Addressing Therapeutic Challenges of AMR in Neonates

ESCMID/ASM Conference on Antimicrobial Resistance

September 22, 2016
Vienna

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Therapeutic Challenges in Neonates

- Children are not small adults
- Neonates are not small children
  - There are Differences and Similarities to adults and older children concerning drug exposures, PK/PD targets and simulation target attainment
Therapeutic Challenges in Neonates

• Neonates are immune-compromised and have increased infection morbidity and mortality compared with children
• “Exposures” associated with positive outcomes in adults (extrapolation) may not apply to neonates
  • Rather than 40% T > MIC for modeling the PK/PD breakpoint of meropenem, we arbitrarily selected 60% T > MIC for simulations, as we believed it needed to be higher than that used for adults, but had no data regarding how much higher
Therapeutic Challenges in Neonates

- Once you have your PK/PD target, how do you pick the neonatal population ‘target attainment,’ because you **cannot afford to fail** in your treatment for a baby.

- What target attainment in modeling is appropriate for neonates? 90%? 95%? 98%?

- If that target is higher, you will need more exposure to match that T>MIC or AUC:MIC (with each dose linked to age: gest/chronologic/PMA)

- What about safety at an increased exposure that has never been studied in adults?
Therapeutic Challenges in Neonates

- Dr Steve Baker (September 21, 2016):
  - “Socialist Dosing to achieve high target attainment is problematic as it increases the doses we need to use”
Therapeutic Challenges in Neonates

- What is the necessary duration of therapy for microbiologic cure?
  - Short course therapy in adults may be linked to a host immune response (neutrophils) that is adequate to respond to a low residual pathogen burden documented at 5-7 days into treatment (Drusano and colleagues)
- Do the neonates have that ability?
Therapeutic Challenges in Neonates

- Neonates are a heterogeneous population!
  - Birthweights of 500 grams are not uncommon (going down to 400 gm now... how low can it go?)
  - LBW, VLBW (< 1.5 kg), ELBW (< 1.0 kg), ?ILBW
- Organ function (renal, hepatic) matures with gest/chron age
- Volume of distribution varies with gest/chron age
- Diffusion constants between compartments differ in neonates (eg, the “blood-brain barrier” is not much of a barrier for either pathogens or drugs)
- In sepsis, organ perfusion can change quickly: poor renal clearance may change into enhanced renal clearance (or just the opposite) over a few hours
Similarities Between Neonates and Adults

- The MDR pathogens that cause infection in babies are similar to those in adults; mostly healthcare-associated
  - Neonatal ICU-acquired
  - Mothers with premature rupture of membranes, with fever, on broad spectrum antibiotics for many days prior to delivery
Differences Between Neonates and Adults

Can we EXTRAPOLATE microbiologic efficacy from adults to neonates?

- Sepsis/Meningitis
- Pneumonia/Chronic Lung Disease
- Necrotizing enterocolitis (NEC)
- Surgical infections
- ABSSI
Differences Between Neonates and Adults

• How would you like to prescribe “short course therapy” of 5 days for this baby girl?

MRSA breast abscess
Clinical Trial Design in Neonates

• Babies have different pathophysiology and clinical infection presentation
  • Babies are more likely to become bacteremic from the GI tract (NEC), or a renal focus of infection
  • Meningitis (and other secondary sites) occurs more frequently as a consequence of bacteremia than in older children (so you need to look for it in bacteremia/fungemia)
Differences Between Neonates and Adults

- Is NEC the same as cIAI in adults?
- Different pathophysiology?
- Different organisms?
What microbiologic endpoints should be reached for a successful outcome for Gram Negative meningitis?

- Sterile CSF at 3d? 5d? 7d?
- Decreased CSF inflammatory parameters?
  - How many LP’s in the 500 gram infant?
  - Timing of LP’s: at day 3?, day 5? Day 7? At EOIV? (treatment course of 2 weeks or 3 weeks? Longer in the 500 gm neonate?)
Clinical Trial Design in Neonates

• What clinical endpoints for a successful outcome for Gram Negative meningitis?
  • Survival at 4 weeks? 52 weeks?
  • Morbidity at 4 weeks? 52 weeks? 5 years?
  • Developmental outcomes?
  • No long term seizure disorder?
  • Motor function? Cerebral Palsy?
Clinical Trial Design in Neonates

- How much blood can a baby provide to use for research in an era where RBC transfusions are kept to a minimum?
- How many blood draws for PK?
  - Sparse sampling is a wonderful technique, with modeling, to assess PK plasma exposures
  - Heel stick blood filter paper sampling... close, but more variance than sampling from plasma (how much variance is acceptable?)
- How many blood draws for safety?
Clinical Trial Design in Neonates

- How to collect urine?
  - An indwelling bladder catheter is not considered ethical for drug concentration data
  - “Special wood fiber drug study diapers” ...bound colistin in urine!
  - Cotton balls placed into a diaper... seems to be a current compromise
Clinical Trial Design in Neonates

- To study “late onset neonatal sepsis” we hope to evaluate safety and efficacy of new antibiotics in neonates who develop infection between 5 and 60 days of age.

- In fact, most babies who are admitted from the community with “Rule Out Sepsis” do not have bacterial infections.

- They go home in 1 – 2 days, and may be categorized statistically as “investigational drug treatment failures” if enrolled in a study!
Therapeutic Challenges in Neonates

• Obtaining consent from the parents to participate in a study? Both parents?
• Parents are worried sick about their baby, and you are asking them to take on more RISK by using a new antibiotic that may not work as well as Standard of Care!
• You are required to share a long list of possible adverse events from the antibiotic, as well as “possible adverse events of an unknown nature.”
Therapeutic Challenges in Neonates

• The parents trust you. What if the baby gets worse while on a treatment protocol?
  • Is it the infection or a ‘bad’ antibiotic? You may ruin their baby’s life forever… every pediatric investigator in this conference knows what I am talking about…

• But we need data if we are to provide safe and effective therapy to babies

• “We” means all of us: clinicians, academicians, pharma, NIH, and regulators
Therapeutic Challenges in Neonates

- Simulations to assess neonatal meropenem exposures against *Pseudomonas aeruginosa* (Crystal Ball, 2008)
Therapeutic Challenges in Neonates

- We need to more forward together quickly to be able to use agents (old and new) effective against MDR pathogens in neonates.

- The US FDA (CDER) held a public workshop September 15, 2016) on Neonatal Clinical Trial Design to address these complicated scientific and ethical issues (Dr. S. Nambiar).
Questions???