Scaling pharmacodynamics in children: Lessons from immunology, infectious diseases and critical care

Joe Standing

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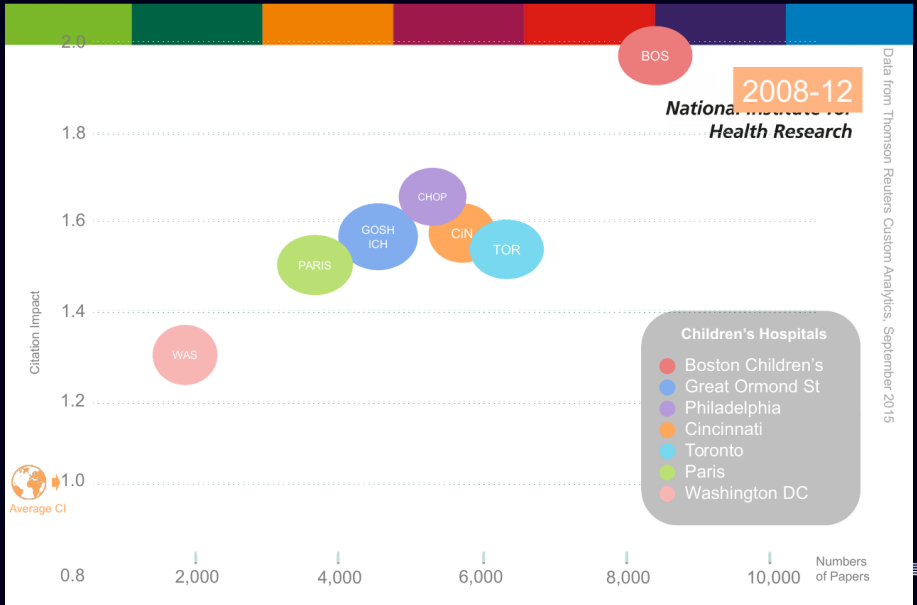
Antimicrobial Pharmacist: Great Ormond Street Hospital for Children
Honorary Senior Lecturer: St George's University of London

7/6/17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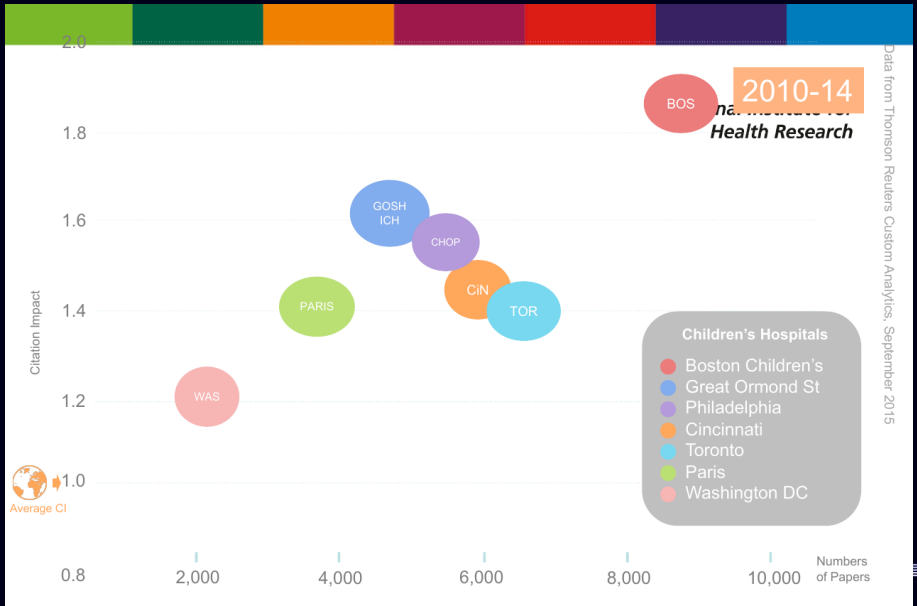
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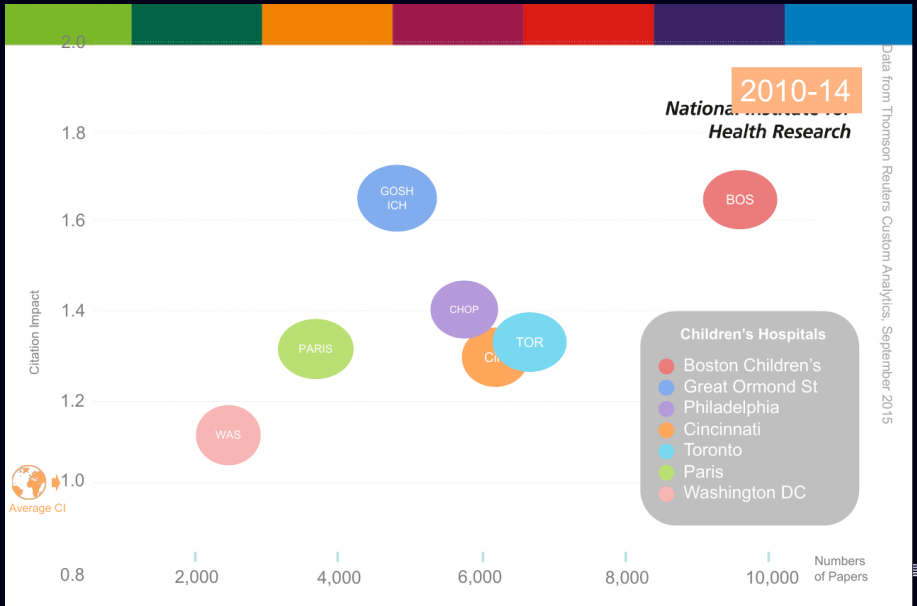
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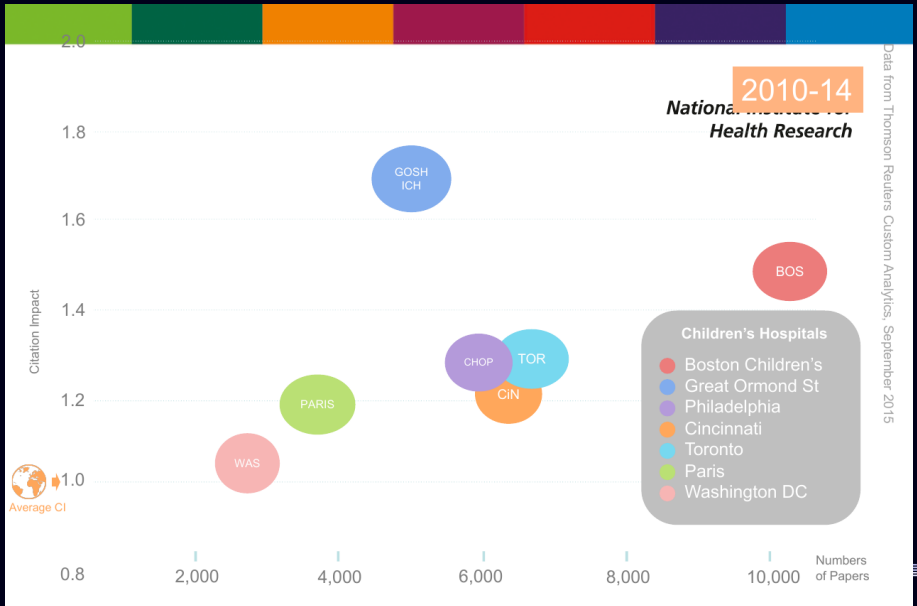
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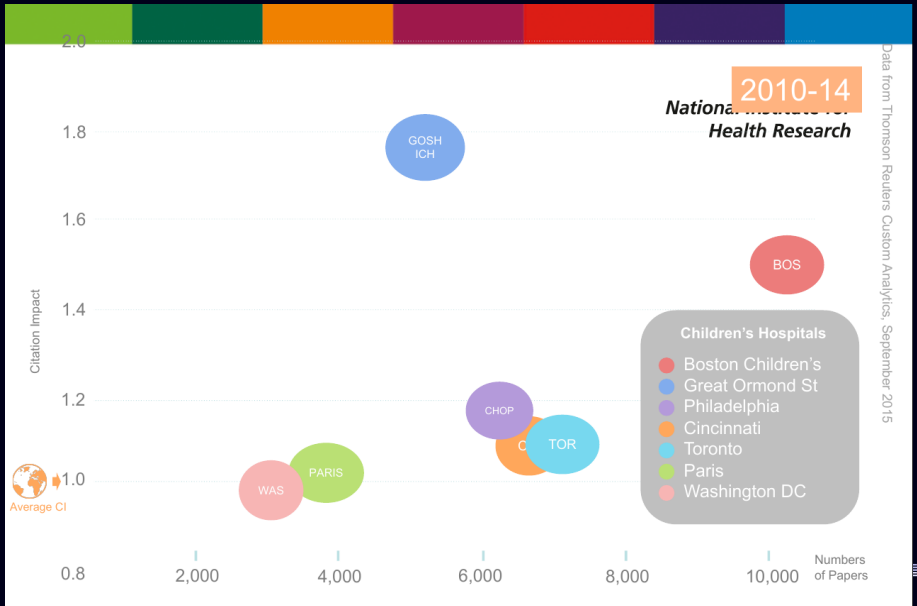
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Data for today:

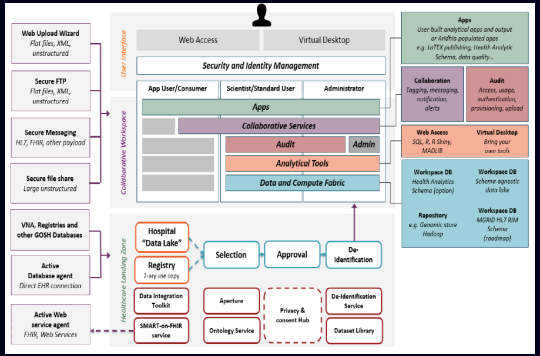
Prospective clinical trials, e.g.:

- NeoMero
- Treosulfan PKPD myeloablative stem cell transplant conditioning
- Dexmedetomidine sedation
- (PENTA network HIV studies)

Retrospective cohort studies (prospective evaluation sometimes):

- From the GOSH "**data lake**"

Great Ormond Street Hospital (GOSH) data lake:



e.g. current projects:

- B-cell suppression with rituximab in rheumatology
- Immune reconstitution post stem-cell transplant
- Antimicrobial PKPD studies

Definition 1

Scaling pharmacodynamics in **children**

- pre-term neonate (born before 37 weeks)
- neonate (age $<$ 1 month)
- infant (age 1 month to $<$ 2 years)
- child (age $\geq$ 2 to $<$ 12 years)
- adolescent (age $\geq$ 12 to $<$ 18 years)
- adult (age $\geq$ 18 years)

gestational age + post natal age = post menstrual age

Definition 2

Scaling **pharmacodynamics** in children

- measured response to drug, and how evolves with time
- pharmacokinetics drives pharmacodynamics

General question:

- How to choose the PK endpoint $C(t)$, C_{max}, C_{min}, AUC?
- What is the pharmacological rationale?

Definition 3

Scaling pharmacodynamics in children

- i.e. can we predict PD in children knowing adult PD?

What do paediatricians say?

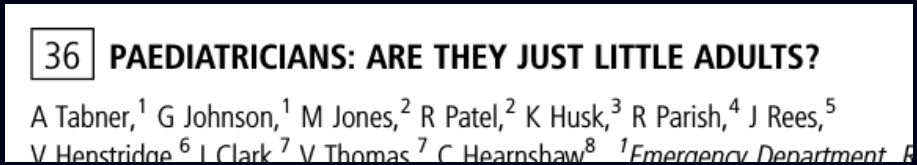
- Children are not small adults

What do we say?

- Agree (since Child $\notin$ Adult - see Definition 1 slide)

Definition 3

Aside: Turns out paediatricians *are* small adults (Tabner 2016):



36 **PAEDIATRICIANS: ARE THEY JUST LITTLE ADULTS?**

A Tabner,[1] G Johnson,[1] M Jones,[2] R Patel,[2] K Husk,[3] R Parish,[4] J Rees,[5]
V Henstridge [6] L Clark [7] V Thomas [7] C Hearnshaw[8] [1]*Emergency Department*

Does repeating "children are not small adults" get us anywhere?

History lesson: Scaling PK

Regulatory changes $\rightarrow \uparrow$ PK studies from early 2000s

QUIZ

- Who first suggested CL may not scale per kg?

Clue 1:

- Surname ends in "_ _ _ _ ford"

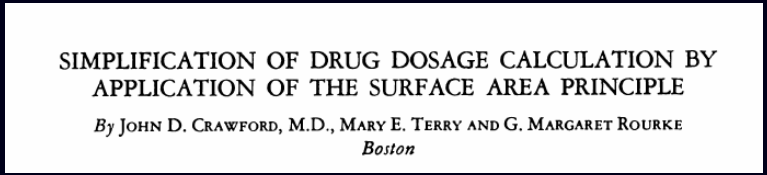
Clue 2:

- Suggested link with allometric metabolic rate scaling

History lesson: Scaling PK

ANSWER:

- Crawford Pediatrics 1950:



SIMPLIFICATION OF DRUG DOSAGE CALCULATION BY APPLICATION OF THE SURFACE AREA PRINCIPLE

By JOHN D. CRAWFORD, M.D., MARY E. TERRY AND G. MARGARET ROURKE
Boston

Is “Crawford” the 1950 pseudonym for a small adult named “Holford”?

