OBJECTIVES

• Describe medication use in neonates and mothers (pre and postnatal)
• Identify characteristics of maternal drugs that may impact fetus/neonate
• Define the impact of pharmacokinetics on neonatal drug exposure
• Review examples of medication use in neonates where neonatal pharmacology is important
DRUG THERAPY

- Goal is to administer a given drug at a given dose to achieve a desired therapeutic effect while minimizing risk of toxicity.
MEDICATION USE IN NEONATES

• Nearly all medications used in the NICU are done so off-label
• Limited clinical data in neonates leads to extrapolation from more extensively studied patient populations
  – Clinical data from other patient populations with animal data and known developmental pharmacology of neonates to determine best guess for drug and dosing regimens
• Maturation of organ systems leads to differences in dosing needs throughout spectrum of NICU stay
  – Up to 1-log value of variability seen intra- and interpatient weights (0.5 to 5 kg)
HISTORY OF UNEXPECTED ADVERSE EFFECTS

- Kernicterus (sulfonamides, ceftriaxone, ibuprofen?)
- Gray baby syndrome (chloramphenicol)
- Gasping syndrome (benzyl alcohol—enoxaparin, midazolam)
- Apnea (promethazine)
- Metabolic acidosis (propylene glycol)
NEONATAL PHARMACOLOGY

• Prediction of drug-specific effects and adverse effects based on pharmacokinetics and pharmacodynamics
  – Pharmacokinetics: concentration/time profile
  – Pharmacodynamics: concentration/effect profile
MATERNAL DRUG EXPOSURE

- More than 90% of pregnant women self-report taking at least one medication during pregnancy\textsuperscript{1}
  - Average number of medications: 4.2
  - Half of all pregnant women take more than 4 medications

\textsuperscript{1}Koren et al. JPPT 2013
Exposure to teratogen during a specific developmental stage

- **Gamete**
  - sterility

- **Blastocyst**
  - death

- **Embryo**
  - death

- **Fetus**
  - death

- **Normal Newborn**

  - **Major structural abnormalities**
  - **Functional abnormalities**
Figure 6-8 Schematic illustration of the sensitive or critical periods in prenatal development. Dark boxes denote highly sensitive periods; light boxes indicate states that are less sensitive to teratogens. (From Moore KL: Before We Are Born: Basic Embryology and Birth Defects, 2nd ed. Philadelphia, WB Saunders, 1977.)
DRUG TRANSFER ACROSS THE PLACENTA

• Most drugs ingested by pregnant women cross the placenta
  – Most women expose fetus to 1-8 drugs during pregnancy
• Human placenta unique from other species as organ of drug transfer
  – Higher permeability after 16 weeks gestation
  – Later in gestation, increases in uterine blood flow → higher passage across the placenta
Most drugs cross via passive diffusion

- Characteristics of highly diffused drugs:
  - Low molecular weight (≤ 600 d), non-ionized, lipid soluble
- Strongly ionized compounds poorly diffuse
  - Exceptions: ampicillin, methicillin
DRUG TRANSPORT ACROSS THE PLACENTA

• Facilitated diffusion: concentration gradient, requires no energy, inhibited by competitive analogues, saturable

• Occurs with drugs structurally similar to endogenous compounds
  – Cephalosporins, gancyclovir, and corticosterone
PLACENTAL PROTECTION FOR FETUS

- Placental function
  - Semipermeable barrier
  - Limited drug metabolism by placenta
- Drugs enter the fetus through the umbilical vein
  - 40-60% of the umbilical blood flow enter into the fetal liver
<table>
<thead>
<tr>
<th>Category</th>
<th>Animal Data</th>
<th>Human Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No risk</td>
<td>No risk</td>
</tr>
<tr>
<td>B</td>
<td>No risk</td>
<td>No data</td>
</tr>
<tr>
<td>C*</td>
<td>Risk</td>
<td>No data</td>
</tr>
<tr>
<td>D*</td>
<td>Harmful</td>
<td>Harmful</td>
</tr>
<tr>
<td>X</td>
<td>Harmful</td>
<td>Harmful</td>
</tr>
</tbody>
</table>

