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A Clinical Perspective of Therapeutic Drug Monitoring of Cyclosporine in Pediatric Patients with Kidney Transplant

Maša Roganović, Marija Jovanović, Katarina Vučićević*

University of Belgrade – Faculty of Pharmacy, Department of Pharmacokinetics and Clinical Pharmacy, Vojvode Stepe 450, 11221 Belgrade, Serbia

*Corresponding author: Katarina Vučićević, e-mail: katarina.vucicevic@pharmacy.bg.ac.rs

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Abstract

Cyclosporine A (CsA) is an immunosuppressive used in both children and adult transplant recipients, as well as patients with autoimmune diseases such as nephrotic syndrome. Therapeutic drug monitoring (TDM) of CsA is essential due to its significant interindividual and intraindividual pharmacokinetic variability, narrow therapeutic index and the risk of organ rejection or autoimmune disease relapse at subtherapeutic levels, as well as the potential for serious adverse effects with overexposure. In pediatric patients, CsA pharmacokinetics can be significantly influenced by developmental physiological factors, necessitating even greater attention to TDM in this vulnerable population. This paper explores the key challenges associated with TDM in children, the clinical rationale for its use, clinical settings where it is applied and future perspectives, including the potential of model-informed precision dosing (MIPD).

Key words: cyclosporine, children, therapeutic drug monitoring, transplantation

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Introduction

Cyclosporine A (CsA) is a potent immunosuppressive drug used in the management of patients undergoing solid organ transplantation (kidney, liver, heart, lung) and hematopoietic stem cell transplantation to prevent graft rejection and graft-versus-host disease. Additionally, it is used in the treatment of immune-mediated diseases such as rheumatoid arthritis, atopic dermatitis, psoriasis and nephrotic syndrome (1). CsA mechanism of action involves inhibition of calcineurin, resulting in the downregulation of interleukin-2 (IL-2) gene transcription and suppression of T-cell activation (2).

Due to substantial interindividual and intraindividual pharmacokinetic variability and its narrow therapeutic index, CsA is categorized as a drug that requires therapeutic drug monitoring (TDM). TDM is essential to achieve optimal therapeutic outcomes, particularly the prevention of graft rejection in transplant recipients, while minimizing the risk of adverse drug reactions (3–5).

The use of immunosuppressive drugs can induce serious adverse effects, which can be more prominent in vulnerable populations such as pediatric patients, who require immunosuppressive therapy from an early age and throughout critical periods of growth and development, in contrast to adults. A key adverse effect associated with CsA and other calcineurin inhibitors (CNIs) like tacrolimus is nephrotoxicity, which may be classified as acute or chronic (6). Acute CNI-induced nephrotoxicity is dose-dependent, reversible and more likely to occur at trough levels (C_0) exceeding 400 ng/mL, although it can manifest at lower levels as well (6–8). Therefore, it is crucial to monitor C_0 levels of CsA. Conversely, chronic nephrotoxicity is irreversible and often contributes to long-term graft dysfunction. Other CsA-related adverse effects include hypertension, gingival hyperplasia which is specific to CsA, increased risk of post-transplant diabetes mellitus and electrolyte disbalance, although the last two are more commonly associated with tacrolimus (9). Therefore, in addition to TDM, regular monitoring of renal function is essential, particularly in pediatric kidney transplant recipients. Parameters that need to be monitored are urine output, proteinuria, serum albumin levels, serum creatinine and estimation of glomerular filtration rate using the Schwartz formula in children and adolescents. Routine assessment of growth parameters (height and weight) is also critical due to their relevance in pediatric development (10).

Drug disposition in children is influenced by multiple factors, including body size, developmental stage, physiological changes, and genetic factors (11, 12). Additionally, outcomes such as one-year and long-term allograft and patient survival are affected by patient age, weight, and particularly adherence, which tends to be more challenging during adolescence (9, 13). Given these complexities, the importance of TDM in pediatric patients treated with CsA, regardless of the indication, is even more pronounced. TDM plays a crucial role in ensuring therapeutic efficacy, minimizing toxicity, and supporting individualized treatment strategies in this sensitive population.