Lamivudine, Burger 2007

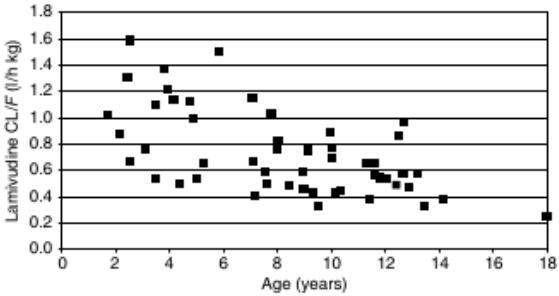


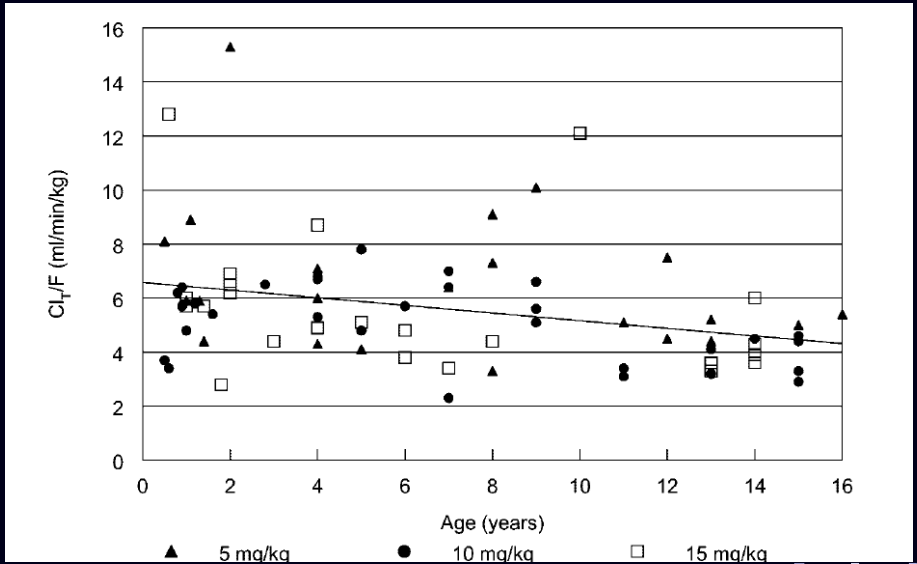
Figure 1 Association of lamivudine body weight corrected CL/F and age.

- 4 year old CL $\approx$ 1 L/h/kg
- 12 year old CL $\approx$ 0.5 L/h/kg
- These PK studies changed ART dosing, why???

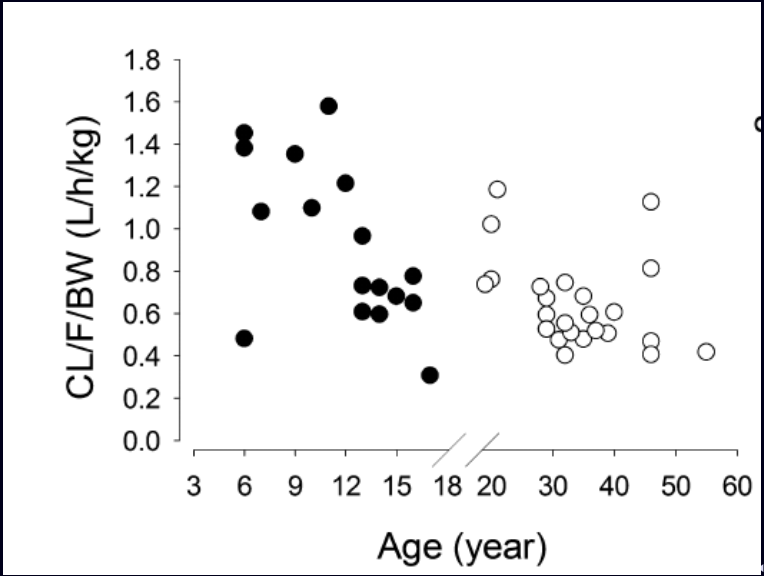
Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study

Esse N Menson, A Sarah Walker, Mike Sharland, Carole Wells, Gareth Tudor-Williams, F Andrew I Riordan, E G Hermione Lyall, Diana M Gibb, for the collaborative HIV paediatric study steering committee