*Potential benefit may outweigh potential risk to fetus
FDA PROPOSED CHANGES TO LABELING

• Elimination of the 5 categories
  – Misleading to providers and women
  – Risk for C, D, and X are based on risk and benefits to patient, not just risk
  – Categories do not distinguish differences in frequency, severity, and type of fetal toxicities

• Two subsections: pregnancy and lactation
  – Labor and delivery section eliminated
  – Three components: risk summary, clinical considerations, and data section

BREASTFEEDING AND MEDICATION USE

• Rates of breastfeeding in the US per CDC 2013 report card:
  – 77% infants begin life breastfeeding; 49% breastfeeding at 6 months, 27% at 12 months
• ~90% of women take some form of medication during the first week postpartum
  – In a study of 14,000 pregnant/breastfeeding women, 79% used meds while breastfeeding, avg intake: 3.9 drugs
• Maternal compliance with drug therapy can be erratic while breastfeeding secondary to infant concerns
Most drugs cross into breast milk but amount and concentration transferred are low and relatively safe for infant.

Maternal and infant characteristics influence amount of drug transferred into milk.
MATERNAL FACTORS

• Dose and duration of therapy
  – Low dose, infrequent dosing, short duration
  – If drug contraindicated, may consider “pump and dump”

• Route of administration
  – Drugs given IV before of poor PO bioavailability are usually poorly absorbed by infant through milk

• Drug pharmacokinetics
  – Drugs with long half-life may result in cumulative exposure in infant
INFANT FACTORS

• Total amount of drug exposure to infant:
  – Concentration in breast milk and volume of milk ingested per day

• Gestational age and postnatal age determine infants ability to absorb, metabolize, and excrete drug
  – Preterm infant less able to metabolize and excrete drugs because of less mature liver and kidneys
PHARMACOKINETICS

• What the body does to the drug
• Describes the movement of drug into, through, and out of the body
  – Absorption: translocation of drug from site of administration into blood
  – Distribution: space within the body that drug must fill to reach steady-state
  – Metabolism: biotransformation of drug to metabolites
  – Excretion: removal of drug from the body
• Must consider both maternal and neonatal pharmacokinetic profiles to predict fetal/neonatal outcomes of medication use
MATERNAL ABSORPTION

• Increased gastric emptying time
• Decreased intestinal motility
• Result: delayed absorption time, delayed peak effect, negligible effect on steady-state
MATERNAL DISTRIBUTION

• Body composition
  – Increase in maternal fat relatively constant with weight gain
  – Result: increased doses needed for fat-soluble drugs, accumulation may occur in adipose tissue (increased half-life, prolonged drug effects)

• Body volume
  – Increased total body water, extracellular water, and plasma volume
  – Increased cardiac output, heart rate, stroke volume
  – Result: decreased serum concentrations water-soluble drugs
MATERNAL DISTRIBUTION

- Serum proteins decreased
- Increased free fraction of highly bound drugs
- Result: increased exposure across placenta to protein-bound drugs
MATERNAL METABOLISM

• Increased hepatic enzyme activity
• Result: increased metabolism, clearance
  – Higher doses needed of drug to maintain effect
NEONATAL PHARMACOKINETICS

• Important clinical features
  – Absorption
  – Distribution
  – Metabolism
  – Excretion
NEONATAL ABSORPTION

- Enteral
- Percutaneous
- Subcutaneous
- Intramuscular
- Intrapulmonary
- Rectal
**NEONATAL ABSORPTION-ENTERAL**