Formulations of cyclosporine and dosage recommendations

CsA is available on the market in two different formulations: self-emulsifying system, known as Sandimmun®, which was developed first, and self-microemulsifying system Sandimmun Neoral®. Both formulations are available as an oral solution (100 mg/mL) and soft gelatin capsules (10, 25, 50 and 100 mg). Additionally, CsA is available as a concentrate for solution for infusion (50 mg/mL) (1, 14). Sandimmun Neoral® exhibits a significantly improved absorption profile and, consequently, better clinical efficacy compared to the previous formulation, Sandimmun® (15). Its superiority has been confirmed in the pediatric population, with Sandimmun Neoral® demonstrating an absolute bioavailability of approximately 43% (range: 30–68%) vs. 28% (range: 17–42%) (1, 14). Switching from Sandimmun® to Sandimmun Neoral® requires careful dose adjustment. According to the Summary of Product Characteristics (1), the initial dose of Sandimmun Neoral® should match the previous daily dose of Sandimmun®, accompanied by mandatory monitoring of CsA C_0 levels. It is recommended that whole blood CsA concentrations should be measured within 4 to 7 days following conversion to allow timely dose adjustments if levels fall outside the target therapeutic range. This caution is necessary because the peak concentration (C_{max}) and overall drug exposure, expressed as area under the concentration-time curve (AUC), can increase substantially after switching to Neoral.

Dosage recommendations for CsA in pediatric kidney transplant recipients are summarized in Table I.

Table I Dosage recommendation for cyclosporine (CsA) in pediatric transplant patients (1)

Tabela I Preporuke za doziranje ciklosporina (CsA) u pedijatrijskoj populaciji pacijenata sa transplantiranim organom (1)

Formulation	Pediatric dosing, SOT	Dosage forms
Self-emulsifying system	PO • 4–12 h pretransplant: 10–15 mg/kg PO divided BID • 1–2 weeks post-transplant: 10–15 mg/kg/day PO divided BID • reduce gradually until 2–6 mg/kg/day PO divided BID IV • approximately one third of the corresponding oral dose • patients should be switched as soon as possible to the oral route of administration	Oral solution (100 mg/mL) Soft gelatin capsules (10, 25, 50 and 100 mg in Europe, 25 mg and 100 mg in the United States of America) IV solution (50 mg/mL)
Self-microemulsifying system		Oral solution (100 mg/mL) Soft gelatin capsules (10, 25, 50 and 100 mg in Europe, 25 mg and 100 mg in the United States of America)

SOT – solid organ transplant, PO – per os, BID – two times a day, IV – intravenous

Pharmacokinetics of cyclosporine in pediatric patients

The bioavailability of CsA is highly variable in the pediatric population (16). In both children and adults, C_{max} is typically reached approximately 2 hours after oral administration. However, due to delayed or variable absorption, time to peak can be extended to 3 or 4 hours in some individuals (1, 5, 16). Due to its lipophilic nature, CsA has a large volume of distribution, with a reported mean of approximately 3,5 L/kg (1). However, literature values can range from 3 to 5 L/kg (17). CsA is also extensively bound to plasma proteins (~90%), and a substantial proportion (41–58%) is distributed within erythrocytes, which explains the influence of hematocrit levels on CsA pharmacokinetics (18).

CsA is primarily metabolized in the liver by cytochrome P450 enzymes, specifically CYP3A4 and CYP3A5. Polymorphism of the genes encoding CYP3A5 and CYP3A4 contributes significantly to the observed interindividual variability in CsA pharmacokinetics, with a more pronounced and well-established effect of CYP3A5 variants on tacrolimus than on CsA (1, 5, 19). The CYP3A5*3 allele is the most common allele in the white population and patients who are homozygous carriers produce a nonactive enzyme (nonexpresser phenotype), whereas the homozygous and heterozygous carriers of CYP3A5*1 allele (wild type) produce an active enzyme form (expresser phenotype) (19–22). Therefore, compared to the patients with the nonexpresser phenotype, patients with the expresser phenotype possibly need higher doses to achieve target CsA levels (22–25). Homozygous and heterozygous carriers of CYP3A4*22 allele produce a CYP3A4 enzyme of reduced activity, which can consequently lead to higher C_0 concentrations compared to noncarriers of this allele (22, 26, 27). Furthermore, CsA is a known substrate of P-glycoprotein (5). As with other proteins, a polymorphism of the multidrug resistance gene (MDR1 gene), whose product is P-glycoprotein, can alter CsA pharmacokinetics by changing its intestinal expression and activity (16, 28).

