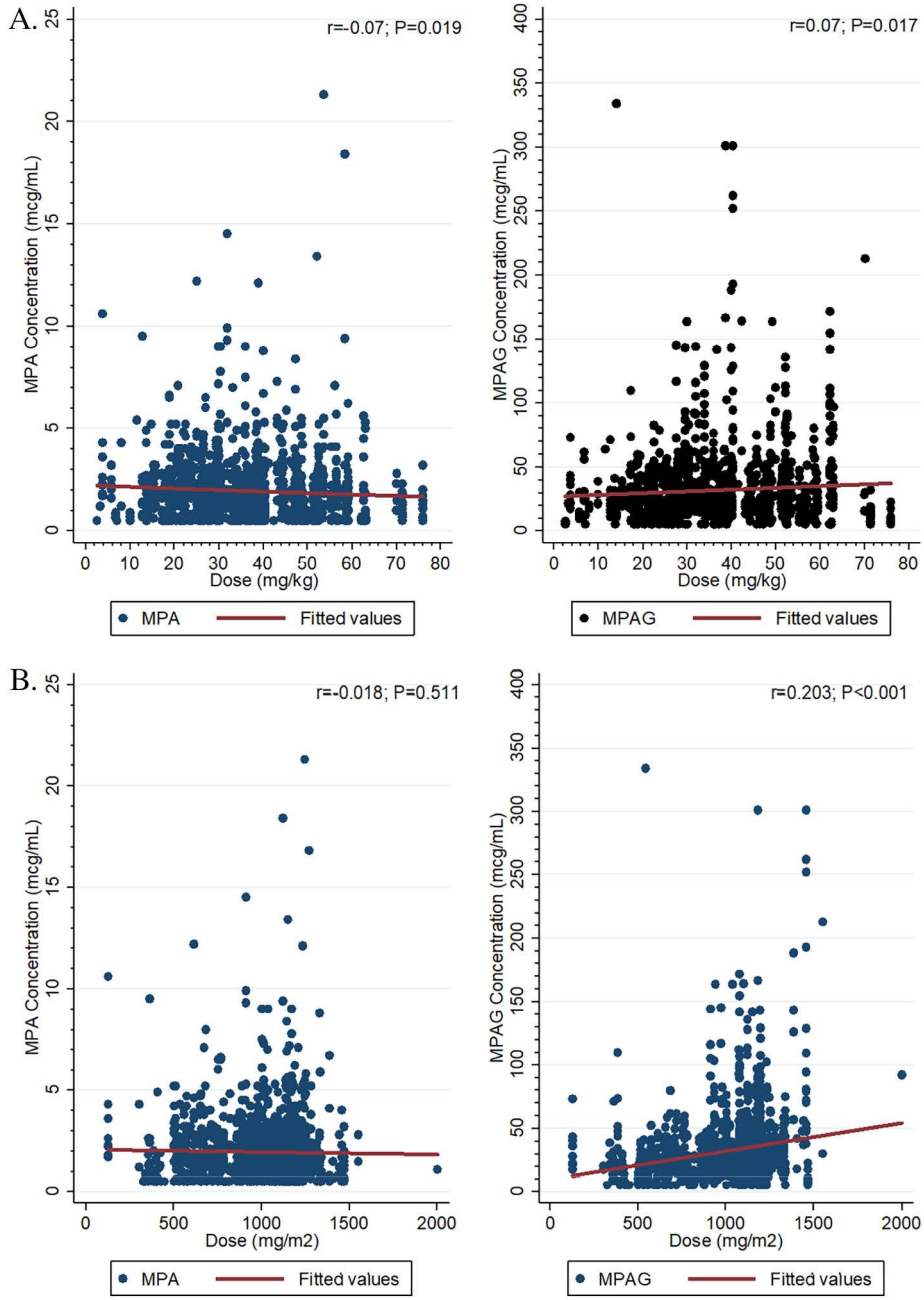
Discussion

This study is the first large, retrospective analysis of mycophenolate serum trough concentration monitoring in pediatric OHT recipients. The complicated pharmacokinetic profile of MMF is due to many factors that affect drug exposure, and therefore subsequent trough concentrations. Mycophenolic acid and MPAG are extensively bound to albumin (97% for MPA, 82% for MPAG) and any changes in a patient's albumin concentration directly affect its distribution. In addition, poor kidney function can lead to the accumulation of MPAG, which can subsequently displace MPA from albumin. As previously noted, MPA undergoes glucuronidation by the liver to its inactive metabolite, MPAG. This is followed by deglucuronidation of MPAG by gut flora back to MPA, which then undergoes enterohepatic recirculation. Therefore, multiple patient factors, such as liver function, ontogenic enzyme activity, pharmacogenomics, and antibiotic use, can affect the exposure of MMF. These complex factors make mycophenolate trough concentration monitoring unreliable. Because of the clinical variability of our patient population and the retrospective nature of this study, we did not note these differences because they are not routinely accounted for in our clinical decision to adjust MMF dosing based on trough concentrations.[7]

