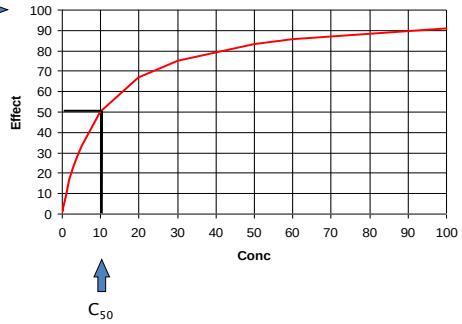
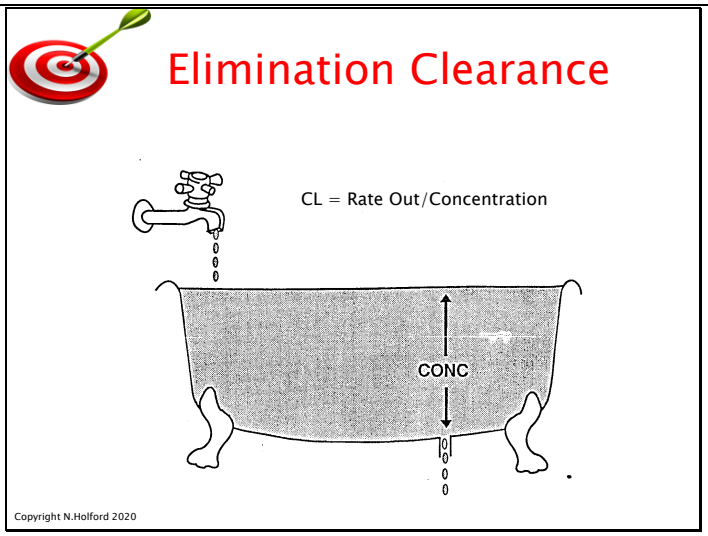
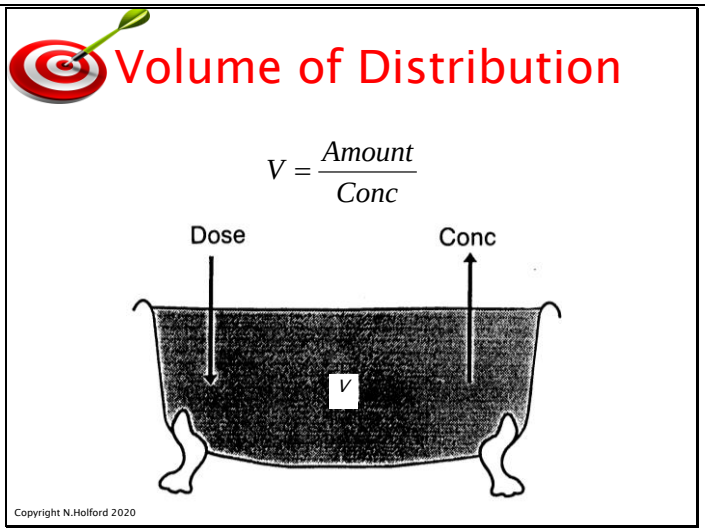
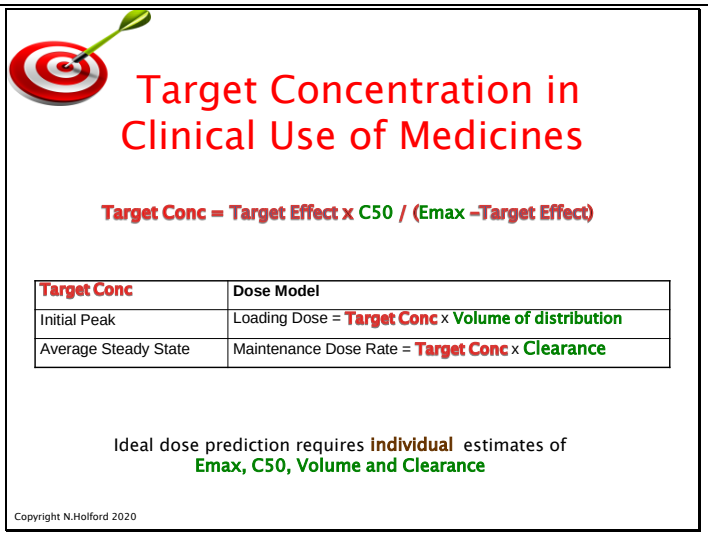
Slide 1	# The Target Concentration Approach to Dosing in Children and Adults -- Application to Busulfan Nick Holford MBChB, FRACP https://www.pkpdrx.com/	
Slide 2	 ## Clinical Pharmacology Pharmacokinetics Pharmacodynamics CL V Emax C50 Dose Concentration Effect Copyright N.Holford 2020	Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (C50).
Slide 3	 ## Conc and Effect Emax  C_{50} Copyright N.Holford 2020	http://clinpharmacol.fmhs.auckland.ac.nz/docs/immediate-time-course-of-drug-effect.pdf http://clinpharmacol.fmhs.auckland.ac.nz/docs/ligand-binding.pdf Based on the law of mass action principle the binding of a drug to a receptor should follow a hyperbolic curve (as shown here). If it is assumed that the effect is directly proportional to the binding then the C50 will be the same as the Kd (the equilibrium binding constant). Notice that Emax can never be directly observed. It is the asymptotic effect of the drug at infinite concentration. Even 10 times the C50 only reaches 90% of Emax.

