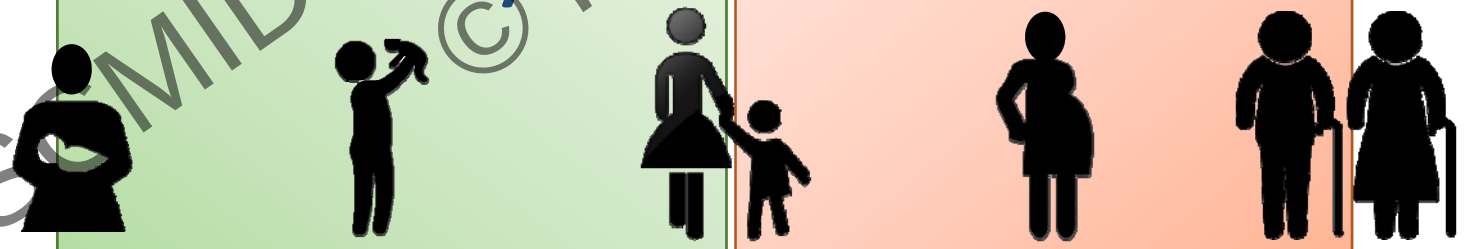
PK-PD Dosing Issues in Special Patient Populations

ASM/ESCMID 2017



Prof. Mike Sharland
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Catarrhal Bronchitis, Stubborn Coughs and Colds

"Not Miniature Men and Women"

Abraham Jacobi

Contains 12% of alcohol by weight or 14% per volume. Use as a solvent

DIRECTIONS:
For adults: Take a teaspoonful about one-half hour before meals and when retiring.

For children: Half dose. If the taste is not liked, it may be combined with a mouthful of water.

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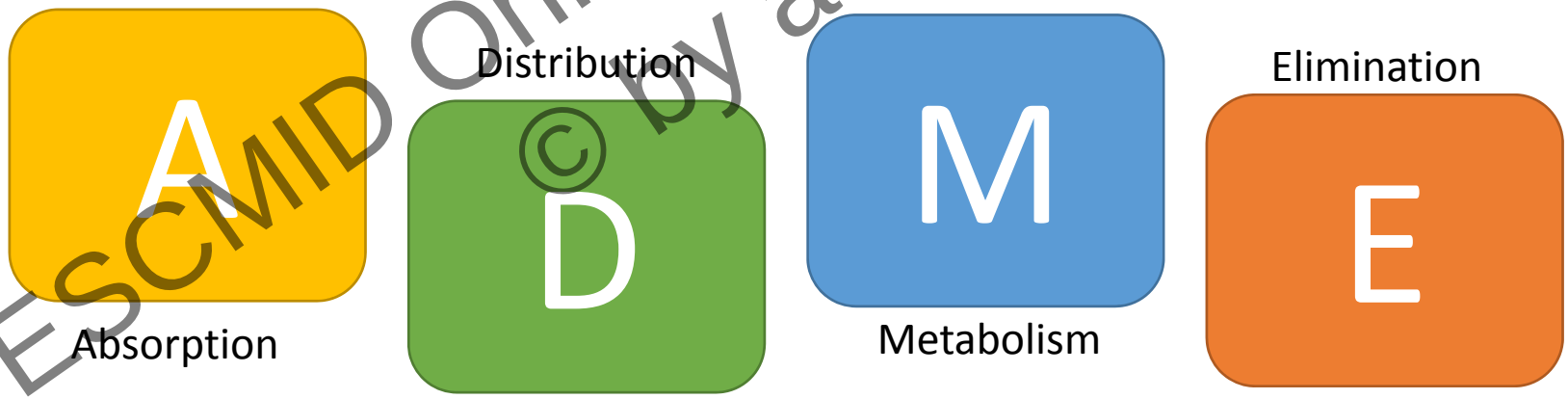
Factors that influence tissue drug concentrations over time include Absorption, Distribution, Metabolism and Excretion (ADME). (Formulation!)

These ADME processes differ in ***neonates, children, pregnancy and elderly*** populations with major consequences on the pharmacokinetic profile of a drug.

High VARIABILITY in ADME have direct effect on antibiotic PK/PD – concern especially in older drugs with a narrow therapeutic index



EMA. 2001. ICH Topic E11. Clinical investigation of medicineal products in the paediatric population. CPMP/ICH/2711/99. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf (last accessed 11 October 2013)

- **Neonates and children**
- **Pregnancy**
- **Elderly**

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The continuous development

- Preterm newborn
- Newborn (0–28 days)
- Infant (>28 days–12 months)
- Toddler (>12 months–23 months)
- Preschool child (2–5 years)
- School age child (6–11 years)
- Adolescents (12-18 years)

Many physiological changes take place during childhood which may have an impact on the pharmacokinetics and dynamics of a compound

