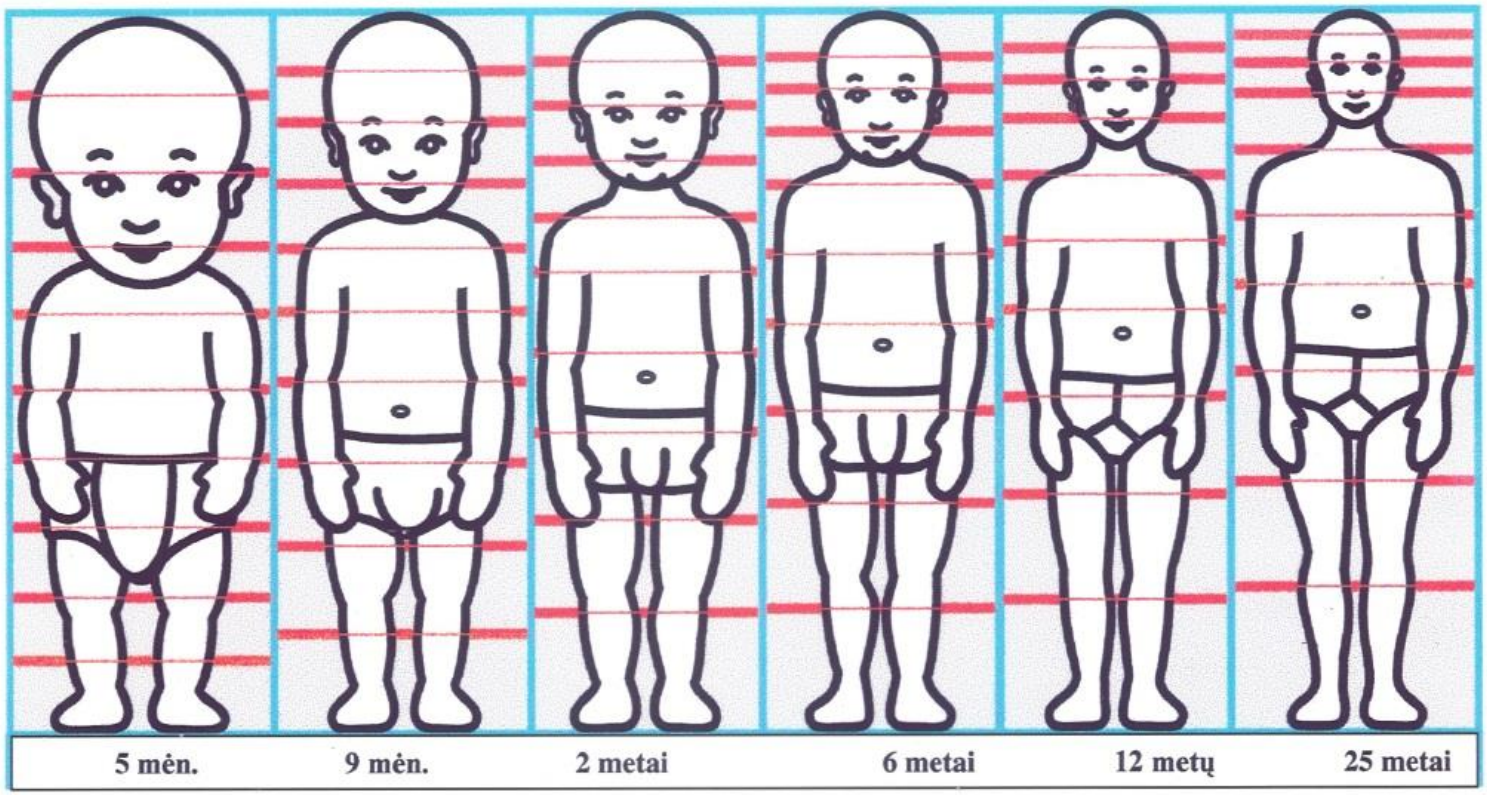
Paediatric clinical pharmacology

Prof. Dr. Jolanta Gulbinovič



Pav. Vaikas – tai ne suaugusio žmogaus maža kopija

Illness, disease, disorder

Treatment of children vs. adults

Safety and efficacy of medicines?

Clinical trials

Pharmaceutical formulation

Dosage

Duration of treatment

PEDIATRICS Vol. 104 No. 3 September 1999 583

Editorial Comment: Therapeutic Orphans

Harry Shirkey, MD

<...> However, many of the drugs released since 1962 carry an "orphaning" clause, eg, "Not to be used in children . . . is not recommended for use in infants and young children since few studies have been conducted in this age group... clinical studies have been insufficient to establish any recommendations for use in infants and children . . . should not be given to children."

Despite such clear cautions, many physicians have ignored the warnings and have prescribed the restricted drugs. It requires little imagination to wonder what a jury of laymen would decide after a defending physician admitted in court to the use of a drug despite such a clear warning.<...>

1. NAME OF THE MEDICINAL PRODUCT

Xydalba 500 mg powder for concentrate for solution for infusion

4.1 Therapeutic indications

Xydalba is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults (see sections 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Recommended dose and duration of treatment for adults

The recommended dose of dalbavancin in adult patients with ABSSSI is 1500 mg administered as either a single infusion of 1500 mg or as 1000 mg followed one week later by 500 mg (see sections 5.1 and 5.2).

Paediatric population

The safety and efficacy of dalbavancin in children aged from birth to < 18 years has not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

ARTICLE

Off-label Drug Use in Hospitalized Children

Samir S. Shah, MD; Matthew Hall, PhD; Denise M. Goodman, MD, MS; Pamela Feuer, MD; Vidya Sharma, MBBS, MPH; Crayton Fargason, Jr, MD; Daniel Hyman, MD, MMM; Kathy Jenkins, MD, MPH; Marjorie L. White, MD; Fiona H. Levy, MD; James E. Levin, MD, PhD; David Bertoch, MHA; Anthony D. Slonim, MD, DrPH

Objectives: To describe the magnitude of off-label drug use, to identify drugs most commonly used off-label, and to identify factors associated with off-label drug use in children hospitalized in the United States.

Design: Retrospective cohort study.

Setting: Administrative database containing inpatient resource utilization data from January 1 to December 31, 2004, from 31 tertiary care pediatric hospitals in the United States.

Participants: Hospitalized patients 18 years or younger.

Main Exposures: Institution and patient characteristics.

Main Outcome Measures: Off-label drug use was defined as use of a specific drug in a patient younger than the Food and Drug Administration–approved age range for any indication of that drug.

Results: At least 1 drug was used off-label in 297 592 (78.7%) of 355 409 patients discharged during the study. Off-label use accounted for $270 275 849 (40.5%) of the total dollars spent on these medications. Medications classified as central or autonomic nervous system agents or as fluids or nutrients, or gastrointestinal tract agents were most commonly used off-label, whereas antineoplastic agents were rarely used off-label. Factors associated with off-label use in multivariate analysis were as follows: undergoing a surgical procedure, age older than 28 days, greater severity of illness, and all-cause in-hospital mortality.

Conclusions: Most patients hospitalized at tertiary care pediatric institutions receive at least 1 medication outside the terms of the Food and Drug Administration product license. Substantial variation in the frequency of off-label use was observed across diagnostic categories and drug classes. Despite the frequent off-label use of drugs, using an administrative database, we cannot determine which of these treatments are unsafe or ineffective and which treatments result in substantial benefit to the patient.

Arch Pediatr Adolesc Med. 2007;161:282-290

Table 1 Off-label categories

Off-label category	Description
Age	Drug not recommended in the SmPC below a certain age
Weight	Drug not recommended in the SmPC for children below a certain weight
Absence of pediatric information	No mention at all in the SmPC regarding pediatric use
Lack of pediatric clinical data	Stated lack of evidence of efficacy and safety in pediatric patients in the SmPC
Contraindication	Statement in the SmPC that the drug is contraindicated in children
Indication	Drug prescribed for indications outside of those listed in the SmPC
Route of administration	Drug administered by a route not described in the SmPC

SmPC, Summary of Product Characteristics.

I

(Acts whose publication is obligatory)