Slide 4		http://clinpharmacol.fmhs.auckland.ac.nz/docs/clearance.pdf The bathtub provides a physical model to explain how clearance determines drug elimination. This bathtub has fixed rate of water flowing in from the tap (rate in = 4 drops/unit time). Water is lost from the bathtub at the same rate (rate out = 4 drops/unit time) which keeps the bath water level constant (steady state). Clearance is determined by the size of the hole in the bathtub.
Slide 5		http://clinpharmacol.fmhs.auckland.ac.nz/docs/volume-of-distribution.pdf The bathtub provides a physical model to explain how physical factors can influence the apparent volume. In this example there is no loss of water from the bathtub. By putting a known amount of drug (the dose) into the bathtub and measuring the concentration it is easy to calculate the apparent volume.
Slide 6		The target concentration approach links PKPD to prediction of the right dose for a patient.

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Three Ways to Dose

- Population
  - Same dose for everyone
    - The dream dosing method! (often used in adults)
- Group (Covariate guided)
  - Same dose for similar group
    - e.g. same weight, CLcr, genotype (usually used for children)
- Individual
  - Dose determined by individual response
    - e.g. BP, INR, blood conc

Holford & Buclin 2012

CLcr = Creatinine clearance, BP = Blood Pressure, INR=International Normalized Ratio

Holford NHG, Buclin TMD. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit 2012; 34: 565-68.

There are 3 ways to think about choosing the dose.
The population dosing method uses the same dose for everyone. It is the most commonly used method but usually just for convenience. This means that some patients are either under-dosed or over-dosed.
The group dosing method uses patient factors (also known as covariates) to predict the dose suitable for a group of patients with similar factors. Dosing in children is nearly always based on weight or age. The use of weight or renal function to adjust the dose is recommended for some medicines but probably not used as often as it should be.
Individual dosing based on patient response is widely used when the response is easily measured. For example anti-hypertensive doses are usually adjusted based on the blood pressure response. The use of other response markers such as the international normalized ratio (INR) response to warfarin or the concentration of an antibiotic such as gentamicin are also examples.

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Group Dosing Methods Busulfan

Age Group	Method	Acceptable	Age Group	Method	Acceptable
All Ages	Age & Size	72%	Age>=1 and <2	Age & Size	69%
	EMA	70%		EMA	72%
	FDA	57%		FDA	54%
Age Group	**Method**	**Acceptable**	**Age Group**	**Method**	**Acceptable**
Age>=5 and <10	Age & Size	78%	Age<1	Age & Size	62%
	EMA	71%		EMA	61%
	FDA	49%		FDA	54%

Acceptable if within 80–125% of individual Bayesian TCI predicted dose

Age & Size method (McCune et al 2014) overall better than EMA method. FDA method markedly inferior.

