Dynamic Pediatric Physiology – Affects on Pharmacokinetics, Pharmacodynamics and Development of Long-Acting Therapeutics

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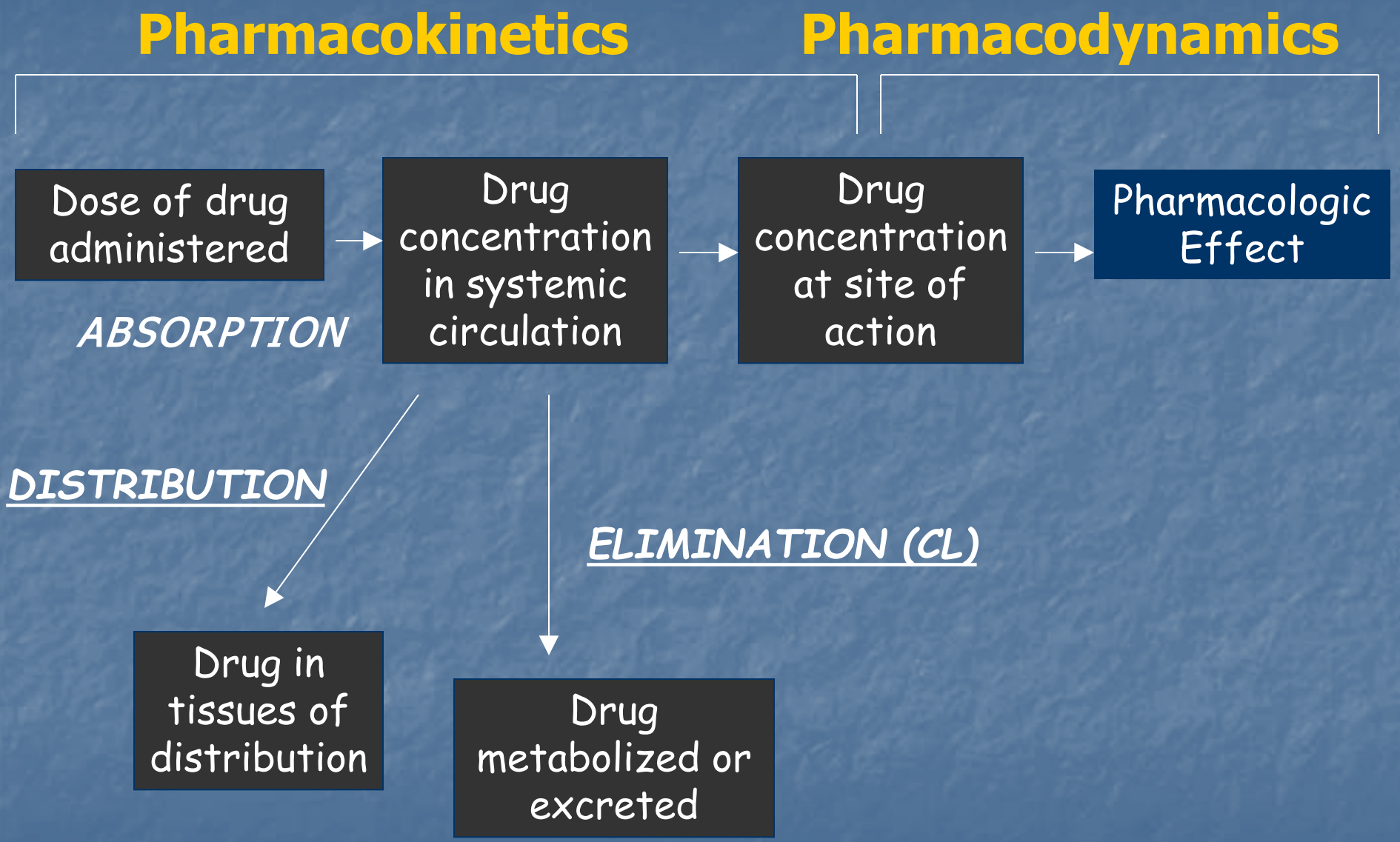
ADME - PD

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion
- **P**harmaco**D**ynamics (Response)

Age Can Impact All !

