DEVELOPMENTAL PHARMACOKINETICS

Viewpoint of a neonatal clinical pharmacologist

John N. van den Anker, MD, PhD

- Evan and Cindy Jones Endowed Chair of Pediatric Clinical Pharmacology, Vice Chair of Pediatrics for Experimental Therapeutics, and Chief of the Division of Clinical Pharmacology, Children's National Medical Center, Washington, DC
- Eckenstein-Geigy Distinguished Professor of Pediatric Pharmacology, and Chair of the Department of Pediatric Pharmacology and Pharmacometrics, University of Basel Children's Hospital, Basel, Switzerland

Disclosure(s)

- No conflict to disclose
- Off label drug use in neonates, treated in NICUs, is the current standard and therefore will be presented


25
20
15
10
5
0
5
10
15
20
25

Medication Use in NICUs – Pediatrix, Inc. Data for 2007: 72,647 Patients - Rate/1000 Discharges

Drug	Rank	Use
Gentamicin	1	822
Ampicillin	2	726
Surfactants	3	234
Caffeine	4	224
Furosemide	5	199
Vancomycin	6	177
Metoclopramide	7	82
Fentanyl	8	95
Dopamine	9	89
Midazolam	10	80
Morphine	11	71
Ranitidine	12	70
Cefotaxime	13	62
Phenobarbital	14	59
Indomethacin	15	54

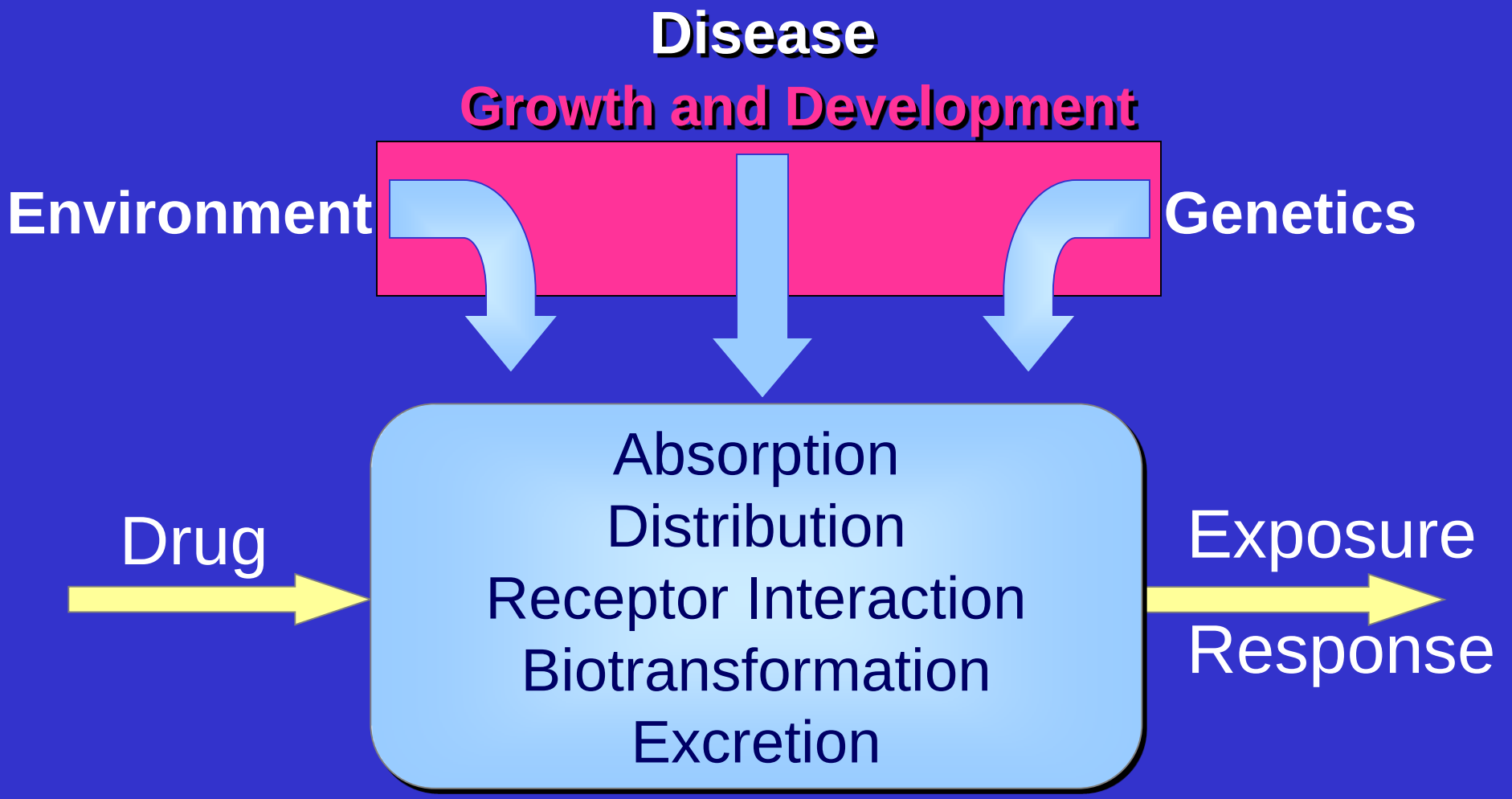
Data from Reese Clark 2007

Medication Use in NICUs, 2014

Drug	Rank	
Ampicillin	1	
Gentamicin	2	
Caffeine	3	
Vancomycin	4	
Beractant	5	
Furosemide	6	
Fentanyl	7	
Dopamine	8	
Midazolam	9	
Calfactant	10	
Metoclopramide	11	
Ranitidine	12	
Poractant alpha	13	
Morphine	14	
Cefotaxime	15	

