

Development and Evaluation of an Optimized Busulfan Dosing Strategy in Hematopoietic Stem Cell Transplantation



UPPSALA
UNIVERSITET

Razan Sakran, PharmD^{1,2}, Xiaomei Chen, PhD^{2,3}, Daniel Kurnik, MD¹, Elisabet Nielsen²

¹Clinical Pharmacology, Rambam Health Care Campus, Haifa, Israel

²Department of Pharmacy, Uppsala University, Sweden

³Department of Pharmacology, University of Gothenburg, Sweden



RAMBAM
Health Care Campus

Introduction

- Busulfan is a key drug in conditioning regimens prior to hematopoietic stem cell transplantation (HCT).
- Busulfan has a narrow therapeutic window and high interindividual variability (IIV).
- Clinical efficacy and toxicity are strongly associated with cumulative exposure, expressed as the area under the concentration–time curve (AUC).
- Initial dosing is commonly selected using weight-based dosing tables derived from population pharmacokinetic (PopPK) models; however, these dosing tables have key limitations:
 - They were developed from relatively small and selected cohorts, excluding adults and underrepresenting infants.
 - They rely solely on body weight and assume a typical age–weight relationship.

Objectives

- To develop an optimized IV busulfan initial dosing regimen, applicable from infancy to adulthood, targeting a cumulative AUC_{cum} of 79 mg·h/L over 4 days of treatment.
- To evaluate the newly proposed dosing regimen versus standard dosing regimens used in clinical practice.

Methods

Step 1. PopPK model development

One-compartment PopPK model developed using:

- 3025 samples, 527 HCT patients
- Age: median 22 years (IQR 5–53.5; range 0.2–75)
- Weight: median 57 kg (IQR 17.5–74.4; range 4.6–125.8)
- Age ~ CL: sigmoid Emax model
- Weight allometrically scaled on CL and Vd using fixed exponents

Step 2. Development of alternative dosing regimen

- Using the final PopPK model, cumulative exposure was predicted for the typical patient
- Target AUC_{cum} = 79 mg·h/L
- Doses linearly adjusted to achieve target exposure
- Dosing recommendations summarized by weight ± age

Step 3. Evaluation of alternative dosing regimen:

Monte Carlo simulations (10,000 iterations):

- Developed alternative dosing regimen
- European Medical Agency (EMA) dosing¹ and Bartelink et al.² dosing (adjusted to target AUC_{cum} = 79 mg·h/L)

Evaluation metrics:

- Probability of target (AUC_{cum} = 79 mg·h/L) attainment (PTA)
- Sub- and supratherapeutic exposure (<75 and >83 mg·h/L)
- Extreme exposure (<60 or >100 mg·h/L)

Results

- Our combined weight- and age-based dosing regimen achieved the target exposure with acceptable bias and precision (median AUC_{cum} = 78.9 mg·h/L; MPE: 2.7%; RMSE: 19.5 mg·h/L; Figure 1).
- All evaluated dosing regimens showed low PTA: 13% (95% CI: 12.6–13.2), 15% (95% CI: 15.1–15.7), and 17% (95% CI: 16.7–17.3) for Bartelink, EMA, and our new regimen.
- Standard dosing regimens tended toward underexposure in higher weight/age groups (>34 kg and age > 20 years; Figure 2). The new dosing regimen reduced extreme under- and overexposure to 27.5%, vs. 39.7% and 42.5% with the EMA- and Bartelink-based regimens (Figure 2).

References:

1. Nguyen et al. Bone Marrow Transplant. 2004;33:979. 2. Bartelink et al. Clin Pharmacokinet. 2012;51:331

- The new dosing regimen reduced extreme under- and overexposure to 27.5%, vs. 39.7% and 42.5% with the EMA- and Bartelink-based regimens (Figure 2).