- Most drugs absorbed in small intestine
- Gastrointestinal pH, transit time, and gastric emptying play important roles in total drug exposure time and absorption
- Gastric acidity
  - Does not reach adult levels until 2-3 years of age
  - Introduction of nutrition helps regulate GI function
  - Acid production function of postnatal age, not PCA
  - Length/frequency of feeding can impact pH
  - Drugs that are weak acids absorbed more slowly than weak bases
## Table 1. Comparative Intestinal Variables Affecting Gastrointestinal Drug Absorption

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Full-term Newborn</th>
<th>1-day to 1-month-old Infant</th>
<th>1-month to 2-year-old Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric pH</td>
<td>1-3</td>
<td>&gt;5</td>
<td>Adult</td>
</tr>
<tr>
<td>Gastric Emptying time</td>
<td>Variable/reduced</td>
<td>Variable/reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Intestinal Transit Time</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Intestinal Surface Area</td>
<td>Reduced</td>
<td>Reduced</td>
<td>~Adult</td>
</tr>
<tr>
<td>Bacterial Flora</td>
<td>Very limited</td>
<td>Limited</td>
<td>Developing</td>
</tr>
<tr>
<td>Transporter Maturity</td>
<td>Immature</td>
<td>Immature</td>
<td>Developing</td>
</tr>
<tr>
<td>Rectal Absorption*</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Adult</td>
</tr>
</tbody>
</table>

*Rectal Absorption*
FACTORS AFFECTING GASTRIC EMPTYING

• Gestational and postnatal age
• Increased:
  – Extensively hydrolyzed formula compared to intact or partially hydrolyzed
• Decreased:
  – Increasing caloric density and medium-chain triglycerides
• Does not approach adult times until 6-8 months of life
NEONATAL ABSORPTION-PERCUTANEOUS

• Degree of skin hydration and relative absorption surface area
  – Inversely related to thickness of stratum corneum

• Term infants
  – Intact skin barrier function
  – Ratio of surface area to body weight much higher than adults
  – 2.7 x greater amount drug exposure
NEONATAL ABSORPTION-
SUBCUTANEOUS

• Subcutaneous injection goes into the fatty layer of tissue under the skin
  – Little blood flow to fatty tissue
  – Injected medication absorbed more slowly

• Premature neonates generally lack the fatty tissue of the subcutaneous space that makes this dosing method effective
NEONATAL ABSORPTION - INTRAMUSCULAR

- Physicochemical and physiologic factors affect rate
  - Drug pH, lipophilicity
  - Blood flow, total surface area of muscle at injection site
- Rate of absorption may be lower
  - Extent of absorption may be higher secondary to higher density of skeletal muscle capillaries compared to older children and adults
Intrapulmonary
- Final stages of normal lung development interrupted in premature infants
  - Decreased lung volumes, gas exchange, capillary surface area
- Potentially altered patterns of drug disposition and absorption
  - Ventilatory type and settings (high-frequency vs. conventional)

Rectal
- Rapid, complete absorption
- Dosage formulations often problematic
NEONATAL DISTRIBUTION

• Occurs after reaching systemic circulation
• Factors affecting distribution:
  – Body compartment size and composition
  – Hemodynamics (cardiac output, regional blood flow)
  – Membrane permeability
  – Fat/water solubility of drugs
  – Plasma protein binding
NEONATAL DISTRIBUTION-PROTEIN BINDING

• Affinity of albumin for acidic drugs increases from birth to early infancy
• Alpha1-acid glycoprotein binds basic drugs
  – Neonates have half the adult concentration
• Overall binding affinity lower
  – Increased free fraction of drug, increased availability of active compound
  – Increased adverse effects, increased drug clearance
• Free fatty acids and unconjugated bilirubin displace drugs from protein binding sites
  – Ampicillin, sulfonamides, phenytoin, diazepam
NEONATAL DISTRIBUTION-BODY COMPOSITION