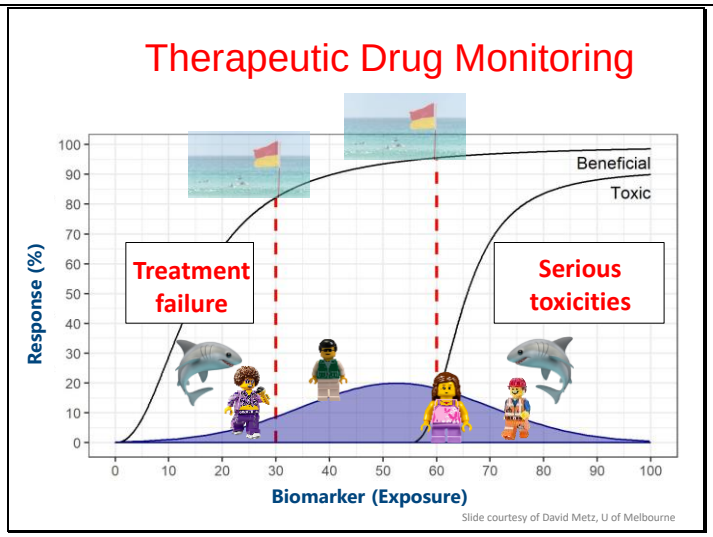
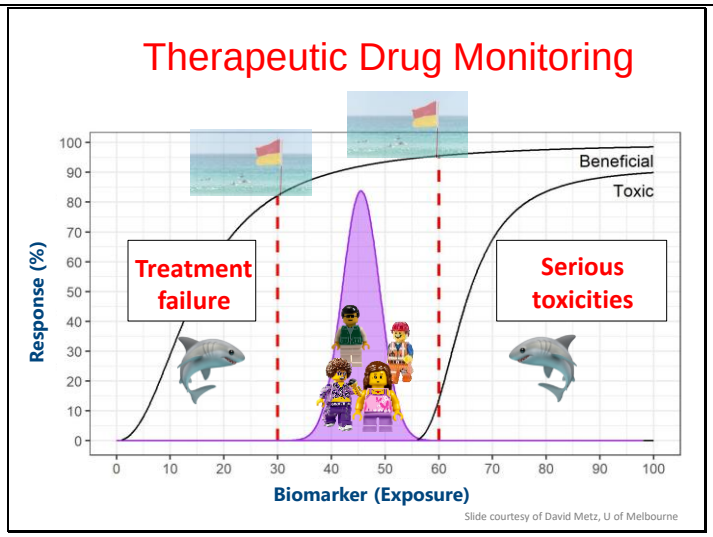
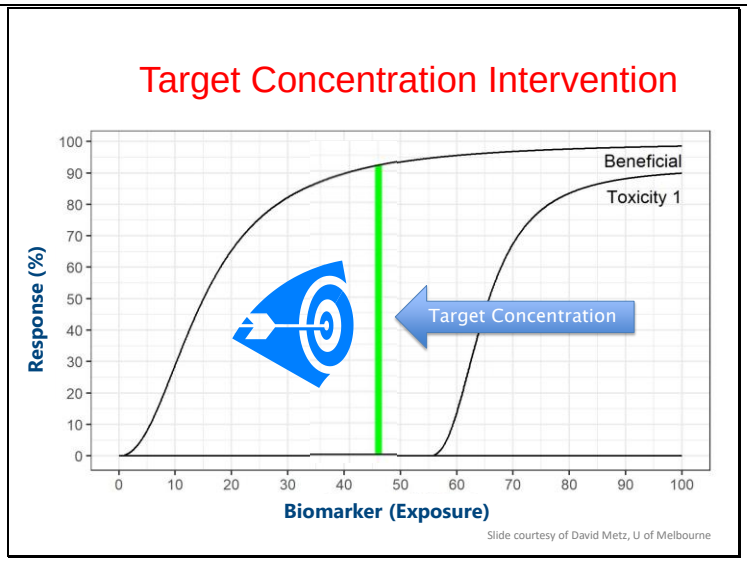
McCune et al Clin Canc Res 2014