Data from PTN network 2014

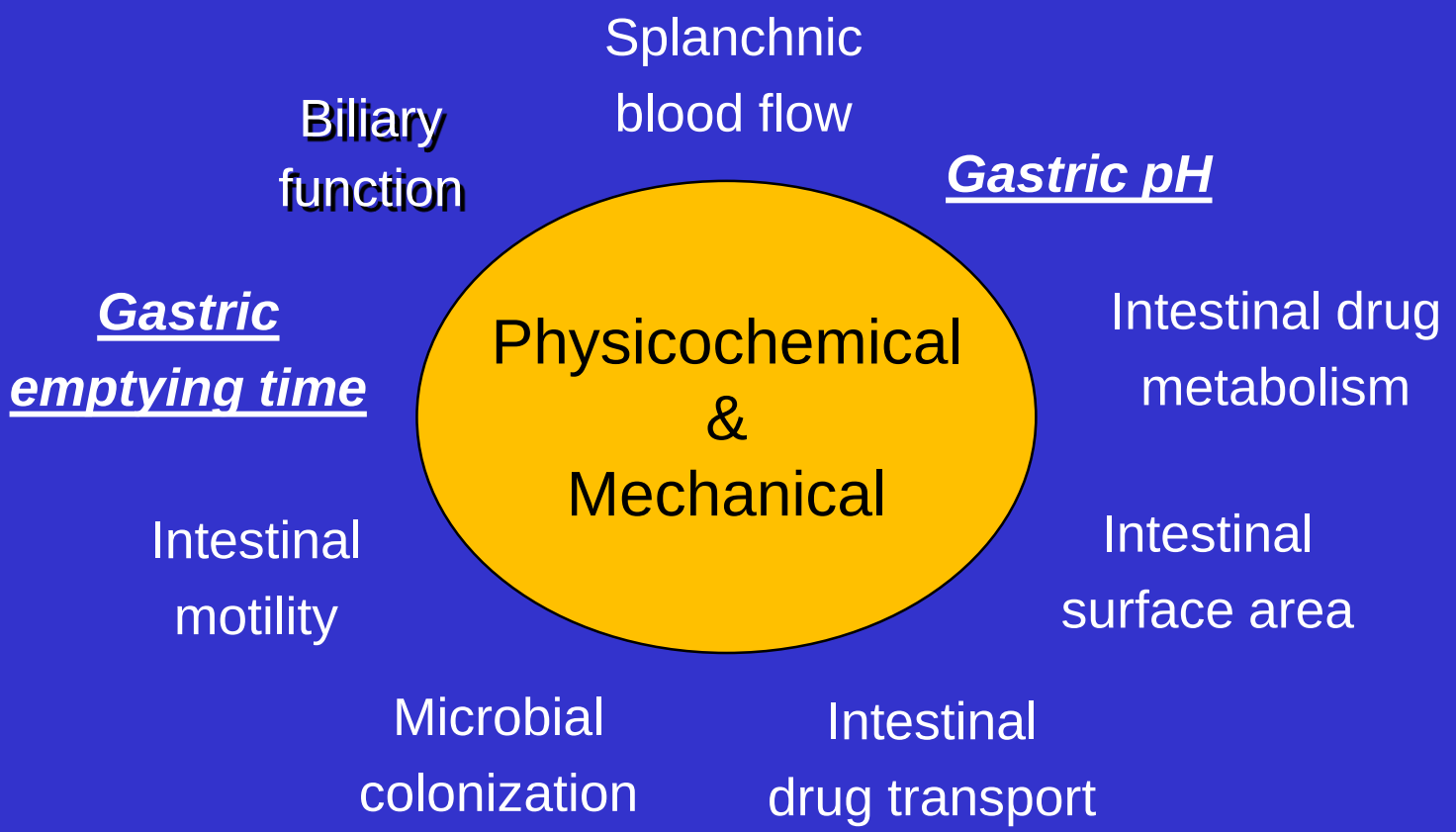
Determinants of Drug Response in Neonates



The Challenge of Neonatal Clinical Pharmacology: Determining the Source(s) of Variability

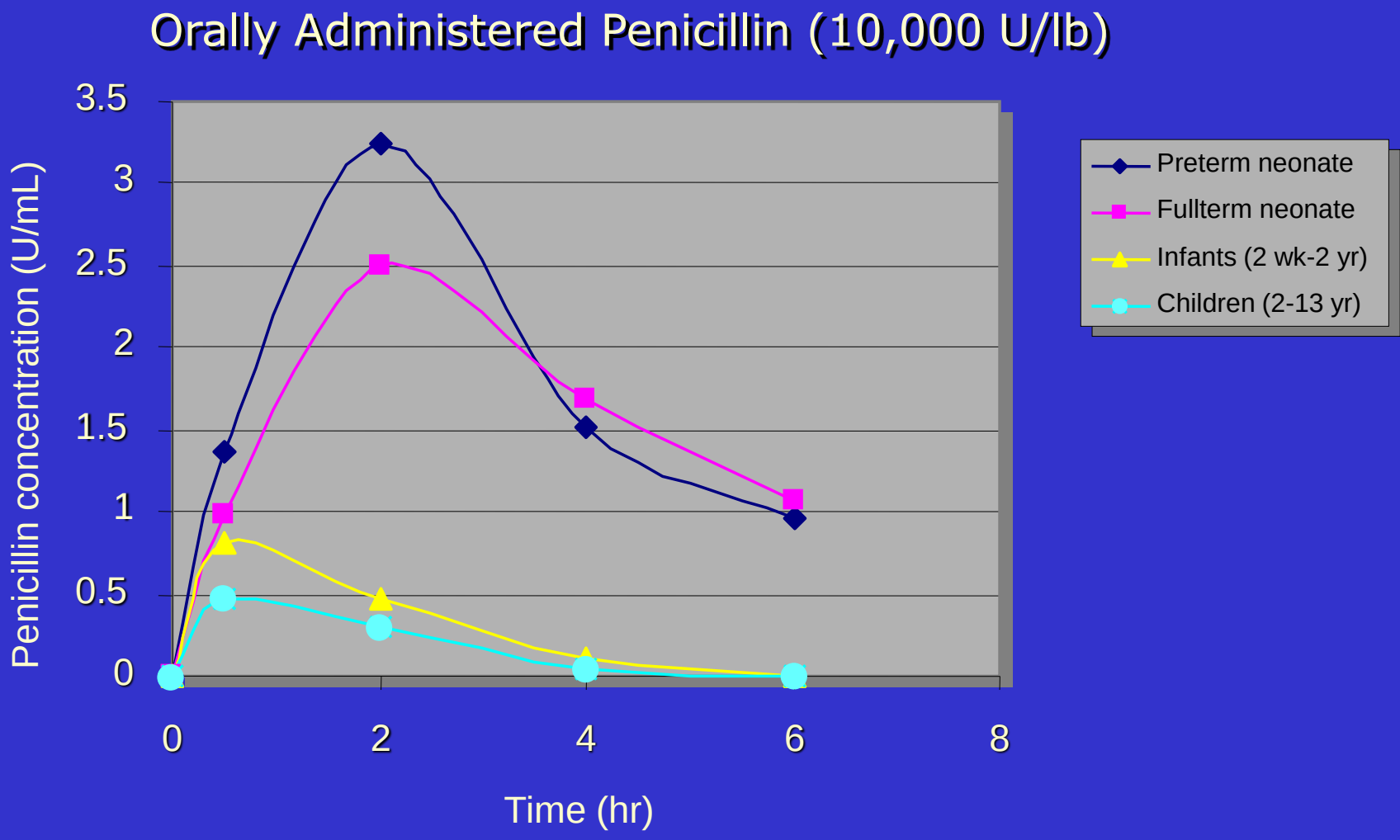
Ontogeny

Factors Influencing Oral Drug Absorption



Biopharmaceutical, Interactions, etc

Developmental Alterations in Intestinal Drug Absorption Influence of Higher Gastric pH



Huang NN and High RH. J Pediatr 1953;42(6):657-8

Influence of Developmental Alterations in Gastric Emptying and Intestinal Transit

	Postconceptional Age		
	28-36 wks. (n = 17)	36-42 wks. (n = 13)	42-54 wks. (n = 5)
Cmax (ng/ml)	30.0(17.5)	23.3(11.7)	44.5(19.5)
Tmax (hr)	5.0(2.6)	4.3(3.3)	2.2(1.1)
T1/2 (hr)	11.6(3.0)	11.5(3.0)	4.8(3.0)
AUC (ng/ml*hr)	568(257)	362(198)	364(249)
VDss/F (L/kg)	7.4(4.7)	12.7(9.1)	4.1(1.5)
Cl/F (L/hr/kg)	0.45(0.26)	0.75(0.46)	0.85(0.69)