In pediatric patients undergoing transplantation, CsA clearance per kilogram of body weight tends to be higher than in adults, resulting in the need for higher weight-based dosing (22, 29). A possible explanation for CsA exhibiting such pharmacokinetic characteristics is not completely clear. According to many studies, the activity of CYP3A5 and CYP3A4 enzymes reaches adult levels after the first year of life (11, 30).

In general, toddlers often require higher doses per kilogram than adults for many metabolized drugs, suggesting increased enzyme activity. This has been linked to a higher liver-to-body mass ratio in children. However, evidence is inconsistent, and this needs to be addressed in further research (22). Another explanation is that once the enzymatic capacity has fully matured, the increased clearance of many drugs is attributable to size-related factors and reflects the overall body metabolism.

Clearance values reported in the Summary of Product Characteristics (1) are based on a limited pediatric sample size. The study included only 7 renal pediatric transplant patients aged 2–16 years, with the reported mean clearance value of 11.8 mL/min/kg (range: 9.8–15.5 mL/min/kg) and elimination half-life ranging from 6.1 to 16.6 h (1, 14,

31). In pediatric liver transplant patients, the reported mean clearance was 9.3±5.4 mL/min/kg (1, 14). Another study in a similar population reported a clearance value of 8.4 (1.9–13.9) mL/min/kg (32), once again highlighting the extent of pharmacokinetic variability in this population.

Drug interactions are also an important factor in CsA variability. CYP3A4 and P-glycoprotein inhibitors can increase CsA concentrations (14). For example, glucocorticoids, which are part of the posttransplant immunosuppressive therapeutic protocol, increase CsA concentration. Macrolide antibiotics, azole antifungals, calcium channel blockers (verapamil, diltiazem) and metoclopramide can also increase CsA concentrations and cause side effects such as nephrotoxicity due to CsA overexposure (14). Rifampin, anticonvulsants such as carbamazepine, oxcarbazepine and phenytoin, on the other hand, have an opposite effect and can cause CsA underexposure and consequently graft rejection by enzyme induction (14). Moreover, grapefruit juice and St. John's wort can increase and decrease CsA levels, respectively (14). Therefore, in patients receiving the abovementioned drugs, CsA TDM should be performed more frequently at initiation, during dose adjustments, or upon discontinuation of the interacting drug; once steady-state CsA concentrations are achieved, TDM may return to the standard schedule.

Bearing in mind that CsA is mostly eliminated by metabolic transformation, any abnormality in liver functioning requires additional caution as it can also alter CsA pharmacokinetics by changing CYP3A4 and CYP3A5 enzyme activity (14, 17).

Therapeutic drug monitoring of cyclosporine

TDM of CsA involves measuring drug concentrations in the whole blood, plasma or serum (with whole blood samples being used most frequently due to the distribution of CsA in the erythrocytes) to ensure they remain within a target range that balances efficacy and safety. It includes scheduled sampling, interpretation of results based on clinical context, and dose adjustment to avoid underexposure (risk of graft rejection or disease relapse) or overexposure (risk of nephrotoxicity and other adverse effects). TDM is essential due to the narrow therapeutic index of CsA and high interindividual and intraindividual pharmacokinetic variability, especially in pediatric patients.