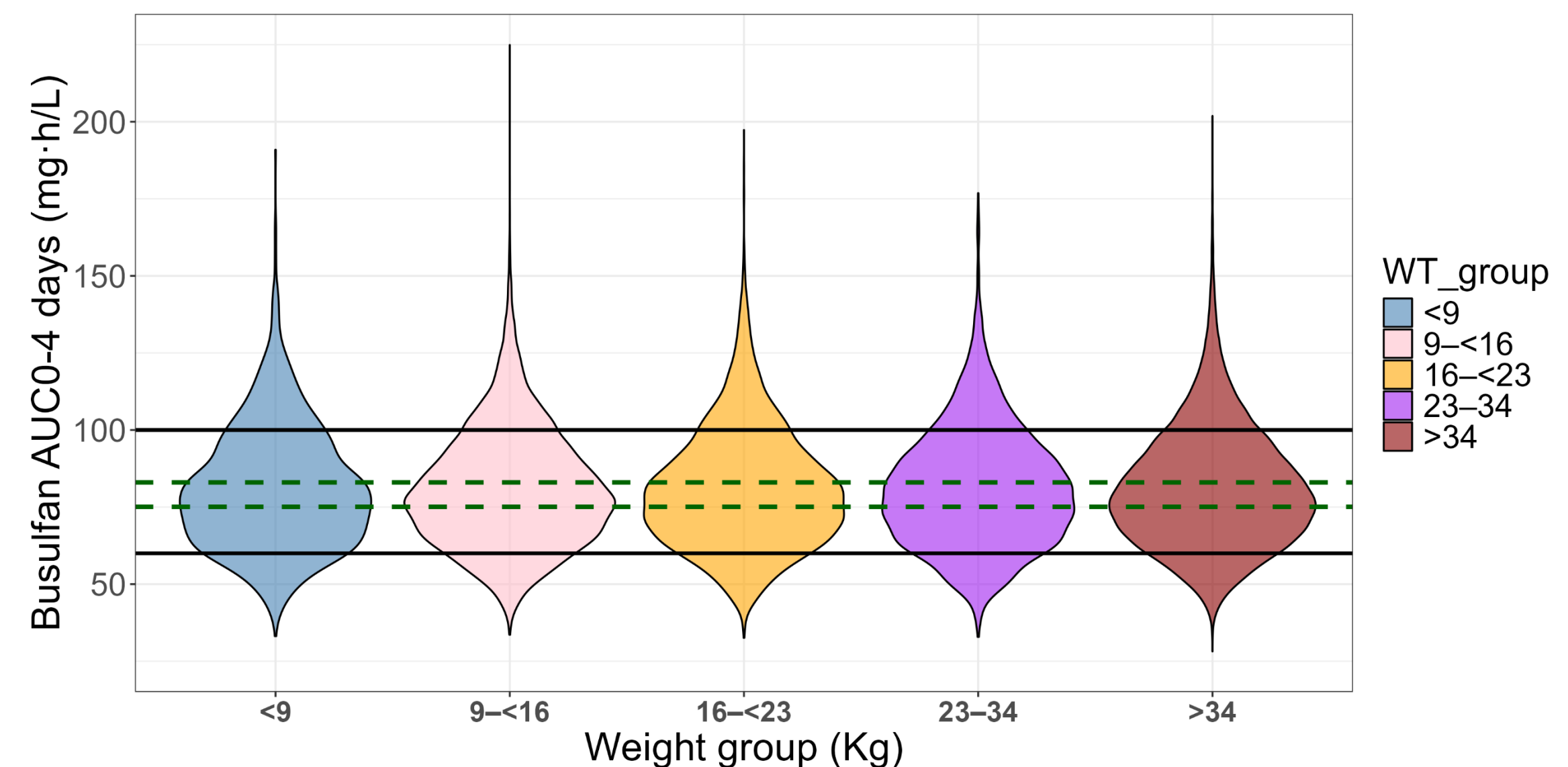


Figure 1. Distribution of simulated cumulative busulfan exposure (AUC_{cum}) across weight groups using the new dosing regimen