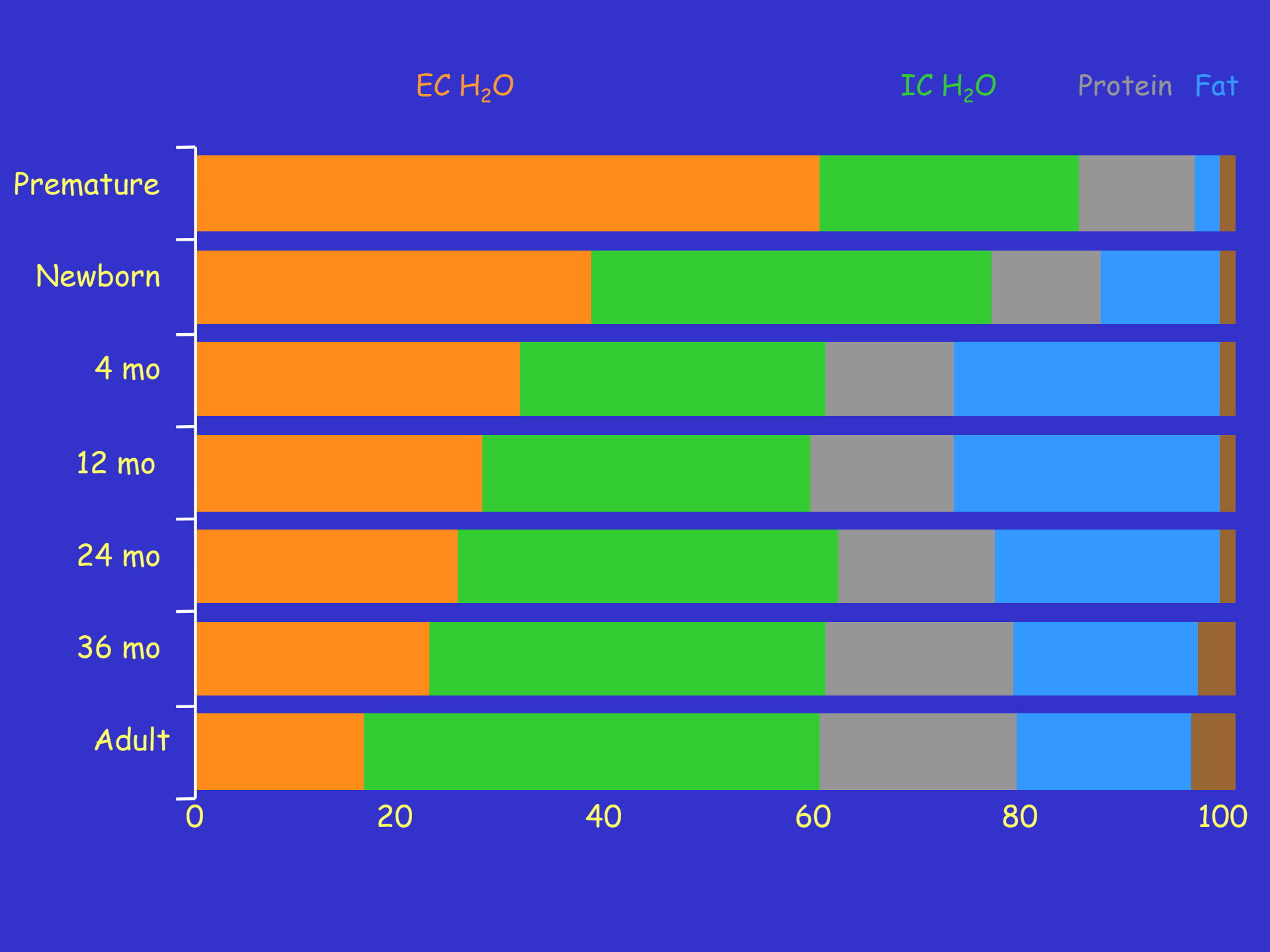
Kearns, Robinson, Wilson-Costello, Knight, Ward, van den Anker. *Clin Pharmacol Ther 2003;74:312-325*

65 Years Later!!

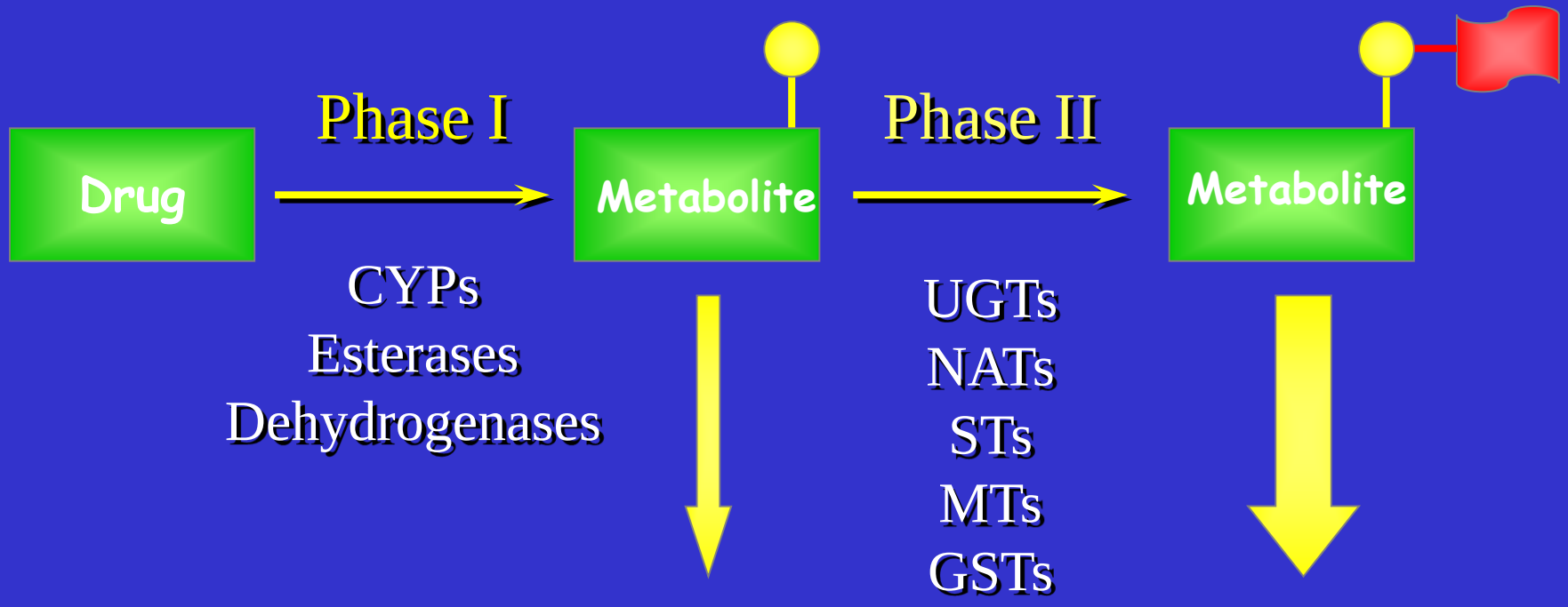
No consensus about the ontogeny of gastric acid production (rate and amount) and secretion or on its impact on drug absorption in the preterm/full term neonate and during infancy

Very limited understanding of the effect of age on the rate and extent of gastric emptying in the neonate and during early infancy

Van den Anker, Reed, Allegaert, Kearns. J Clin Pharmacol 2018;58(S10):S10-S25)


EC H_2O
IC H_2O
Protein
Fat
Premature
Newborn
4 mo
12 mo
24 mo
36 mo
Adult
0
20
40
60
80
100