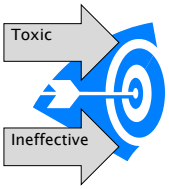
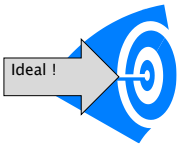
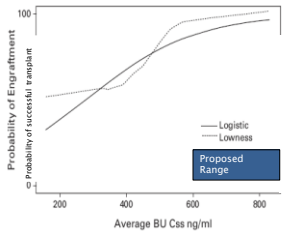
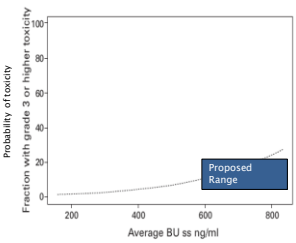
McCune JS, Bemer MJ, Barrett JS, Scott Baker K, Gamis AS, Holford NHG. Busulfan in Infant to Adult Hematopoietic Cell Transplant Recipients: A Population Pharmacokinetic Model for Initial and Bayesian Dose Personalization. Clin Cancer Res. 2014;20(3):754-63.

Slide 9

But …

- Only 2/3 of patients will get a suitable busulfan dose
- So 1/3 of patients will be either over-treated or undertreated
- What can we do for them?

Slide 10		In the clinic patients will have exposure within, at the limit of, and outside the acceptable range. They will be distributed within and across the therapeutic window. The therapeutic drug monitoring approach, assumes, that all our patients sit within the flags. This assumption is not correct.
Slide 11		The second fallacy of TDM is what is done with a concentration measurement; what should be the magnitude of the dose change given a measured concentration? What should we do if the measurement is just inside or outside the acceptable range (e.g. 28 or 31 in this example)? Furthermore this approach assumes that there is a range of doses which match the acceptable range of concentrations. The maintenance dose rate is related to the target concentration and clearance. Clearance will time with time, but is constant at a single point in time. The target concentration can only be achieved by a single maintenance dose. It is not possible to have a range of targets (e.g. 28 to 31) as this will require a range of maintenance dose rates.
Slide 12		We can be more accurate and precise if we remove the flags and aim for a specific target. In the target concentration intervention approach, every measurement is used to guide dose adjustment to achieve a target concentration a measure which is correlated with improved outcomes. As described previously, maintenance dose rate is related to the target concentration and clearance. Therefore if we know the clearance for an individual, then the maintenance dose rate is known. Target concentration intervention also provides a method to link target concentration with dose. This means that the clinician is provided a proposed dose that will achieve the target.