- Physiologic space for drug distribution displays changes early in neonatal life
  - Ratio of total body water to body weight is greater in newborns
  - Total body fat lower (1% premature vs. 15-20% term)
- Higher weight-based doses of hydrophilic drugs needed
  - Aminoglycosides
- Lower weight-based doses of lipophilic drugs needed
  - Propofol
NEONATAL DISTRIBUTION - BLOOD COMPONENTS

- Blood flow
- Organ perfusion
- Cell membrane permeability
  - BBB more permeable in premature infants, passive diffusion of drugs
- Acid-base balance
- Cardiac output
# Developmental Fluid Compartments

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>% of Total Body Water*</th>
<th>% of Extracellular Fluid*</th>
<th>% of Intracellular Fluid*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 month fetus</td>
<td>92</td>
<td>65</td>
<td>25</td>
</tr>
<tr>
<td>Term gestation</td>
<td>75</td>
<td>35-44</td>
<td>33</td>
</tr>
<tr>
<td>4-6 months</td>
<td>60</td>
<td>23</td>
<td>37</td>
</tr>
<tr>
<td>12 months</td>
<td>-</td>
<td>26-30</td>
<td>-</td>
</tr>
<tr>
<td>Puberty</td>
<td>~60</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Adult</td>
<td>50-60</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>
# VOLUME OF DISTRIBUTION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume of Distribution (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neonate (1-30 days old)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>8-10</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.7-1.5</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.2-0.38</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>2.5-4</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1.2-2</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>0.8-1.2</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>1.2-1.4</td>
</tr>
</tbody>
</table>
NEONATAL METABOLISM

• Action:
  – Conversion of drugs to water soluble metabolite for easier excretion
  – Inactive drug into active metabolite, toxic metabolite

• Sites of metabolism:
  – GI tract
  – Kidney
  – Liver
  – Lungs
NEONATAL METABOLISM

• Expression of intestinal drug metabolizing enzymes markedly different in neonates
  – Duodenal and jejunal CYP450 enzymes age-dependent (3A4, 1A1)
  – Other metabolic enzymes (epoxide hydrolase, glutathione peroxidase) demonstrate little dependence on age
  – Beta-glucuronidase in small intestine 7-fold higher in children
• Oral bioavailability impacted by GI enzyme expression
NEONATAL HEPATIC METABOLISM

• Overall rate of biotransformation of drugs much slower
  – Rapid physiologic changes occur in first week of life that change capacity of hepatic drug metabolism and oral bioavailability
    • Changes in hepatic blood flow, increased portal venous flow, closure of ductus venosus
• Phase I:
  – Oxidation, reduction, and hydrolysis
  – Mediated by cytochrome enzymes
• Phase II:
  – Conjugation pathways
  – Acetylation, glucuronidation, sulfation, methylation
PHASE I REACTIONS

- Total hepatic cytochrome P450 concentration is 30% adult values
  - All isoenzymes display age-dependent maturation
- CYP3A7 is major isoform present in fetus and neonate
  - Disappears 1-4 weeks after birth
  - CYP3A4 begins to overtake expression, reaching 30-50% adult levels at 3-12 months of age
# Development of Metabolic Enzyme Activity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fetal Liver*</th>
<th>1 month*</th>
<th>Time to Adult Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP 2D6</td>
<td>Low to absent</td>
<td>~20%</td>
<td>3-5 years</td>
</tr>
<tr>
<td>CPP 2C9/C19</td>
<td>Low to absent</td>
<td>Low</td>
<td>6 months</td>
</tr>
<tr>
<td>CYP 1A2</td>
<td>Low to absent</td>
<td>Low</td>
<td>4 months</td>
</tr>
<tr>
<td>CYP 3A4</td>
<td>Low to absent</td>
<td>30%-40%</td>
<td>6 months</td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAT</td>
<td>Poor</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>TPMT</td>
<td>~30% Adult</td>
<td>Highly variable†</td>
<td>1-3 years</td>
</tr>
<tr>
<td>UGT</td>
<td>Limited</td>
<td>Highly variable†</td>
<td>6-24 months</td>
</tr>
<tr>
<td>ST</td>
<td>Developed</td>
<td>Highly variable†</td>
<td>Isoform specific</td>
</tr>
</tbody>
</table>
PHASE II REACTIONS