International Conference on Harmonization (ICH) E11 classifications

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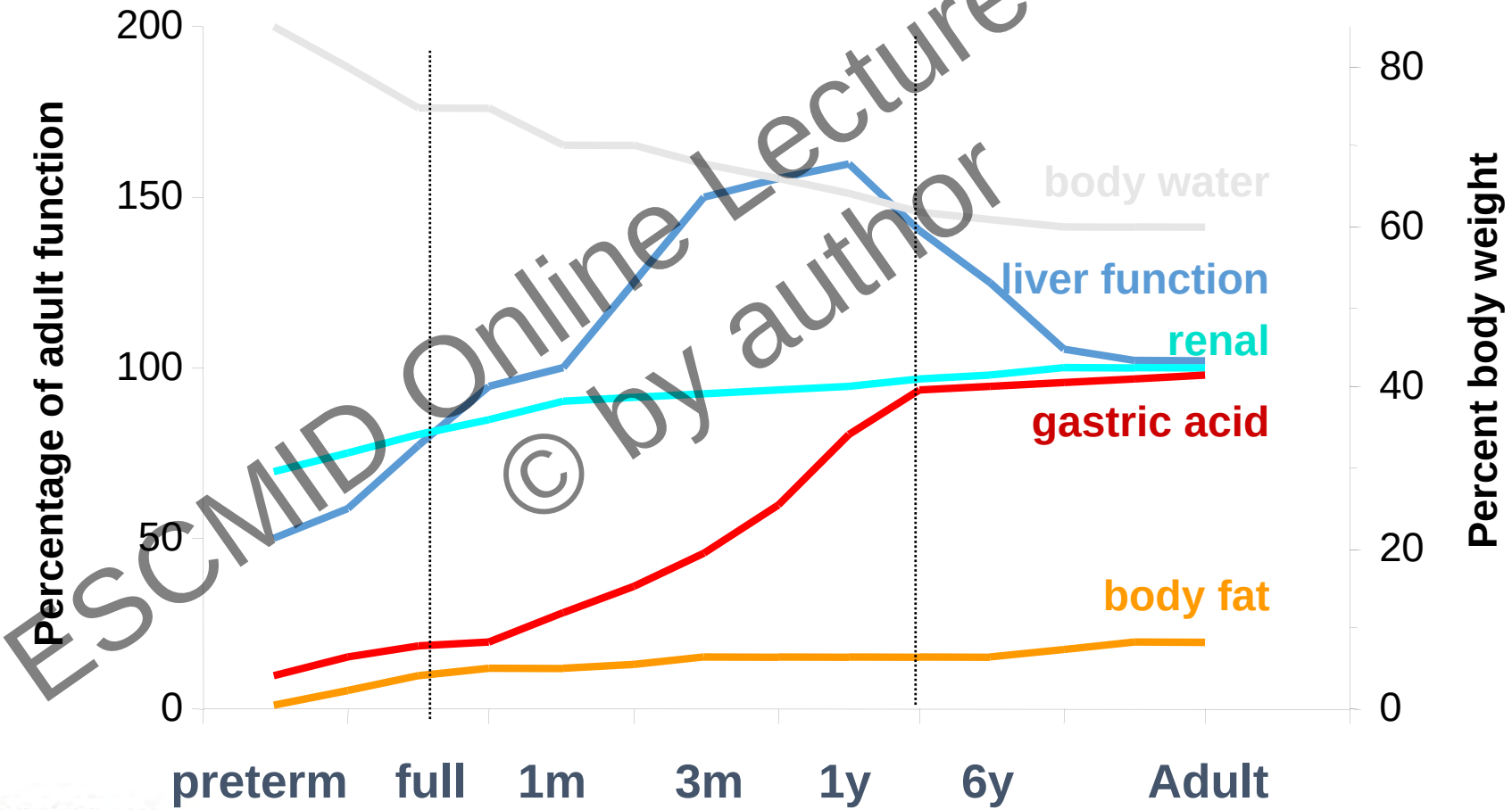
Changes in Antimicrobial pharmacokinetics with age



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Source: Dr Saye Khoo, Liverpool

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Children and neonates

A

Absorption

Developmental change	PK consequence
↓Gastric pH	↑C_{max} for weak acids
↓Intestinal transit	↓C_{max} and ↓AUC
↓Intestinal bile concentration	↓C_{max} and ↓AUC

	Newborn (full-term)	Neonate (1 day–1 month)	Infant (1 month–2 years)
Physiological factor			
Gastric pH	1–3	>5	~Adult
Gastric emptying time	Reduced (variable)	Reduced (variable)	Increased
Intestinal surface area	Reduced[b]	Reduced[b]	~Adult
Intestinal transit time	Reduced	Reduced	Increased
Pancreatic and biliary function	Very immature	Immature	~Adult
Bacterial flora	Very immature	Immature	Immature
Enzyme/transporter activity	Very immature	Immature	Approaching adult