Slide 13	 **TDM or TCI?** • Therapeutic Drug Monitoring – TDM Therapeutic Range ☹ **Imprecise** – Sub-optimal at borders of the range  Target Concentration Intervention » TCI Single Target ☺ **Accurate** » Optimal – do the best you can  Copyright N.Holford 2020	http://clinpharmacol.fmhs.auckland.ac.nz/docs/target-concentration-intervention.pdf Note the difference between precision and accuracy. It is possible to have group shots at a target so that they are close together and thus precise – but not at the centre of the target. An accurate group of shots will be centred on the target. The term "precision dosing' is not the same as "accurate dosing". That is why target concentration intervention is a better description of individualized dosing method than precision dosing.
Slide 14	 **Busulfan Pharmacodynamics**  Figure 1 Probability of engraftment compared to Bu Css (ng/ml).  Figure 2 Fraction of patients with toxicity as related to Bu Css (ng/ml). Proposed Range 0.6 to 0.9 mg/L; Target Concentration 0.77 mg/L Corresponds to Target AUCssDI of 1125 umoL*min q6h dosing Bolinger et al Bone Marrow Transplantation 2000 Copyright N.Holford 2020	Bolinger AM, Zangwill AB, Slattery JT, Glidden D, DeSantes K, Heyn L, et al. An evaluation of engraftment, toxicity and busulfan concentration in children receiving bone marrow transplantation for leukemia or genetic disease. Bone Marrow Transplant. 2000;25(9):925-30. AUCssDI = Area under the concentration time curve at steady state over the dosing interval
Slide 15	 **AUC Dose Adjustment from Busulfex label (PDL 2006)** **Dose Adjustment Based on Therapeutic Drug Monitoring** Instructions for measuring the AUC of busulfan at dose 1 (see Blood Sample Collection for AUC Determination), and the formula for adjustment of subsequent doses to achieve the desired target AUC (1125 µM•min), are provided below. Adjusted dose (mg) = Actual Dose (mg) x Target AUC (µM•min)/Actual AUC (µM•min) For example, if a patient received a dose of 11 mg busulfan and if the corresponding AUC measured was 800 uM•min, for a target AUC of 1125 µM•min, the target mg dose would be: Mg dose = 11 mg x 1125 µM•min / 800 µM•min = 15.5 mg Busulfex dose adjustment may be made using this formula and instructions below. ***Blood Sample Collection for AUC Determination:*** Calculate the AUC (µM•min) based on blood samples collected at the following time points: For dose 1: 2 hr (end of infusion), 4 hr and 6 hr (immediately prior to the next scheduled BUSULFEX administration). Actual sampling times should be recorded. For doses other than dose 1: Pre-infusion (baseline), 2 hr (end of infusion), 4 hr and 6 hr (immediately prior to the next scheduled BUSULFEX administration). AUC calculations based on fewer than the three specified samples may result in inaccurate AUC determinations. For each scheduled blood sample, collect one to three mL of blood into heparinized (Na or Li heparin) Vacutainer® tubes. The blood samples should be placed on wet ice immediately after collection and should be centrifuged (at 4°C) within one hour. The plasma, harvested into appropriate cryovial storage tubes, is to be frozen immediately at -20°C. All plasma samples are to be sent in a frozen state (i.e., on dry ice) to the assay laboratory for the determination of plasma busulfan concentrations. **Calculation of AUC:** BUSULFEX AUC calculations may be made using the following instructions and appropriate standard pharmacokinetic formula: Dose 1 $AUC_{infinity}$ Calculation: $AUC_{infinity} = AUC_{0-6hr} + AUC_{extrapolated}$ where AUC_{0-6hr} is to be estimated using the linear trapezoidal rule and AUC extrapolated can be computed by taking the ratio of the busulfan concentration at Hour 6 and the terminal elimination rate constant, λ_z. The λ_z must be calculated from the terminal elimination phase of the busulfan concentration vs. time curve. A "0" pre-dose busulfan concentration should be assumed, and used in the calculation of AUC. If the AUC is assessed subsequent to Dose 1, steady-state AUC_{ss} (AUC_{0-6hr}) is to be estimated from the trough, 2 hr, 4 hr and 6 hr concentrations using the linear trapezoidal rule. ***Instructions for Drug Administration and Blood Sample Collection for Therapeutic Drug Monitoring:*** An administration set with minimal residual hold up (priming) volume (1-3 mL) should be used for drug infusion to ensure accurate delivery of the entire prescribed dose and to ensure accurate collection of blood samples for therapeutic drug monitoring and dose adjustment. Prime the administration set tubing with drug solution to allow accurate documentation of the start time of BUSULFEX infusion. Collect the blood sample from a peripheral IV line to avoid contamination with infusing drug. If the blood sample is taken directly from the existing central venous catheter (CVC), DO NOT COLLECT THE BLOOD SAMPLE WHILE THE DRUG IS INFUSING to ensure that the end of infusion sample is not contaminated with any residual drug. At the end of infusion (2 hr), disconnect the administration tubing and flush the CVC line with 5 cc of normal saline prior to the collection of the end of infusion sample from the CVC port. Collect the blood samples from a different port than that used for the BUSULFEX infusion. When recording the BUSULFEX infusion stop time, do not include the time required to flush the indwelling catheter line. Discard the administration tubing at the end of the two-hour infusion. Copyright N.Holford 2020	The FDA label is complex and detailed. It recommends an AUC using umol/L*h derived from the target from the literature average steady state concentration (0.77 mg/L) with a 6 h dosing interval. There is no rationale for using molar units (umol/L) but there is a rational argument for using mass units because they are the same units as the dose (mg). This simplifies the calculation of the dose.