The reference range of drug concentration depends on the choice of biological material and the analytical method used to determine concentration. The analytical methods used for the determination of CsA concentration include immunoassay methods (most commonly in the routine clinical practice), high pressure liquid chromatography (HPLC) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) as a reference method (33, 34). Additionally, the target concentration of CsA in blood is influenced by several factors: the type of transplanted organ, the patient's clinical condition, age, concomitant medications and the specific protocol of the transplant center, as there are different internal protocols and no consensus on clear target concentration recommendations. TDM in children presents unique challenges, such as difficulties in frequent blood sampling, limited blood volume and adherence issues, especially among adolescent patients (13).

CsA is usually administered twice daily, in the morning and evening, and two blood samples are taken, corresponding to C_0 and 2-hour post-dose (C_2) levels. Some studies suggest that C_2 better reflects drug absorption and correlates more strongly with clinical efficacy, due to the highly variable bioavailability of CsA (35).

Moreover, there is a known correlation between CsA exposure (AUC) and its clinical efficacy (36, 37). Most interindividual and intraindividual variations in drug exposure occur during the first four hours post-dose, which corresponds to the absorption phase (38). This supports the use of exposure in the 0–4 h period ($AUC_{0\text{-}4}$) as a meaningful marker of exposure, with strong correlations to outcomes such as acute rejection (39–41). Despite its clinical utility, calculating $AUC_{0\text{-}4}$ is impractical in routine settings due to the need for multiple blood draws, making it resource- and time-intensive. Thus, studies have focused on identifying single time points that correlate well with $AUC_{0\text{-}4}$, and pharmacokinetic data indicate that C_2 is a reliable surrogate across various organ transplant types (42, 43). Conversely, C_0 has been shown to be a poor predictor of acute rejection (39, 42, 44), but it remains useful for assessing drug elimination (10). Additionally, some studies showed that interindividual variability is lower with C_2 than with C_0 (42). Pharmacodynamic studies also suggest a strong correlation between calcineurin inhibition and CsA blood levels, with peak inhibition occurring approximately two hours post-dose (45). Given these findings, guidelines recommend monitoring both C_0 and C_2 concentrations to optimize therapeutic outcomes (10). Time-course of the CsA concentration is shown in the Figure 1.

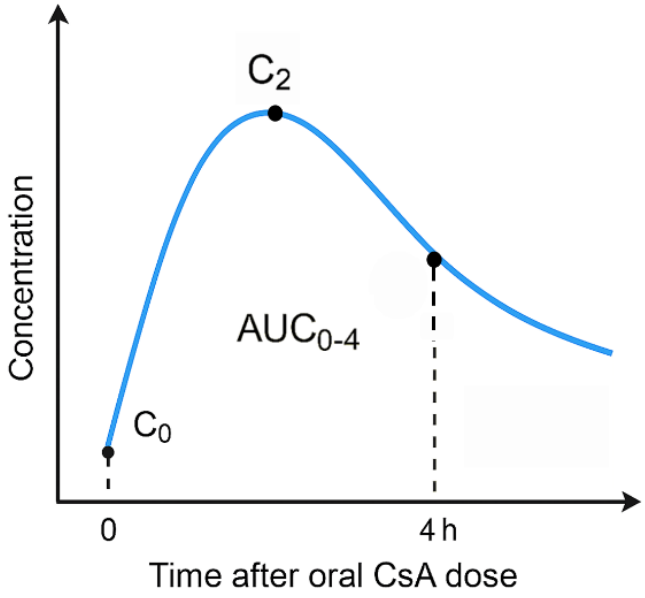

Figure 1. **Pharmacokinetic profile of cyclosporine (CsA) at steady state (SS), showing C_0 (pre-dose trough concentration), C_2 (concentration at 2 hours post-dose), and $AUC_{0\text{–}4}$ (area under the concentration-time curve from 0 to 4 hours).**

Slika 1. **Farmakokinetički profil ciklosporina (CsA) u stanju ravnoteže (SS), koji prikazuje C_0 (nivo leka pre doze – *trough* koncentraciju), C_2 (koncentraciju 2 sata nakon doziranja) i $AUC_{0\text{–}4}$ (površinu ispod krive koncentracije tokom vremena od 0 do 4 sata).**

Currently, TDM-guided dosing of CsA in the pediatric population is largely based on experience gained from adult patients (9). For example, at the University Children's Hospital Tiršova, recommended target whole-blood levels for pediatric transplant recipients, measured by chemiluminescent microparticle immunoassay are: C_0 150–200 ng/mL, C_2 1200–1400 ng/mL during the first month post-transplantation; C_0 100–150 ng/mL, C_2 800–1200 ng/ml during months two and three; and after one year, C_0 100–130 ng/mL, C_2 800–1000 ng/mL (22).