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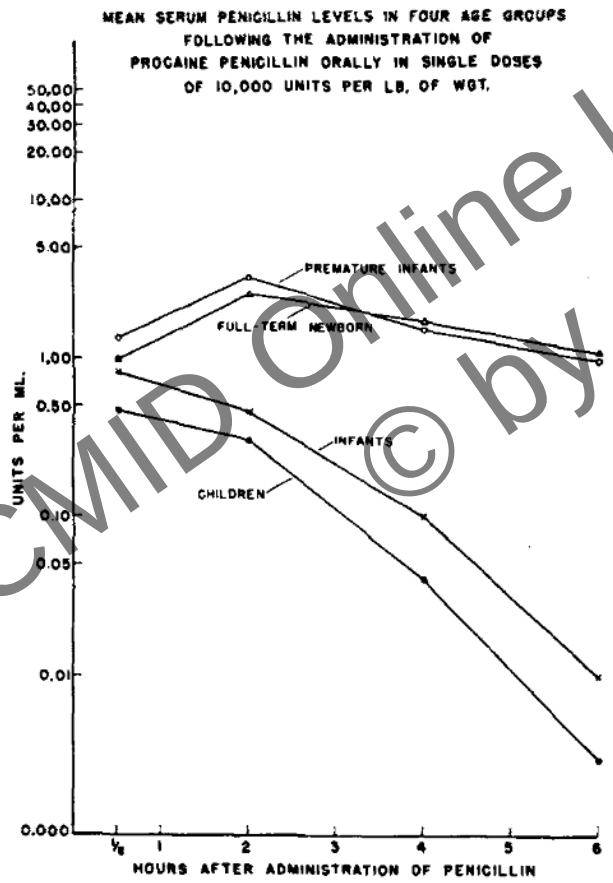
Children and neonates

Comparison of serum levels following the administration of oral and parenteral preparations of penicillin to infants and children of various age groups

A

Absorption



This higher pH in neonates and young infants may have a protective effect on acid-labile drugs and may at least partially account for the higher bioavailability of beta-lactam antibiotics.

(Huang et al, J paediatrics 1953)

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Children and neonates

D

Distribution

Developmental change	PK consequence
Body composition	↔V_d • **neonates** have relatively **reduced fat** • **infants** have increased fat compared with adults • **extracellular water is relatively higher in neonates – immature blood brain barrier**
↓plasma protein	↑free fraction of drug in plasma ↑V_d

Parameter	Neonate	Infant	Child
Total protein	Decreased	Decreased	Equivalent
Plasma albumin	Decreased	Equivalent	Equivalent
Plasma globulin	Decreased	Decreased	Equivalent
α_1-acid glycoprotein	Decreased	No data available	Equivalent
Free fatty acids	Increased	Equivalent	Equivalent
Unconjugated bilirubin	Increased	Equivalent	Equivalent

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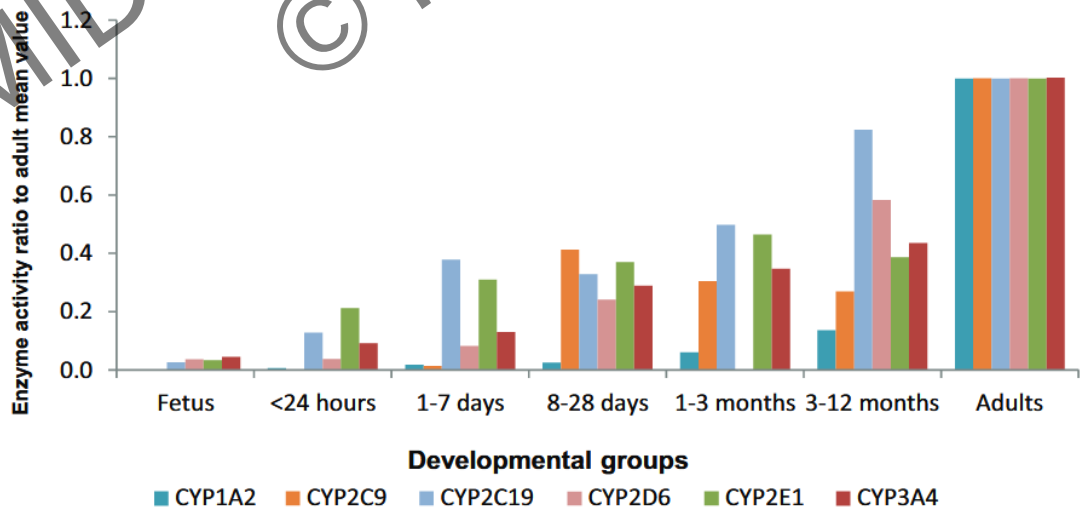
Children and neonates

M

Metabolism

Developmental change	PK consequence
Hepatic metabolism Phase I enzyme activity ↓	Hepatic clearance
Hepatic metabolism Phase II UGT enzyme activity ↓	Hepatic clearance
Bacterial colonization of the intestine	↑C_{max} and ↑AUC