Drug Biotransformation

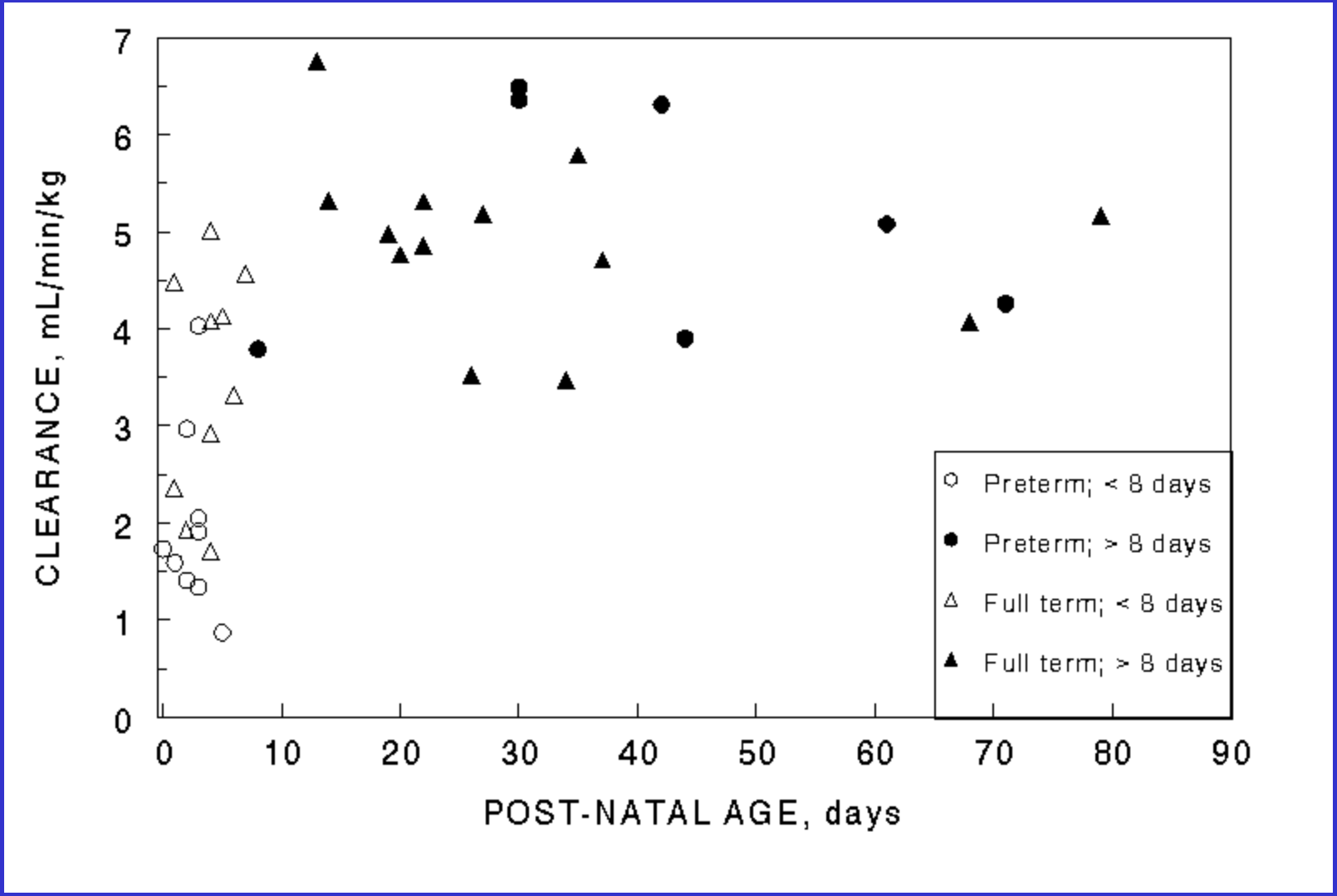


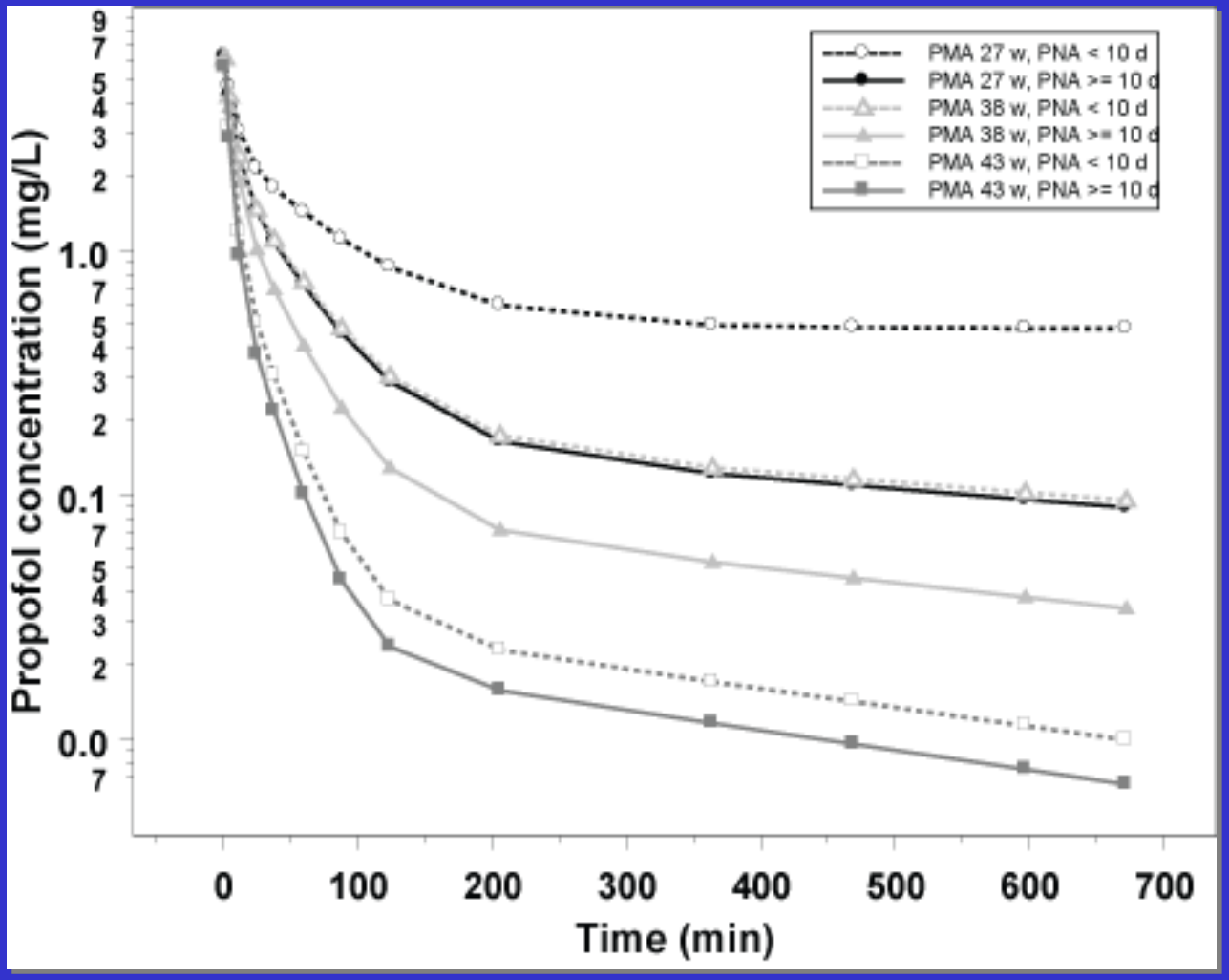
Impact of Age on Linezolid Pharmacokinetics