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 12 December 2006

on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission,

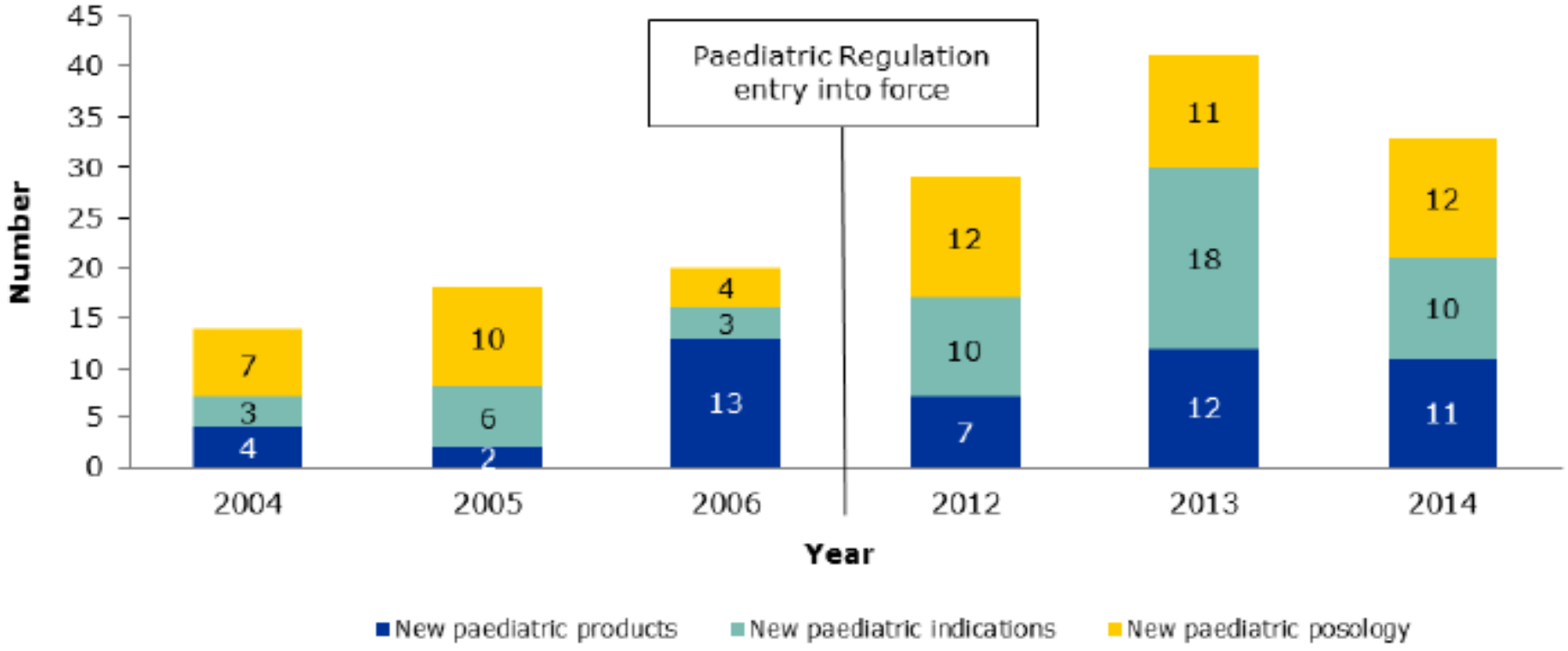
Having regard to the Opinion of the European Economic and Social Committee ([1]),

Having consulted the Committee of the Regions,

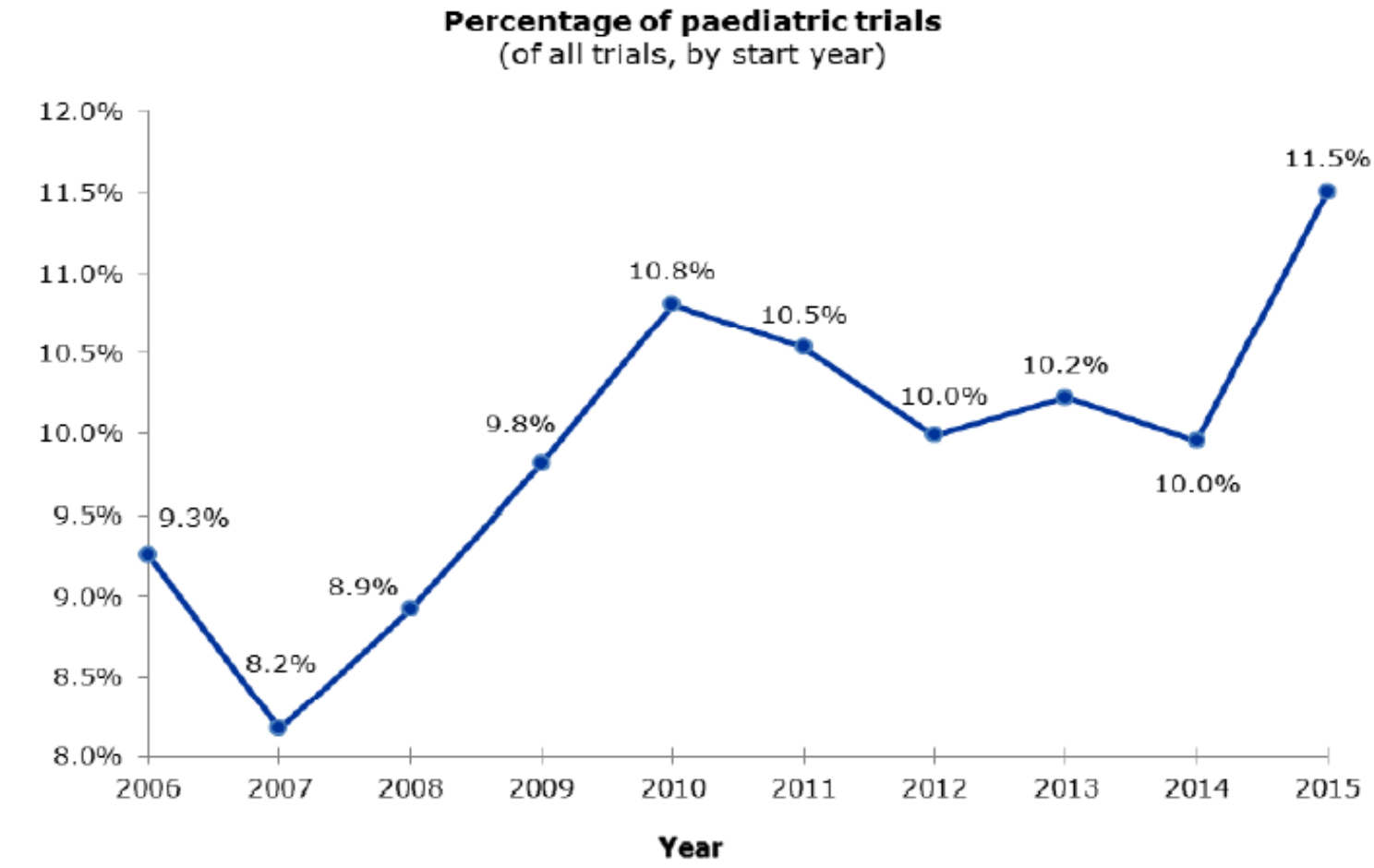
(4) This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations.

Number of new paediatric products, indications and posology

2004-2006 and 2012-2014



Source: EMA database (SIAMED)



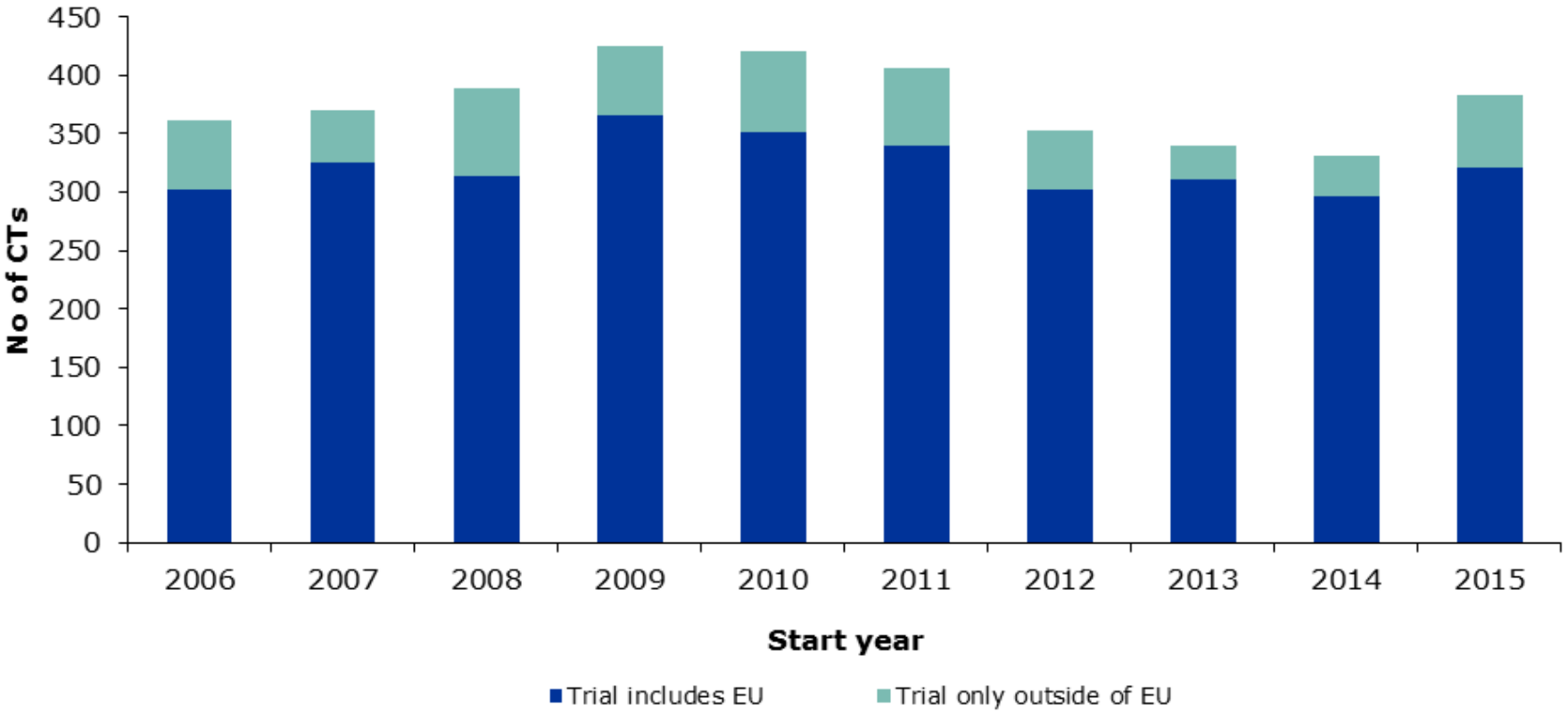
Note: A paediatric trial is a trial that includes at least one participant below 18 years of age.

Source: EudraCT database

Ref. Ares(2016)6395061 - 14/11/2016

Number of authorised paediatric clinical trials

(inside/outside of EU)



Ref. Ares(2016)6395061 - 14/11/2016

Is the problem solved?