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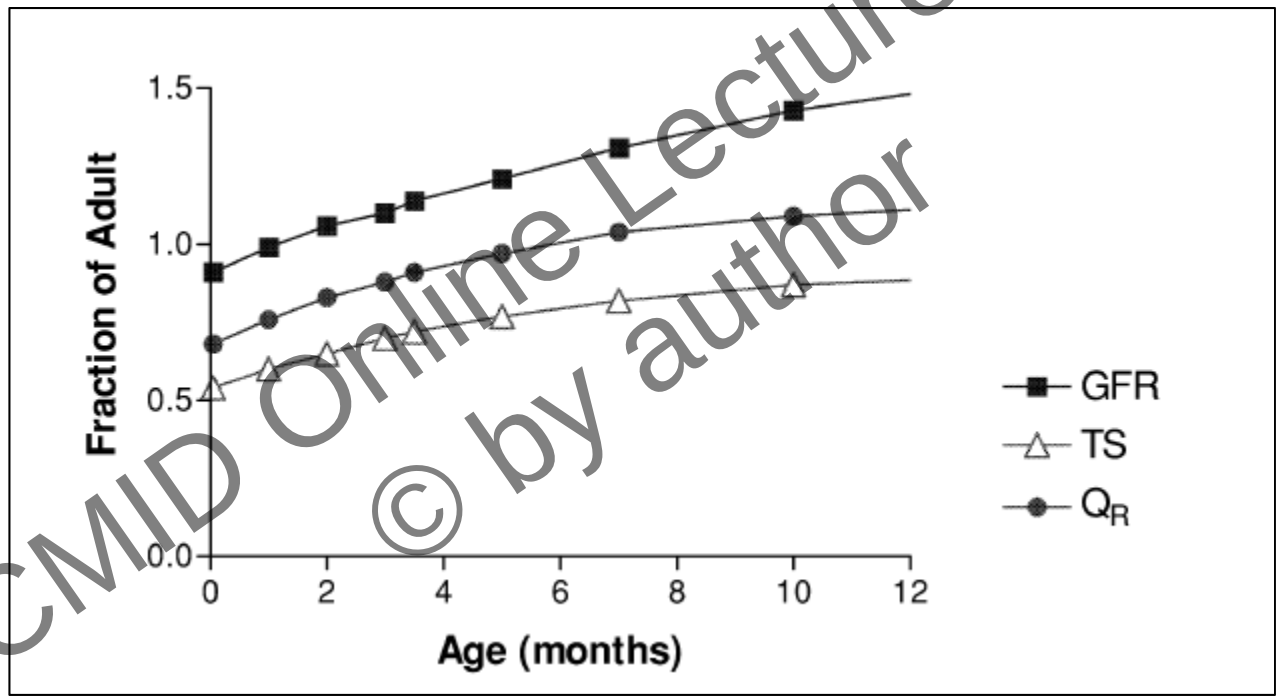
Children and neonates

E

Elimination



Excretion of drugs by the kidneys is dependent on three processes, glomerular filtration (GFR), tubular secretion and reabsorption (TS/R) (colistin high TR).

They are dependent on renal blood and renal plasma flow Q, which increase with age as a result of an increase in cardiac output and a reduction in peripheral vascular resistance.