In adults, the therapeutic range also varies depending on the post-transplantation phase. Target C_0 levels range from 50 to 350 ng/mL, typically 200–300 ng/mL in the first three months, and then they are gradually reduced to 75–125 ng/mL after six months. The corresponding target C_2 levels range from 480 to 2000 ng/mL, typically 1000–1500 ng/mL in the first three months, gradually decreasing to 400–600 ng/mL after six months (34). As reported in the cited reference, these CsA concentration ranges were derived from different assays (34).

Beyond traditional therapeutic drug monitoring of cyclosporine

Model-informed precision dosing (MIPD) represents a clinical approach that combines patient-specific data, TDM measurements, and pharmacokinetic/pharmacodynamic models to optimize drug therapy on an individual basis. In the context of CsA, MIPD enables tailoring the dosing regimen to account for the significant interindividual and intraindividual variability observed in pediatric patients, where developmental physiology, body weight, and organ function play a major role (46, 47).

Population pharmacokinetic models are mathematical models developed from concentration-time data across diverse patient populations, quantifying typical pharmacokinetic parameters (e.g., clearance, volume of distribution) and their variability. These models also identify covariates that explain part of the observed variability (48, 49). Table II shows some examples of population pharmacokinetic models of CsA with identified covariates that affect CsA pharmacokinetics.

Table II Examples of population pharmacokinetic models of cyclosporine (18, 50–52)

Tabela II Primeri populacionih farmakokinetičkih modela ciklosporina (18, 50–52)

Population	Number of patients	Software/Model	Identified covariates	Reference
Pediatric, solid organ transplant and autoimmune disease patients	53	Monolix®/two-compartment	CLcr on oral clearance	(50)
Pediatric, kidney transplant patients	98	NONMEM/two-compartment	POT on oral clearance, WT on central volume of distribution	(51)
Pediatric, pretransplant patients	162	NONMEM/three-compartment	WT, HCT, Scr, CHL on systemic clearance; WT, HCT, Scr, CHL on distribution volume	(18)
Pediatric, HSCT	74	NONMEM/one-compartment	WT, POT, FLUC, VORI, POSA, RBC on clearance	(52)

CLCr – creatinine clearance, POT – postoperative time, WT – body weight, HCT – hematocrit, Scr – serum creatinine, CHL – cholesterol, HSCT – hematopoietic stem cells transplantation, FLUC – fluconazole, VORI – voriconazole, POSA – posaconazole, RBC – red blood cell count

In pediatric populations, models often include maturation functions and/or allometric scaling models to describe age and weight-related changes in drug clearance or distribution (18, 52, 53). When applied in clinical practice, population pharmacokinetic models are integrated with Bayesian forecasting, a statistical method that combines prior knowledge (the model and population parameters) with observed TDM data from the patient, to estimate the most likely individual pharmacokinetic parameters (54). Based on these parameters, the model predicts future drug exposure (e.g., AUC, C_0, or C_2 levels), and the dosing regimen is adjusted to reach and maintain therapeutic targets (54, 55).

This model-based approach reduces the risks associated with empirical dosing: underexposure, which may lead to graft rejection or autoimmune relapse, and overexposure, which increases the likelihood of nephrotoxicity, hypertension, and other adverse effects. Importantly, MIPD is particularly beneficial in pediatric settings where frequent blood sampling is challenging, and precise dosing is critical (46).