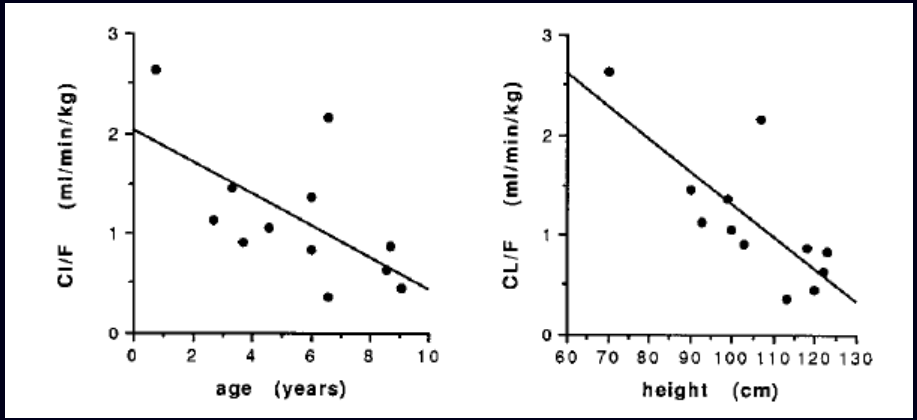
Gatifloxacin, Caparelli 2005



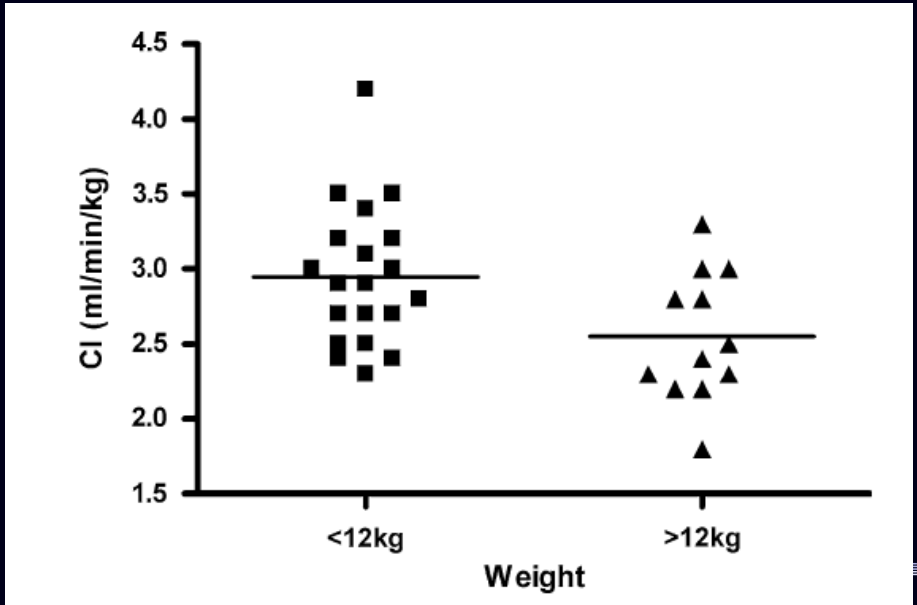
Hydrocodone, Liu 2015



Dapsone, Gatti 1995



Carboplatin, Veal 2010



Busulfan, Tran 2004

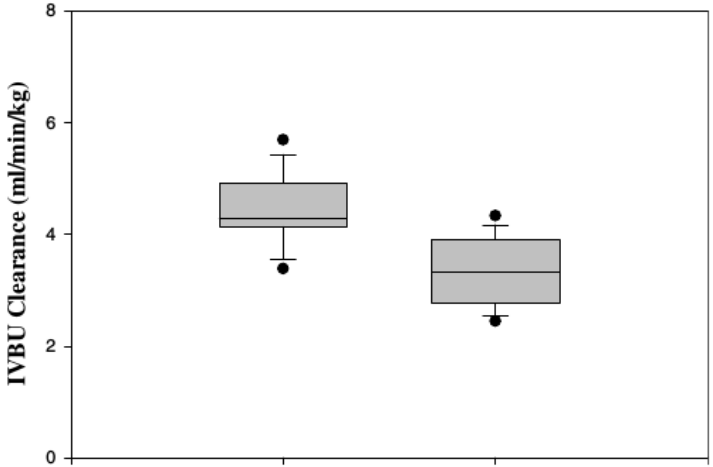
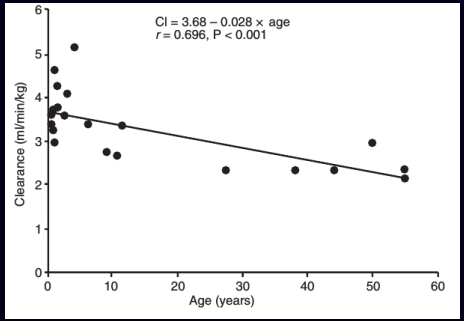
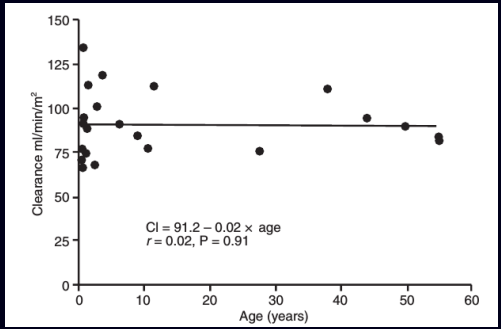


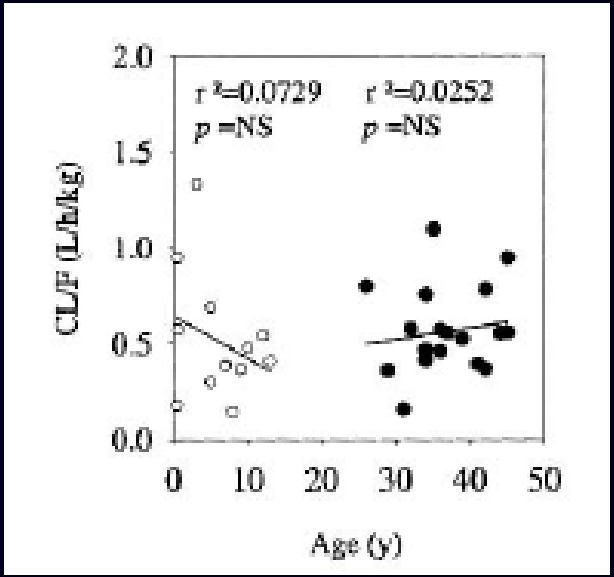
Figure 1. IBVU clearance by age group. Comparison of final clear-