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Bayesian Dose Adjustment

- Well established methodology for TDM based dose prediction
  - Sheiner 1977
  - Applied to busulfan paedatric BMT (Bleyzac 2001, Salinger 2010)
- Flexible
  - Not affected by sampling times (provided they are accurate)
  - First dose can be loading dose > maintenance dose
- Output
  - Estimate of patient's clearance (CL) and dose
  - Any dosing interval (e.g. q6h, daily, continuous infusion)

Dose mg q interval h	= Target Conc (mg/L)	* CL (L/h)	* interval (h)
265 mg q 24 h	= 0.770 mg/L	* 14.3 L/h	* 24 h

Sheiner LB, Rosenburg B, Marathe VV. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. J Pharmacokinet Biopharm. 1977;5:445-79.

Bleyzac N, Souillet G, Magron P, Janoly A, Martin P, Bertrand Y, et al. Improved clinical outcome of paediatric bone marrow recipients using a test dose and Bayesian pharmacokinetic individualization of busulfan dosage regimens. Bone Marrow Transplant. 2001;28(8):743-51.

Salinger DH, Vicini P, Blough DK, O'Donnell PV, Pawlikowski MA, McCune JS. Development of a Population Pharmacokinetics-Based Sampling Schedule to Target Daily Intravenous Busulfan for Outpatient Clinic Administration. The Journal of Clinical Pharmacology. 2010;50(11):1292-300.

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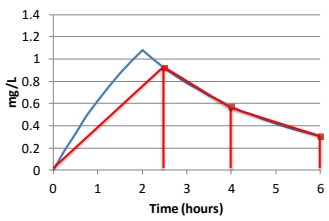
AUC vs Bayesian Dose Adjustment



Method	Sampling Times (h)	Dose Error
AUC lin	2,4,6	-2.3%
AUC lin	2.5,4,6	8.2%
AUC lin/log	2,4,6	2.5%
AUC lin/log	2.5,4,6	13.2%
Bayesian	2,4,6	0.3%
Bayesian	2.5,4,6	0.3%

- Simulated concentrations without error
- AUC linear or linear/log trapezoidal
- Bayesian pharmacokinetic model

AUC method sensitive to sampling time but Bayesian PK is not

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The Evidence – Tacrolimus

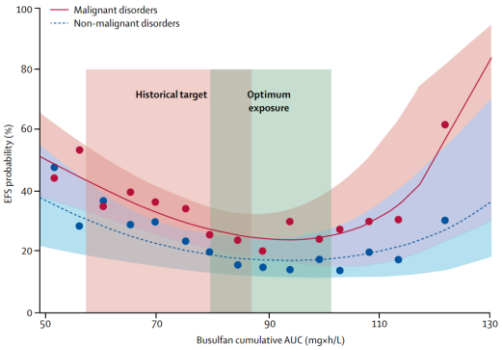
- TDM
  - Use of TDM had no effect in reducing renal transplant rejection
    - Thervet (2010): Fixed dose vs Genotype dosing (increased fraction within therapeutic range)
    - Anutrakulchai (2019): Fixed dose vs Genotype dosing (increased fraction within therapeutic range, more delayed graft function)

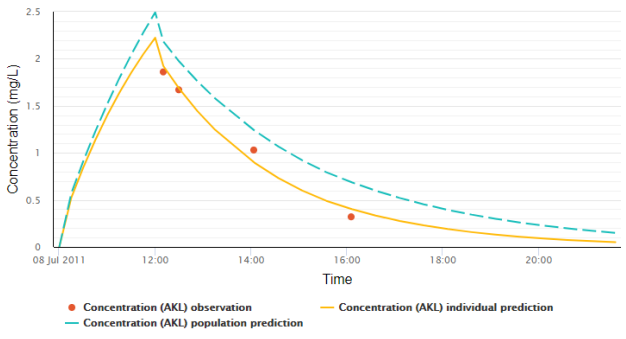
TDM = goal was to reach exposure within therapeutic range in every patient. Clinicians were given dosing advice.