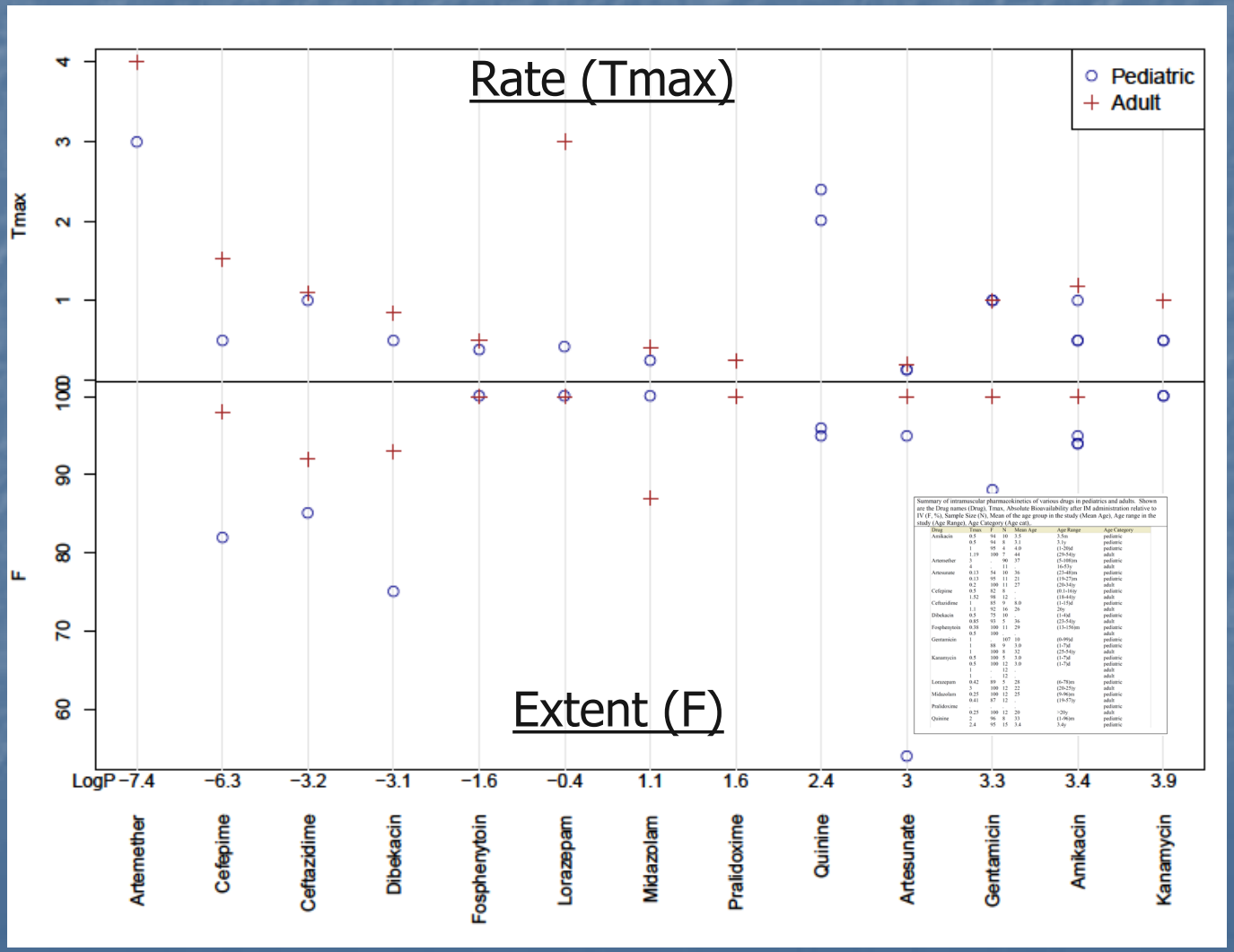

Pharmacokinetics
Pharmacodynamics
Dose of drug administered
ABSORPTION
Drug concentration in systemic circulation
Drug concentration at site of action
Pharmacologic Effect
DISTRIBUTION
ELIMINATION (CL)
Drug in tissues of distribution
Drug metabolized or excreted

Drug Absorption

Maturation of Drug Absorption

- **Rate** (KA, Tmax, Cmax) and **Extent** (F, Cmax) can be Affected by Age
- Maturation Changes Seen in Various Routes
  - **Oral Absorption**
    - Maturation in gut function may have large impact on drug absorption both KA and F
    - Multiple factors involved – GI motility, gastric pH, transporters and drug metabolizing enzymes, bile acid pool, lipolytic activity, microbiome, diet etc.
    - Largest changes in first 3 years of life
  - **IM Absorption**
    - Variable effects of age – Muscle mass, location, needle length, injection method etc.
  - **SC Absorption**
    - Mostly depends on convection though pericellular pores. Faster mAb (bNAb) absorption seen in infants
    - mAb (bNAb) absorption, distribution and metabolism driven by lymphatic (not blood) flow and lysosomal (not hepatic) enzymes

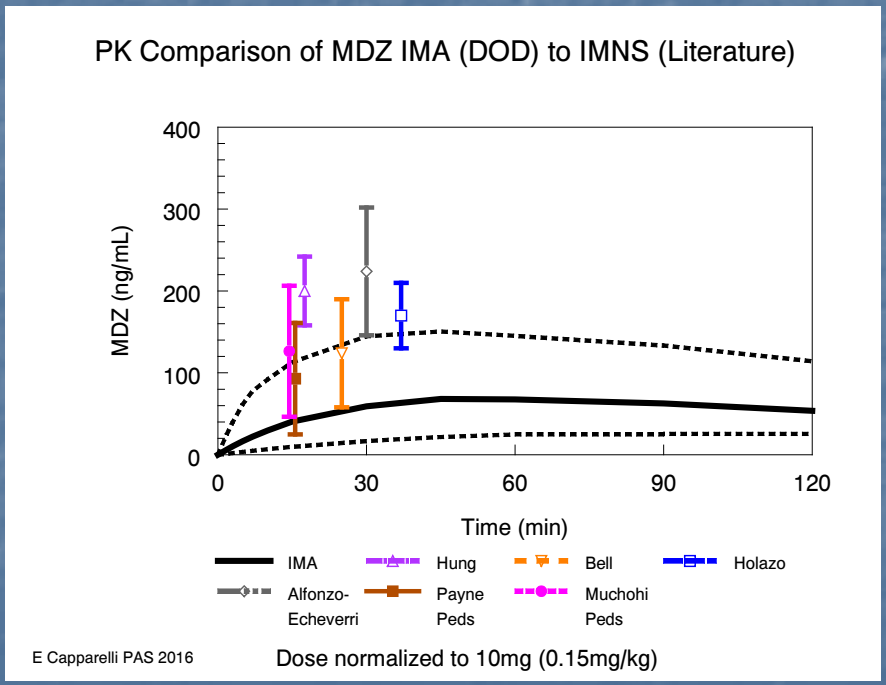
IM Absorption – Pediatric vs Adults
Rate (Tmax) and Extent (F) Drug Dependent