Busulfan, Hassan 2002

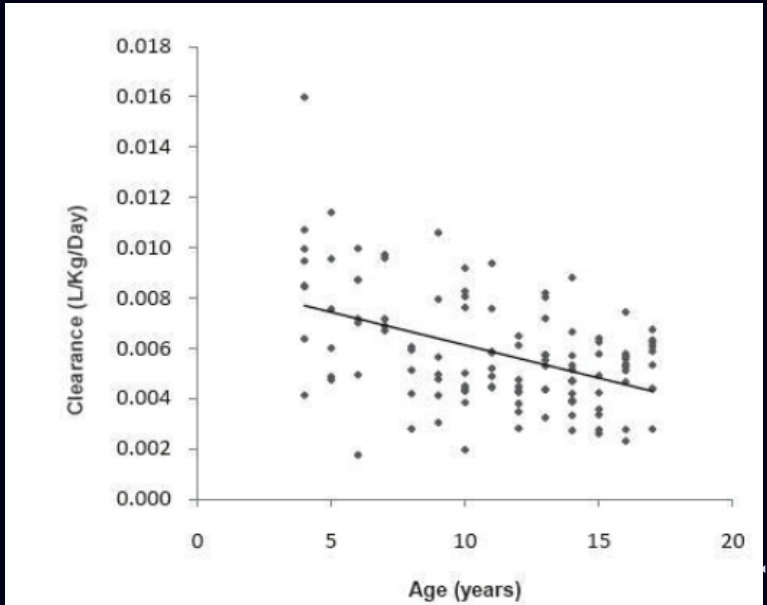




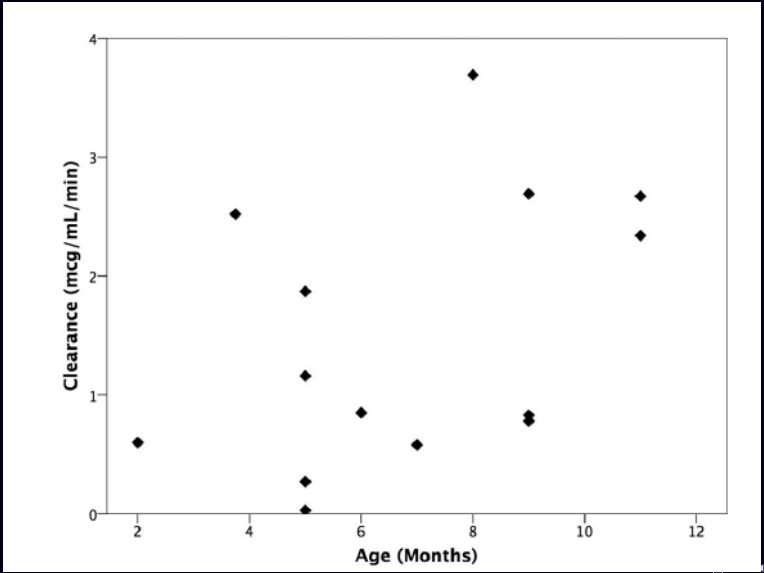
Omeprazole, Marier 2004



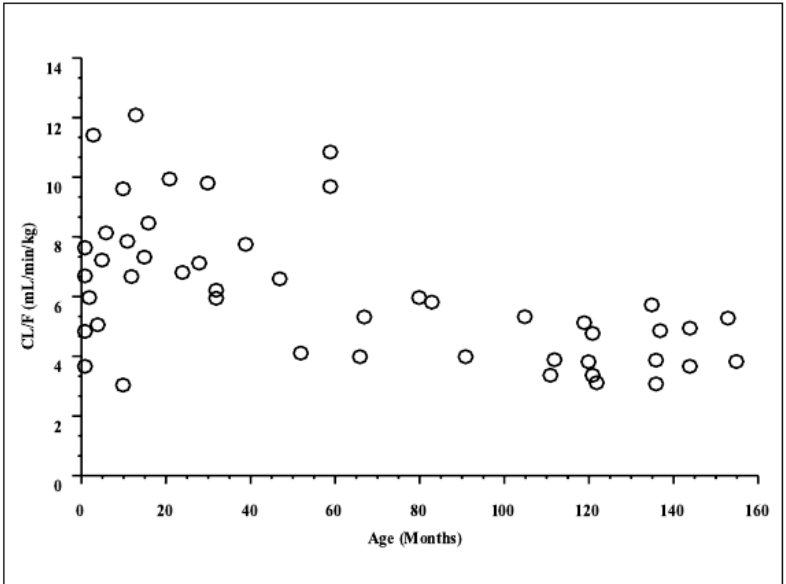
Infliximab, Goldman 2012



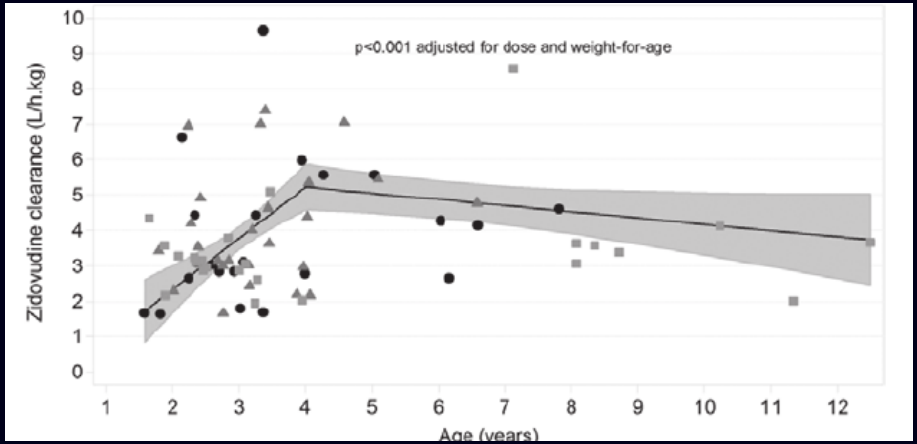
Ketorolac, Cohen 2011



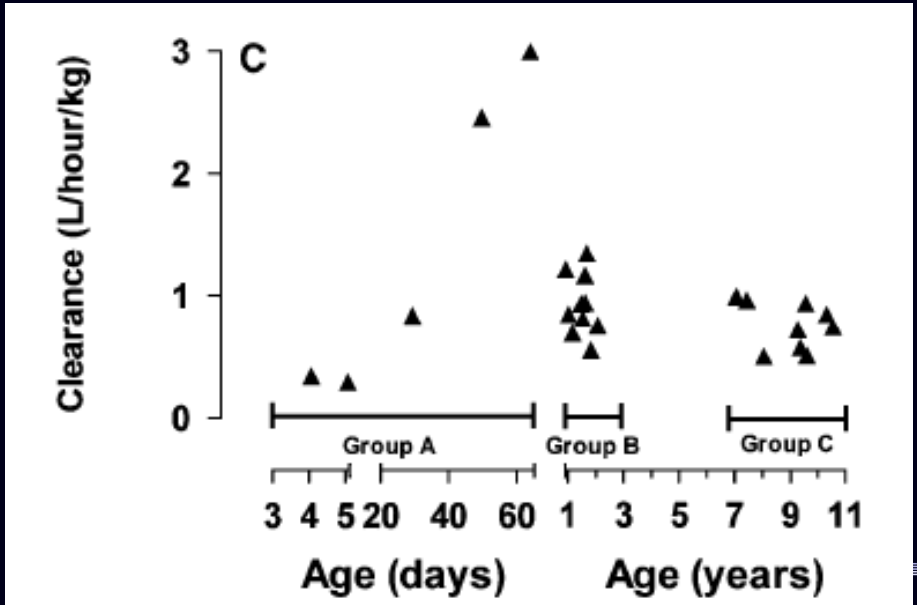
Gabapentin, Haig 2001



Zidovudine, Fillekes 2014



Ketobemidone, Lundeberg 2009



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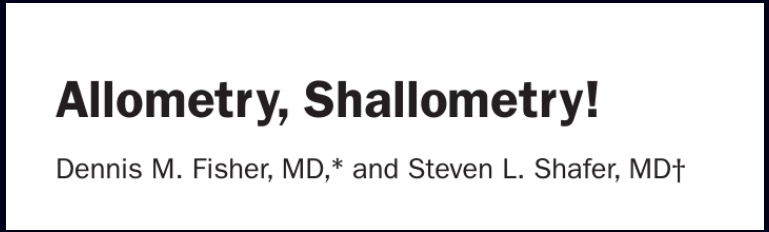
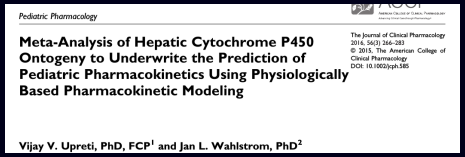


We have biological prior information ...

CL scaling

Biological "priors" on PK scaling:

- liver size scales with weight$^{0.78}$ (Johnson 2005)
- glomerular filtration scales with weight$^{0.63}$ (Rhodin 2009)
- understanding maturation: e.g. Upreti 2016 shows how; Calvier 2017 explores why (with PBPK):



Pediatric Pharmacology

Meta-Analysis of Hepatic Cytochrome P450 Ontogeny to Underwrite the Prediction of Pediatric Pharmacokinetics Using Physiologically Based Pharmacokinetic Modeling

Vijay V. Upreti, PhD, FCP[1] and Jan L. Wahlstrom, PhD[2]

The Journal of Clinical Pharmacology 2016, 56(3) 266-283

DOI: 10.1002/jcph.585

Clin Pharmacokinet (2017) 56:273–285
DOI 10.1007/s40262-016-0436-x

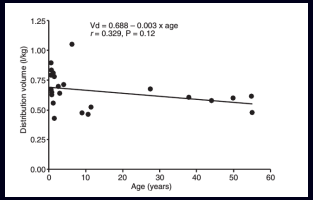
ORIGINAL RESEARCH ARTICLE

Allometric Scaling of Clearance in Paediatric Patients: When Does the Magic of 0.75 Fade?

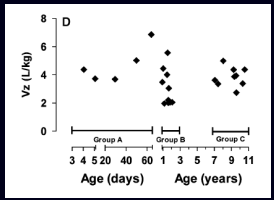
Elisa A. M. Calvier[1] · Elke H. J. Krekels[1] · Pyry A. J. Välitalo[1] · Amin Rostami-Hodjegan[2] · Dick Tibboel[3] · Meindert Danhof[1] · Catherijne A. J. Knibbe[1,4]

Volume (generally) linear (Price 2003)

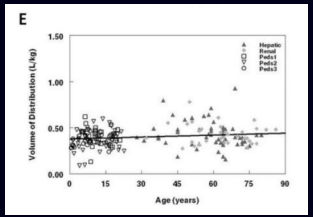
Busulfan, Hassan 2002



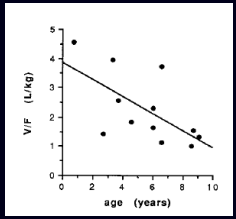
Ketobemidone, Lundeberg 2009



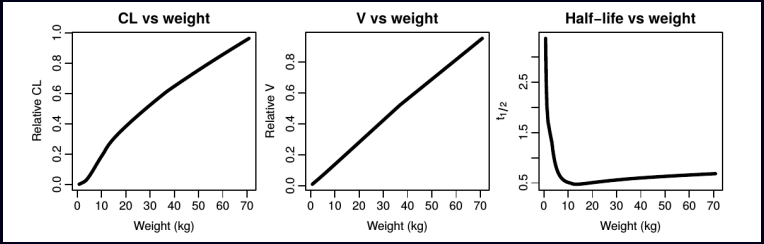
Oxaliplatin, Nikanjam 2015



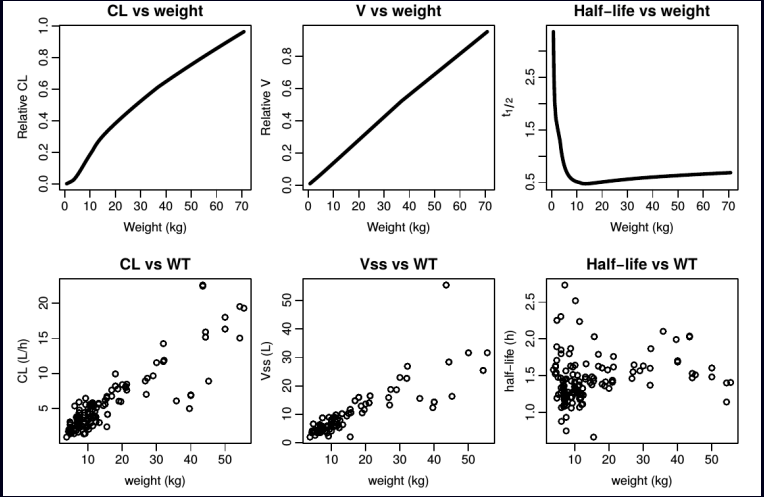
Dapsone, Gatti 1995 (not always)



PK scaling theory



PK scaling reality (treosulfan)



What about pharmacodynamics?