Parameter	Adult (n=57)	Child (n=44)	Infant (n=10)
Vdss (L/kg)	0.63 ± 0.13	0.71 ± 0.18	0.83 ± 0.18
Cl (L/hr/kg)	0.10 ± 0.03	0.30 ± 0.12	0.52 ± 0.15
$t_{1/2}$ (hr)	4.6 ± 1.7	3.3 ± 0.9	2.0 ± 0.9
$Cmax_{norm}$ (mg/L)	19.7 ± 4.9	17.0 ± 5.2	12.5 ± 3.5
$C_{12\ pred}$ (mg/L)	3.3 ± 2.1	0.41 ± 0.72	0.03 ± 0.05
$T>MIC_{90}$ (%)	70-100%	35-70%	20-35%

Kearns, Jungbluth, Abdel-Rahman, Hopkins, Welshman, Grzebyk, Bruss, van den Anker.
Clin Pharmacol Ther 2003;74:413-422

Linezolid Plasma Clearance Association with PNA



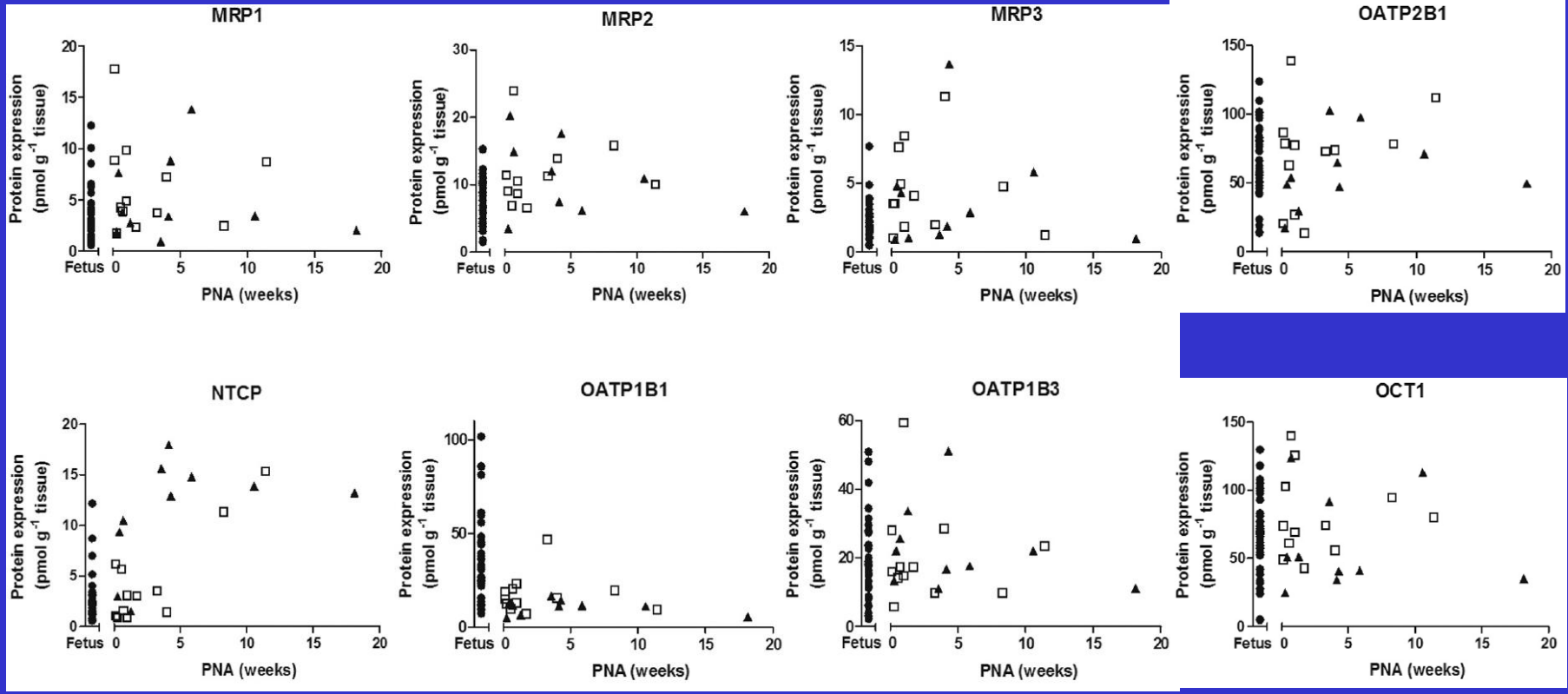


Allegaert K, et al. Br J Anesth 2007 dec 99(6):864-70

Ontogeny of Drug Disposition in Neonates: Recent Developments

- Shift from studies describing ontogeny of drug disposition genes using mRNA expression data to those presenting quantitative proteomic data
  - *CYPs, UGTs and other drug metabolizing enzymes*
  - *Transporters*

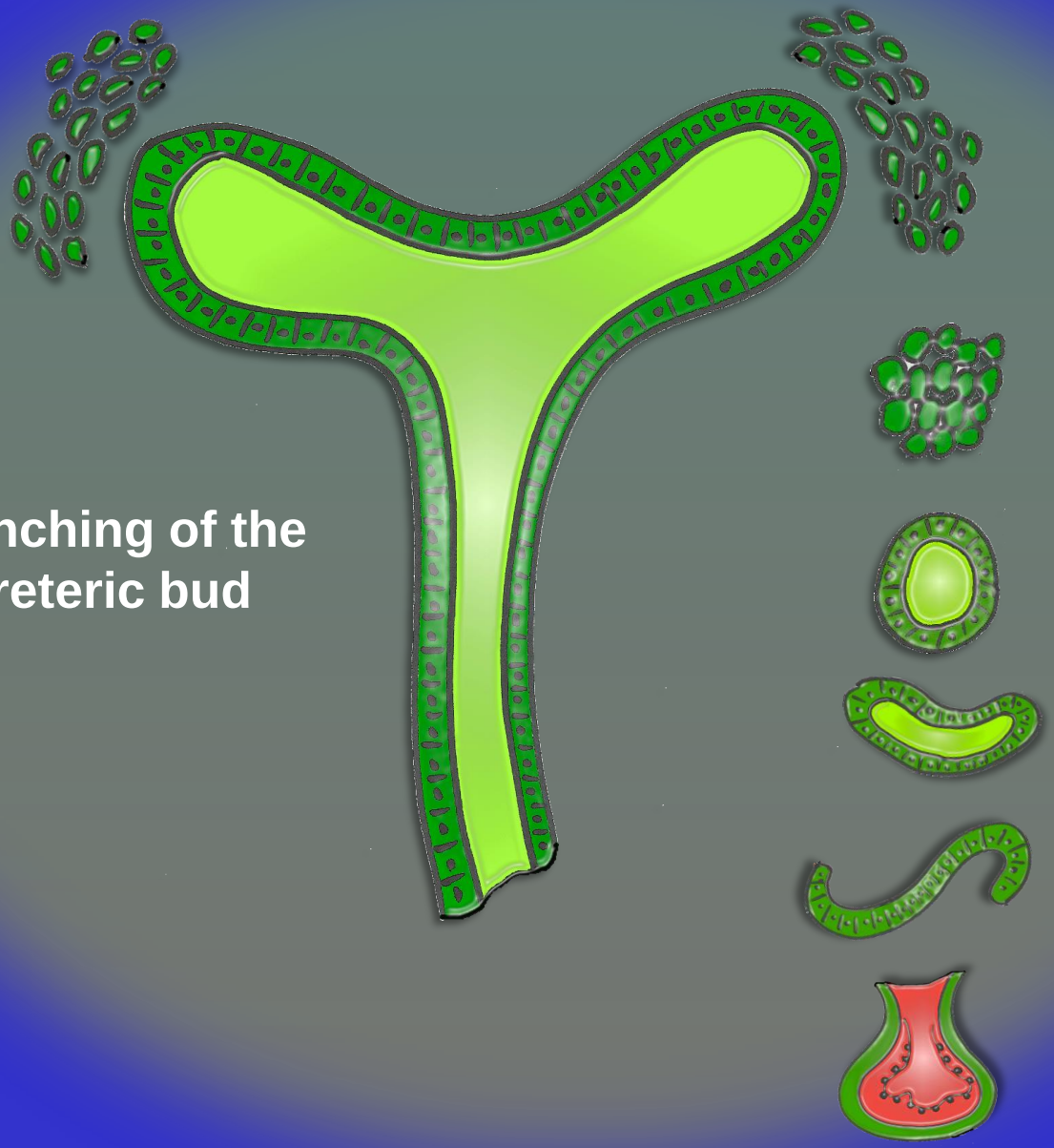
Ontogeny of Transporters: Proteomic Data