- Doctors are still inevitably forced to prescribe children unauthorized medicines
- These drugs account for about 40% of all GPs prescriptions and up to 90% of appointments in hospitals
- This leads to suboptimal treatment, the risk of overdose in children, adverse reactions, and inadequate efficacy due to the potential for underdose
- In addition, the prescribing physician is left unconscious; it is difficult to find the right dose for children

van der Zanden TM, et al. Arch Dis Child 2017;102:357–361

- Preterm newborn, g.a. 32 weeks, 4 weeks; 1,7 kg
- Hospital infection
- Blood sample - *Pseudomonas aeruginosa,* susceptible to piperacillin and tazobactam

- Dosage regimen (SmPC)

Paediatric population (2–12 years)

Dosage regimen	Indication
piperacillin 80 mg /tazobactam 10 mg / kg body mass every 6 hours	Febrile neutropenia*.
piperacillin 100 mg /tazobactam 12,5 mg / kg body mass every 8 hours	Complicated intra-abdominal infection*.

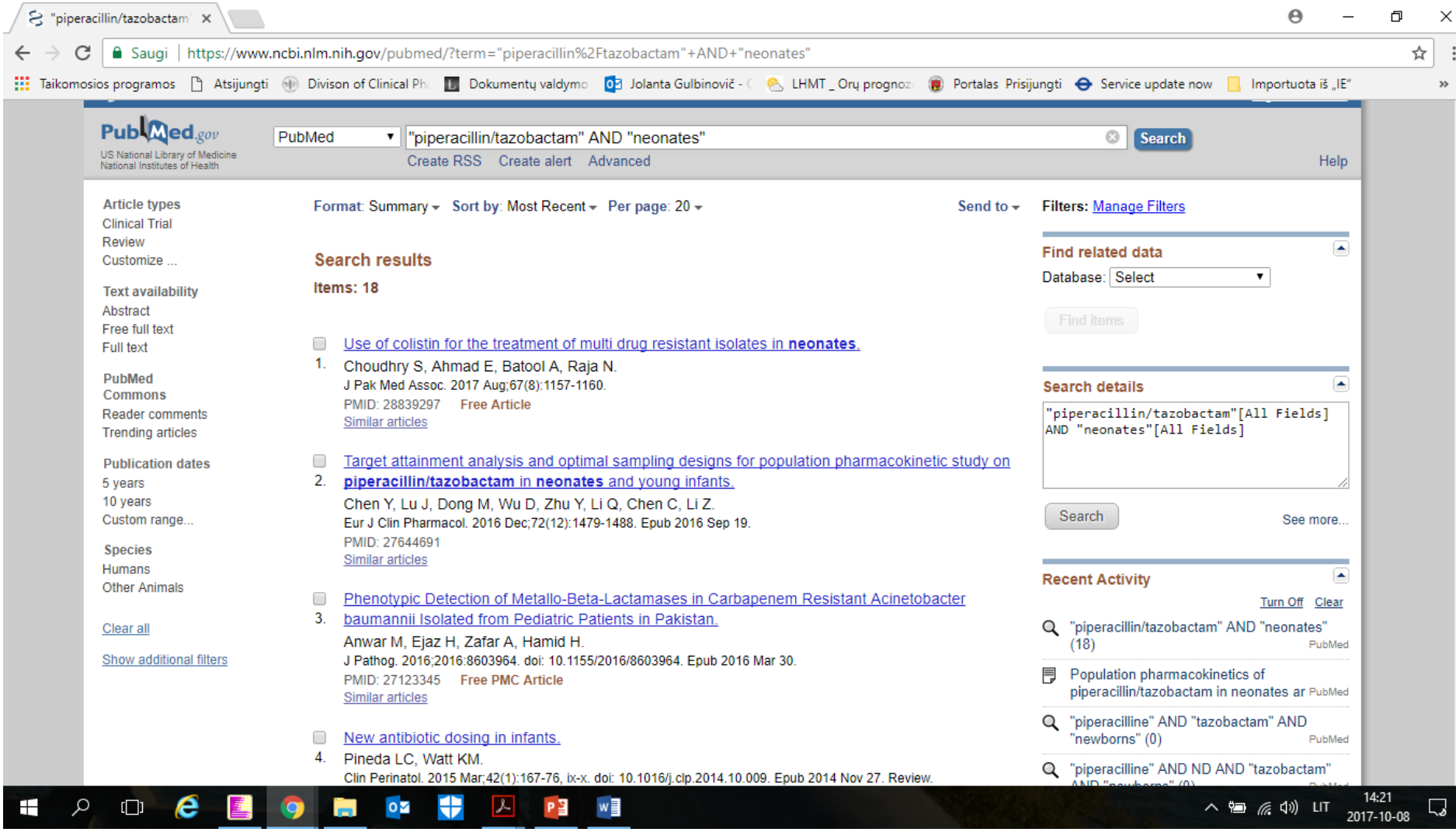
Dosage of medicines for children

Von Harnack table

Age	Part of adult dose
1 month	1/10
6 months	1/5
12 months	1/4
3 years	1/3
7 years	1/2
12 yeras	2/3

Dose factor (mg/kg)

Age in years	coefficient
0-1	1,8
1-6	1,6
6-10	1,4
10-14	1,2
Adult	1,0


"piperacillin/tazobactam"
Saugi
https://www.ncbi.nlm.nih.gov/pubmed/?term="piperacillin%2Ftazobactam"+AND+"neonates"
Taikomosios programos
Atsijungti
Divison of Clinical Ph
Dokumentų valdymo
Jolanta Gulbinovič -
LHMT _ Orų prognoz
Portalas Prisijungti
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Full text
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Trending articles
Publication dates
5 years
10 years
Custom range...
Species
Humans
Other Animals
Clear all
Show additional filters
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Filters: Manage Filters
Search results
Items: 18
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Choudhry S, Ahmad E, Batool A, Raja N.
J Pak Med Assoc. 2017 Aug;67(8):1157-1160.
PMID: 28839297 Free Article
Similar articles
2. Target attainment analysis and optimal sampling designs for population pharmacokinetic study on piperacillin/tazobactam in neonates and young infants.
Chen Y, Lu J, Dong M, Wu D, Zhu Y, Li Q, Chen C, Li Z.
Eur J Clin Pharmacol. 2016 Dec;72(12):1479-1488. Epub 2016 Sep 19.
PMID: 27644691
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3. Phenotypic Detection of Metallo-Beta-Lactamases in Carbapenem Resistant Acinetobacter baumannii Isolated from Pediatric Patients in Pakistan.
Anwar M, Ejaz H, Zafar A, Hamid H.
J Pathog. 2016;2016:8603964. doi: 10.1155/2016/8603964. Epub 2016 Mar 30.
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Pineda LC, Watt KM.
Clin Perinatol. 2015 Mar;42(1):167-76, ix-x. doi: 10.1016/j.clp.2014.10.009. Epub 2014 Nov 27. Review.
Find related data
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Find items
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Population pharmacokinetics of piperacillin/tazobactam in neonates ar PubMed
"piperacilline" AND "tazobactam" AND "newborns" (0) PubMed
"piperacilline" AND ND AND "tazobactam"
LIT
14:21
2017-10-08

Eur J Clin Pharmacol. 2013 Jun;69(6):1223-33. doi: 10.1007/s00228-012-1413-4. Epub 2013 Jan 26.

Population pharmacokinetics of piperacillin/tazobactam in neonates and young infants.

Li Z[1], Chen Y, Li Q, Cao D, Shi W, Cao Y, Wu D, Zhu Y, Wang Y, Chen C.

⊕ Author information

Abstract

OBJECTIVES: To develop population pharmacokinetic (PK) models for piperacillin/tazobactam in neonates and infants of less than 2 months of age in order to determine the appropriate dosing regimen and provide a rational basis for the development of preliminary dosing guidelines suitable for this population.

METHODS: A two-stage, open-label study was conducted in neonates and infants less than 2 months of age in the neonatal intensive care unit (NICU). A total of 207 piperacillin and 204 tazobactam concentration-time data sets from 71 patients were analyzed using a nonlinear mixed-effect modeling approach (NONMEM VII). PK models were developed for piperacillin and tazobactam. The final models were evaluated using both bootstrap and visual predictive checks. External model evaluations were made in 20 additional patients.

RESULTS: For neonates and young infants less than 2 months of age, the median central clearance was 0.133 and 0.149 L/h/kg for piperacillin and tazobactam, respectively. Postmenstrual age (PMA) was identified as the most significant covariate on central clearance of piperacillin and tazobactam. However, the combination of current bodyweight (BW) and postnatal age proved to be superior to PMA alone. BW was the most important covariate for apparent central volume of distribution. Both internal and external evaluations supported the prediction of the final piperacillin and tazobactam PK models. The dosing strategy 44.44/5.56 mg/kg/dose piperacillin/tazobactam every 8 or 12 h evaluated in this study achieved the pharmacodynamic target (free piperacillin concentrations >4 mg/L for more than 50 % of the dosing interval) in about 67 % of infants.

CONCLUSIONS: Population PK models accurately described the PK profiles of piperacillin/tazobactam in infants less than 2 months of age. The results indicated that higher doses or more frequent dosing regimens may be required for controlling infection in this population in NICU.