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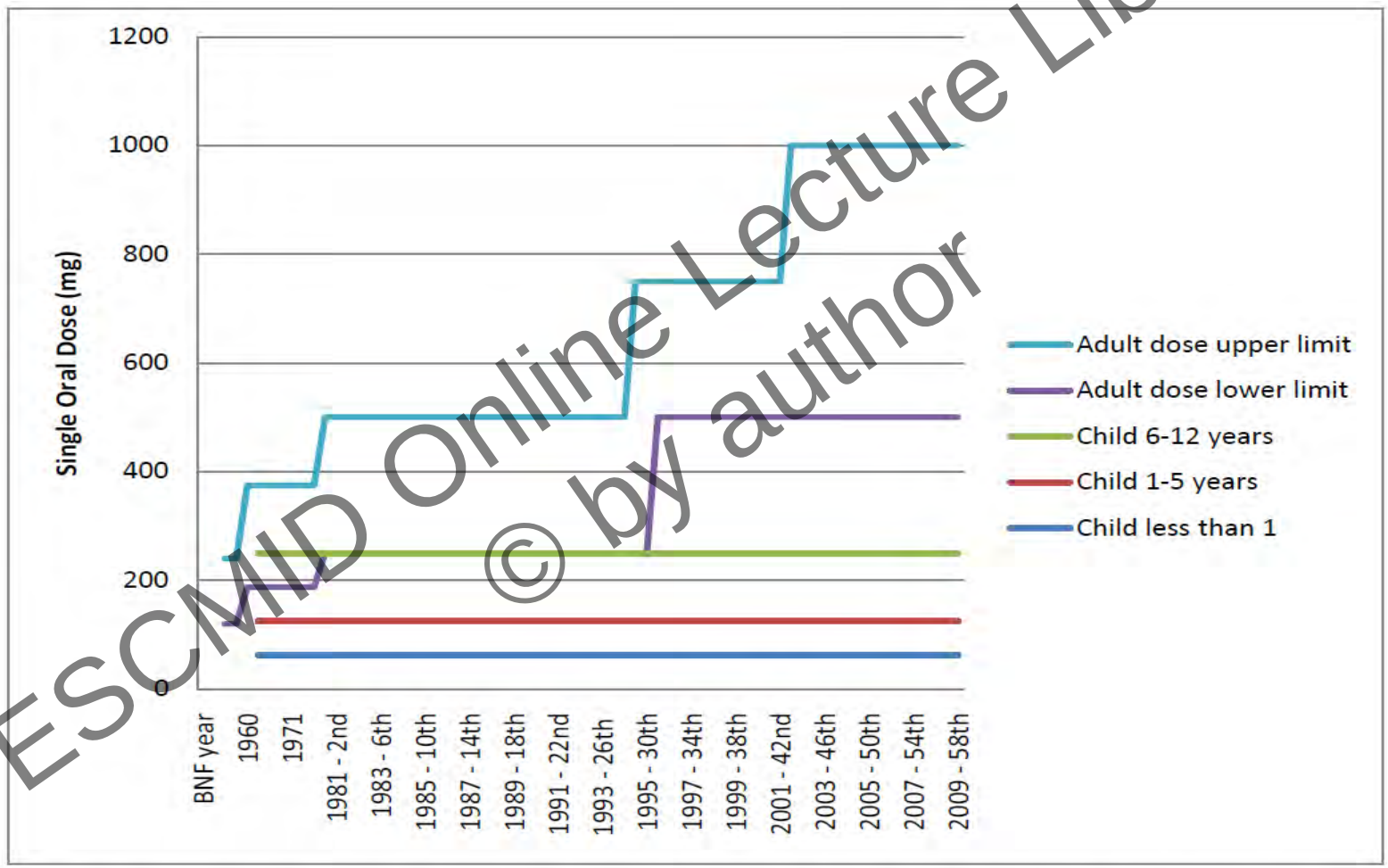

Figure 1: Timeline showing changes in the single oral child and adult dose of penicillin V

Dosing of oral penicillins in children: is big child=half an adult, small child=half a big child, baby=half a small child still the best we can do? Ahmed U et al, BMJ 2011

PK methods: why population PK?

Traditional PK	Population PK studies
Rich sampling	Sparse sampling
Ethical issues	Between subject variability
Practical challenges	Explain drug disposition
Recruitment issues	Modelling and simulation (M&S)
Generalisability varies	Now standard in paediatrics

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Challenges to studies with children and neonates

Neonatal and Paediatric Pharmacokinetics of Antimicrobials Study

NAPPA

- Recruited **216 neonates and 212 children**
- PopPK successfully integrated into routine care
- Opportunistic (and optimal) sampling strategies
- Methods feasible in NHS setting

An open label, multicenter, pan-European, randomised active-comparator controlled phase III superiority trial

NeoMero

- European multicenter network to evaluate pharmacokinetics, safety and efficacy of Meropenem in neonatal sepsis and **meningitis**
- Recruited **272 neonates**

NeoVanc-1- Hollow fibre infection and rabbit models

NeoVanc-2 - Population PK meta-analysis of previous neonatal, vancomycin pharmacokinetics data

neoVanc

NeoVanc-3 Open label European, multi-centre, Phase IIb, randomised, active control, parallel group, non-inferiority trial

- Compare the efficacy, safety and pharmacokinetics of an optimised dosing to a standard dosing regimen of vancomycin
- **300 participants** is planned to be enrolled from five EU countries

- Children and neonates
- **Pregnancy**
- Elderly

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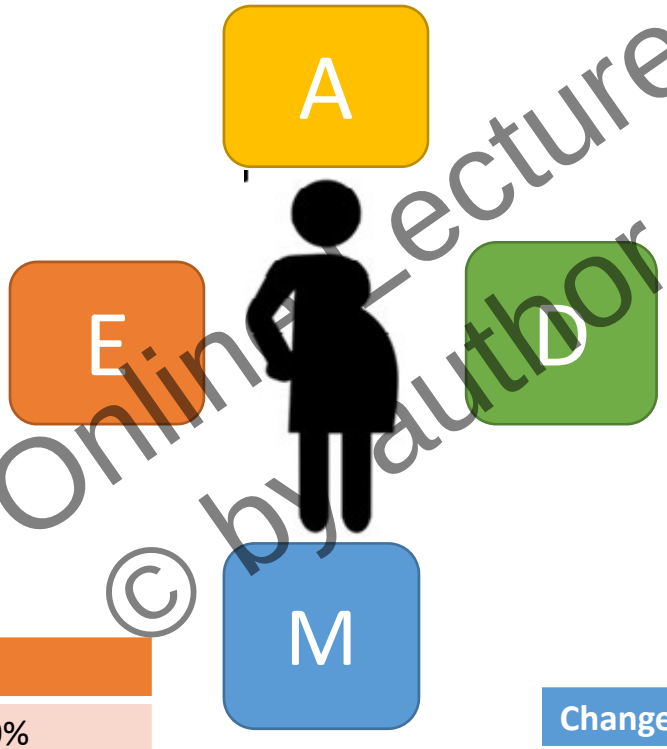
Pregnancy (maternal sepsis)