• Lack of data for impact of neonatal development on phase II enzymes
  – Appears to be age-dependent

• Clinical importance
  – Bilirubin UGT is immature in almost all neonates
  – Gray baby syndrome with chloramphenicol
  – Morphine metabolism
  – Paracetamol metabolism
ACETAMINOPHEN METABOLISM

Acetaminophen

Glucuronide (47-62%)

Sulfate (25-36%)

Cytochrome P450 2E1

Glutathione

Active Repletion Process

N-(Acetyl-p-benzoquinoneimine) (NAPQI)

Cysteine & Mercapturic Acid Conjugates (5-8%)

Glutathione
ACETAMINOPHEN OVERDOSE IN PREMATURE NEONATES

- Eur J Clin Pharmacol 2012
  - 25.5 week GA infant (DOL 12) given 446 mg/kg
- Pediatric Anesthesia 2010
  - 28 week GA (35 weeks corrected) given 146 mg/kg
- Arch Dis Child Fetal Neonatal Ed 2001
  - 29 week GA (DOL 55) given 136 mg/kg
- NO hepatic toxicity seen in any patient
  - Due to slow oxidative metabolism and rapid glutathione synthesis
NEONATAL EXCRETION

• Renal excretion primary route for most drugs
  – Nonvolatile, water soluble, low molecular weight
• Three processes
  – Glomerular filtration
  – Tubular secretion
  – Active or passive tubular reabsorption
• Nephrogenesis
  – Begins at 9 weeks gestation, complete at 34 weeks gestation
  – May be impacted in utero by fetal growth retardation, maternal nephrotoxic medications, renal/urologic malformations
NEONATAL GLOMERULAR FILTRATION RATE

• GFR in first week of life
  – Preterm: 0.6 to 0.8 mL/min/1.73 m²
  – Term: 2 to 4 mL/min/1.73 m²

• Rapid increases in GFR over first 2 weeks of life
  – Drop in renal vascular resistance
  – Increase in renal blood flow

• Other factors influencing GFR
  – Vasoactive systems (RAAS)
  – Plasma protein concentration
  – Arteriolar resistance
  – Surface area of glomerular membrane
## Gentamicin Pharmacokinetics

<table>
<thead>
<tr>
<th>GA (wk)</th>
<th>Number of Patients</th>
<th>BW (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>9</td>
<td>571.2</td>
</tr>
<tr>
<td>24</td>
<td>23</td>
<td>646.5</td>
</tr>
<tr>
<td>25</td>
<td>29</td>
<td>722.2</td>
</tr>
<tr>
<td>26</td>
<td>27</td>
<td>796.3</td>
</tr>
<tr>
<td>27</td>
<td>41</td>
<td>944.6</td>
</tr>
<tr>
<td>28</td>
<td>33</td>
<td>1014.4</td>
</tr>
<tr>
<td>29</td>
<td>41</td>
<td>1202.7</td>
</tr>
</tbody>
</table>

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## GENTAMICIN PHARMACOKINETICS

<table>
<thead>
<tr>
<th>GA (wk)</th>
<th>ke (hr⁻¹)</th>
<th>Vd (L/kg)</th>
<th>Cl (mL/kg/min)</th>
<th>T ½ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>0.069</td>
<td>0.53</td>
<td>0.036</td>
<td>12.9</td>
</tr>
<tr>
<td>24</td>
<td>0.058</td>
<td>0.58</td>
<td>0.035</td>
<td>12.5</td>
</tr>
<tr>
<td>25</td>
<td>0.056</td>
<td>0.60</td>
<td>0.033</td>
<td>13.2</td>
</tr>
<tr>
<td>26</td>
<td>0.061</td>
<td>0.58</td>
<td>0.038</td>
<td>11.8</td>
</tr>
<tr>
<td>27</td>
<td>0.069</td>
<td>0.56</td>
<td>0.040</td>
<td>10.3</td>
</tr>
<tr>
<td>28</td>
<td>0.076</td>
<td>0.54</td>
<td>0.045</td>
<td>9.6</td>
</tr>
<tr>
<td>29</td>
<td>0.073</td>
<td>0.58</td>
<td>0.043</td>
<td>9.7</td>
</tr>
</tbody>
</table>

