Anti-Infectives and Neonates

Danny Benjamin MD PhD
Kiser-Arena Distinguished Professor of Pediatrics, Duke University
Chair, Pediatric Trials Network

Summary of Neonatal Anti-infective drug development

1. Assess exposure (PK)
2. Extrapolate efficacy
3. The real (primary) safety question is: does the product get into the (CNS) central nervous system?

Dosing in the NICU: 2005

Lessons of history: chloramphenicol, bactrim, ceftriaxone

- 23 week estimated gestational age DOL 3, vs. 28 week DOL 40
- 2005, we did not know the dosing (let alone safety) in the ELBW infant

Medication	Rank-use in NICU	PK studies <28 wks
Ampicillin	1	6 infants, 26-28 wks
Erythromycin	27	0
Clindamycin	47	0
Nafcillin	67	0
Metronidazole	81	0
Cefazolin	95	0
Meropenem	141	1 infant, 27 wks
Piperacillin-tazobactam	144	0

Dosing surprises

- Need for clinical pharmacology
- Most (but not all) safety and efficacy surprises related to exposure
- Exposure in one compartment, let alone tissue distribution

Drug	Preferred adult dosing (mg/kg/day)	Pediatric or infant dosing (mg/kg/day)
Ampicillin	30–50	~50
Piperacillin	250–340	150–300
Ciprofloxacin	10	30
Gentamicin	3–7	3.5–7.5
Daptomycin	4–6	12
Metronidazole	30	15
Fluconazole	3–6	12
Micafungin	3	10

2005-2018 Antibiotics and Antifungals in the NICU in Babies < 28 weeks EGA

RED indicates FDA-NIH BPCA off-patent work through the Pediatric Trials Network

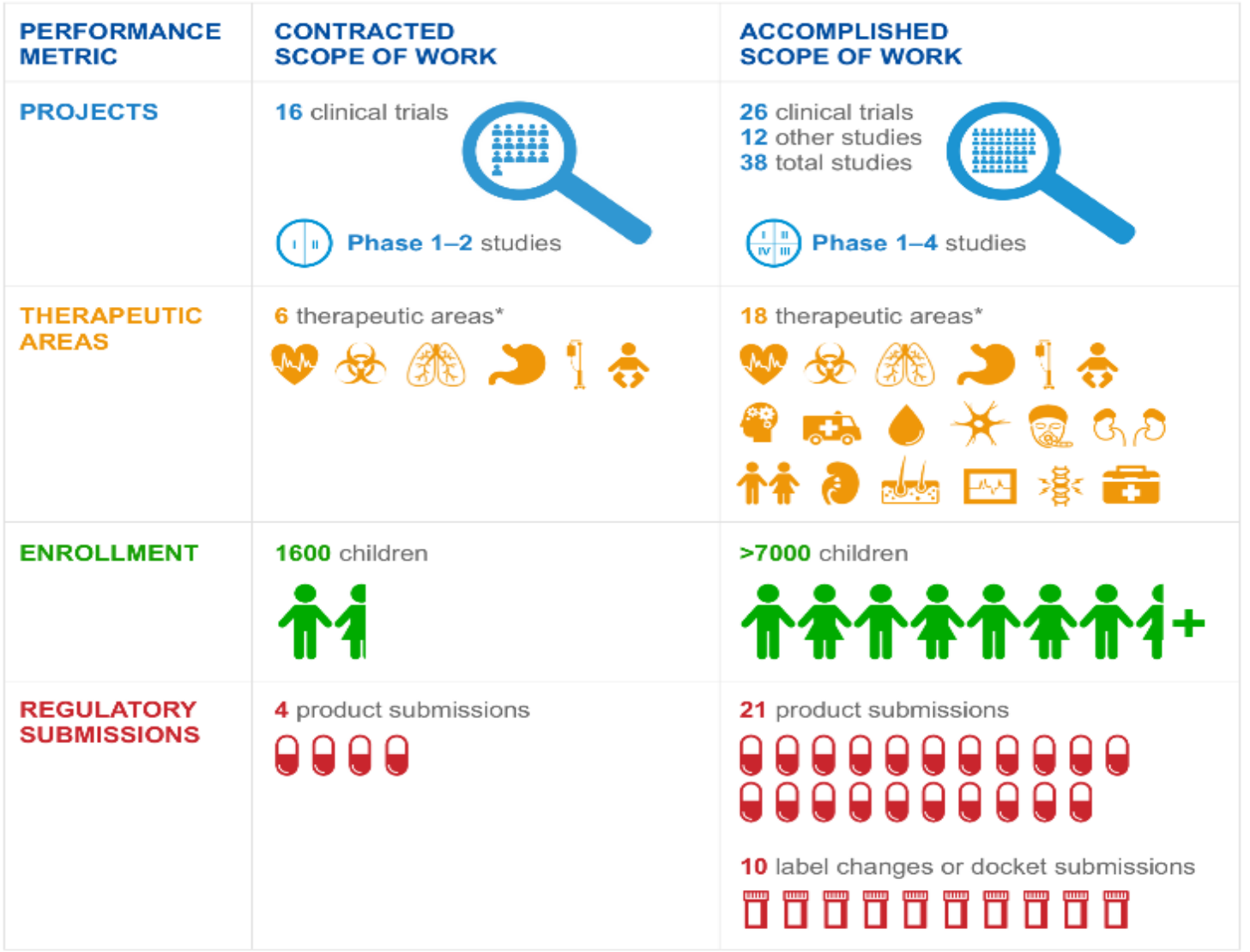
1. *Acyclovir*
2. *Ampicillin*
3. Anidulafungin
4. Cefipime
5. *Cefazolin*
6. Ceftazidime
7. *Clindamycin*
8. Daptomycin
9. *Fluconazole*
10. *Gentamicin*
11. *Metronidazole*
12. Micafungin
13. *Meropenem*
14. *Piperacillin-tazobactam*
15. *Rifampin*
16. *Ticarcillin-clavulaunic acid*
17. *Trimethoprim-sulfa*
18. Tobramycin
19. Vancomycin (shunts)
20. Voriconazole (TDM)

Three Stages of Research & Innovation

1. You can't do that (2006)
   - It's impossible
2. We're not going to do that (2012)
   - It's expensive
3. Anybody can do that (2018)
   - It's easy, required by law, etc.