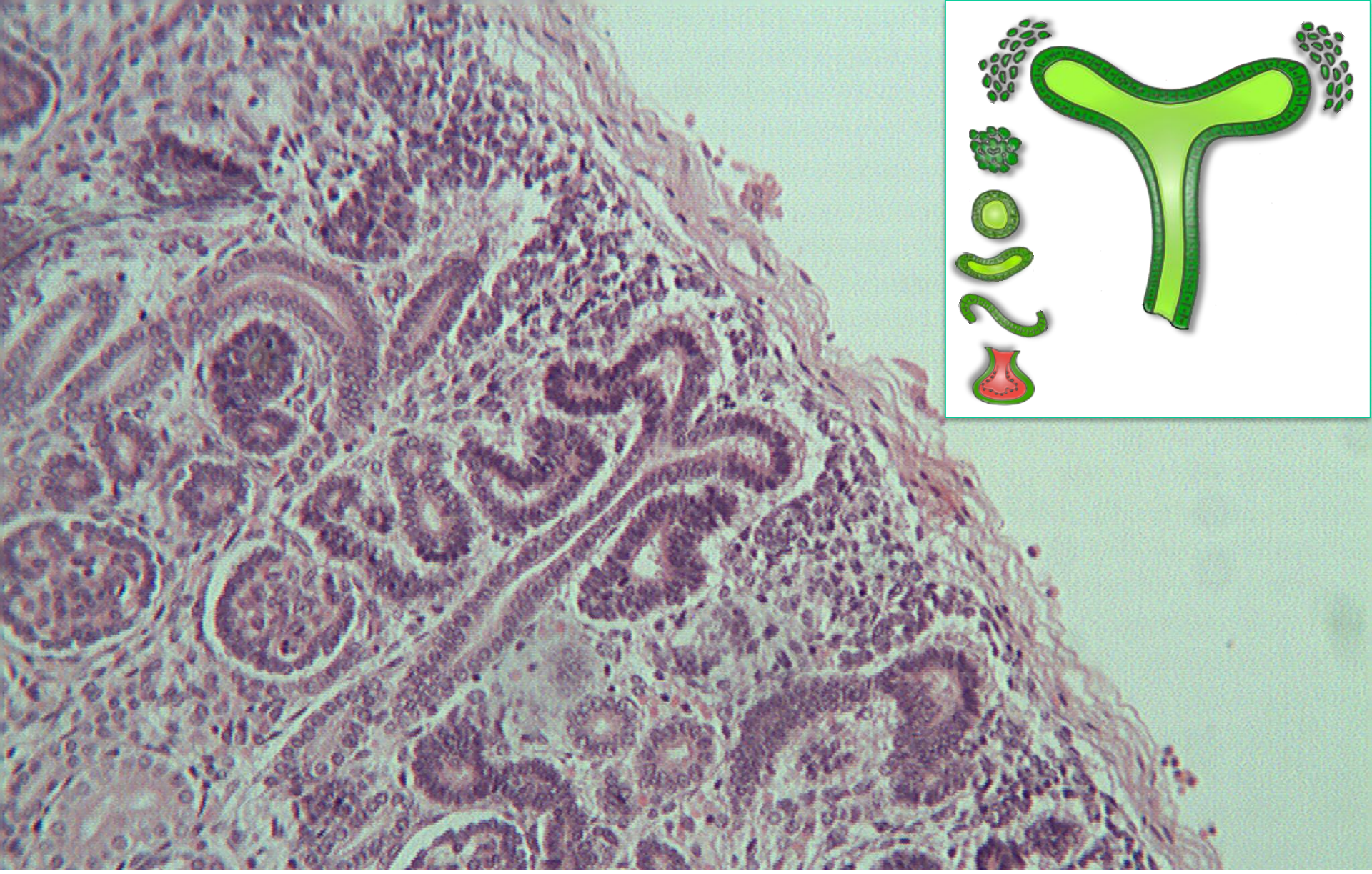
Van Groen B et al. Eur J Pharm Sci 2018;124:217-227

