Slide 1	# Systems Pharmacology Learning from GAVamycin Nick Holford University of Auckland	
Slide 2	## Outline •What is Systems Pharmacology •What is GAVamycin? •PK and Disease Progression •Lessons for Systems Biology ©NHG Holford, 2017, all rights reserved.	

Slide 3	## Systems Pharmacology
	= Systems Biology + Pharmacology
	
	• Systems Biology
	  • Quantitative description of biological processes in the whole living organism
	
	• Size and Maturation Approach
	  • Scaling of structure and function using the living organism mass
	  • Describing maturation of structure and function using biological age
	
	• Specific System Biology Features
	  • Glomerular filtration rate
	  • Creatinine production rate
	  • Renal function
	
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Slide 4

GAVamycin

- Gentamicin
- Amikacin
- Vancomycin

- Three similar antibiotics
- Eliminated primarily by the renal route
- Used extensively in neonates
- Standard size and maturation model approach

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Slide 5

Collaborators and Data

Study	Description	Location	Principal Investigator	Patients
ALL	Pooled gentamicin, amikacin, vancomycin,GFR	International	Holford,N. 2017	2356
STDY1	Vancomycin	Leuven	Allegaert,K. 2007	273
STDY2	Vancomycin	Coimbra	Falcao,A.	33
STDY3	Vancomycin	Marseille	Simon,N.	53
STDY4	Pooled GFR	International	Rhodin,M. 2009	108
STDY5	Vancomycin	Kuala Lumpur	Lo,L. 2010	116
STDY6	Vancomycin	Glasgow	Thomson,A. 2009	94
STDY7	Amikacin	Dunedin	Sherwin,C.	80
STDY8	Amikacin	Dunedin	Sherwin,C.	80
STDY9	Amikacin	Leuven	Allegaert,K.	711
STDY10	Gentamicin	Dunedin	Sherwin,C.	439
STDY11	Gentamicin	Dunedin	Sherwin,C. 2009	244
STDY12	Vancomycin	Dunedin	Sherwin,C.	47
STDY13	Vancomycin	Paris	Zhao,W. 2013	78

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Allegaert K, Anderson BJ, van den Anker JN, Vanhaesebrouck S, de Zegher F. Renal drug clearance in preterm neonates: relation to prenatal growth. Ther Drug Monit. 2007;29(3):284-91.
Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009;24(1):67-76.
Lo YL, van Hasselt JG, Heng SC, Lim CT, Lee TC, Charles BG. Population pharmacokinetics of vancomycin in premature malaysian neonates: identification of predictors for dosing determination. Antimicrob Agents Chemother. 2010;54(6):2626-32.
Sherwin CM, McCaffrey F, Broadbent RS, Reith DM, Medlicott NJ. Discrepancies between predicted and observed rates of intravenous gentamicin delivery for neonates. J Pharm Pharmacol. 2009;61(4):465-71.
Thomson AH, Staatz CE, Tobin CM, Gall M, Lovering AM. Development and evaluation of vancomycin dosage guidelines designed to achieve new target concentrations. J Antimicrob Chemother. 2009;63(5):1050-7.