Anutrakulchai S, Pongskul C, Kritmetapak K, Limwattananon C, Vannaprasaht S. Therapeutic concentration achievement and allograft survival comparing usage of conventional tacrolimus doses and CYP3A5 genotype-guided doses in renal transplantation patients. Br J Clin Pharmacol. 2019;85(9):1964-73.

Thervet E, Loriot MA, Barbier S, Buchler M, Ficheux M, Choukroun G, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther. 2010;87(6):721-6.

Slide 19	 **The Evidence – Vancomycin** • Three studies compared TCI with historical TDM • All showed TCI achieved more exposure in the therapeutic range than TDM • All showed reduced nephrotoxicity with TCI TCI = goal was to reach target AUC in every patient. Clinicians were given dosing advice using Bayesian estimation. TDM = goal was to reach target trough within therapeutic range in every patient. Clinicians may have been given dosing advice (varied by study). Truong et al. Int Med J (2012), Neely et al. Antimicrob Agents Chemo (2018), Meng et al. Pharmacotherapy (2019) Copyright N.Holford 2020	Meng L, Wong T, Huang S, Mui E, Nguyen V, Espinosa G, et al. Conversion from Vancomycin Trough Concentration–Guided Dosing to Area Under the Curve–Guided Dosing Using Two Sample Measurements in Adults: Implementation at an Academic Medical Center. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2019;39(4):433-42. Truong J, Levkovich BJ, Padiglione AA. Simple approach to improving vancomycin dosing in intensive care: a standardised loading dose results in earlier therapeutic levels. Internal Medicine Journal. 2012;42(1):23-9. Neely MN, Kato L, Youn G, Kraler L, Bayard D, van Guilder M, et al. Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing. Antimicrob Agents Chemother. 2018;62(2):e02042-17.
Slide 20	 **The Evidence – Mycophenolate** • TCI – Use of TCI reduced renal transplant rejection • Hale 1998 (Phase 3): Randomized Concentration Controlled Trial. 3 Target AUCs. • Le Meur 2008 (APOMYGYRE): Fixed Dose vs Target AUC • TDM – Use of TDM had no effect in reducing renal transplant rejection • van Gelder 2008 (FDCC): Fixed dose vs Therapeutic Range AUC • Gaston 2009 (OPTICEPT): Fixed dose vs Therapeutic Range Trough TCI = goal was to reach target in every patient. Clinicians were given dosing advice using Bayesian estimation. TDM = goal was to reach exposure within therapeutic range in every patient. Clinicians were not given dosing advice. Copyright N.Holford 2020	Hale M, Nicholls A, Bullingham R, Hene R, Hoitsman A, Squifflet J, et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. Clin Pharmacol Ther. 1998;64:672-83. Le Meur Y, Buchler M, Thierry A, Caillard S, Villemain F, Lavaud S, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant. 2007;7(11):2496-503. van Gelder T, Silva HT, de Fijter JW, Budde K, Kuypers D, Tyden G, et al. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. Transplantation. 2008;86(8):1043-51. Gaston RS, Kaplan B, Shah T, Cibrik D, Shaw LM, Angelis M, et al. Fixed- or controlled-dose mycophenolate mofetil with standard- or reduced-dose calcineurin inhibitors: the Opticept trial. Am J Transplant. 2009;9(7):1607-19. Rousseau A, Laroche M-L, Venisse N, Loichot-Roselmac C, Turcant A, Hoizey G, et al. Cost-Effectiveness Analysis of Individualized Mycophenolate Mofetil Dosing in Kidney Transplant Patients in the APOMYGRE Trial. Transplantation. 2010;89(10):1255-62.