Back to the future: embryology

MET: Mesenchymal Epithelial Transition

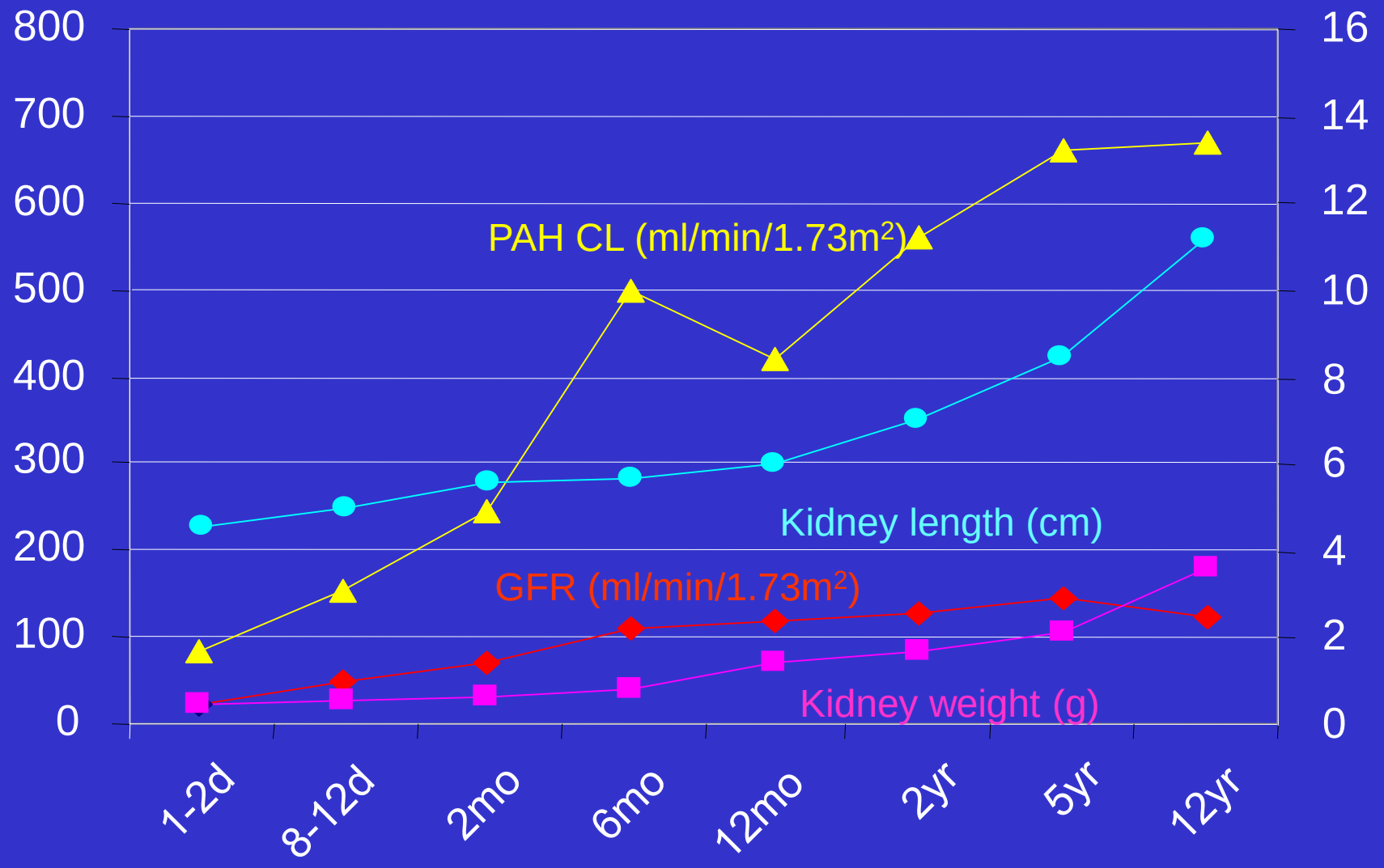


Branching of the ureteric bud

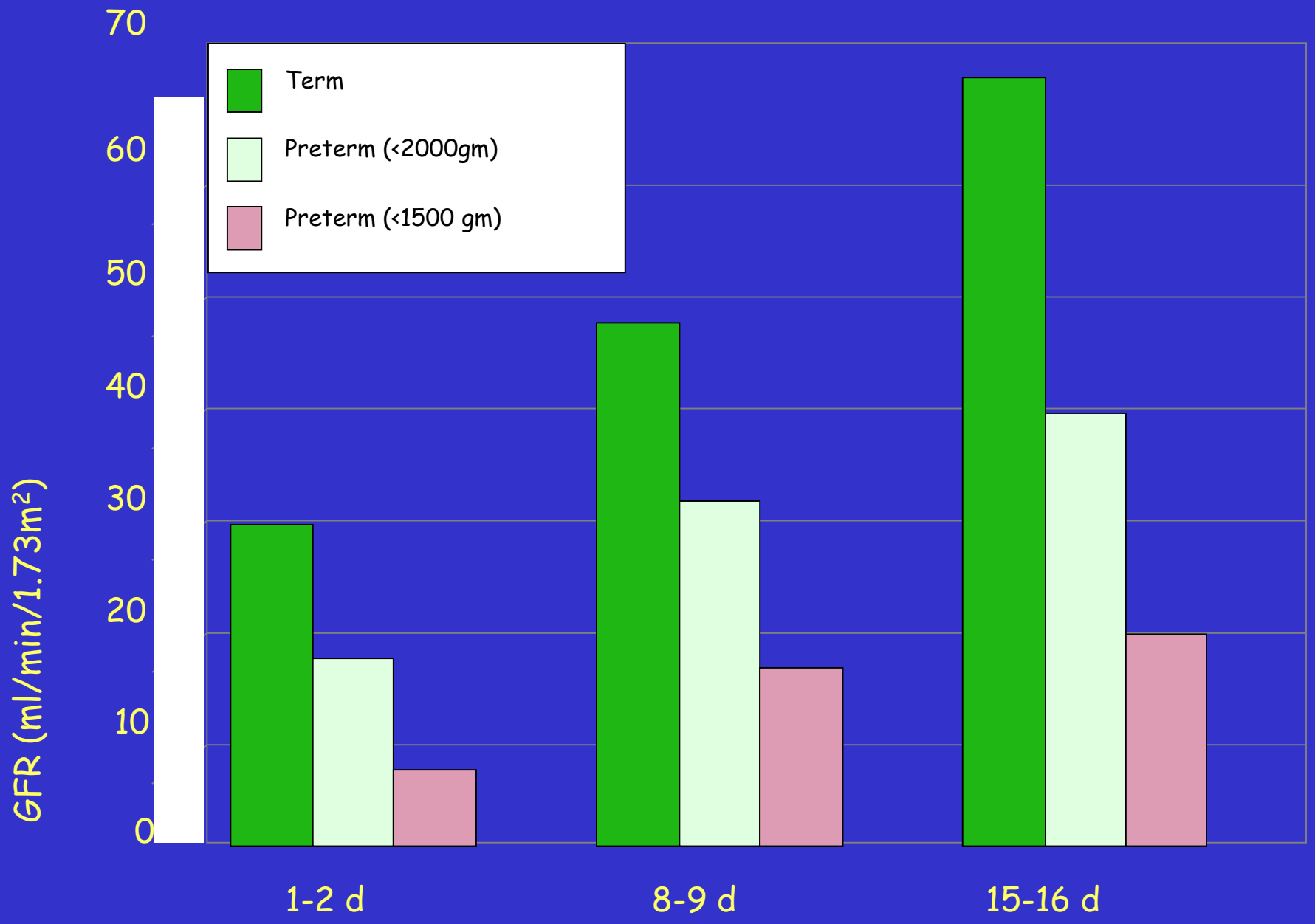


Active glomerulogenesis

Maturation of Renal Function



John TR, Moore WM, Jeffries JE (eds.). Children are Different: Developmental Physiology,2nd edition, Ross Laboratories, 1978


70
60
50
40
30
20
10
0
GFR (ml/min/1.73m²)
Term
Preterm (<2000gm)
Preterm (<1500 gm)
1-2 d
8-9 d
15-16 d