Change in Pregnancy
↓ gastric acidity Slower gastric emptying
↑ Increased oro-cecal transit time in third trimester



Change in Pregnancy
↑ Plasma volume
↓ Albuminemia
↑ Hepatic blood flow
Changes to regional blood flow
↓ serum creatinine and urea
↑ activity of renin-angiotensin system

Change in Pregnancy
Cardiac output ↑ 30%-50% ↑respiration rate
↑ in stroke volume and heart rate
↓ functional reserve capacity
GFR ↑ 50%

Change in Pregnancy
Increased levels of estrogen and progesterone modulate enzymatic: **CYP P450 activity which can be ↑** (ie, CP3A and CYP2A6) or ↓ (ie, CYP1A2)
Increased hepatic blood flow

A European clinical pharmacology network to investigate the Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNAnt women

- Was almost no data on ARVs in pregnancy – critical to optimise dosing to reduce MTCT
- PENTA network developed for PK of mothers taking ARVs in pregnancy
- Combination antiretroviral treatment (cART): 2 NRTI's and integrase inhibitor, protease inhibitor/r, or NNRTI now have optimal doses
- Could be adapted for antimicrobials

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Feasible

PENTA ID www.penta-id.org

The pharmacokinetics, safety and efficacy of tenofovir and emtricitabine in HIV-1-infected pregnant women

AIDS 2013, **27**:739–748

Maraviroc Pharmacokinetics in HIV-1–Infected Pregnant Women

CID 2015:61 (15 November)

Raltegravir in HIV-1–Infected Pregnant Women: Pharmacokinetics, Safety, and Efficacy

HIV/AIDS • CID 2015:61 (1 September)

AIDS 2014, Vol 28 No 2

Pharmacokinetics, safety and transplacental passage of rilpivirine in pregnancy: two cases

J Antimicrob Chemother 2015; **70**: 534–542
doi:10.1093/jac/dku400 Advance Access publication 17 October 2014

Journal of Antimicrobial Chemotherapy

Pharmacokinetics of total and unbound darunavir in HIV-1-infected pregnant women

Antiviral Therapy 2015; **20**:57–64 (doi: 10.3851/IMP2820)

Original article

Atazanavir exposure is effective during pregnancy regardless of tenofovir use

First reported use of elvitegravir and cobicistat during pregnancy

AIDS 2016, **30**:807–812

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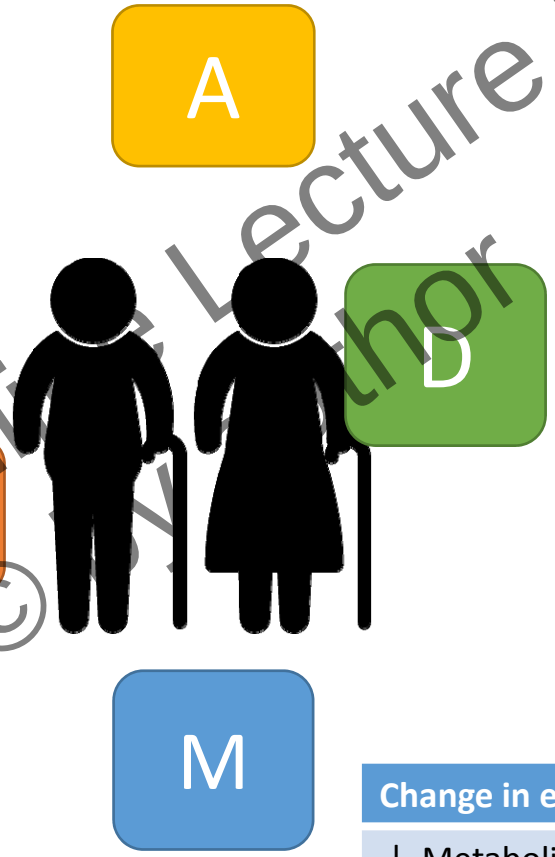
- Children and neonates
- Pregnancy
- **Elderly**

PK-PD Dosing Issues in Special Patient Populations

Elderly

(dose adjustment, toxicity, polypharmacy)



Change in elderly
↓ gastric acidity
↓ due to certain comorbidities (e.g.,diabetes, Parkinson's Disease) and certain medications (e.g.,anticholinergics and opioids)

Change in elderly
↓ muscle mass ↓body fat ↓total body water
↓in plasma albumin (further reduction may be due to age-related chronic conditions) a1-acid glycoprotein may be increased (due to acute illness or chronic inflammatory disease states)
↓ first-pass metabolism due to reduced liver blood flow and mass