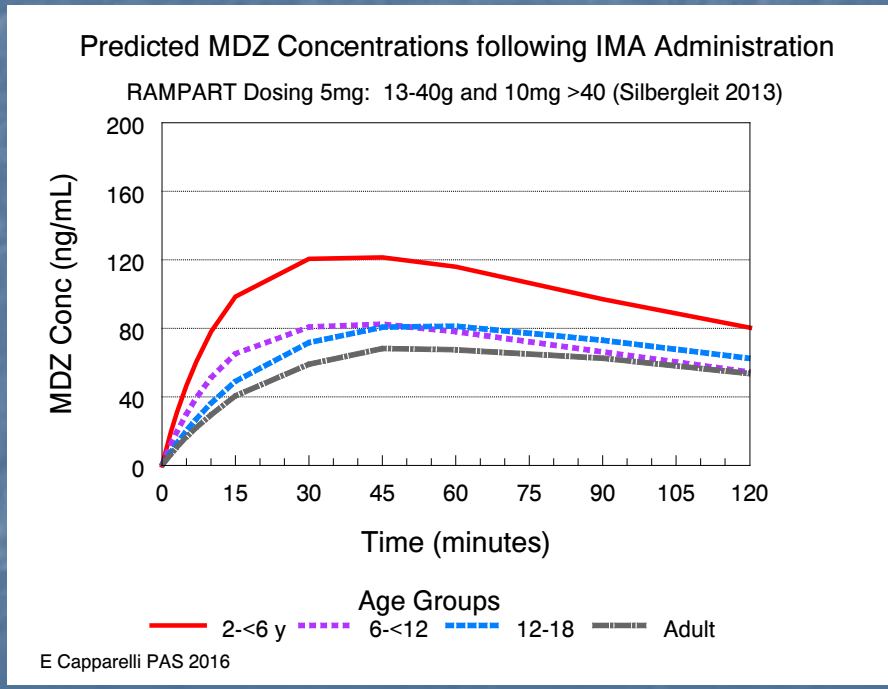
IM Absorption of Midazolam

Autoinjector IM (IMA) vs Needle Syringe (IMNS) Administration

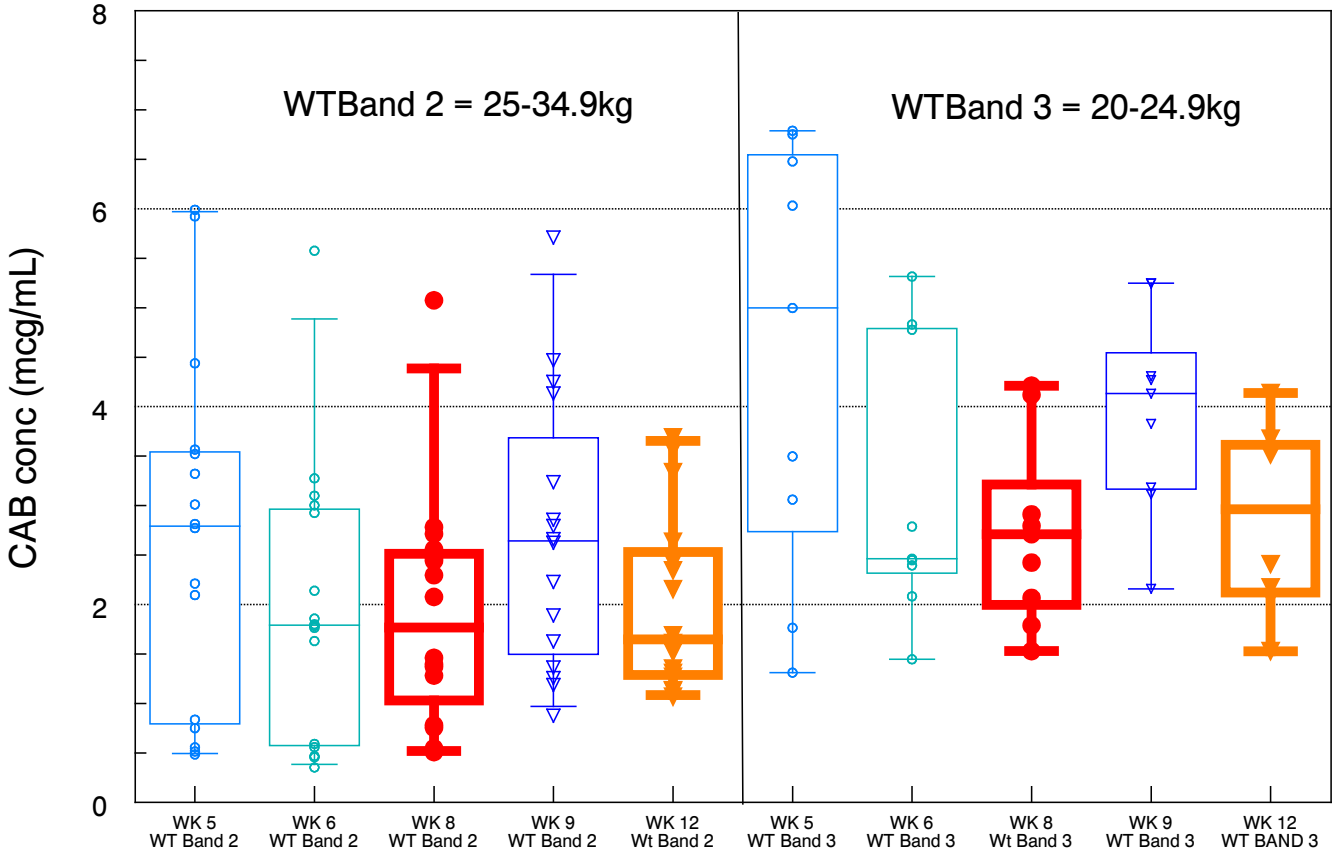
Injection Method



Age Effect



IMPAACT 2036/CRAYON IM PK (Q4W) Initial CAB Conc in Children

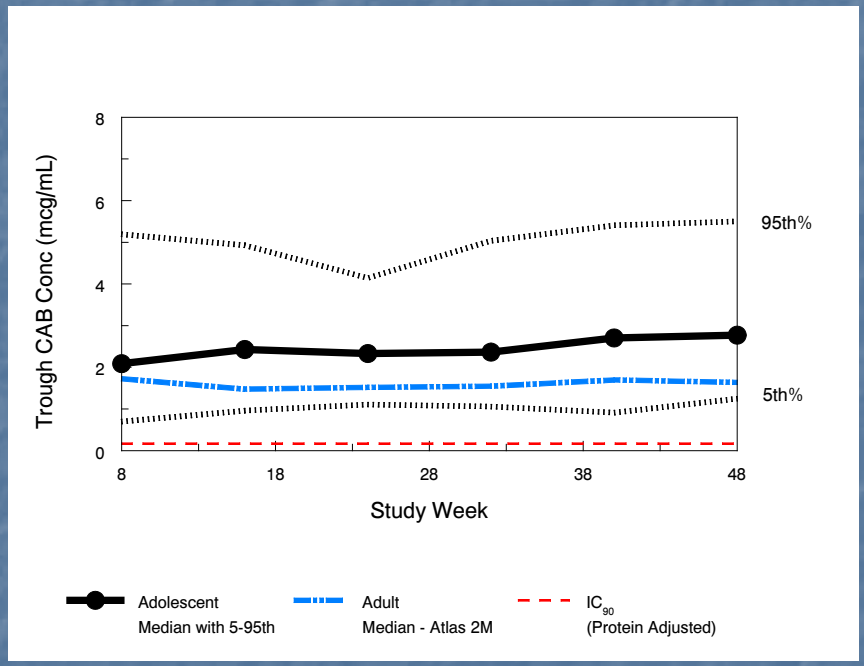


IM Dose 300mg/200mg

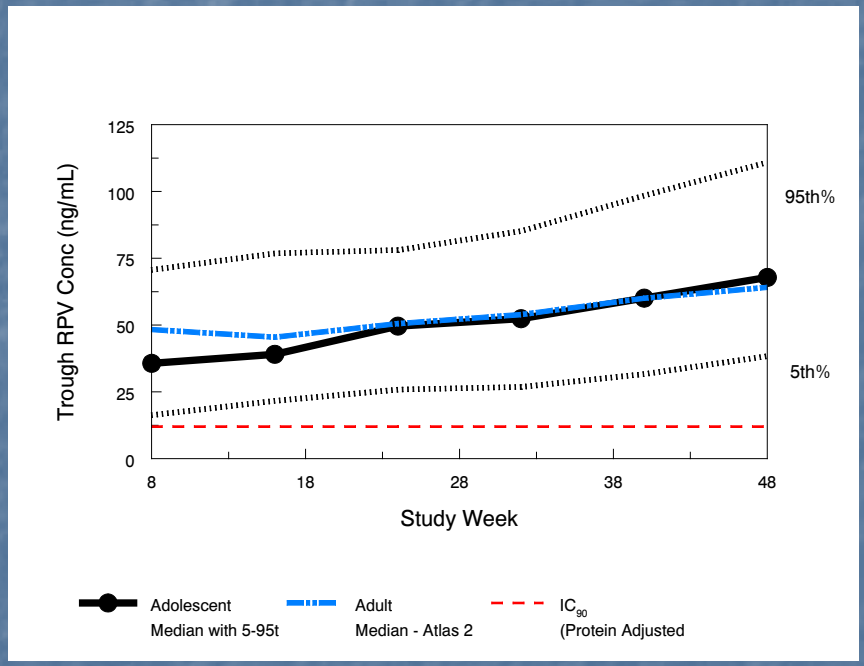