O’Mara et al. ASHP poster presentation 2007
GENTAMICIN PHARMACOKINETICS

O’Mara et al. ASHP poster presentation 2007
NEONATAL TUBULAR SECRETION

- Immature at birth, approaches adult values at 7-12 months
- Limited tubular function in premature neonates
  - Renal elimination of pencillins, cephalosporins
- Active transport process dependent on:
  - Blood flow
  - Affinity of drug carrier proteins in proximal tubule
  - Rate of transport across tubular membranes
  - Rate of delivery of drug to the site of secretion
## PHARMACOKINETICS OF AMPICILLIN IN NEONATES

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value for the indicated gestational age (wk) and PNA (days)</th>
<th>≤34</th>
<th>8–28</th>
<th>&gt;34</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤7</td>
<td>8–28</td>
<td>≥7</td>
<td>8–28</td>
</tr>
<tr>
<td>Group no.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>n</td>
<td>21</td>
<td>7</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Postnatal age (days) at day of first plasma PK sample</td>
<td>Mean (SD)</td>
<td>2.6 (2.3)</td>
<td>15.4 (4.0)</td>
<td>2.9 (2.6)</td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>1.0 (0.0, 7.0)</td>
<td>16.0 (9.0, 21.0)</td>
<td>2.0 (0.0, 7.0)</td>
<td>12.5 (8.0, 25.0)</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>Mean (SD)</td>
<td>30.3 (3.4)</td>
<td>26.9 (2.5)</td>
<td>38.2 (2.0)</td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>32.3 (24.0, 34.0)</td>
<td>26.1 (25.0, 32.0)</td>
<td>38.0 (34.0, 41.0)</td>
<td>38.8 (35.0, 41.0)</td>
</tr>
<tr>
<td>No. (%), male</td>
<td>9 (43)</td>
<td>3 (43)</td>
<td>18 (67)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Ethnicity, no. (%)</td>
<td>Hispanic or Latino</td>
<td>3 (14)</td>
<td>1 (14)</td>
<td>6 (22)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>18 (86)</td>
<td>5 (71)</td>
<td>19 (70)</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Not reported</td>
<td>0</td>
<td>1 (14)</td>
<td>2 (7)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td>Black</td>
<td>4 (19)</td>
<td>3 (43)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>White</td>
<td>16 (76)</td>
<td>3 (43)</td>
<td>23 (85)</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Not reported</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (5)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*PK, pharmacokinetic; PNA, postnatal age.*
# PHARMACOKINETICS OF AMPICILLIN IN NEONATES

**TABLE 5 Individual empirical Bayesian *post hoc* parameter estimates**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Clearance (liters/h/kg)</th>
<th>Volume (liters/kg)</th>
<th>Half-life (h)</th>
<th>Steady-state concn (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>0.055 (0.03–0.07)</td>
<td>0.40 (0.40–0.40)</td>
<td>5.0 (3.9–9.4)</td>
<td>77 (36–320)</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>0.070 (0.03–0.07)</td>
<td>0.40 (0.40–0.41)</td>
<td>4.0 (3.8–8.3)</td>
<td>33 (21–145)</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>0.086 (0.04–0.13)</td>
<td>0.40 (0.40–0.40)</td>
<td>3.2 (2.2–6.2)</td>
<td>48 (5–173)</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>0.11 (0.06–0.13)</td>
<td>0.40 (0.40–0.41)</td>
<td>2.4 (2.1–4.7)</td>
<td>28 (5–129)</td>
</tr>
<tr>
<td>Overall</td>
<td>73</td>
<td>0.072 (0.03–0.13)</td>
<td>0.40 (0.40–0.41)</td>
<td>3.3 (2.1–9.4)</td>
<td>47 (5–320)</td>
</tr>
</tbody>
</table>