Slide 6	**Allometric Size using Normal Fat Mass** GFR NFMGFR=FFM + GFR_FFAT*(WTKG - FFM) $NFMGFR_{STD}$=56.1 + FFTGFR*13.9 FSZGFR=(NFMGFR/$NFMGFR_{STD}$)^(3/4) Creatinine production NFMCPR=FFM + CPR_FFAT*(WTKG - FFM) $NFMCPR_{STD}$=56.1 + CPR_FFAT*13.9 FSZCPR=(NFMCPR/$NFMCPR_{STD}$)^(1) Non-renal clearance NFMCLNR=FFM + CLNR_FFAT*(WTKG - FFM) $NFMCLNR_{STD}$=56.1 + CLNR_FFAT*13.9 FSZCLN=(NFMCLNR/$NFMCLNR_{STD}$)^(3/4) Central volume NFMVC=FFM + VC_FFAT*(WTKG - FFM) $NFMVC_{STD}$=56.1 + VC_FFAT*13.9 FSZVC=(NFMVC/$NFMVC_{STD}$)^(1) Peripheral volume NFMVP=FFM + VP_FFAT*(WTKG - FFM) $NFMVP_{STD}$=56.1 + VP_FFAT*13.9 FSZVP=(NFMVP/$NFMVP_{STD}$)^1) Inter-compartmental clearance NFMQ=FFM + Q_FFAT*(WTKG - FFM) $NFMQ_{STD}$=56.1 + Q_FFAT*13.9 FSZQ=(NFMQ/$NFMQ_{STD}$)^(3/4) GFR_FAT=0 from Rhodin et al (2009) updated with neonatal and child FFM predicted using Sumpter & Holford (2012) GREEN parameters from literature RED parameters estimated in this study ©NHG Holford, 2017, all rights reserved.	
Slide 7	**Maturation** GFR $FMAT_{GFR}$=1/(1+($TM50_{GFR}$/PMAW)^-$Hill_{GFR}$ Non-renal clearance $FMAT_{CLNR}$=1/(1+($TM50_{CLNR}$/PMAW)^-$Hill_{CLNR}$ Creatinine production $FMAT_{CPR}$=1 + CPRSL*(1080 - PMAW) ; <=20 y Central volume $FMAT_{VC}$=1 Peripheral volume $FMAT_{VP}$=1 Inter-compartmental clearance $FMAT_{Q}$=1 $TM50_{GFR}$ =46.5 w and $Hill_{GFR}$ =3.43 from Rhodin et al (2009) updated with neonatal and child FFM predicted using Sumpter & Holford (2012 ©NHG Holford, 2017, all rights reserved.	.Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009;24(1):67-76. Sumpter A, Holford NHG. A model for fat free mass in humans from very premature neonates to young adults. PAGANZ https://wwwpaganzorg/abstracts/a-model-for-fat-free-mass-in-humans-from-very-premature-neonates-to-young-adults/. 2012 ; Accessed 7 Jan 2017
Slide 8	**Creatinine Production Rate** STDCPR ; mmol/h/70kg male 40 PNAY Jaffe [C&G] FSCR ; conversion of Scr Jaffe to enzymatic STDCPRZ=STDCPR*FSCR ; enzymatic standard creatinine production rate CPR_{STD}=STDCPRZ*CPR_FSDY4 ; SDY4 is GFR study CPR=CPR_{STD}*FSZCPR*FMATCPR ; allometric size and maturation FCLcr=CLcr/GFR ; true CLcr as fraction of true GFR GFR=CLcr/FCLcr Apparent CPR estimation with FCLcr assumed to be 1 $aCPR_{obs}$=GFR_{obs}*SCr_{obs} ; observed GFR and SCr from SDY4 aCPR=FCLcr*CPR ; estimation STDCPR =0.516 from Cockcroft & Gault (1976) FSCR =0.75 from Peake & Whiting (2006) ©NHG Holford, 2017, all rights reserved.	Peake M, Whiting M. Measurement of serum creatinine - current status and future goals. Clin Biochem Rev. 2006;27(4):173-84. Roche results are corrected with an “average” 26.5 µmol/L offset for non-creatinine chromogens (NCR) An offset of -18 µmol/L is recommended for the Olympus method in Australia. NCRSTD=26.5 ; Roche FSCR=0.700 at 1 mg/dL/88.4 umol/L NCRSTD=18 ; Olympus FSCR=0.796 at 1 mg/dL/88.4 umol/L NCRSTD=22.25 ; Conversion at average FSCR=0.75 FSCR= (88.4-NCRSTD)/88.4 =0.75 ; typical C&G Scr=1 mg/dL=88.4 umol/L Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41. Matthews I, Kirkpatrick C, Holford N. Quantitative justification for target concentration intervention--parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. Br J Clin Pharmacol. 2004;58(1):8-19.

Slide 9	## Renal Function CLcr=FCLcr*CPR/Scr ; True CLcr aCLcr=aCPR/Scr ; Apparent CLcr with FCLcr=1 GFR=STDGFR*FSZ_{GFR}*$FMAT_{GFR}$; Size and maturation Renal function (RF) defined as ratio of CLcr to GFR RF=aCLcr/GFR If SCr missing or within 48 h of birth: RF=FRFSDY ; group RF estimate for each study with missing aCLcr STDGFR =6.8 L/h (119 mL/min) from Rhodin et al (2009) updated with neonatal and child FFM predicted using Sumpter & Holford (2012) ©NHG Holford, 2017, all rights reserved.	
Slide 10	## Clearance In general: CL = $CLNR_{STD}$ * FSZ_{CLNR}* $FMAT_{CLNR}$ + RF * STDGFR* FSZ_{GFR}* $FMAT_{GFR}$ If aCLcr can be calculated then this is equivalent to: CL = $CLNR_{STD}$ * FSZ_{CLNR}* $FMAT_{CLNR}$ + aCLcr Drug specific CLNR, CLR relative to GFR and VC, VP and Q relative to vancomycin were estimated. STDGFR =119 mL/min from Rhodin et al (2009) updated with neonatal and child FFM predicted using Sumpter & Holford (2012 ©NHG Holford, 2017, all rights reserved.	
Slide 11	## Renal Function Disease Progress When aCLcr can be calculated: RF=aCLcr/GFR Study specific RF, FRFSDY, only estimable if aCLCr cannot be calculated. In a second step the empirical Bayes estimates of RF obtained with CPR & PK model were used as DV in a second step to refine estimates of FRFSDY. These RF estimates were used to describe RF time course, i.e. disease progress, for all subjects. RF=FRFSDY ; group RF estimate by SDY with EBE as DV for RF ©NHG Holford, 2017, all rights reserved.	