M Archary CROI 2025

IMPAACT 2017/MOCHA IM PK (Q8W)
CAB and RPV Pre-dose Conc Adolescents vs Adults

Cabotegravir



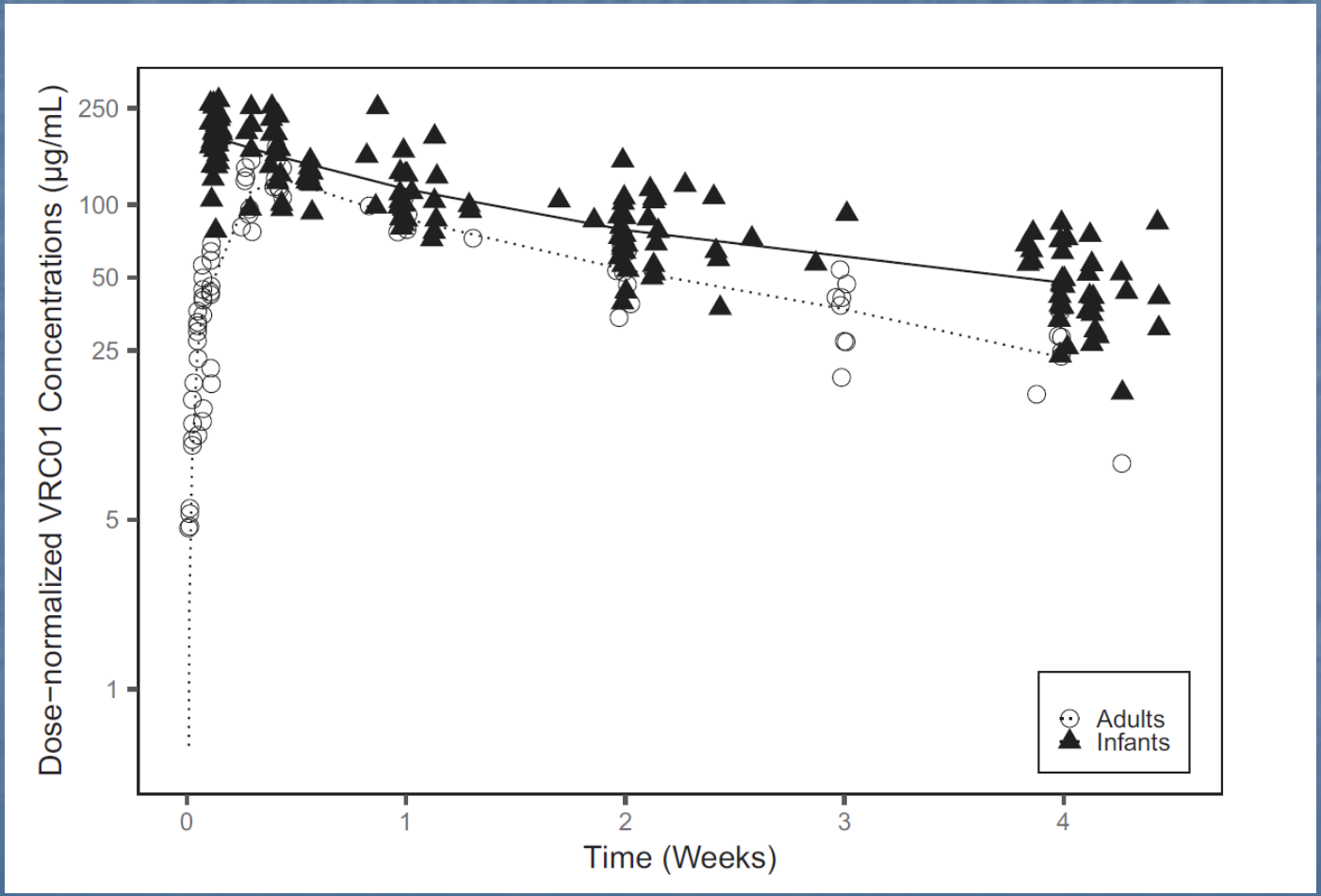
Rilpivirine



C Bolton-Moore Lancet HIV 2025, A Gaur IAS 2024

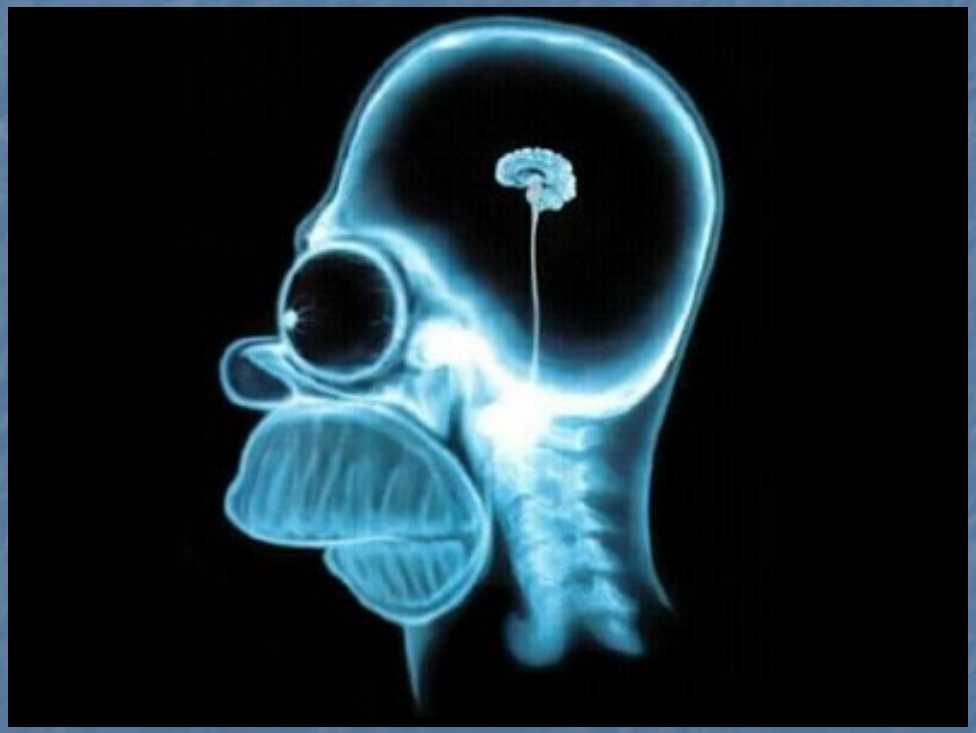
SC Absorption of VRC01 in Infants vs Adults

Faster Tmax, Higher Cmax and Lower CL/F in Infants – IMPAACT P1112