Slide 21	 **Busulfan Target Exposure AUC vs Event Free Survival**  Acceptable Range 78 to 101 mg/L*h over 4 days Target AUC 90 mg/L*h over 4 days Bartelink et al Lancet Haematol 2016 EFS=event-free survival	Bartelink IH, Lalmohamed A, van Reij EM, Dvorak CC, Savic RM, Zwaveling J, et al. Association of busulfan exposure with survival and toxicity after haemopoietic cell transplantation in children and young adults: a multicentre, retrospective cohort analysis. Lancet Haematol. 2016;3(11):e526-e36 Figure 2: Polynomial Weibull models of the association between busulfan cumulative area under the curve and event-free survival (A) The polynomial Weibull model of the association between busulfan cumulative AUC and EFS (using uncensored data) is able to reproduce the central tendency, because all raw EFS data of the Δ 5 mg × h/L AUC groups (dots) in the training (blue solid line) and internal validation datasets (blue dashed line) fall within the 95% CI of the model predicted association between busulfan cumulative AUC and EFS. (B) The busulfan cumulative AUC and EFS polynomial Weibull model stratified by malignant (red solid line) and non-malignant (blue dashed line) underlying disease shows that the optimum AUC does not depend on indication. The red shaded rectangles show the historical target, as defined in previous studies.13,15,26,27 The green shaded rectangles show the target defined in the present study. Shaded areas represent 95% CIs. AUC=area under the curve. Css=concentration at steady state.
Slide 22	 **Practical Questions** • Number and timing of blood samples for busulfan measurement? • Should doses be adjusted to achieve – Target AUC – ignoring whether initial doses were too or too low? – The traditional goal or – Total treatment period target AUC – adjust subsequent doses to achieve cumulative dose? – The pharmacological theory goal 	

Slide 23	 **Conclusion** Received: 6 February 2020 | Revised: 28 April 2020 | Accepted: 19 May 2020 DOI: 10.1111/bcp.14434 **REVIEW-THEMED ISSUE** **TDM is dead. Long live TCI!** Nick Holford[1] | Guangda Ma[1] | David Metz[2] Holford et al Brit J Clin Pharmacol 2020 Copyright N.Holford 2020	Holford N, Ma G, Metz D. TDM is dead. Long live TCI! Br J Clin Pharmacol. 2020; Early View (doi:10.1111/bcp.14434).
Slide 24	 **Busulfan NextDose** http://www.nextdose.org NextDose TCI busulfan 19:2020-09-01-195354_conc_NextDose2017_AVG **Target: CONC 0.77 mg/L at steady state** Trapezoid: AUC 6.6 mg/L*h (1615.1 umol/L*min); Interval 0-infinity; Dose Pred maintenance dose 62.7 mg; Comment Bayesian 1: Route IV; Predicted Dose 47.8 mg every 6 hours; Actual Dose 90.0 mg; 11/07/2011 18:11 **Proposed IV maintenance dose 51.3 mg every 6 hours (Bayesian)** McCune JS, Bemer MJ, Barrett JS, Scott Baker K, Gamis AS, Holford NHG. Busulfan in Infant to Adult Hematopoietic Cell 63. Same clearance decrease (-8%)from 36h. CAUTION: This is a prototype. Use in patient care is undertaken at the risk of the treating clinician. Careful interpretation ar up is recommended especially for trough concentration targets. CL L/h: 10.8; fCL%: 36.7; V L: 7.94; fV%: -8.7; F: 1; fF%: 0; FFM kg: 36.5; RF%: . Copyright N.Holford 2020	NextDose target concentration intervention report for a patient after the first dose of busulfan. The trapezoidal AUC and dose predicted from the AUC are shown only to compare with the Bayesian predicted dose which is expected to be more reliable. The Bayesian estimate of clearance is 36.7% higher than expected based on the patients age and size.
Slide 25	 **Busulfan NextDose** http://www.nextdose.org  Copyright N.Holford 2020	The measured busulfan concentrations are shown with population predictions based on the dose, age and size. The yellow line shows the Bayesian predicted concentrations based on the measured concentrations and population prior information.