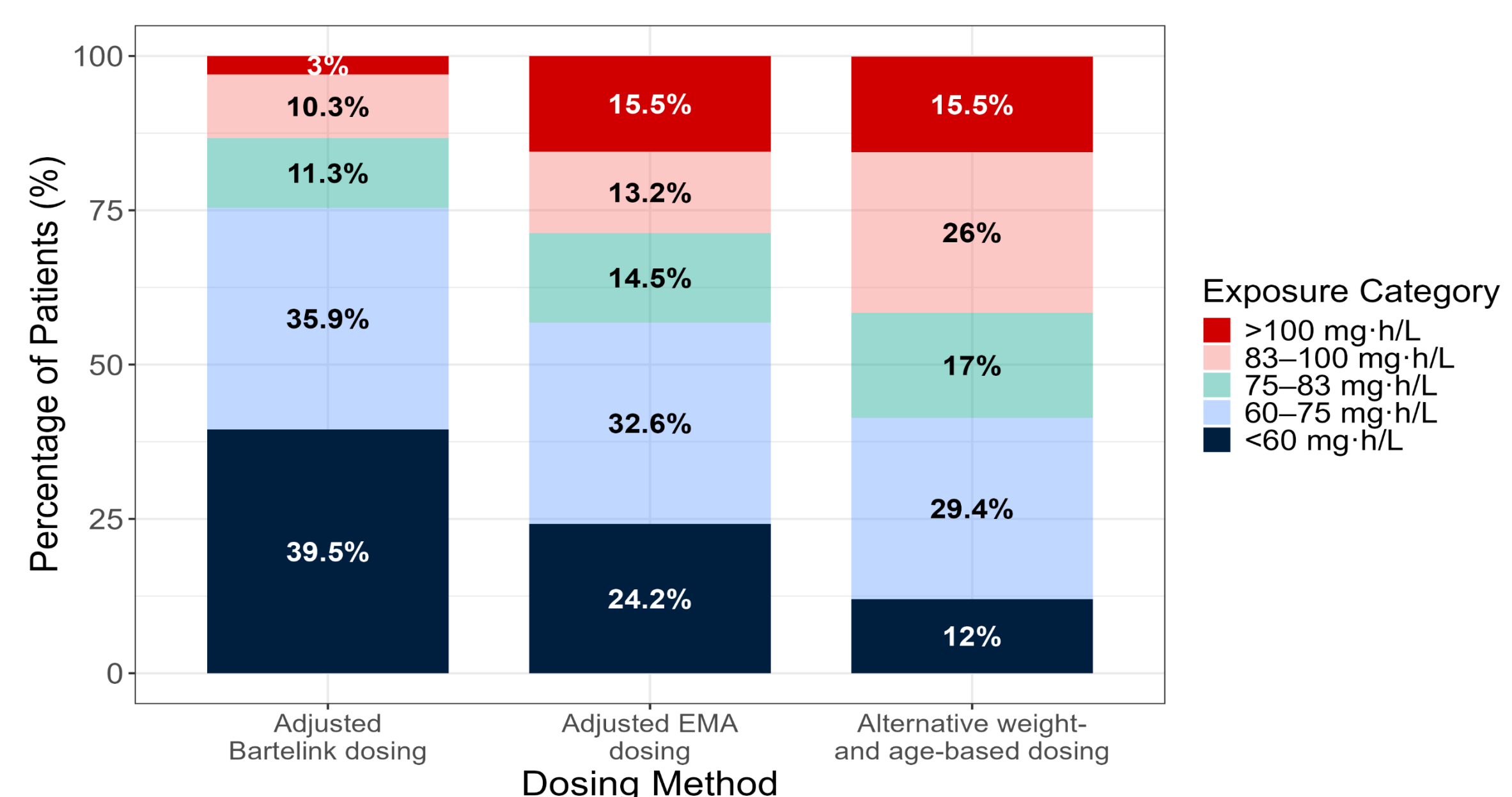


Figure 2. Distribution of simulated cumulative busulfan exposure categories across dosing regimens for patients >34 kg

- Weight-based dosing alone resulted in substantial overexposure in infants (MPE: 24%; RMSE: 40 mg·h/L; Figure 3).