*All values are medians and ranges.*
PHARMACOKINETICS OF AMPICILLIN IN NEONATES

<table>
<thead>
<tr>
<th>Gestational age (wk)</th>
<th>Postnatal age (days)</th>
<th>Maintenance dose (mg/kg)</th>
<th>Dosing interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤34</td>
<td>≤7</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>≤34</td>
<td>≥8 and ≤28</td>
<td>75</td>
<td>12</td>
</tr>
<tr>
<td>&gt;34</td>
<td>≤28</td>
<td>50</td>
<td>8</td>
</tr>
</tbody>
</table>

TABLE 7 Optimal dosing regimen based on Monte Carlo simulations using the final pharmacokinetic model
NEONATAL TUBULAR REABSORPTION

- Immature at birth, especially in preterm infants
  - Development and maturation of glomerular permeability functions and renal tubular reabsorption are gradual process
  - Peak maturation at 1-3 years
- Depends on physiochemical characteristics of drugs
  - Lipophilicity
  - Water solubility
  - Acidic vs. basic pH
  - pH of fluids in proximal and distal tubules
DISEASE STATES THAT IMPACT DRUG BEHAVIOR

- Extremely premature birth
- Peripartum asphyxia
- Therapeutic hypothermia
- Extracorporeal membrane oxygenation
- Sepsis
- Patent ductus arteriosus
- Necrotizing enterocolitis
### PDA IMPACT ON PK

- PK differences between neonates with significant PDA vs. no PDA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 216)</th>
<th>Patent Ductus Arteriosus (n = 106)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ke (hr)</td>
<td>0.8 ± 0.02</td>
<td>0.06 ± 0.03</td>
<td>.0001</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>8.98 ± 2.86</td>
<td>12.24 ± 7.43</td>
<td>.0001</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.54 ± 0.13</td>
<td>0.61 ± 0.15</td>
<td>.0002</td>
</tr>
<tr>
<td>CL (mL/kg/hr)</td>
<td>44.73 ± 14.74</td>
<td>40.02 ± 16.85</td>
<td>.0108</td>
</tr>
</tbody>
</table>

Ke, elimination constant; T<sub>1/2</sub>, half-life; Vd, volume of distribution; CL, clearance.

Williams et al. Crit Care Med 1997

PDA: Patent ductus arteriosus
### VOLUME OF DISTRIBUTION WITH PDA

<table>
<thead>
<tr>
<th>Vd (L/kg)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>48</td>
<td>75</td>
<td>48</td>
<td>75</td>
</tr>
<tr>
<td>0.65</td>
<td>32</td>
<td>86</td>
<td>53</td>
<td>72</td>
</tr>
<tr>
<td>0.7</td>
<td>24</td>
<td>92</td>
<td>60</td>
<td>71</td>
</tr>
<tr>
<td>0.75</td>
<td>17</td>
<td>95</td>
<td>62</td>
<td>70</td>
</tr>
<tr>
<td>0.8</td>
<td>10</td>
<td>96</td>
<td>58</td>
<td>69</td>
</tr>
</tbody>
</table>

Vd: volume of distribution  
PPV: positive predictive value  
NPV: negative predictive value

*Williams et al. Crit Care Med 1997*
Conclusions

• Neonatal response to drug therapy is multi-factorial
  – Maternal factors
  – Gestational age
  – Postnatal age

• Maturational differences in pharmacokinetic profiles leads to different efficacy and toxicity profiles compared to other patient populations
  – Importance of understanding timeline of development of metabolic enzymes and clearance pathways