Paediatric drug formulary (the Netherlands)

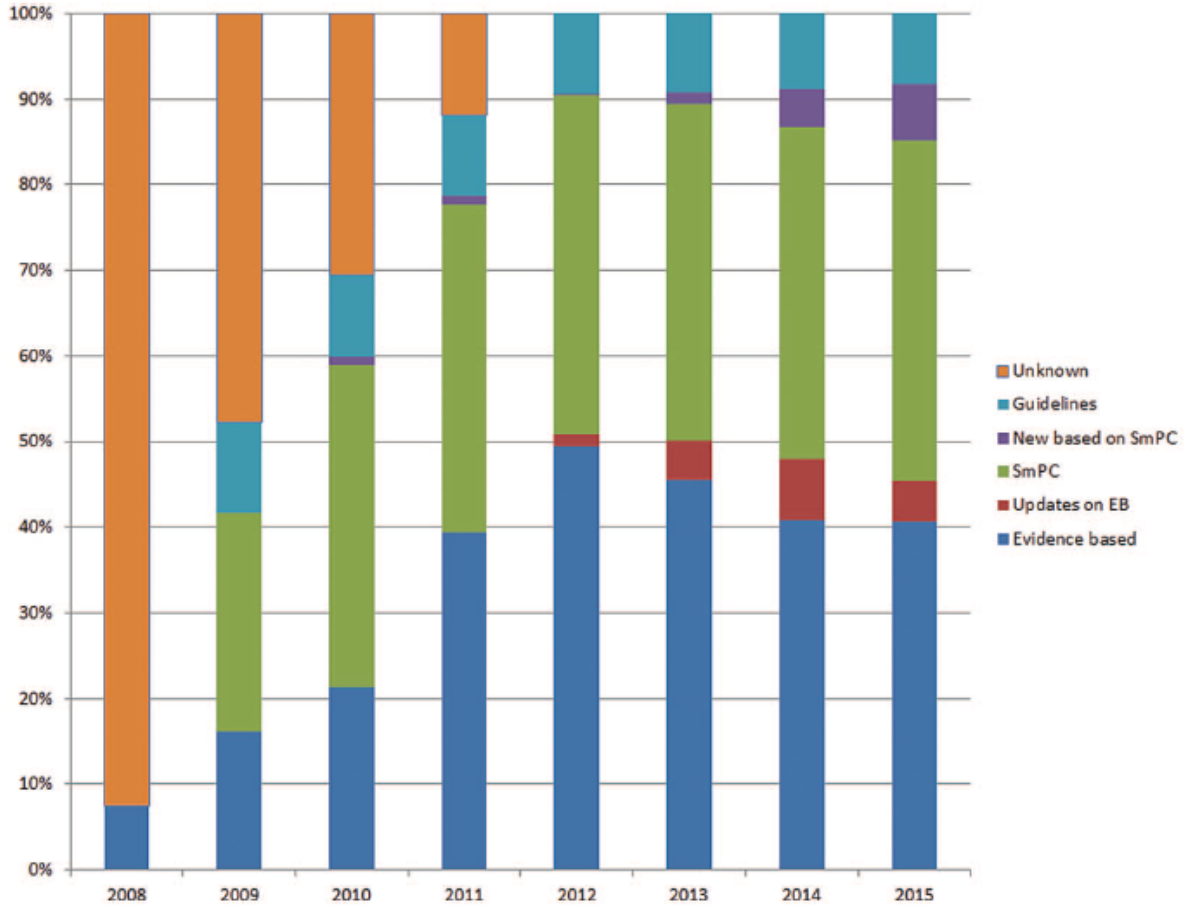


Figure 1 Improving the knowledge base. EB, evidence based; SmPC, Summary of Product Characteristics.

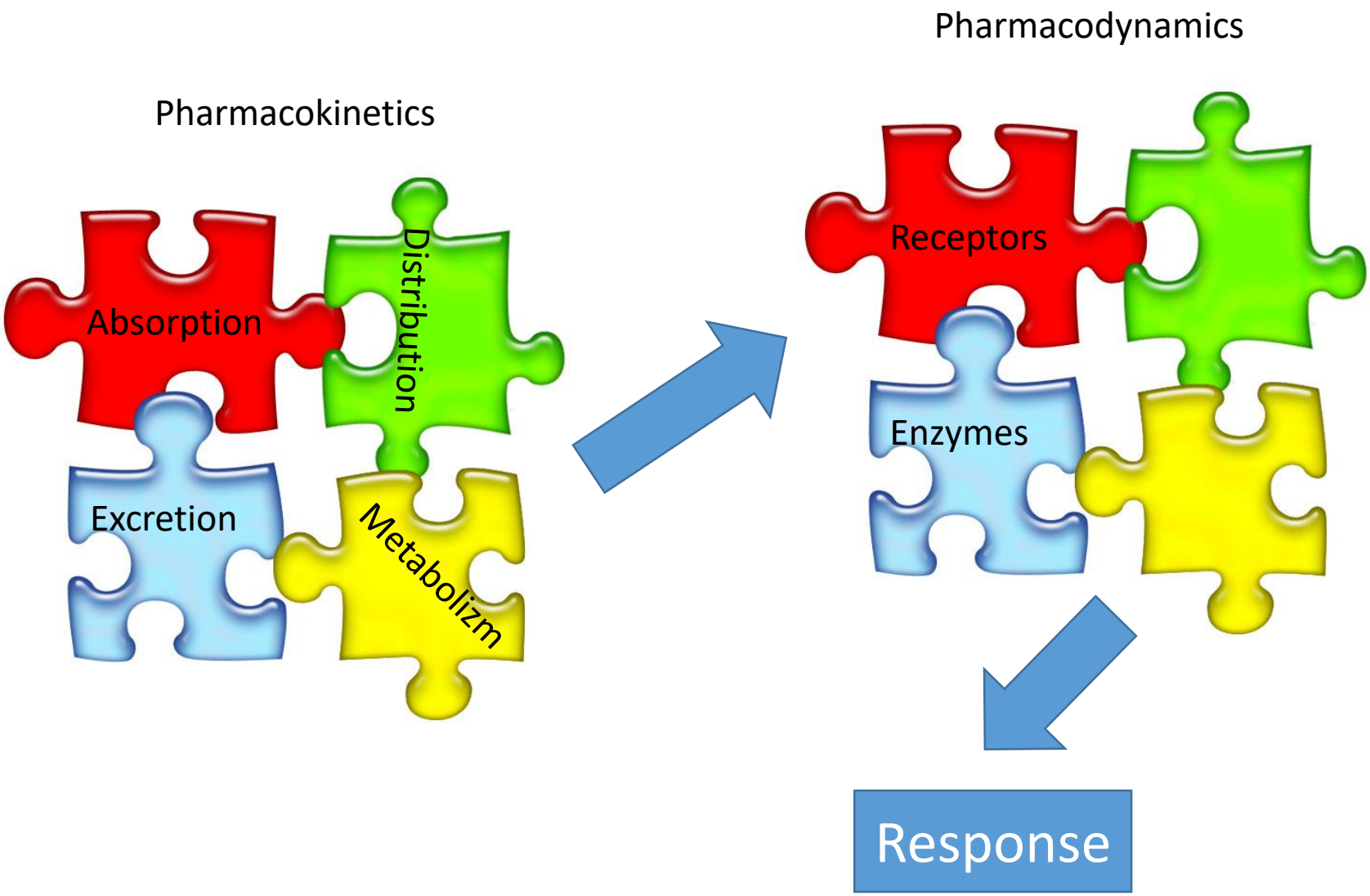
van der Zanden TM, et al. Arch Dis Child 2017;102:357–361

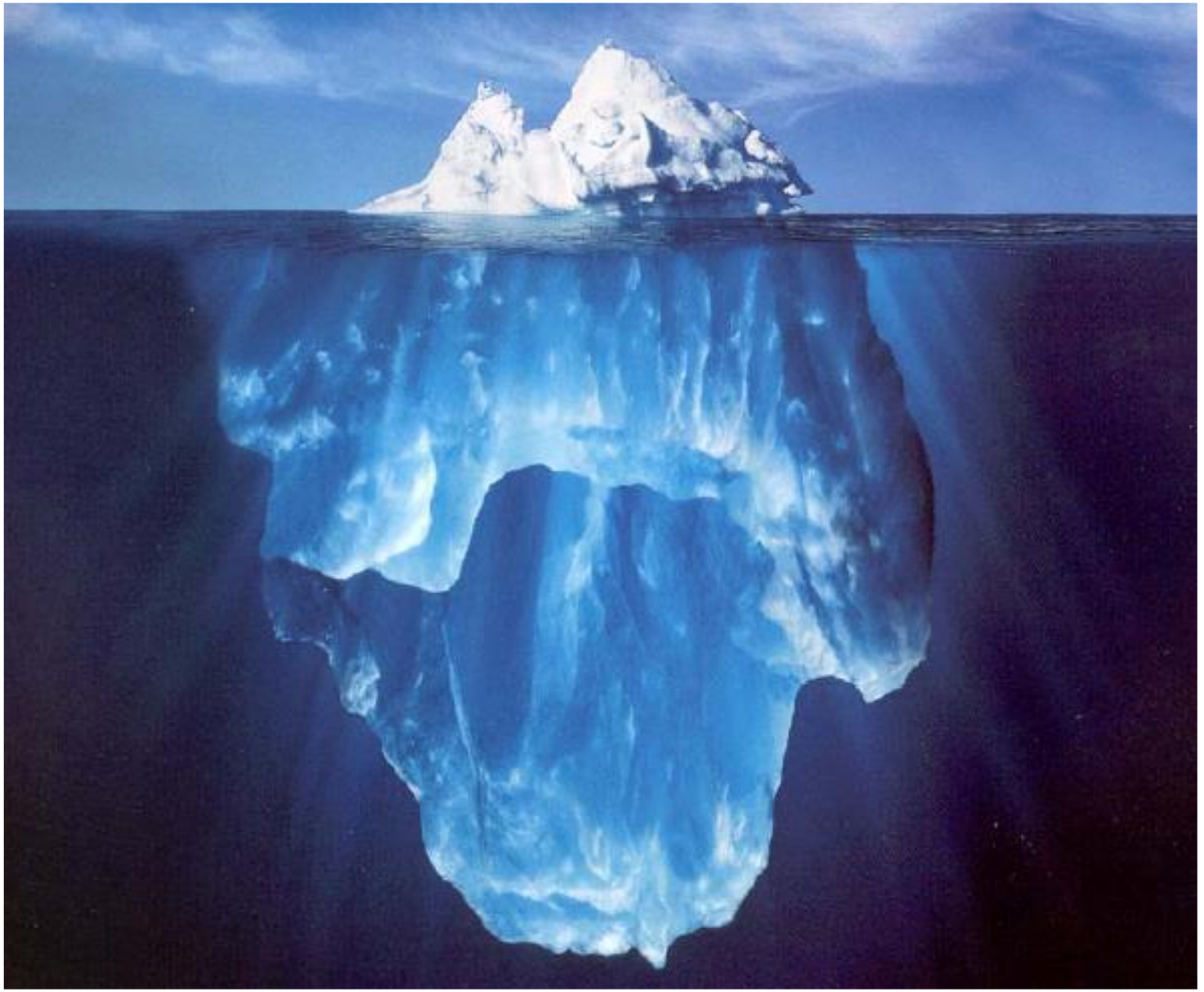
Variability of Drug Response in Children