To address the challenge of invasive blood sampling in pediatric patients, modern microsampling techniques, such as dried blood spots (DBS), offer a less invasive, more

practical alternative. These methods require only small volumes of blood, making them especially suitable for children, and facilitate easier, more frequent sampling for TDM (56). CsA concentrations obtained using the DBS method can differ slightly compared to whole-blood concentrations, mostly due to the hematocrit effect, spot size and analyte recovery during extraction, but with appropriate validation and calibration of the method, DBS can be considered a reliable method for TDM (34, 56, 57, 58).

Besides CsA concentrations as an indirect predictor of organ rejection, some novel non-invasive biomarkers are being considered in the monitoring of solid organ transplants. Knight et al. conducted an extensive review of papers regarding the use of donor-derived cell-free DNA (dd-cfDNA) in the blood or urine of transplant patients as a potential biomarker for prediction of all kinds of graft injuries – acute rejection and infection (59). The review included 47 studies (patients with different transplanted organs – kidney, liver, heart, lungs, and even patients with more than one transplanted organ). It was shown that the elevation of dd-cfDNA can imply acute injury of the graft (59). Further research is needed, but the results seem promising.

Conclusion

TDM of CsA remains a cornerstone in optimizing immunosuppressive therapy in pediatric transplant recipients. Given the significant pharmacokinetic variability associated with CsA, driven by developmental physiology, genetic factors, and formulation differences, individualized dosing is essential to balance efficacy and safety. While C_0 levels have traditionally been used due to practical convenience, growing evidence supports the superior predictive value of C_2 concentrations for clinical outcomes, particularly in the early post-transplant period. However, the lack of standardized target concentrations across institutions and variability in protocols underscores the need for individualized monitoring strategies. Combining both C_0 and C_2 measurements, along with patient-specific factors, enables optimized dosing and minimizes risks of underexposure (organ rejection) and overexposure (nephrotoxicity). Emerging strategies, such as TDM supported by MIPD and minimally invasive microsampling methods, provide promising tools to enhance clinical decision-making and improve outcomes. Future efforts should focus on standardizing target concentrations, validating population pharmacokinetic models across age groups, and integrating these tools into routine care to ensure optimal and personalized treatment.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Author contributions

K.V.: Conceptualization, Writing—review, editing and supervison; M.R.: Literature search, Data curation and Visualization; M.R. and M.J.: Literature analysis and writing—original draft; All authors have read and approved the final version of the manuscript.

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Klinički aspekti terapijskog praćenja ciklosporina u pedijatrijskoj populaciji pacijenata sa transplantiranim bubregom

Maša Roganović, Marija Jovanović, Katarina Vučićević*

Univerzitet u Beogradu – Farmaceutski fakultet, Katedra za farmakokinetiku i kliničku farmaciju, Vojvode Stepe 450, 11221, Beograd, Republika Srbija

*Autor za korespondenciju: Katarina Vučićević, e-mail: katarina.vucicevic@pharmacy.bg.ac.rs

Kratak sadržaj

Ciklosporin A (CsA) je imunosupresiv koji se koristi kod dece i odraslih pacijenata sa transplantiranim organom, kao i kod pacijenata sa autoimunim bolestima kao što je nefrotski sindrom. Terapijsko praćenje ciklosporina (TDM) je ključno za optimizaciju terapije zbog velike interindividualne i intraindividualne farmakokinetičke varijabilnosti, uskog terapijskog indeksa, rizika od odbacivanja organa ili recidiva autoimune bolesti ukoliko su nivoi CsA preniski, ili pojave neželjenih efekata usled prekomerne izloženosti leku. Kod dece, farmakokinetika CsA može biti izmenjena zbog razvojnih fizioloških faktora, tako da treba posvetiti više pažnje sprovođenju TDM u ovoj osetljivoj populaciji. U ovom radu biće opisani ključni izazovi sprovođenja TDM u pedijatrijskoj populaciji, razlog zbog koga se i kada sprovodi u kliničkoj praksi, kao i savremene strategije za optimizaciju terapije kao što je doziranje zasnovano na upotrebi modela.

Ključne reči: ciklosporin, deca, terapijsko praćenje lekova, transplantacija