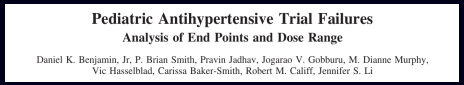
- PD endpoints heterogeneous and lack of standards for a valid/reliable
- Crisis in paediatric drug development: e.g. 42% failure rate in 1998-2012


Impact of Pediatric Exclusivity on Drug Labeling and Demonstrations of Efficacy

WHAT'S KNOWN ON THIS SUBJECT: Most therapeutic products used in children have not been studied in that population. There is a need for special incentives and market protection (pediatric exclusivity) to compromise drug exposure for studying these

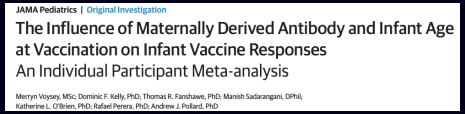
AUTHORS: Gerold T. Wharton, MS,[a] M. Dianne Murphy, MD,[a] Debbie Avant, RPh,[a] John V. Goldsmith, PhD,[a] Grace Chai, PharmD, LCDR, USPHS,[a] William J. Rodriguez, MD, PhD,[a] and Eric L. Eisenstein, DBA[a]

- Matching PK exposure does fail: e.g. 50% of anti-hypertensive trials


Pediatric Antihypertensive Trial Failures
Analysis of End Points and Dose Range

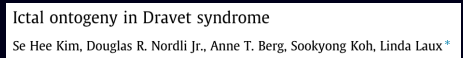
Daniel K. Benjamin, Jr, P. Brian Smith, Pravin Jadhav, Jogarao V. Gobburu, M. Dianne Murphy, Vic Hasselblad, Carissa Baker-Smith, Robert M. Califf, Jennifer S. Li

- Plenty of biological/clinical priors e.g. Vaccines, epilepsy:


JAMA Pediatrics | Original Investigation

The Influence of Maternally Derived Antibody and Infant Age at Vaccination on Infant Vaccine Responses
An Individual Participant Meta-analysis

Merryn Voysey, MSc; Dominic F. Kelly, PhD; Thomas R. Fanshawe, PhD; Manish Sadarangani, DPhil; Katherine L. O'Brien, PhD; Rafael Perera, PhD; Andrew J. Pollard, PhD


Ictal ontogeny in Dravet syndrome

Se Hee Kim, Douglas R. Nordli Jr., Anne T. Berg, Sookyong Koh, Linda Laux *

Epilepsy Center, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg

Overview

Pharmacodynamic scaling in children:

- Introduction
- Lessons from anaesthesia/analgesia
- Lessons from immunology
- Lessons from infectious diseases
- Conclusions

PD scaling of morphine in post-operative pain

Definition:

- "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Biological prior:

- Possible down regulation of μ-opioid receptor in neonates (rat data)


EXPERT REVIEW OF CLINICAL PHARMACOLOGY, 2017
VOL. 10, NO. 1, 111–126
http://dx.doi.org/10.1080/17512433.2017.1254040

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REVIEW

OPEN ACCESS

Paracetamol and morphine for infant and neonatal pain; still a long way to go?

Manuel A. Baarslag[a], Karel Allegaert[a,b], John N. Van Den Anker[a,c,d], Catherijne A.J. Knibbe[e,f], Monique Van Dijk[a,g], Sinno H.P. Simons[g] and Dick Tibboel[a]

Scaling question:

- Do neonates need lower than expected morphine doses?

PD scaling of morphine in post-operative pain

Hypothesis:

- Morphine dosing will follow PK maturation/allometric scaling

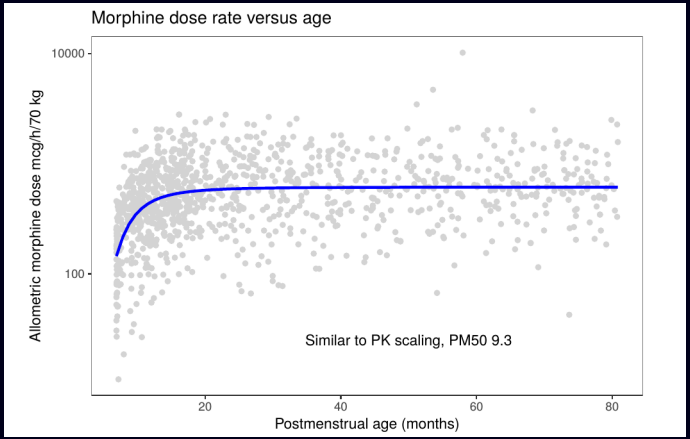
Data:

- GOSH pain registry (1996–), $>$ 35000 episodes, prospective data capture (iPads)
- Choose $<$ 6 year olds, on morphine infusion and paracetamol only, hourly morphine dose sum of background rate and boluses

Methods:

- PK model: as $t \to \infty$, $C(t) = \frac{r}{CL}$, where r is the dose rate
- if analgesic effect $\propto C(t)$ then $r \propto CL$
- for 2–6 year olds fitting $\log(r) = \beta \log(wt) + \alpha$, $\hat{\beta} = 0.79$ i.e. follows allometry
- Now fit: $r \left(\frac{70}{wt}\right)^{0.75} = R \frac{pma^{\gamma}}{pma^{\gamma} + PM_{50}^{\gamma}}$, where R is mature rate, PM_{50}, value of half mature post menstrual age:

PD scaling of morphine in post-operative pain



Blue: data fit

Similar to PK maturation Anderson 2011

PD scaling of dexmedetomidine sedation

Measuring sedation:

- Algorithms for EEG interpretation inappropriate in neonates/infants?