Ceftazidime Pharmacokinetics in Preterm Infants

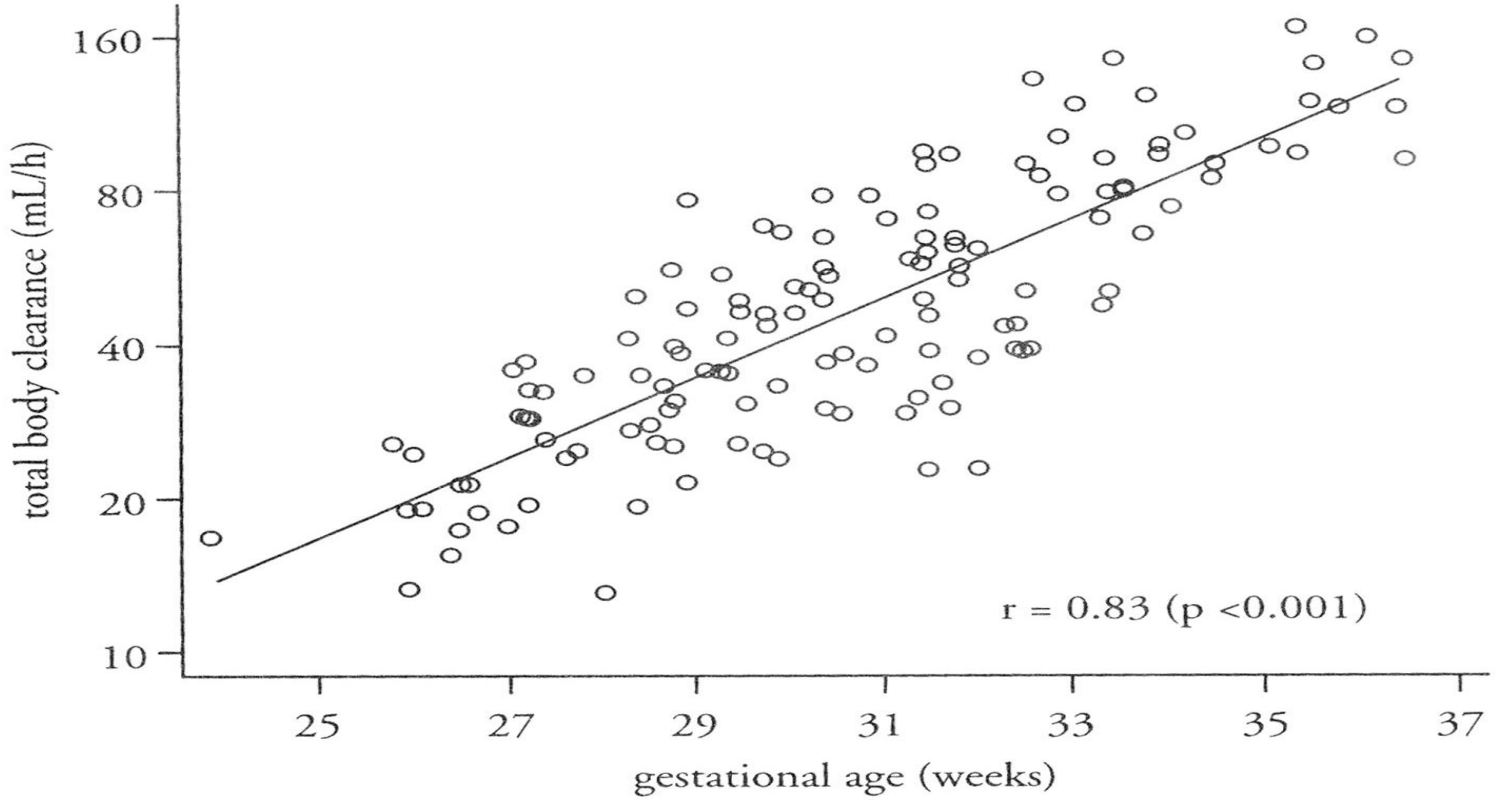


Figure 1. Linear regression analysis of total body clearance of ceftazidime (mL/h) versus gestational age (weeks) in 136 preterm infants on day 3 after birth. Note the logarithmically transformed vertical axis

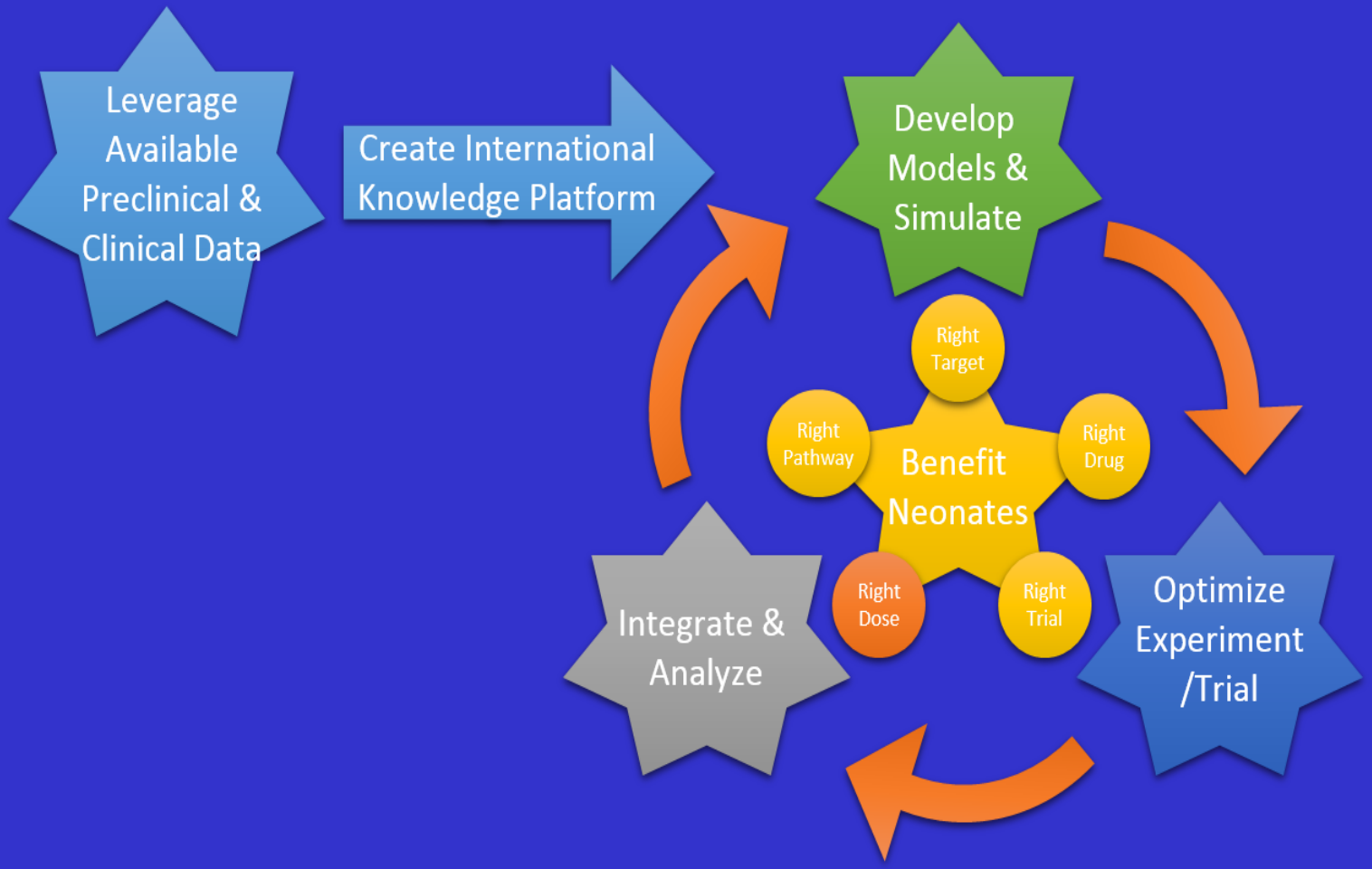
Van den Anker J et al. Clin Pharmacol Ther 1995;58:650-9

Maturation of GFR in neonates as Reflected by Amikacin Clearance

• Langhendries *et al*.	15.5-20 mg/kg; 24-42 hrs
• Sherwin *et al*.	14-15 mg/kg; 24-36 hrs
• Neofax® (2009)	15-18 mg/kg; 24-48 hrs
• *RedBook® (2009)*	*7.5-10 mg/kg; 8-24 hrs*
• *BNFc (2009)*	*15 mg/kg; 24 hrs*
• New regimen	12-20 mg/kg; 20-48 hrs

De Cock R et al. Clin Pharmacokinet 2012;51(2):105-17

Future Perspectives



Allegaert K & van den Anker J. Clin Pharm Ther 2015 Sep;98(3):288-97