Consistent with previously published analyses, this study noted no association between serum MPA or MPAG trough concentrations and dosing. With respect to adverse outcomes, no statistically significant relationship was found besides bone marrow suppression (p = 0.003) and infection (p < 0.001) to serum MPA trough concentrations. We noted higher serum MPA trough concentrations in patients with bone marrow suppression, but we saw lower serum MPA trough concentrations in patients with infection. This statistically significant finding is likely explained by the many patient-specific factors, such as infectious risk and protocolized dosing, that affect overall MMF exposure and therefore trough concentrations. No correlation between dosing and adverse outcomes was identified.

Despite limited guidance, serum mycophenolate trough concentration monitoring is performed after OHT for dose adjustment, usually in the setting of adverse effects, at many transplant centers. Dipchand et al[3] reported the role of mycophenolate drug concentrations in 44 pediatric heart transplant patients with a total of 128 trough MPA concentrations, reporting no significant association between mg/kg dosing or mg/m^2 dosing, aligning with the results of our study. There were no adverse outcomes reported,

Figure 1. Relationship between serum mycophenolic acid (MPA) and MPA glucuronide (MPAG) trough concentrations and mg/kg and mg/m^2 dosing.



and the findings were limited by a small sample size.[3] Tredger et al[8] reported mycophenolate therapeutic drug monitoring in 63 liver transplant recipients, with a weak correlation (r = 0.081) reported between serum MPA concentrations and dosing, corresponding to the findings of our study. Again, too few adverse effects were noted for analysis.[8]

Because of the poor association of MPA and MPAG serum trough concentration monitoring with overall exposure, area under the concentration time curve (AUC) is the preferred method for therapeutic drug monitoring.[9] Van Gelder et al[4] compared fixed and concentration-controlled mycophenolate dosing in adult and pediatric kidney transplant recipients. No difference was found in treatment failure, adverse effects, or difference in MPA AUC. However, a significant relationship was found between MPA AUC and biopsy-proven acute rejection during the first month (p = 0.009)

and first year (p = 0.006) after transplantation. This study indicated a correlation between serum MPA concentrations and rejection.[4] Although limited, published experience with dose modifications of MMF based on AUC monitoring in pediatric OHT recipients supports a reduction in adverse effects and increased tolerability.[10] In non-transplant pediatric use for lupus, graft-versus-host disease prevention following allogeneic hematopoietic cell transplantation, and nephrotic syndrome, MMF AUC monitoring has been described to correlate with efficacy and safety.[11–13] However, at many transplant centers like ours, AUC monitoring is not routinely performed. Although it may be a better marker for total exposure and related outcomes in pediatric OHT recipients, its feasibility may be limited because of multiple blood draws and timing coordination.[9] Based on these results and existing literature in similar patient populations, we discourage the use of routine monitoring of serum mycophenolate trough concentrations and instead recommend use of clinical tolerance to effect dose adjustment.

Table 2. Median Serum Mycophenolic Acid (MPA) Concentrations and Association With Adverse Outcomes

Adverse Outcome	MPA, Median (IQR)	p value*
None	1.6 (0.8–2.5)	—
Rejection	1.15 (0.5–2.25)	0.0153
Gastrointestinal intolerance	1.15 (0.49–2.3)	0.037
Bone marrow suppression	2 (1.1–3.2)	0.003
Infection	0.9 (0.49–1.7)	<0.001

* p < 0.01 is considered significant according to Bonferroni correction. MPA concentrations expressed in mcg/mL

There are several limitations to this study, notably its retrospective nature and limited generalizability to other (non–pediatric heart) solid organ transplant recipients. Additionally, the correlation of serum MPA and MPAG concentrations and adverse effects as ±7 days is not defined in previous literature. This determination was created to capture causative prevalence based on mycophenolate half-life as well as infrequent outpatient clinic visits. Further, we did not serially assess the effect of moderate or severe renal dysfunction on the accumulation of MPA/MPAG metabolites, or drug interactions. Lastly, our center does not routinely perform AUC monitoring, and therefore could not evaluate this practice.