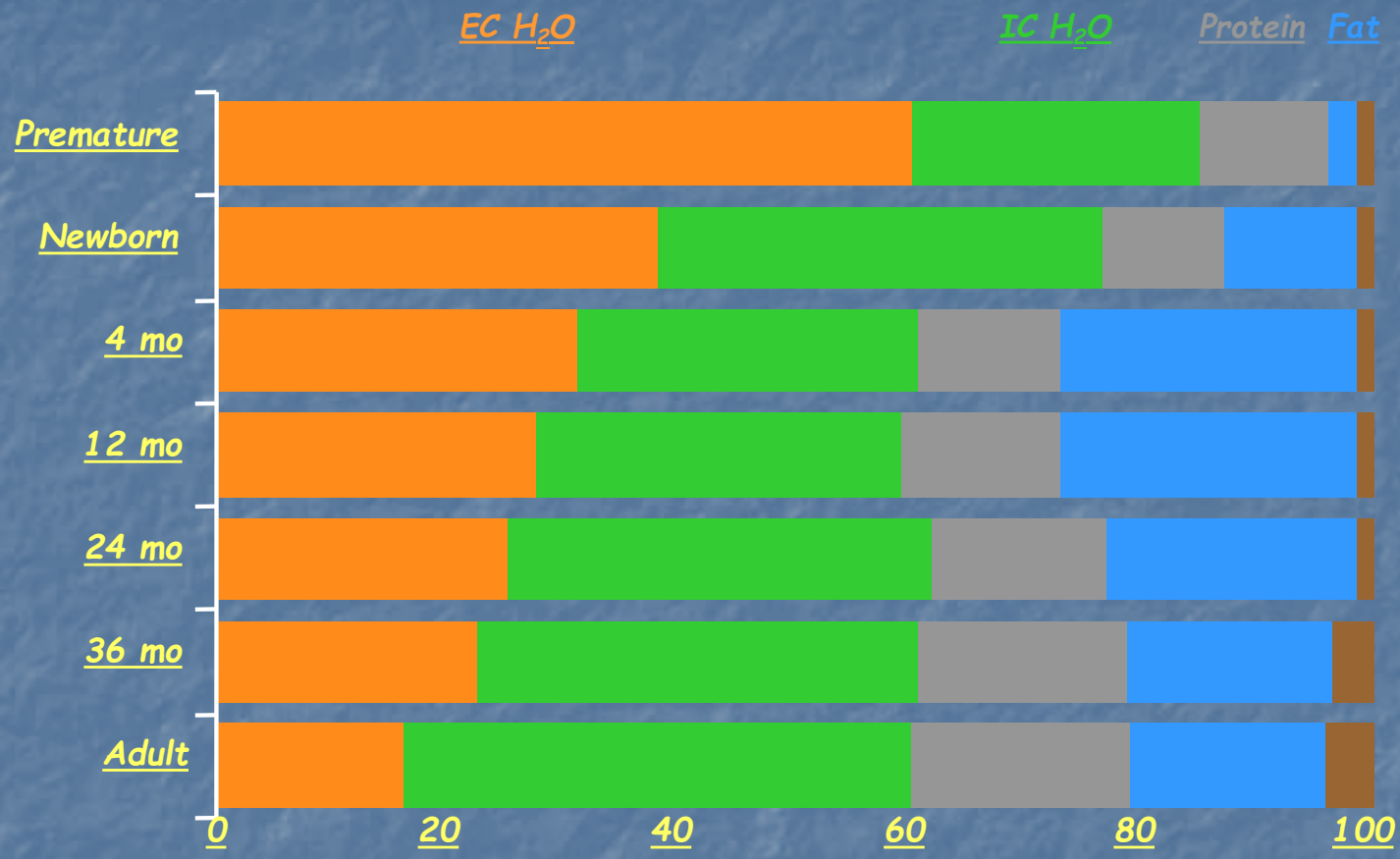


J Li CPT 2020

Distribution



Changes in Body Composition



Comparative Protein Binding

Drug	Percent Bound	
	Newborn	Adult
Ampicillin	10	18
Diazapam	84	99
Digoxin	20	32
Lidocaine	20	70
Morphine	31	42
Nafcillin	69	89
Phenytoin	80	90
Phenobarbital	32	47
Propranolol	60	93
Theophylline	36	56