Ontogeny

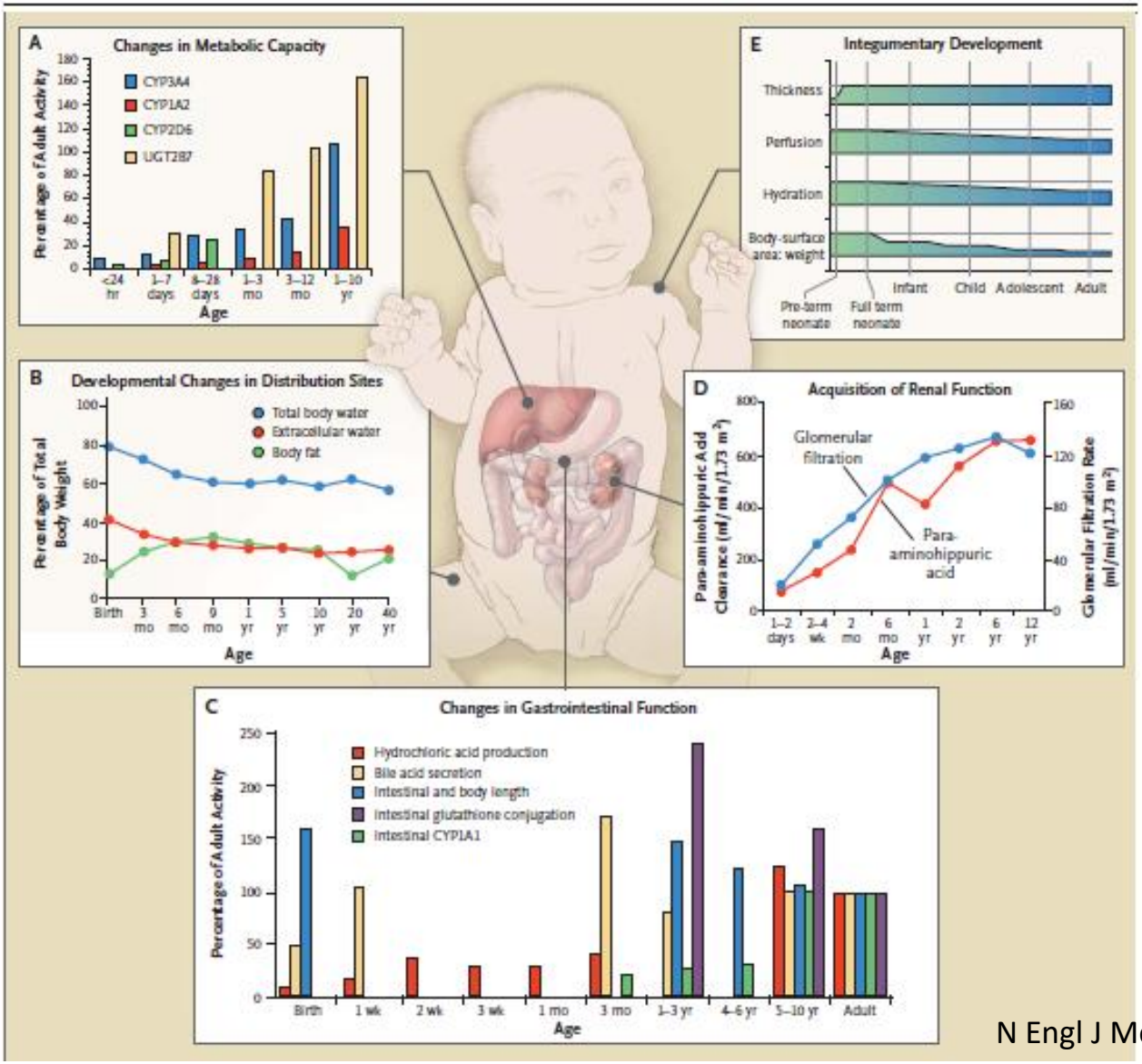
Pharmacogenetics

Variability of Drug Response



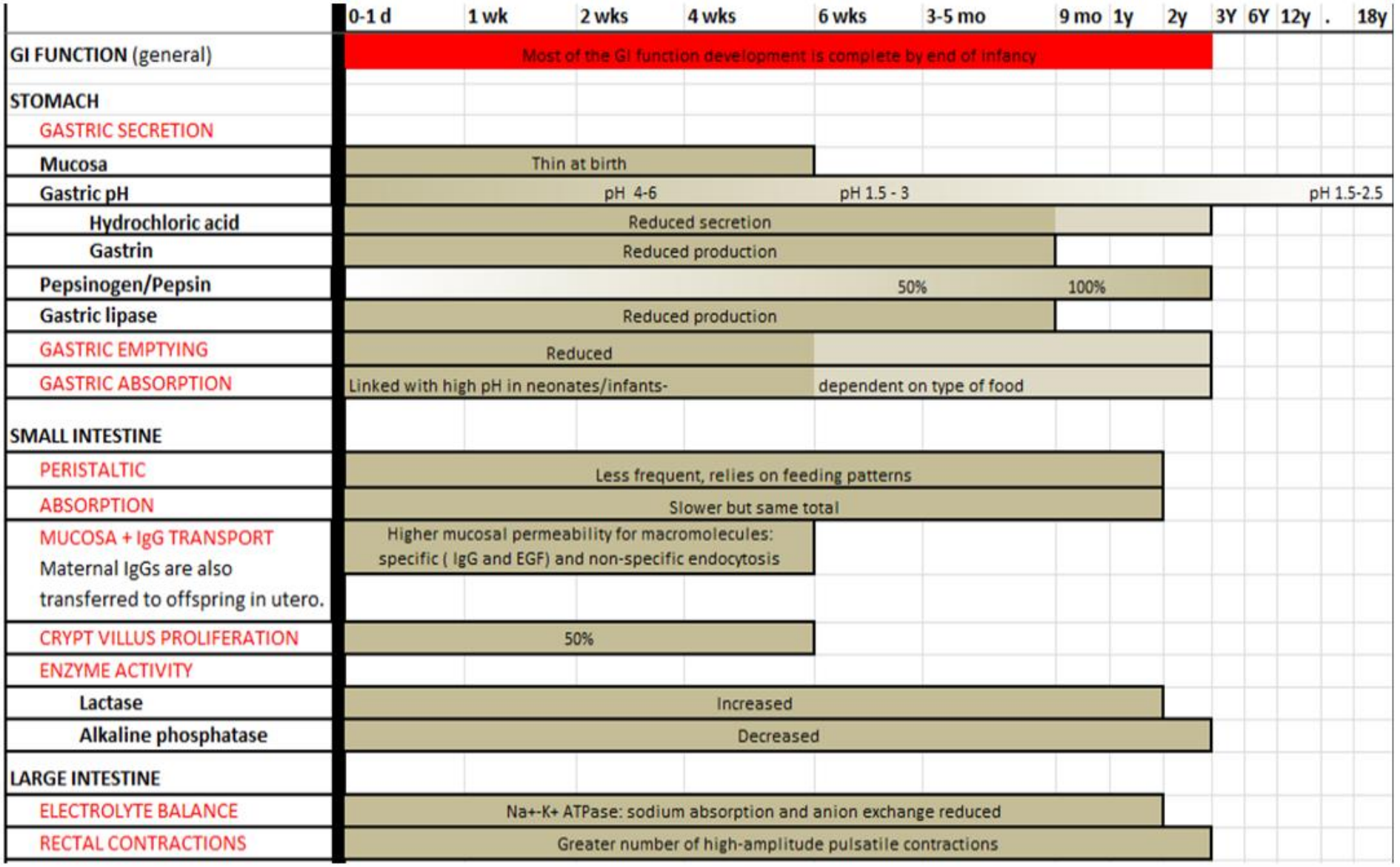


Pharmacotherapy of children - „shooting the moving target“...