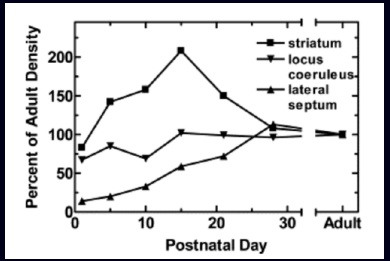
Effect of age on the performance of bispectral and entropy indices during sevoflurane pediatric anesthesia: a pharmacometric study

Alberto Sciusco[1], Joseph F. Standing[2], Yucheng Sheng[3], Pasquale Raimondo[1], Gilda Cinnella[1] & Michele Dambrosio[1]

The impact of age on bispectral index values and EEG bispectrum during anaesthesia with desflurane and halothane in children

O. Tirel[1,3], E. Wodey[1,3]*, R. Harris[4], J. Y. Bansard[2], C. Ecoffey[1] and L. Senhadji[2]

Biological prior: location of α_2 determines excitatory or inhibitory effect:



Scaling question:

- Since dexmedetomidine's sedative effects are largely agonism in the locus coeruleus expect no age scaling

PD scaling of dexmedetomidine sedation

Hypothesis:

- Dexmedetomidine PD will scale with known PK maturation/allometric scaling

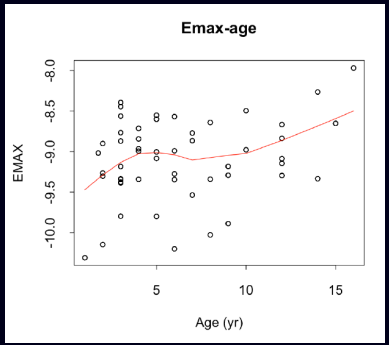
Data:

- Prospective clinical study of dexmedetomidine for MRI sedation
- 53 patients, 428 sedation measurements (1-5 scale)
- Ordered categorical model with first-order Markov

Method:

- Look at whether/how E_{max} scales with age

PD scaling of dexmedetomidine sedation



- weak age effect, but not seen in:

High dose dexmedetomidine as the sole sedative for pediatric MRI

KEIRA P. MASON MD*†, DAVID ZURAKOWSKI PhD*†, STEVEN E. ZGLESZEWSKI MD*, CAROLINE D. ROBSON MB, ChB†, MAUREEN CARRIER RN, BSN†, PAUL R. HICKEY

Haematopoiesis

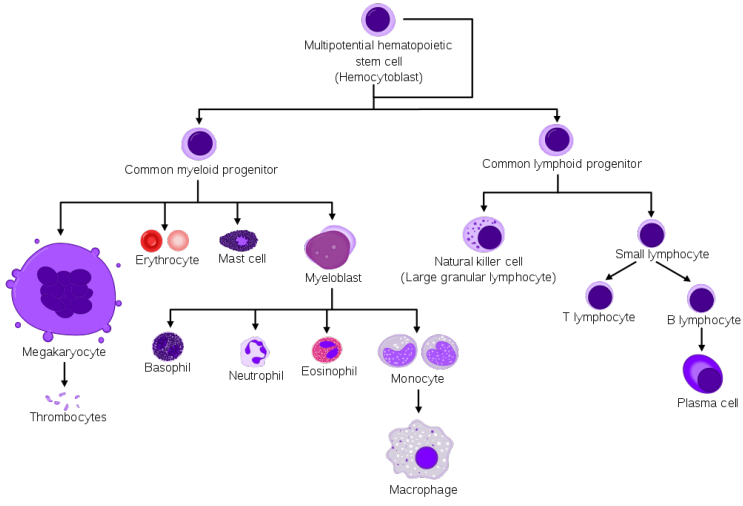


Figure created by Haggstrom, wikipedia

PD scaling of myeloablation

Biomarker:

- Very clear, measured in routine full blood count

Biological prior:

- Normal neutrophil counts do not radically change with age
- Allometric principles suggest dynamics faster in smaller individuals

Scaling question:

- Does drug-induced myeloablation require age scaling?

PD scaling of myeloablation

Hypothesis:

- Drug-induced myeloablation in haematopoietic stem cell transplant (HSCT) does not change with age

Data:

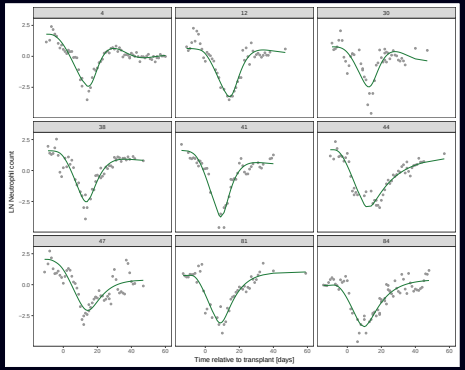
- Prospective Phase II study of treosulfan conditioning
- 84 patients, $\geq$ 6 months follow-up
- Treosulfan PK, daily full blood counts, long-term engraftment measures in myeloid cells

Method:

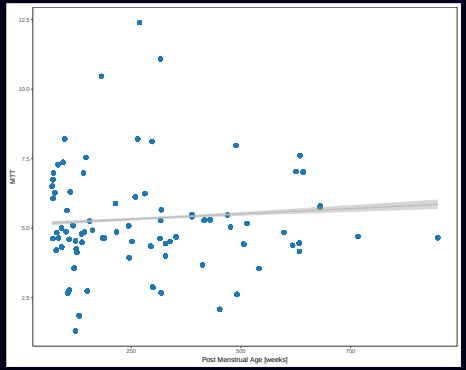
- Use Friberg model for short-term reconstitution
- Age as covariate on myeloid engraftment

PD scaling of myeloablation

Friberg model fits:



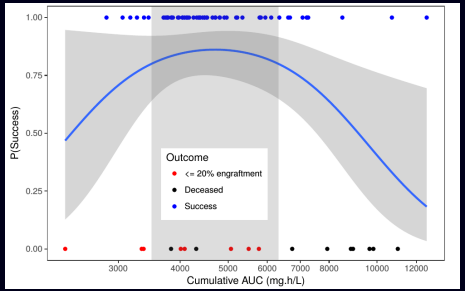
Mean transit time *versus* age



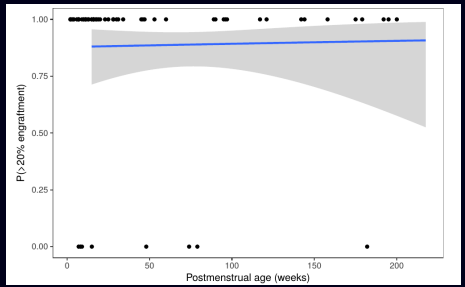
Dynamics slightly faster in smaller individuals, set point similar

PD scaling of myeloablation

- Poor engraftment significantly related with low AUC, death with high AUC:



- P(successful engraftment) *versus* age



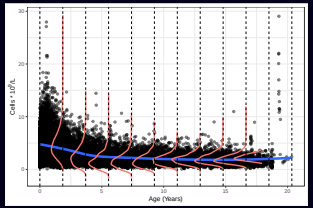
PD scaling of CD4 reconstitution post HSCT

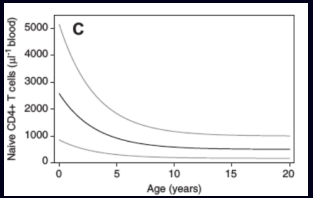
Data:

- 288 HSCT recipients with prospective validation in further 75

Biological prior:

- Normal lymphocyte and CD4 counts ↑ with ↓ age





CD4(t) = thymic out + proliferation − loss

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \lambda + pX - dX \quad (1)$$

- This worries some:

5 years. Monitoring by CD4 cell count in younger children is problematical because age is a highly influential variable.

AIDS 2006, **20**:1289–1294

Scaling question:

- How to incorporate age scaling *a priori*?

PD scaling of CD4 reconstitution post HSCT

Scaling proliferation and loss:

- Ki67 is a marker for proliferation found on CD4 T cells
- Bains 2009 found an exponential decline with age but why not size?