Change in elderly
↓ renal function is common in older adults
↓ in stroke volume and heart rate
↓ functional reserve capacity
↓ GFR

Change in elderly
↓ Metabolizing capacity, PHASE 1: mostly due to reduced hepatic blood flow and mass and reduced oxygen availability

PK-PD Dosing Issues in Special Patient Populations

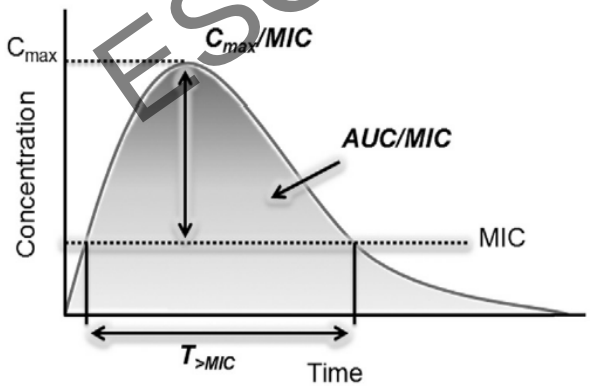
THE FUTURE

PK STUDIES of NEW AB for the PAEDIATRIC POPULATION

- **Populations to cover and age groups:**
  a. 12-18 years
  b. 2-11 years (could be divided into 2-5 years and 6-11 years)
  c. PMA >44 weeks to 2 years
  d. PMA <44 weeks (important to include VLBW and ELBW)

  studies from **2-18 years** could be **conducted in parallel**

- **Study design:**
  - **Sample size** justified **according to expected variability in PK** using **adult** and or **PBPK extrapolation – POSSIBLY ONLY SINGLE/MULTIPLE DOSE PK..**
    a. **7-9 evaluable patients per age cohort** is usually the **minimum requirement**
    b. **50 time-points at different times** are needed in sparse sampling studies



- **Data analysis:**
  - **Population PK models** should be developed first **from adult data to support extrapolation**, and then **updated to cover all studied paediatric age groups**
  - **Probability of target attainment** (**PTA**) should be **simulated for all age groups – RE-CONSIDER PD TARGETS IN SPECIAL POPULATIONS…**

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GARDP Global Antibiotic Research & Development Partnership

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NeoAMR

TPP1

GARDP Global Antibiotic Research & Development Partnership

Indication	**Empiric treatment** of neonatal sepsis, including meningitis (premature and term, early and late onset)
Patient Population	Neonates with pSBI in settings of high prevalence of resistance to first line WHO empiric therapy
Route of Administration	i.v. (intravenous), 30-120 min infusions
Dosing Schedule	2-4 x daily
Efficacy	**Comparable clinical activity to amoxicillin/gentamicin** or ceftriaxone/gentamicin in claimed indication Clinical activity in pathogens resistant to amoxicillin/gentamicin or ceftriaxone/gentamicin
Treatment duration	5-28 days
Safety / Tolerability	Low propensity for resistance development, **large therapeutic window** concerning hepatotoxicity, nephro- and CNS-toxicity, no QT-prolongation
Drug Interactions	Comparable to competitors
Key Countries	Europe, the Americas, Asia, Africa
Price / Day of Therapy	Average ex-factory price at launch: low/DOT (directly observed therapy)
Pharmacoeconomics	Reduction of intensive care unit and hospitalization days (modelling). Reimbursable

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NeoFosfo

Objectives

assess the **safety** of IV fosfomycin with regard to possible elevation of **sodium, calcium and creatinine** at **Day 2 and 7** in neonates

estimate the **PK of IV fosfomycin** in neonates

estimate the **oral bioavailability** of fosfomycin in neonates

Treatment

Randomised to Amp/Gent (SoC) vs Amp/Gent plus a 7-day course of fosfomycin

48 hours (or more) IV fosfomycin, followed by up to 5 days of oral fosfomycin.

Neonates will move to oral fosfomycin once they are tolerating oral feeds.