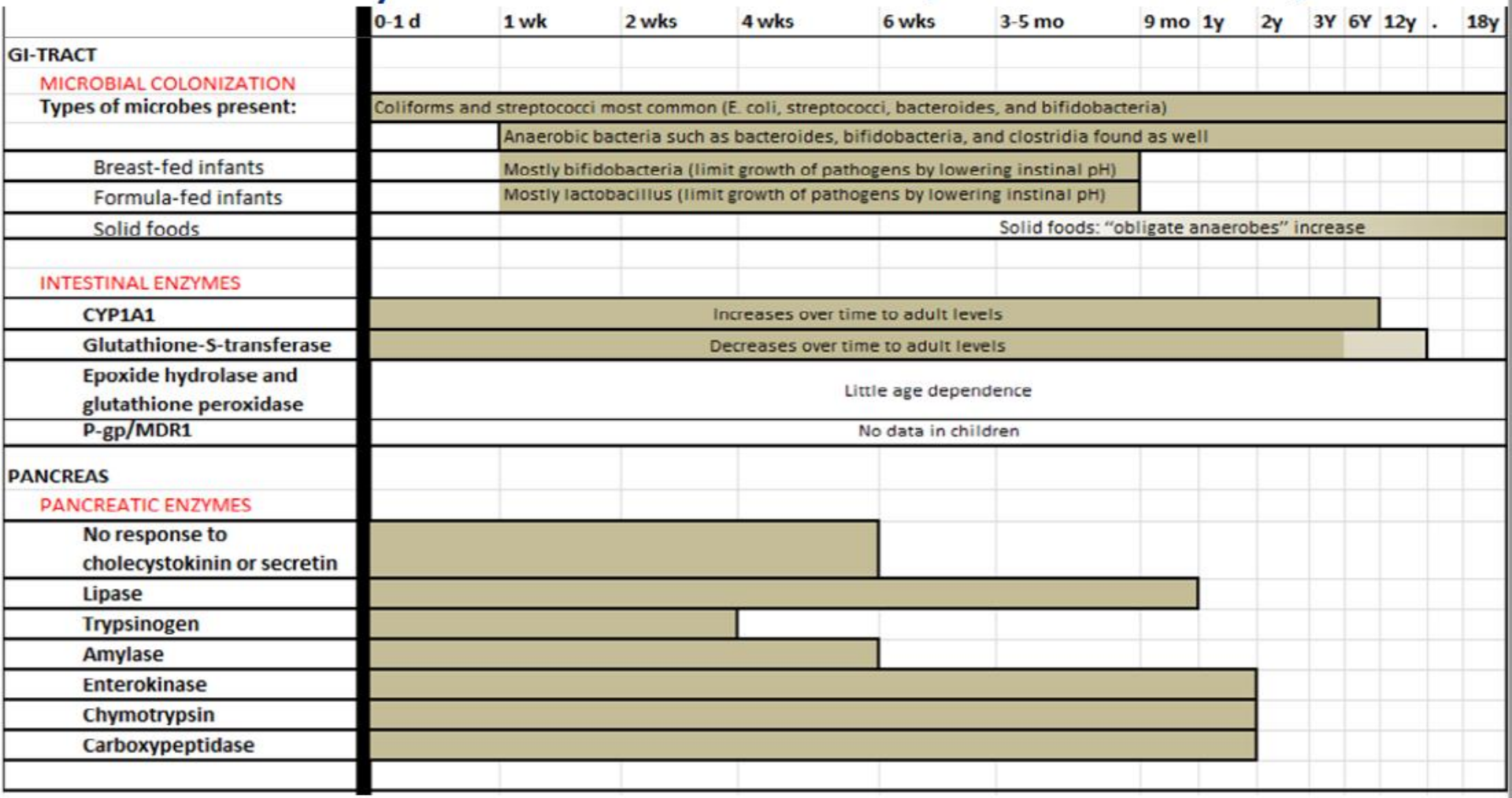


N Engl J Med 2003;349:1157-67

GI-system maturation (under construction)



GI-system maturation (under construction)



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- Walthall K, Cappon GD, Hurtt ME, Zoetis T. Postnatal development of the gastrointestinal system: a species comparison.Birth Defects Res B Dev Reprod Toxicol. 2005 Apr;74(2):132-56.

Liver maturation

	Age (after birth) and maturation period / Hepato-biliary system and metabolic pathways	1 month	2 months	3 months	4 months	5 months	6 months	12 months	15 months	2 years	5 years
Phase I Enzymes	CYP3A4 (midazolam, itraconazole)										
	CYP1A2 (caffeine, theophylline)										
	CYP2D6 (dextromethorphan)										
	CYP2C9/CYP2C19 (benzodiazepines, proton pump inhibitors)										
	CYP2E1 (acetaminophen, halothane, ethanol)										
	FMO (chlorpromazine, promethazine)										
Phase II Enzymes	Glucuronidation UGT1A (acetaminophen)										
	Glucuronidation UGT2B (chloramphenicol, morphine)										
	Sulfation SULT1A1/SULT1A3 (acetaminophen; iodothyronines and catecholamines in foetus)										
	NAT2 (caffeine, isoniazid)										
	Bile flow (reaching up to the adult levels)										

Reference:
Mulberg AE, Silber SA, van den Anker JN; Paediatric Drug Development: Concepts and Applications; Developmental hepatic pharmacology in paediatrics; 2009; p. 243.

Renal system maturation

Renal system Function / Age subsets	0 – 1 year	1 – 2 years	2 – 3 years	Up to 18 years
Glomerular filtration rate (GFR)	Due to haemodynamic changes during and just after birth, GFR increases rapidly in the first two weeks of life. Afterwards, GFR corrected for body surface area increases more slowly to reach adult levels **between 1 to 2 years of age.**			
Tubular secretion	The renal tubular secretion capacity increases over the first months of life and then declines to reach the adult level (per unit of body area) at **~ 7 months to 1 year of age.** The organic anion pathway matures faster than the organic pathway.			
Tubular reabsorption	The development and maturation of the glomerular permeability functions and the renal tubular reabsorption are gradual and continuous processes from **birth** to **adolescence**. The key stage of their maturation is at **~ 1 and 3 years of age.**			

References:

1. **Guideline on the investigation of medicinal products in the term and preterm neonate. CHMP and PDCO, EMEA, London 25 June 2009.**
2. **Paediatric Drug Development. Mulberg AE, Silber SA, Van den Anker JN. John Wiley & Sons, 2009.**

Brain maturation

Brain/brain elements	Period of maturation (postnatal months and years of age)	1 m	6 m	12 m	18 m	24 m	3 y	4 y	5 y	6 y	7 y	8 y	9 y	10 y	11 y	12 y	13 y	14 y	15 y	16 y	17 y	18 y
Neural tube differentiation	Up to 1st month of age																					
Blood brain barrier	Until 6th month of age																					
Proliferation and organization of synapses	50% at 2 yrs; 100% at 4 yrs																					
Myelination	50 % of corpus callosum at 18 months; up to 20-30 yrs																					
Brain size	80% at 2 yrs; 90% at 5 yrs; remodelling of white and gray matter up to 20-30 yrs																					
Cortical gray matter maturation (motor & sensory systems, memory, audio-visual input, object recognition)	1. Frontal lobe: 11 yrs girls & 12.1 yrs boys 2.Temporal lobe: 16.7 yrs girls & 16.2 yrs boys 3. Parietal lobe: 10.2 years girls and 11.8 yrs boys																					
Subcortical gray matter maturation (control of movement and muscle tone, higher cognitive functions, attention, affective states)	Nucleus caudatus size peak: 7.5 yrs girls & 10.0 yrs boys																					
Amygdala and hippocampus maturation (emotion, language, memory)	Between 4 yrs and 18 years																					
White matter maturation	1. Lobar white matter volumes increase up to 30 years 2. Corpus callosum: between 4 yrs and 18 years (integrating left & right hemispheres; unification of sensory fields, memory storage and retrieval, attention & arousal, enhancing language and auditory functions)																					
Prefrontal cortex maturation	Up to the late adolescence – 17-18 yrs																					
Neurotransmitter system maturation (NMDA receptors)	Up to 3 years of age																					
Cholinergic and serotonergic systems	Through childhood and adolescence, in individuals possibly into adulthood																					

1. Volpe JJ, Neurology of the newborn, 5th ed., Elsevier Health Sciences, Philadelphia 2008, p5
2. Benes F, The development of the pre-frontal cortex, the maturation of neurotransmitter systems and their interactions, in: Handbook of developmental cognitive neuroscience (Nelson CA, Luciana M, eds) , MIT press, 2001

Lung maturation (under construction)

Development of the Pulmonary System																		
		Fertilization								Birth								
	Age subset	Embryogenesis		Foetal development						Neonate/ Infant	Child							
		0 w	5 w	10 w	15 w	20 w	25 w	20 w	35 w	40 w	1y	2y	3y	4y	5y	6y	7y	8y
Stage	Embryonic																	
	Pseudo-glandular																	
	Canalicular																	
	Saccular																	
	Alveolar (proliferation)																	
	Microvascular maturation																	
	Alveolar (expansion) (Normal lung growth period)																	

References:

- Zoetis T, Hurtt ME. Species comparison of lung development. Birth Defects Res B Dev Reprod Toxicol. 2003;68(2):121-4. Review.
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Clinical trials in children