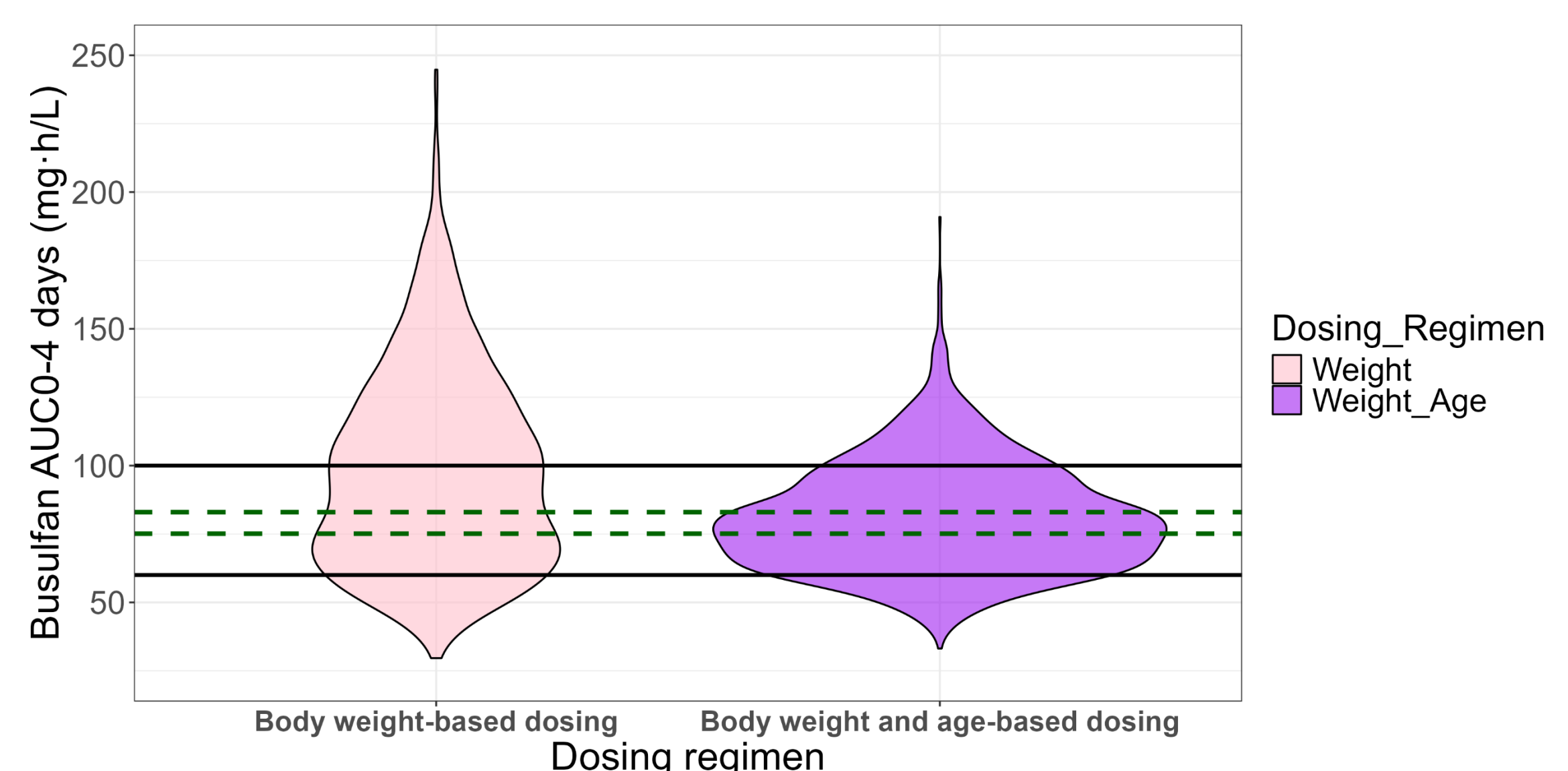


Figure 3. Distribution of simulated cumulative exposure in infants following body weight- or body weight + age-based dosing

Conclusions

- The proposed dosing regimen improved target attainment across a broad range of body weights and ages.
- Incorporating age, in addition to weight, improved target attainment in infants, highlighting the importance of maturation for busulfan dosing in infants.
- Concentration-based dose individualization is indispensable; however, the new first-dose regimen reduces extreme under- and overexposure after the first dose and thus the need for large dose adjustments, potentially decreasing the need for repeat TDM sampling.