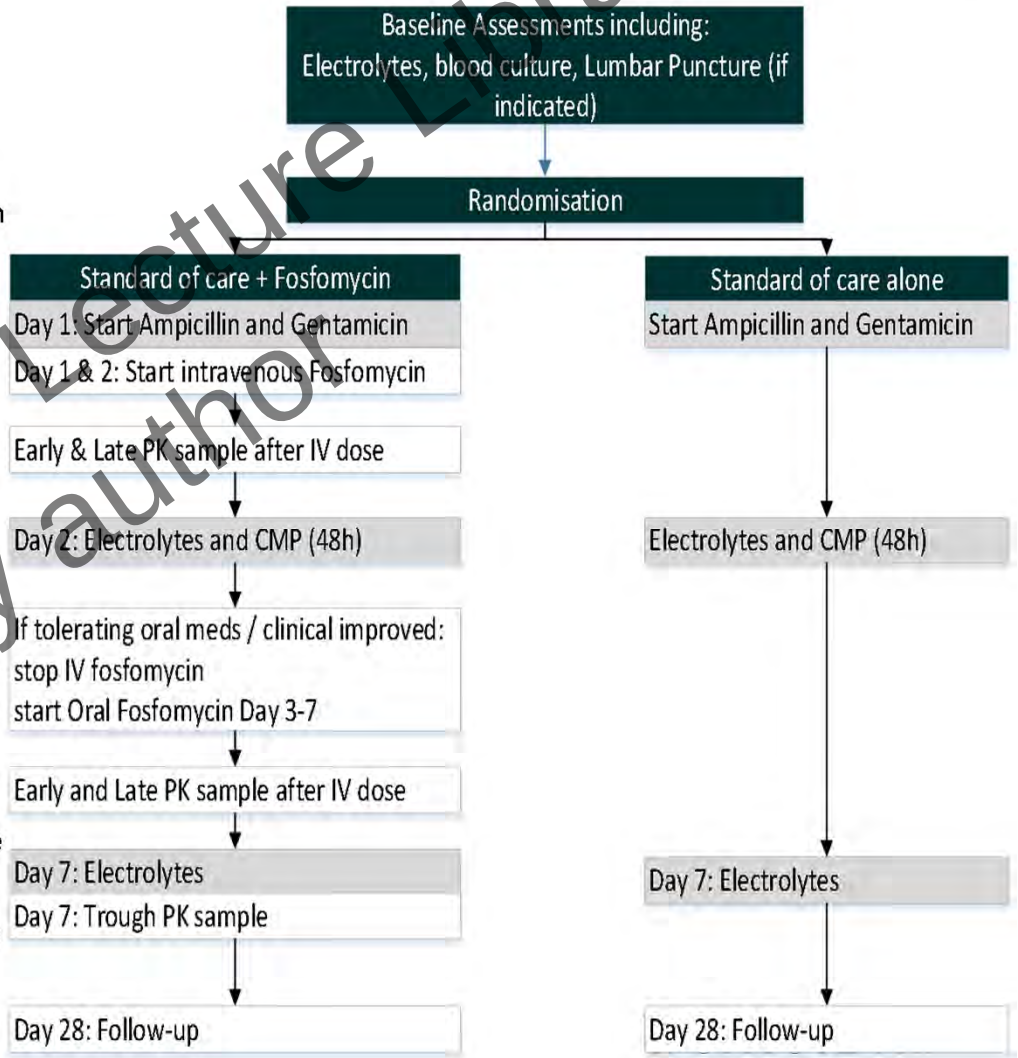
PK and Safety Sampling

Two PK samples will be taken after the first IV and oral doses; the sampling times will be randomly allocated to one of three possible early and late time points

blood sampling for electrolytes including sodium at Day 2 and 7 to assess fosfomycin safety

Statistics

Sample size: 60 babies to get 45 with complete PK



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NeoAMR TPP2

Indication	Neonatal sepsis, where **MDR Gram-negative pathogens** have been demonstrated, including **K. pneumoniae, P. aeruginosa or Acinetobacter spp. Including CROs** Neonatal meningitis
Patient Population	Hospitalized neonates with severe infections, failure on optimal current treatment and proven microbiology
Route of Administration	i.v., 30-120 min infusions
Dosing Schedule	2-4 x daily
Efficacy	Comparable clinical activity to existing options in claimed indication
	Clinical activity in pathogens resistant to carbapenems
Treatment duration	5-28 days
Safety / Tolerability	Low propensity for resistance development, large therapeutic window concerning hepatotoxicity, nephro- and CNS-toxicity, no QT-prolongation
Drug Interactions	Comparable to competitors
Key Countries	Europe, the Americas, Asia, Africa
Price / Day of Therapy	Average ex-factory price at launch: tbd/DOT (directly observed therapy)
Pharmacoeconomics	Reduction of intensive care unit and hospitalization days (modelling). Reimbursable
Main Competitors	Colistin monotherapy

OPTIONS FOR IMPROVING THE PHARMACOVIGILANCE OF NEONATAL AND PAEDIATRIC AB POST MARKETING APPROVAL




- The reporting of pharmacovigilance data on antibiotics in neonates and children is currently limited.
- PENTA has collected extensive PV data through the establishment of a European Pediatric Registry – EPPICC.
- A similar approach could use a Sentinel Survey approach in a network of major children's hospitals, collecting clinical, safety and outcome data on children prescribed specific ABs.
- Post Marketing Authorisation registry data should become an increasingly important component of Pediatric AB DD programs

PK PD IN SPECIAL POPULATIONS

- High unmet clinical need – 2 billion children – quarter global population – 130 million newborns
- Complex PK, but improved study design, M+S, make studies much more feasible
- Continuing need to accelerate studies of new AB…continued pragmatism required – some data better than no data..including neonatal PK
- Major programme to define optimal old AB combinations for MDR infections in pregnancy, neonates and children – GARDP
- Further consideration about PD in special populations..
- Manage risk – inaction is not an option