Problems

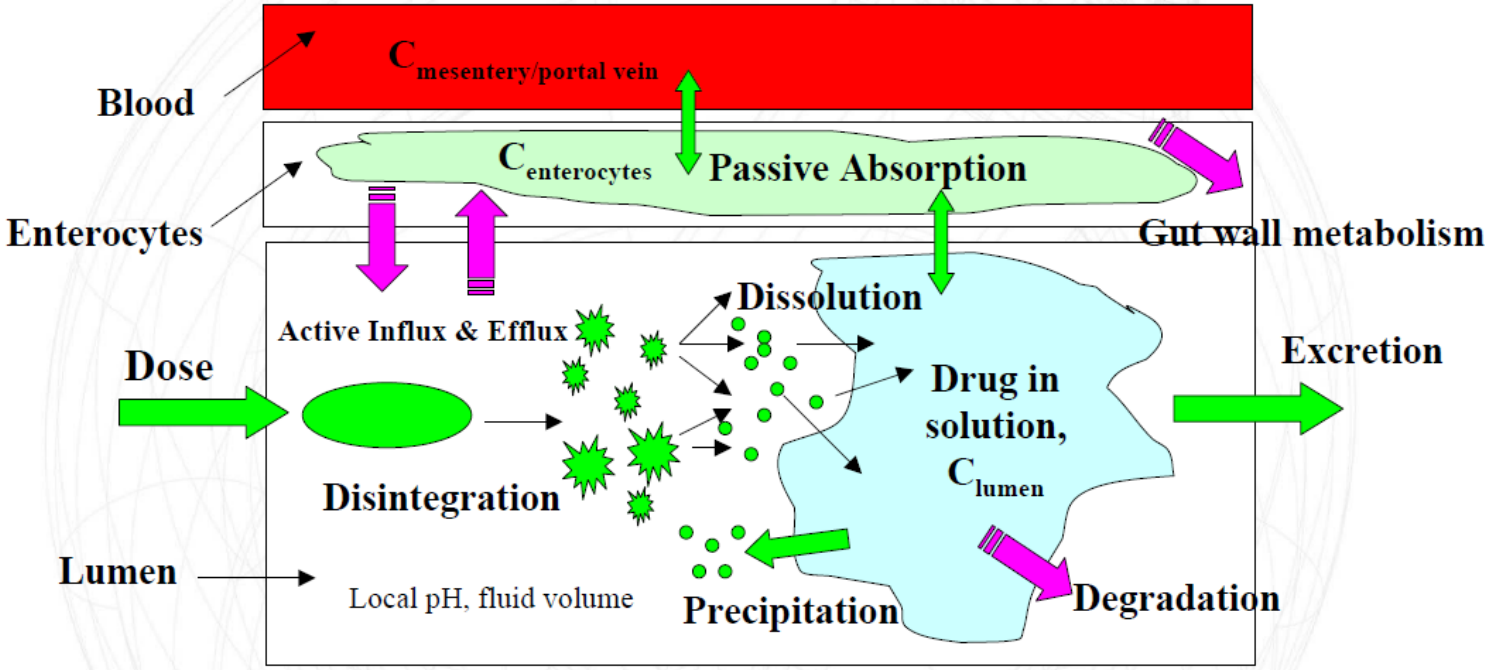
- Ethical problems
- Slight morbidity
- It is difficult to enroll the required number of patients
- Patients of all ages should be studied
- Large expenses

Solutions

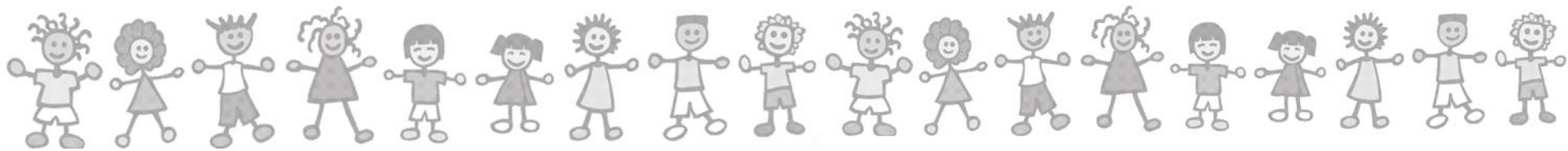
- Free scientific advice
- Patent Extension
- Market protection

- New research methods
  - Extrapolation of data
  - Clinical trials simulation

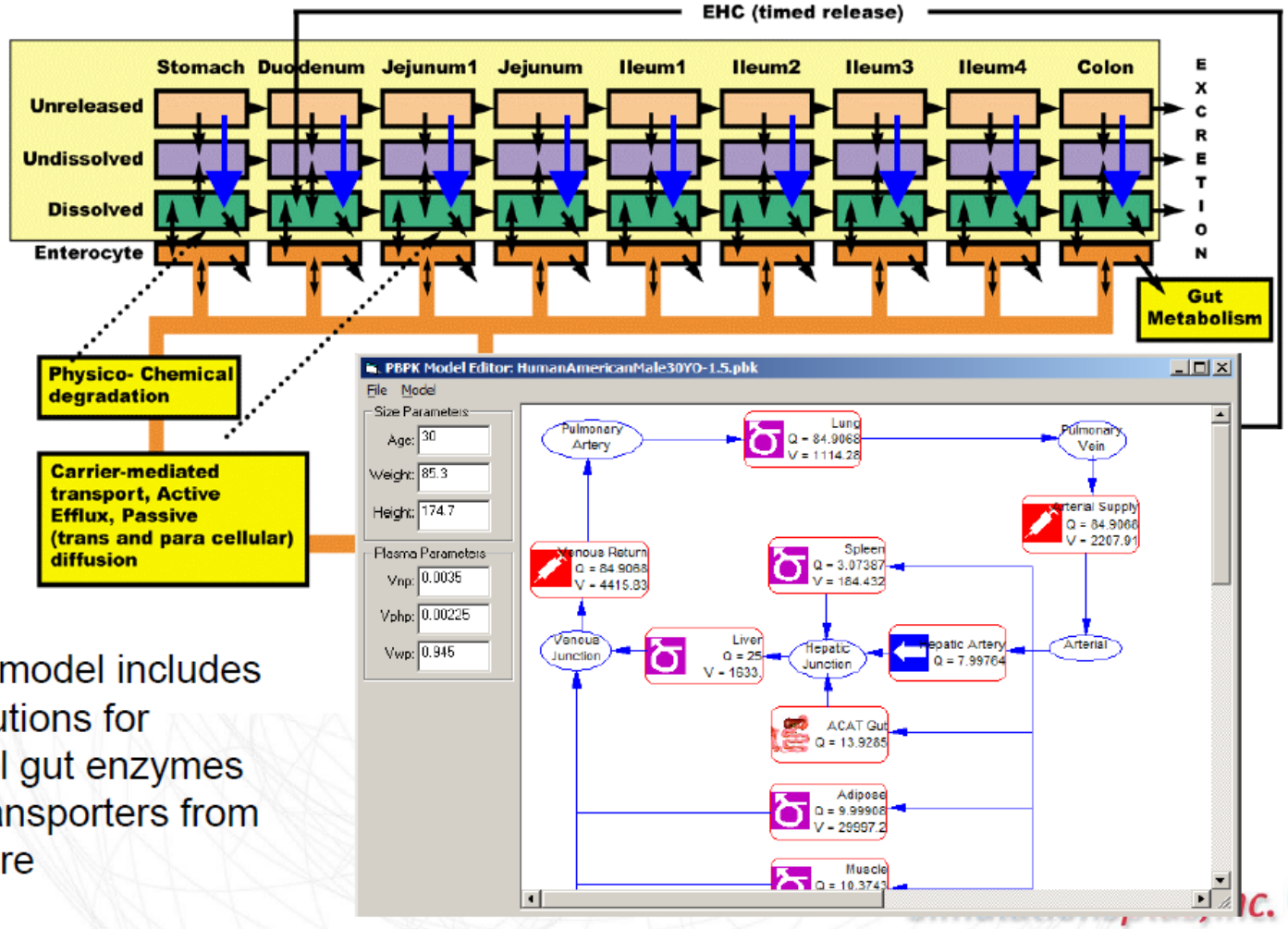
Processes Involved in Oral Absorption



These phenomena are repeated in each of the compartments of the gastrointestinal tract

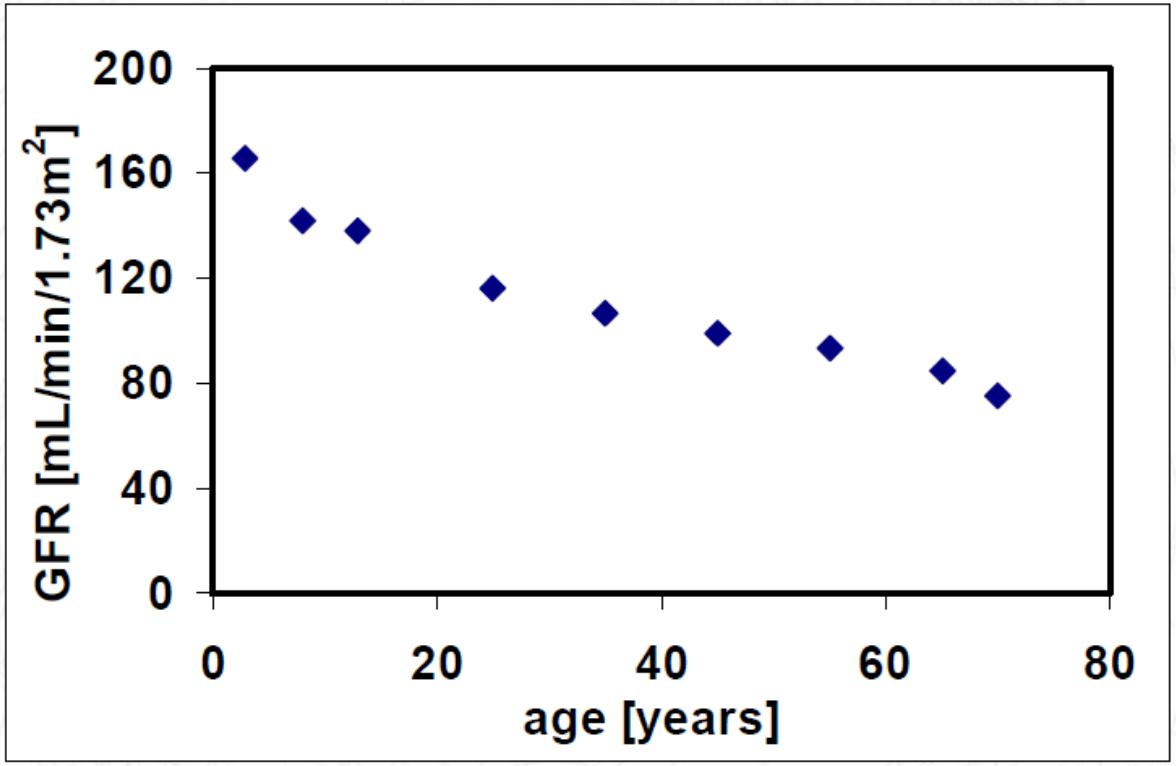


ACAT-PBPK Combined Model



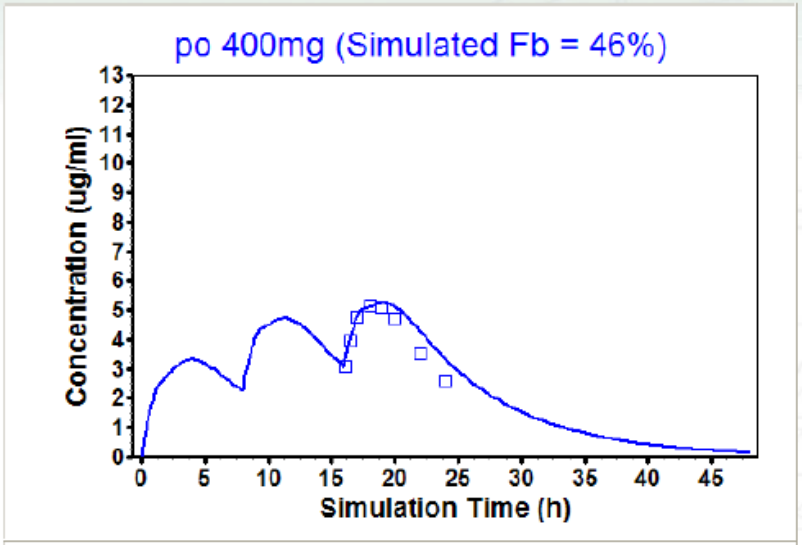
ACAT model includes distributions for several gut enzymes and transporters from literature