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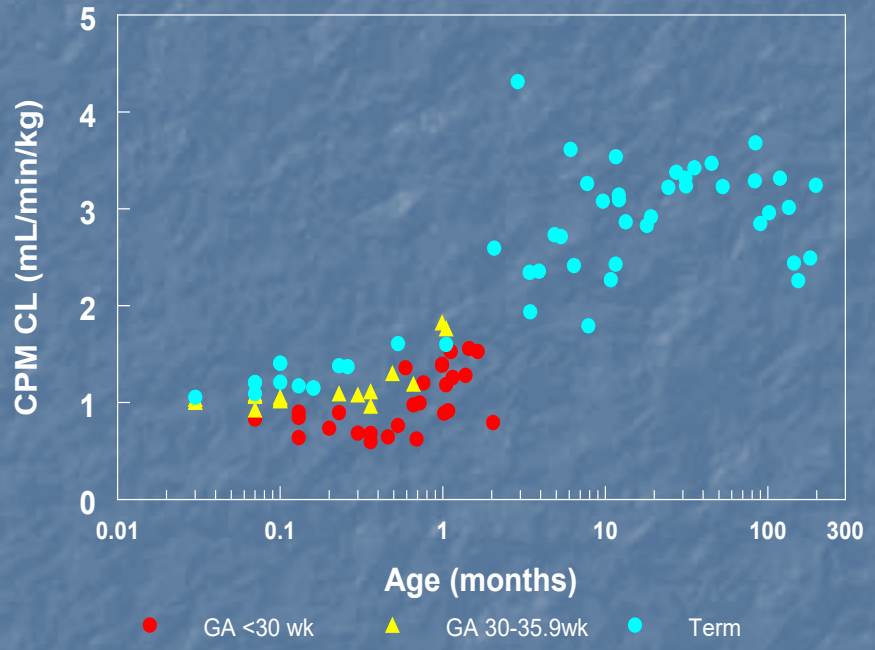
Renal Elimination

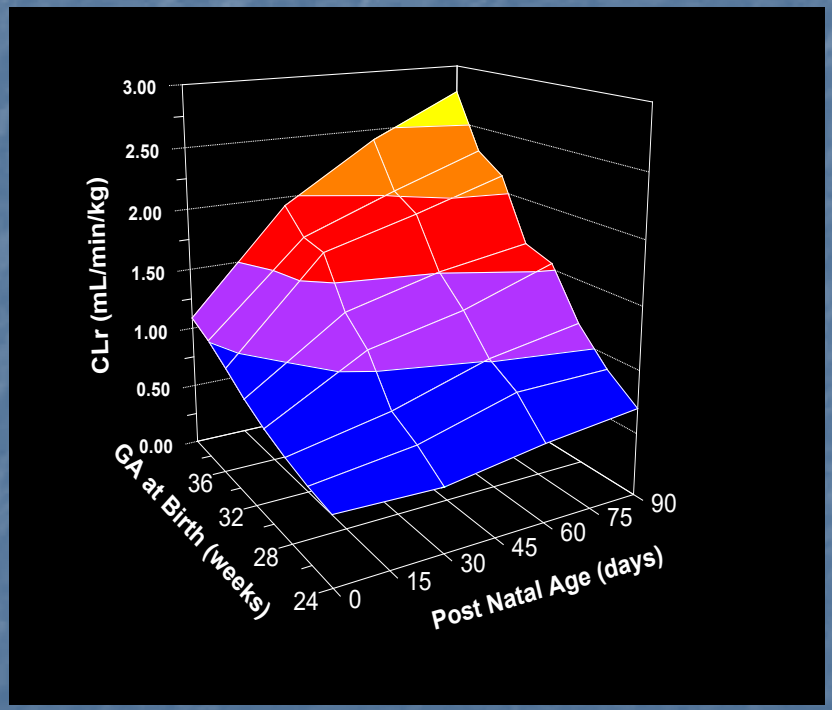
Ontogeny of Renal Drug Elimination

- Kidneys at birth receive only 5-6% of cardiac output compared to 15-25% in adults
- Renal blood flow is ~12 ml/min at birth compared to 1100 ml/min in adults
- GFR is directly proportional to gestational age (GA) beyond 34 weeks GA
- Tubular secretion increases 2 fold over the first week of life and 10 fold over first year of life
- GFR function similar in children (>2 yr) and adults normalized to BSA 80-120mL/min/1.73m^2