Theoretical Article

Some Scaling Principles for the Immune System

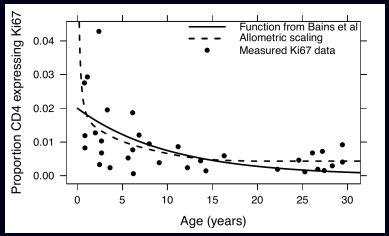
FREDERIK W WIEGEL[1] and ALAN S PERELSON[2]

Scaling aspects of lymphocyte trafficking

Alan S. Perelson[a,*], Frederik W. Wiegel[b]

[a] Theoretical Division, Los Alamos National Laboratory, Los Alamos, NM 87545, USA
[b] Institute of Theoretical Physics, University of Amsterdam, Valckenierstraat 65, 1018XE, Amsterdam, The Netherlands

- Allometric model $y(wt) = 0.0127 * \frac{(wt/70)^{-0.25}}{log(wt) - 1.155}$, gives:



PD scaling of CD4 reconstitution post HSCT

Scaling thymic output:

- Thymus stops growing at 1 year, then epithelial space decreases by 70% by 20 years
- T cell receptor excision circles (TRECs) are a marker of cells released by thymus, progressively lost by division
- An expression for TREC changes with age derived by Bains et al 2009:

$$\lambda(\tau) = \frac{y(\tau)N(\tau)\gamma}{\Delta(c-\gamma)}, \tag{2}$$

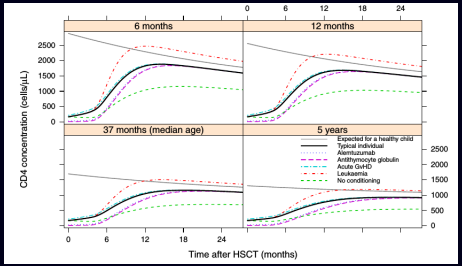
where $\lambda(\tau)$ is number of cells exported from the thymus per day for a person aged τ, Δ, c and γ are constants, $N(\tau)$ is the total number of CD4 cells for a person age τ, and $y(\tau)$ is the proportion of cells expressing Ki67 at age τ.

PD scaling of CD4 reconstitution post HSCT

- Age (size) delineated for multivariable analysis:

Predicting CD4 T-Cell Reconstitution Following Pediatric Hematopoietic Stem Cell Transplantation

RL Hoare[1,2], P Vey[3,4], N Klein[4,5], R Callard[1,2] and JF Standing[1,2,3]



- Extended to HIV (presented at WCoP 2016)
- Lymphocyte scaling used for CMV: I-17 [Ben Margetts] Modelling Cytomegalovirus Growth Kinetics in Immunocompromised Children

Overview

Pharmacodynamic scaling in children:

- Introduction
- Lessons from anaesthesia/analgesia
- Lessons from immunology
- Lessons from infectious diseases
- Conclusions

PD scaling of meropenem in neonatal sepsis

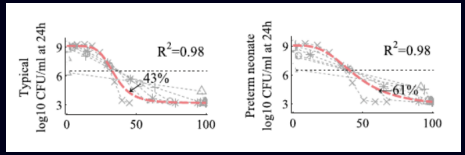
Clinical response in antibiotic trials:

- Often no known source of infection, but resistance rates similar (Bielicki 2015)
- No standardisation of clinical endpoints

Biological prior:

- Neutrophil, macrophage and dentritic function impaired (Cuenca 2013)
- PKPD based on *in vitro* MIC often used: ft>MIC, AUC/MIC, C_{max}/MIC, changing PK profile shape may change most appropriate index (Nielsen 2011)
- Neonates need higher ft>MIC based on *in vitro* (Kristoffersson 2016)

Simulation setting	Benzylpenicillin				
	R^2			$fT_{>MIC}$	
	fC_{max}/MIC	fAUC/MIC	$fT_{>MIC}$	B_{stat} (%)	B_{cid} (%)
Default	0.54	0.84	0.93*	29	38
i *(a)* Reduced CL	0.73	0.94*	0.93	25	33
(b) PK neonate	0.86	0.98*	0.91	24	32



Scaling question:

- Can we rely on *in vitro* derived target?

PD scaling of meropenem in neonatal sepsis

Hypothesis:

- Attaining 61% ft>MIC is sufficient for successful outcome

Data:

- NeoMero 1: Multi centre neonatal sepsis RCT (136 in meropenem arm)
- Optimally designed PK sampling (3 samples or single trough)
- 21 with a Gram negative blood stream infection with MIC
- Treatment failure defined as:
  - modification of treatment
  - death

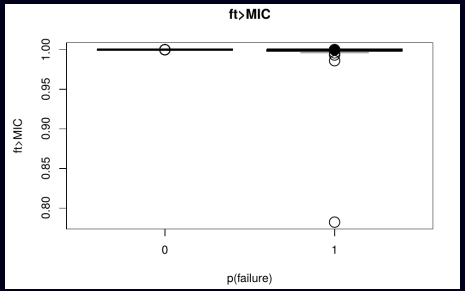
Method:

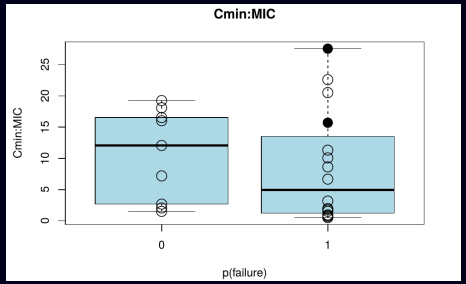
- Investigate ft>MIC *versus* outcome

PD scaling of meropenem in neonatal sepsis

Results:

- All had 61% ft>MIC, possible need for higher target (e.g. 100%>5xMIC as per Li 2007 in adult LRTI)





- For another antimicrobial example see: III-52 [Frank Kloprogge] Pharmacodynamics of vancomycin in children

Overview

Pharmacodynamic scaling in children:

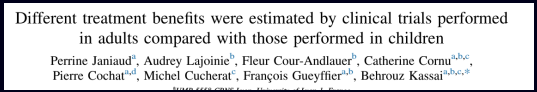
- Introduction
- Lessons from anaesthesia/analgesia
- Lessons from immunology
- Lessons from infectious diseases
- Conclusions

Lessons

- PK-only scaling may/may not be appropriate
- Biological priors useful for scaling (esp. adaptive immune system)
- Antimicrobial *in vitro* targets require further clinical evaluation/scaling

Final thought:

- PD scaling important, but (PK)PD only extrapolation still draws scepticism


Different treatment benefits were estimated by clinical trials performed in adults compared with those performed in children

Perrine Janiaud[a], Audrey Lajoinie[b], Fleur Cour-Andlauer[b], Catherine Cornu[a,b,c], Pierre Cochat[a,d], Michel Cucherat[c], François Gueyffier[a,b], Behrouz Kassai[a,b,c,e]

- Appropriately scaled PKPD-guided small trial design (informing effect size, drug effect as parameter) maybe the future e.g. IDEAL, ASTERIX and INSPIRE consortia

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Main collaborators on work presented here: Robin Callard (UCL), Robert Chiesa (UCL/GOSH), Paul Veys (UCL/GOSH), Nigel Klein (UCL/GOSH), Grant Stuart (GOSH), Irja Lutsar (Tartu), Richard Howard (GOSH), Inaki Troconiz (Pamplona)

Student/Postdoc work presented here: Rollo Hoare, Aiwei Li, Matt Jay, Belen Perez Solans, Eva Germovsek (and see posters of Ben Margetts and Frank Kloprogge)

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London Pharmacometrics Interest Group
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