Conclusion

The results of this study do not support routine monitoring of serum mycophenolate trough concentrations or dose adjustments based on trough concentration monitoring. Median trough concentrations were higher in patients with bone marrow suppression but lower in patients with infection, illustrating that trough concentrations are poorly associated with overall exposure. Based on these results and existing literature in similar

Figure 2. Relationship between mycophenolate dosing (mg/kg/day) and adverse outcomes.

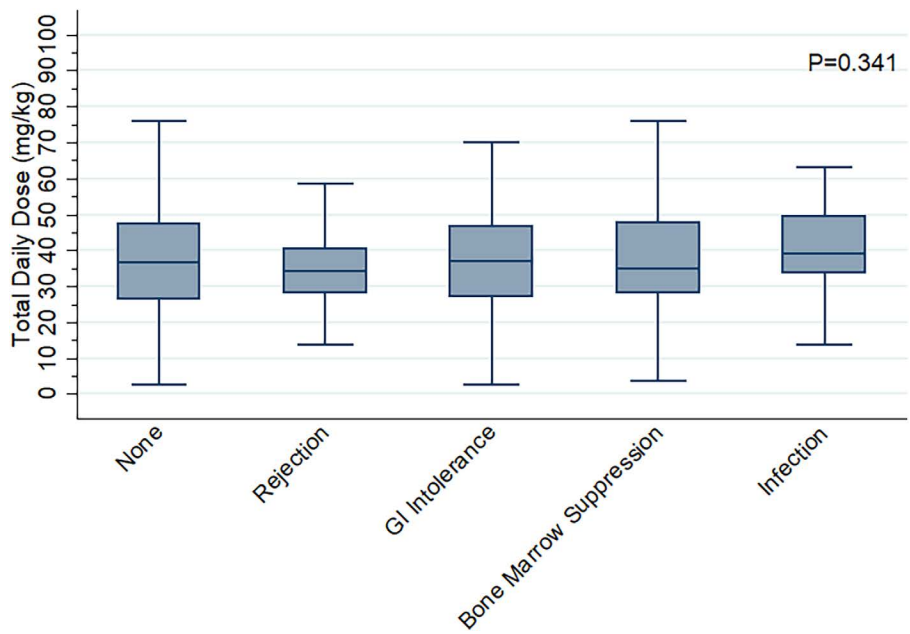
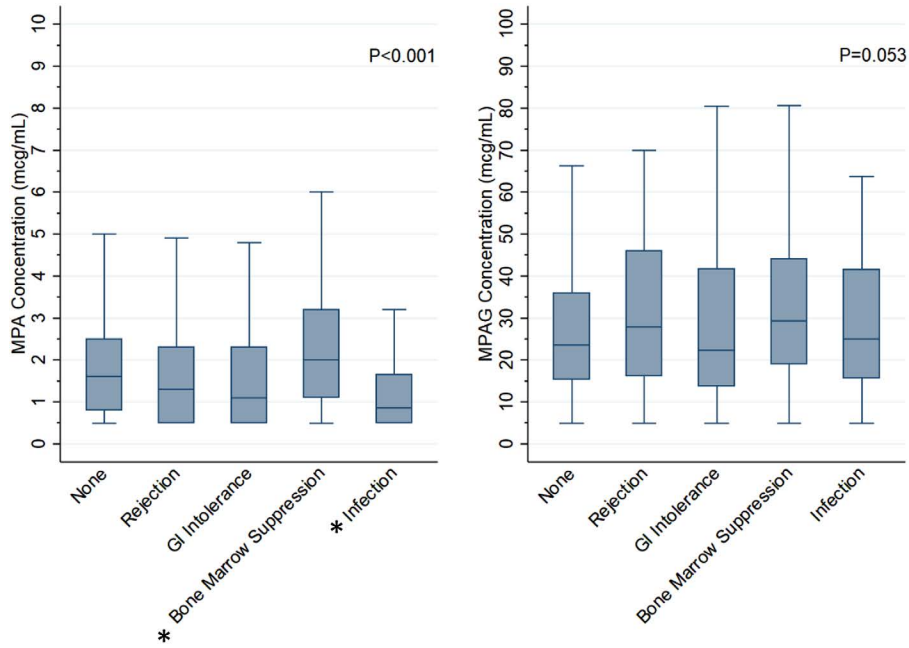


Figure 3. The relationship between serum mycophenolic acid (MPA) and MPA glucuronide (MPAG) trough concentrations and adverse outcomes.



* p < 0.01 (Bonferroni correction).

patient populations, we discourage the use of routine serum mycophenolate trough monitoring in pediatric OHT recipients.

Article Information

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Ethical Approval and Informed Consent. Given the nature of this study, ethics committee review and informed consent were not required.

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