Pediatric Trials Network: Federal and Off-Patent Efforts

- Pediatric Trials Network (PTN) established 2010
- Best Pharmaceuticals for Children Act Off-Patent Program; NICHD-FDA
- >40 molecules under study under an IND
- 22 pediatric therapeutic trials, 4 device trials, 10 longitudinal cohort studies, plus additional secondary analyses,
- From 2010-2018, pediatric labeling changes were agreed upon with the FDA for 10 drugs, of which 7 completed the labeling change.



Priorities for Anti-Infective Use in Neonates

- Exposure in the blood
  - This requires a clinical trial in neonates of varied gestational age
- Exposure in the CNS
  - Neonates do not localize infection
  - Bacteremic neonates develop meningitis ~15%, depending on organism
  - Neonates are pre-verbal, signs are not reliable, and acquisition of the lumbar puncture is extremely variable
  - Pre-clinical work plus a small number of infants who receive product and from whom CSF is obtained
- Exposure in other target tissues (e.g., the lung)
  - Typically can be derived from pre-clinical data, adult data, and primary trial
  - With caution
- General ‘safety data’ for commonly used anti-infectives
  - How much do we learn from randomizing 60 infants

Common hurdles to doing clinical trials in the NICU

- Hurdles
  - Families
    - Blood volume
    - Sticks
    - Uncertainty
  - Physicians
    - Safety
    - Why bother compared to other morbidities
    - High incidence sites, only a small fraction of which are capable sites = very few sites
- The ‘Cs”
  - Contracts
  - Central IRB
  - Case report form

Lesson 1: Basic Design

- Prior method
  - Children with infection
  - 10-20 centers
  - Enroll 8 children 2-3 years
  - 10 samples per child
- Current method
  - At risk of infection
  - Additive therapy (PK study) or compared to standard of care (safety study)
  - Multiple doses
  - 5 centers
  - Across age groups
  - 3-5 samples per child
  - Scavenge sampling; opportunistic sampling
  - Pre-trial modeling, dosing simulation, population modeling
  - Combine data other populations

Lesson 2: Multiple Drugs

- Prior method
  - I have a drug
  - I want to know the dosage
  - Go
- Current method
  - Combination or Master Protocol
  - Pre-consent facilitated
  - Organism: Anti-staphylococcal
  - Indication: Anti-epileptic
  - Patient population: ECMO, Obesity

Trial	# of drugs
POPS	47
Anti-staph	3
Anti-epileptic	4
SCAMP	3
Anti-psychotic	6
Breast Milk	10

Lesson 3: Addressing the CNS

- Prior method
  - Getting cerebrospinal fluid is hard
  - Don’t do it
- Current method
  - Nesting CSF study within larger study
  - CSF is an add-on check box and arm of the protocol
  - Works better for 100-200 infant studies
  - Meropenem example
    - 200 infants, 20 centers, 16 months, 6 infants
  - SCAMP
    - 260 infants
    - Ampicillin, gentamicin, metronidazole, clindamycin, piperacillin-tazobactam
    - 46 sites, 23 samples (3 sites provided most of these samples)

Lesson 4: Electronic Health Record

- The problem
- We knew exposure for several therapeutics including ampicillin
- We wanted to relate dosing to safety: e.g., seizure
- Pivotal study not feasible

- What we did
  - Pediatrix Database
  - Ampicillin cohort
  - Similar demographics as PK
  - Primary outcome seizure
    - 131,723 infants
    - 780 infants with seizure

Challenges Moving Forward

- CNS exposure
  - Few centers responsible for a high fraction of samples
  - Animal data with small amount of human data is feasible
  - A few human samples considerable effort relative to PK study
- Ever decreasing number of centers relative to the obligations
  - Timeline creep: start up, enrollment, submission
- Assessing safety in a meaningful way
  - A single arm study of 100-200 is feasible in neonates, but is it helpful
  - Meaningful—compare to adult endpoint
  - Frequency of use and risk:benefit
  - The use of EHR

FDA-sponsored Program
Industry Collaboration
Pediatric Trials Network

Molecule	Product development	Protocol Design	PSP	PIP	DSMB	Advisory Committee	Dosing optimization
A	X	X					X
B	X	X		X	X		X
C	X			X			X
D	X	X					X
E	X						X
F	X	X	X	X		X	X
G		X					
H	X			X			X
I	X	X					X
J	X	X			X		X
K			X		X		
L	X			X			X
M		X					
N	X						X
O			X				
P		X					
Q	X		X				X
R	X			X	X		X
S	X	X					X
T	X	X		X			X
U	X	X		X	X		X
V		X					
W	X				X	X	X
X	X						X
Y	X	X		X			X
Z		X					
AA	X	X		X			X
BB	X	X					X
CC		X					
DD		X					