Slide 12

Computational Methods

- NONMEM 7.4 alpha
- gfortran 64 bit
- Wings for NONMEM 742
- R to create WFN VPC

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Results

- GAVamycin
  - Bolus or zero-order input, two compartment distribution, first-order elimination
  - Theory based allometric exponents for GFR, VC, VP, Q
  - Ffat=0 for GFR, VC, VP, Q
- Creatinine Production Rate
  - Allometric size exponent=1, Ffat=0 (fat free mass)
  - Linear maturation from birth to 20 years
- Renal Function
  - Study RF varied from 0.836 to 1.55 (only one study < 1)
  - Initial rapid increase (?) then slow decline

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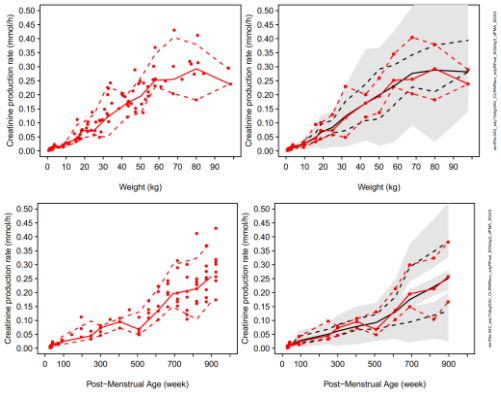
Slide 14

Creatinine Production Rate Size & Maturation



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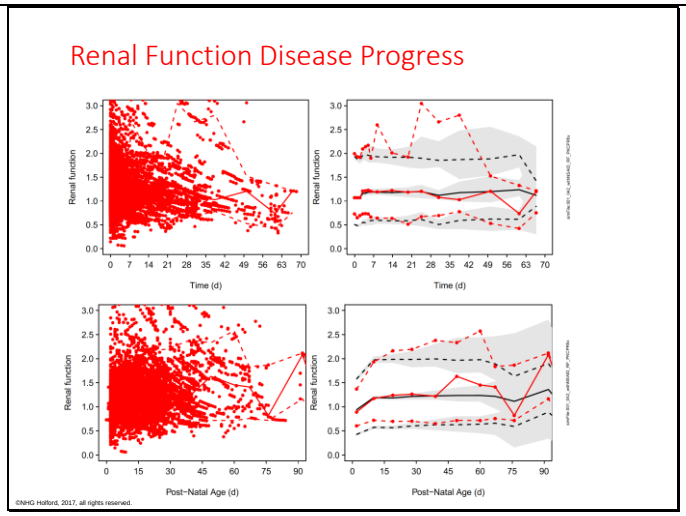
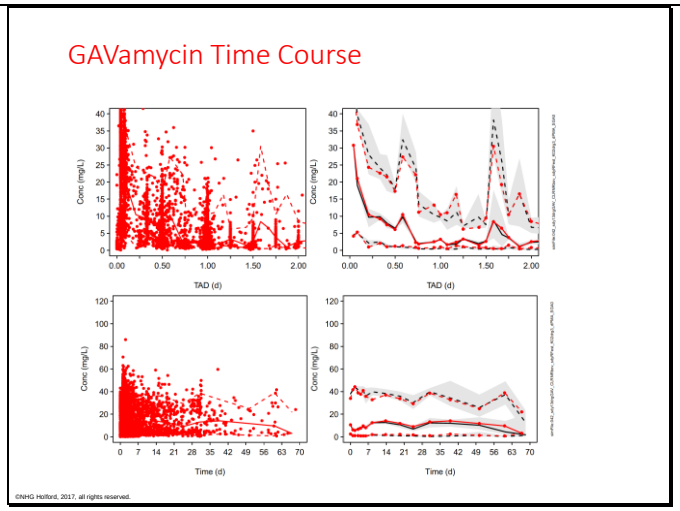
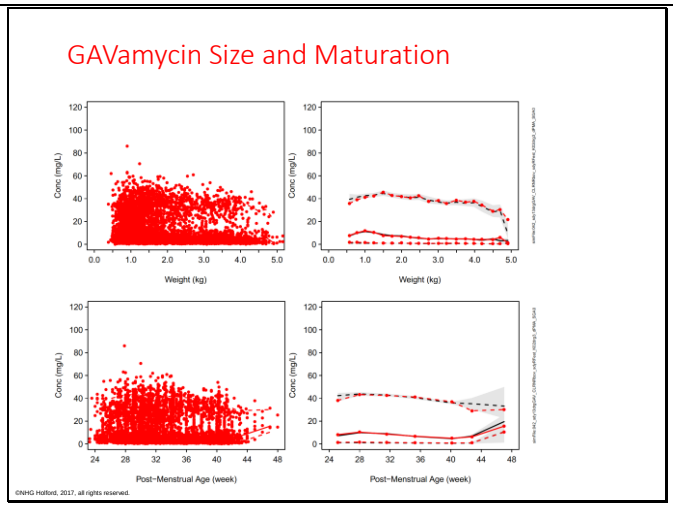
Slide 15		
Slide 16		
Slide 17		

Slide 18	## Conclusion • Gentamicin, amikacin and vancomycin can be described with the same PK model with drug specific parameters. • Creatinine production rate from premature neonates up to young adults can be calculated using fat free mass and post-menstrual age. It can be used predict apparent CLcr. • Renal function declines with continued treatment with gentamicin, amikacin or vancomycin. ©NHG Helford, 2017, all rights reserved.	