Maturation of Renal Drug Clearance



Cefepime

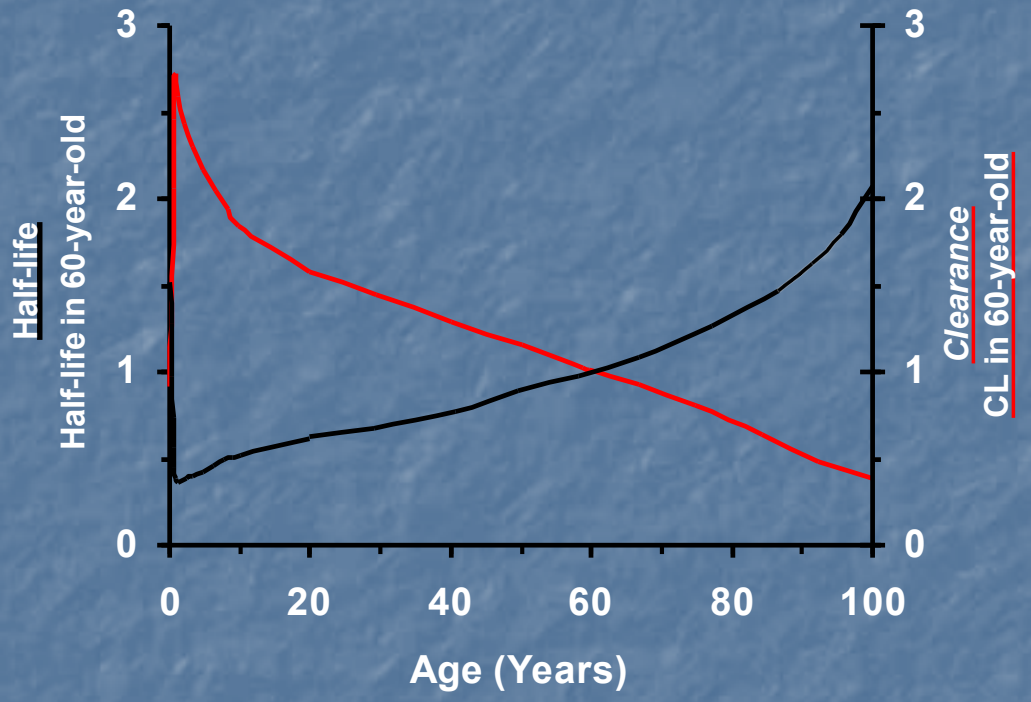


Meropenem

E Capparelli AAC 2005

PB Smith PIDJ 2011

Impact of Age on $T_{1/2}$ and CL For Renal Eliminated Drug



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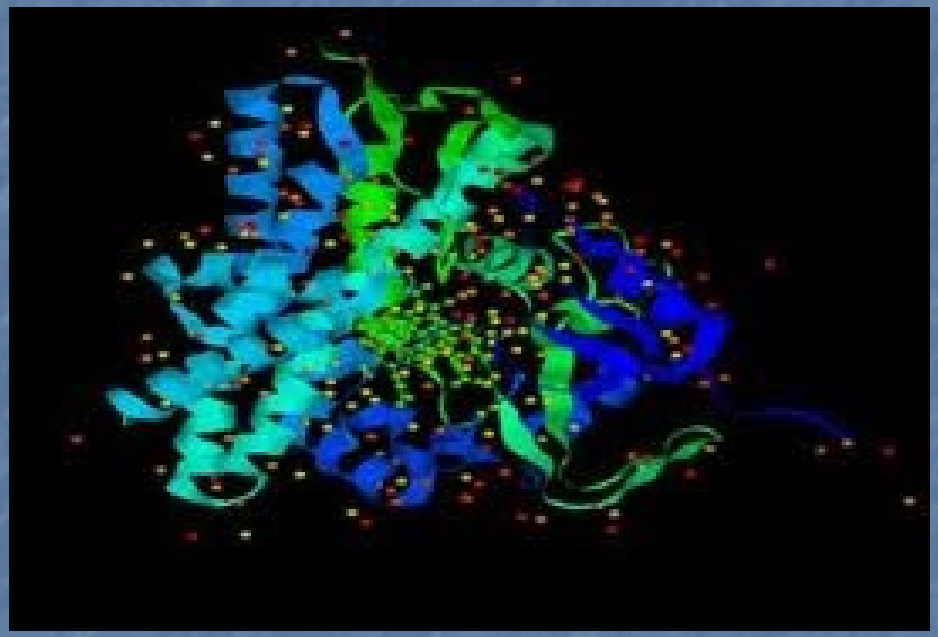
Drug Metabolism

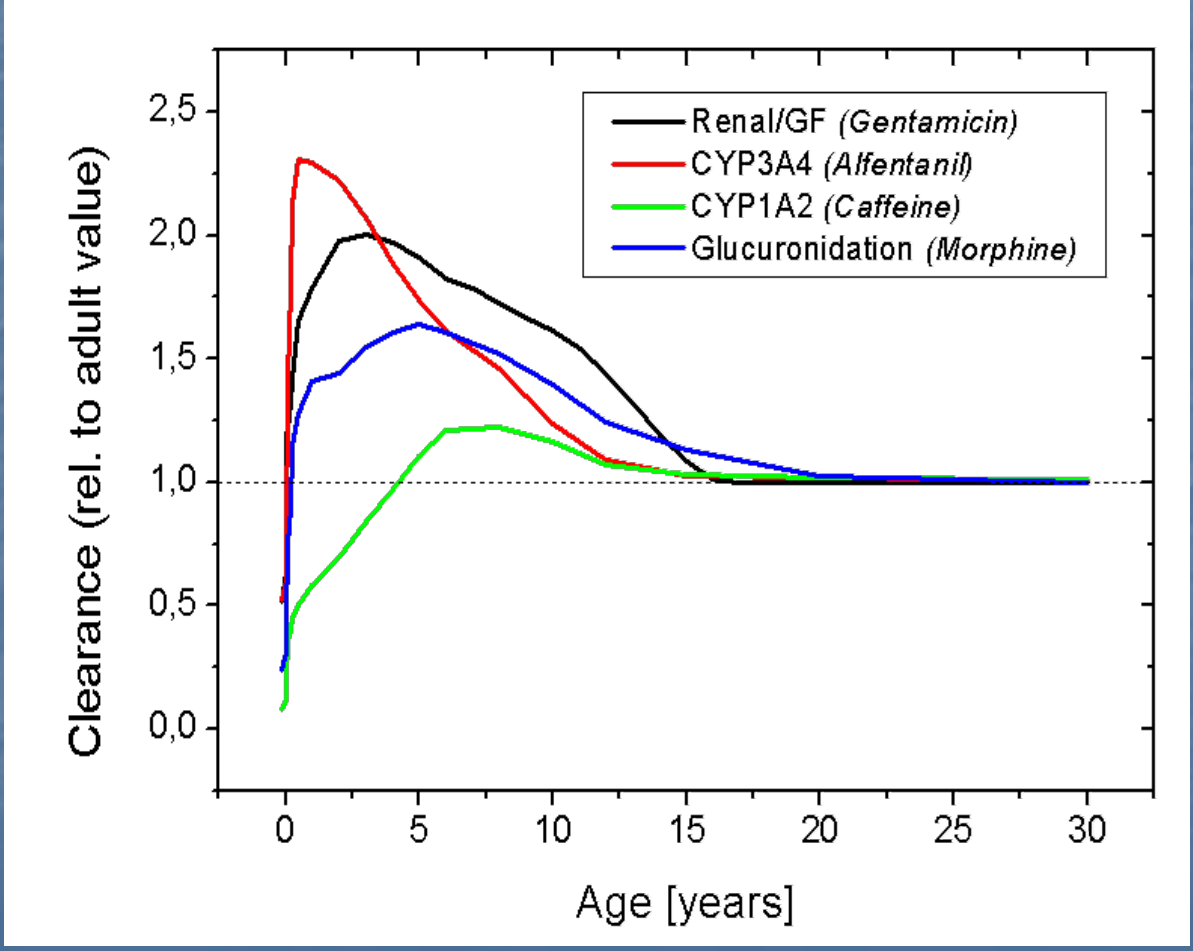


Developmental Changes in Drug Metabolism

- In general, drug metabolism pathways:
  - Are less active in newborns than in older children and adults
  - Increase to peak in young children
  - Decline to "adult" levels later (?puberty)