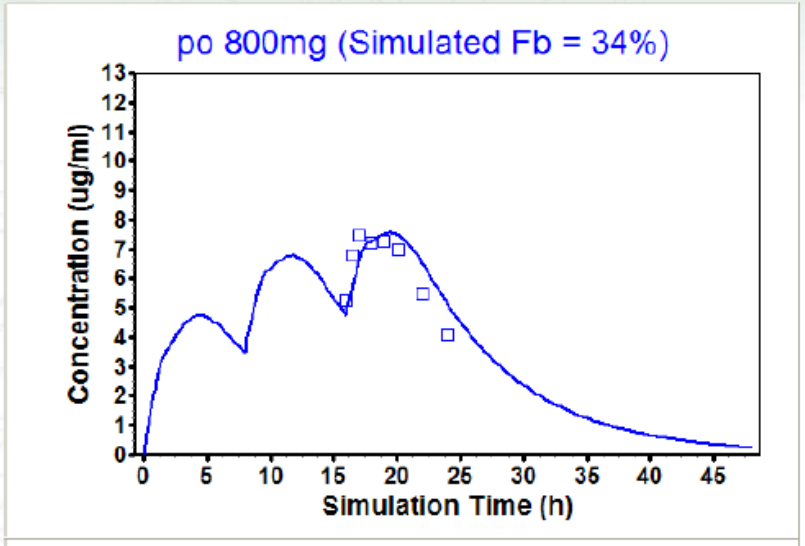
Gabapentin CL Modeled as Function of Glomerular Filtration Rate

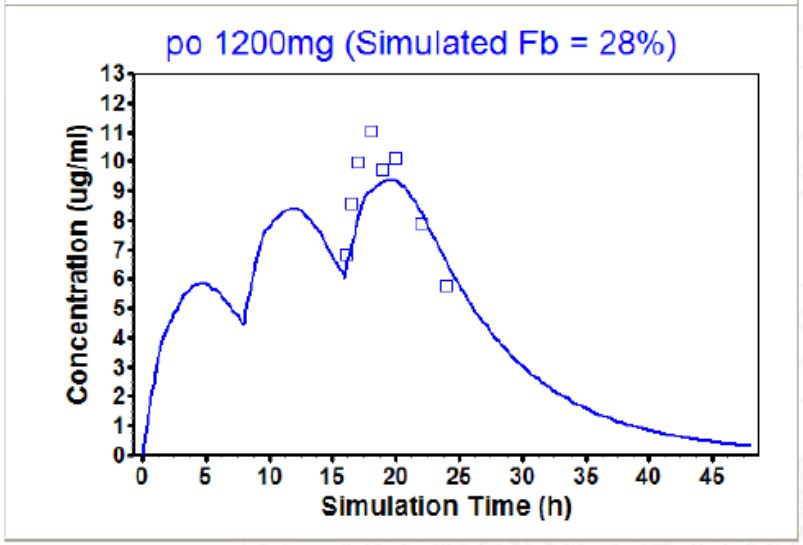


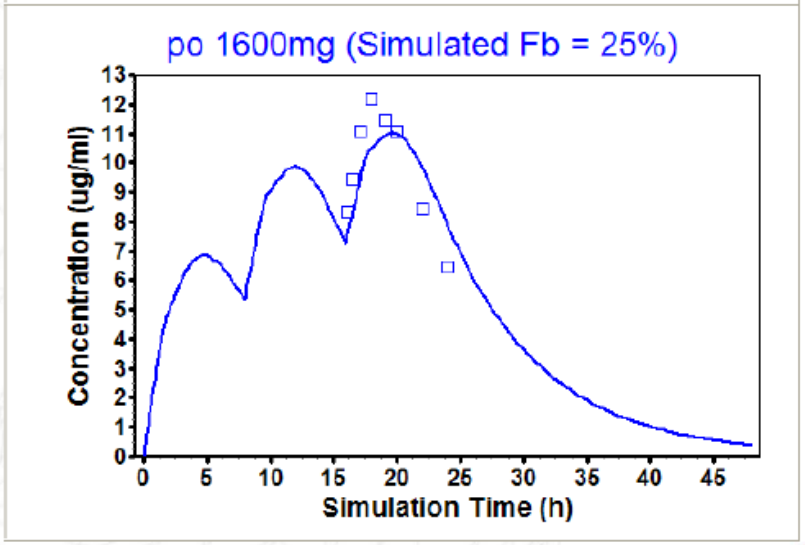
Mego S. 36th Annual Scientific Meeting of the Australian and New Zealand Society of Nuclear Medicine (poster)
Stevens L. FAQ about GFR Estimates (National Kidney Foundation publication)

Gabapentin Nonlinear Dose Dependence in Adults

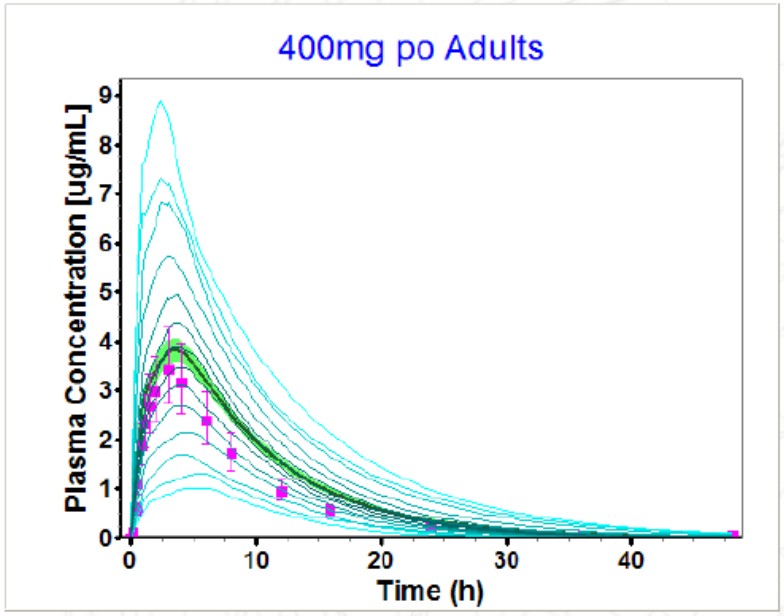




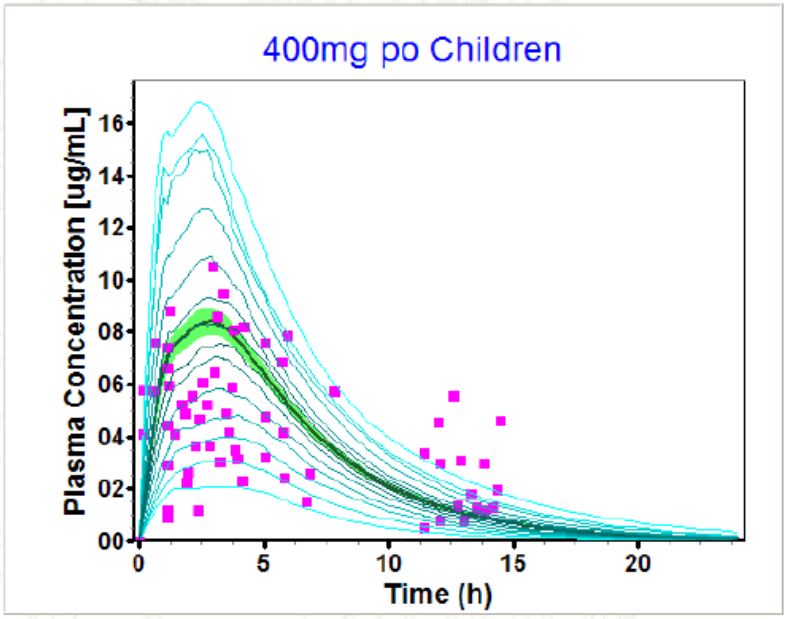




Adult and Pediatric Population Simulations



400 mg solution: 41 yo adult female



400 mg tablet, 7 yo children

Conclusions

- Pharmacokinetics and pharmacodynamics of medicines in children may differ from those of adults (children of other age groups) due to different maturity of organs
- The effects of many new (and not limited to) medicines to children are unknown
- When considering the use of an unlicensed medicine in children, it is necessary to assess the benefits and risks, to try to determine the dose as closely as possible according to age, body weight, body surface area, renal function, maturity, response to the drug
- Prescribe the appropriate pharmaceutical form for children
- Avoid polypharmacy