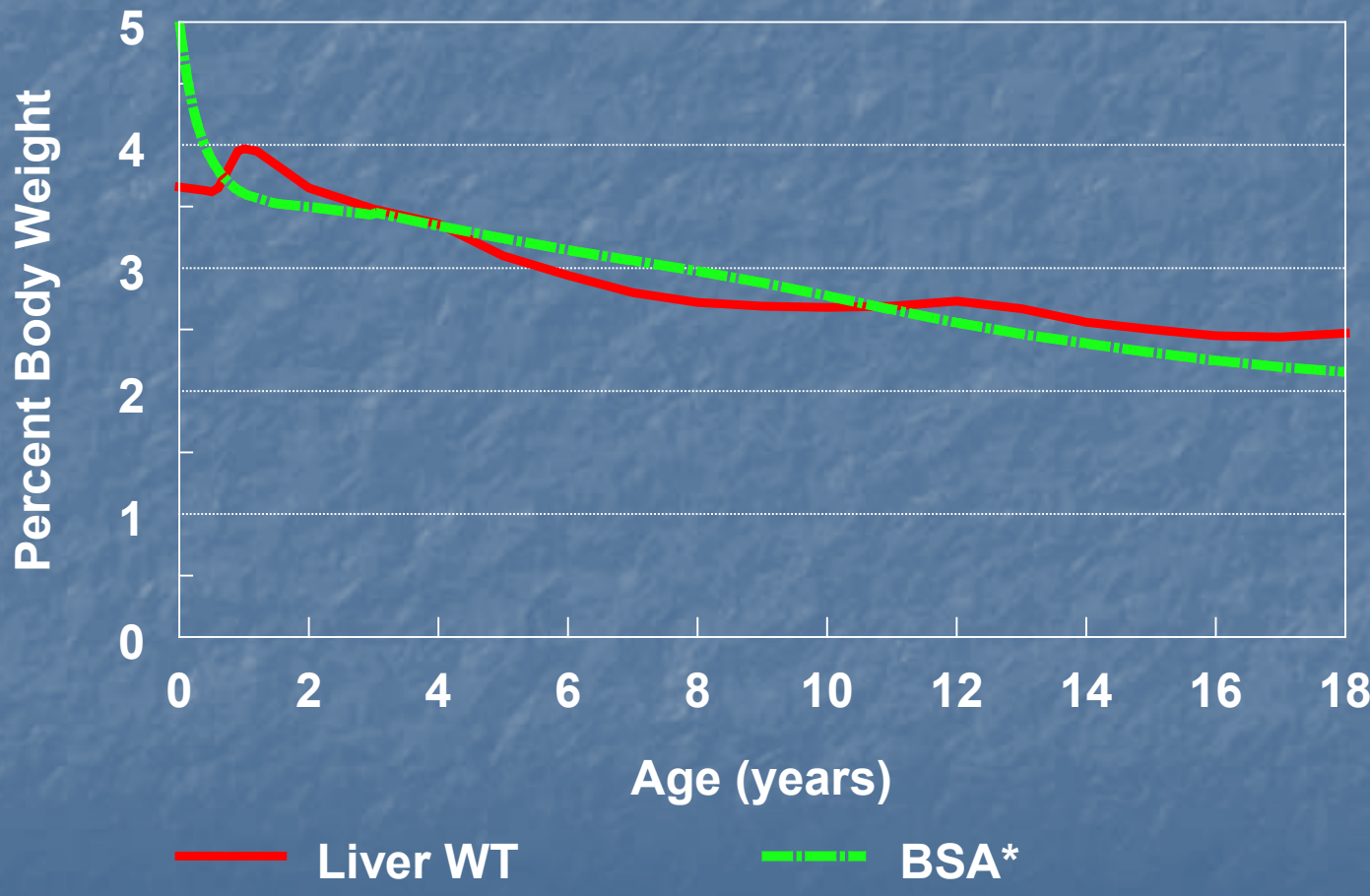
- Pattern of increase depends on the specific pathway
  - Peak activity
  - Time to peak activity

Developmental Changes in Drug Elimination



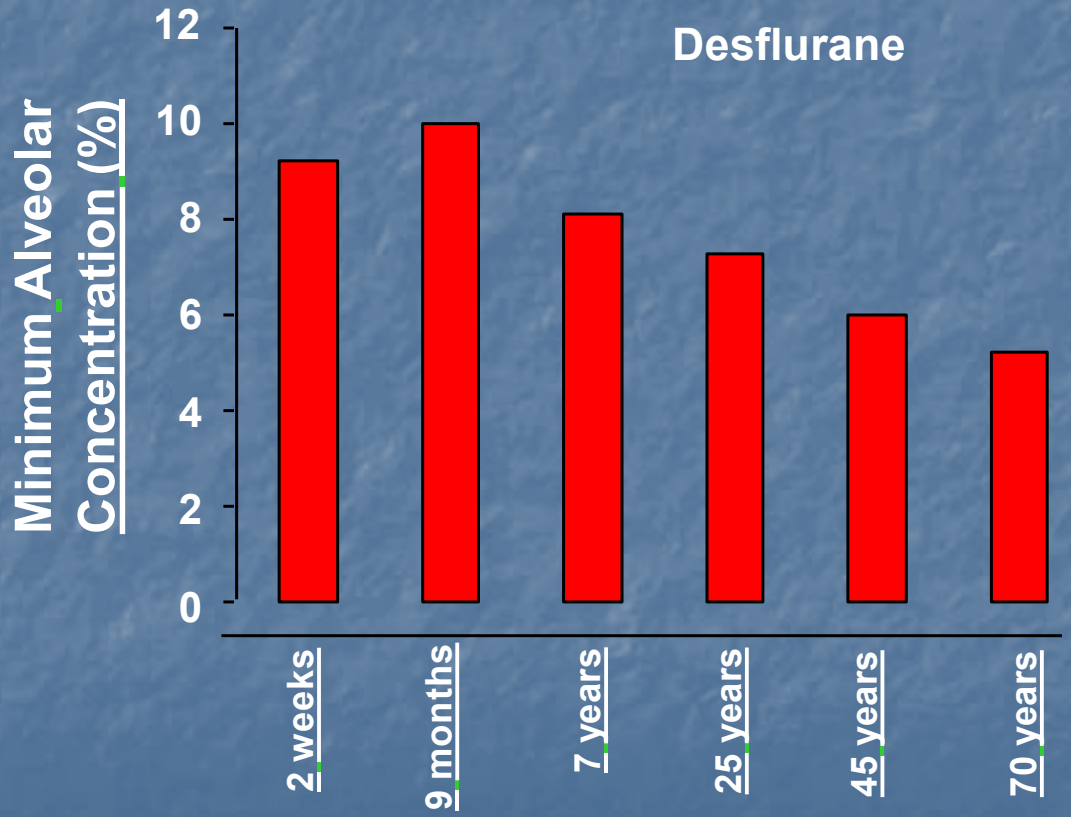
A Edington Clin Pharmacokin 2006

Liver Size as a Source of Developmental Changes in Metabolism



*multiplied x scalar

Changes in PD – Anesthesia at Various Ages



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Summary of Physiological Differences Between Neonates and Adults

Gastric pH	Increased
Gastric Motility	Decreased
Gastric Emptying Time	Increased
Intestinal flora, pancreatic enzymes, bile salts	Decreased
Percutaneous Absorption	Increased
Total body water % & Extracellular water	Increased
Plasma Proteins	Decreased
Hepatic Enzyme capacity	Decreased
Renal Function	Decreased

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NIH National Institute of Allergy and Infectious Diseases

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