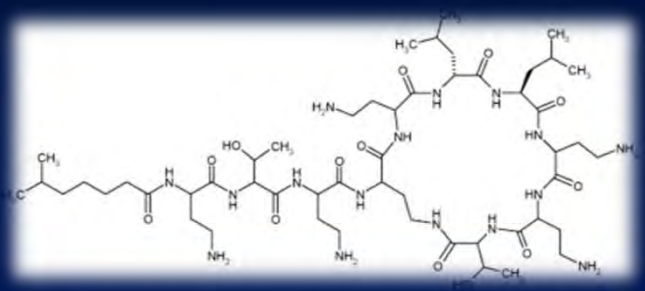
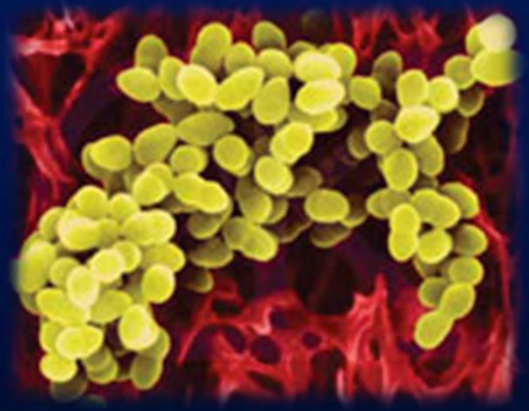
Addressing Therapeutic Challenges of AMR *in Neonates*



ESCMID/ASM Conference on Antimicrobial Resistance



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Vienna

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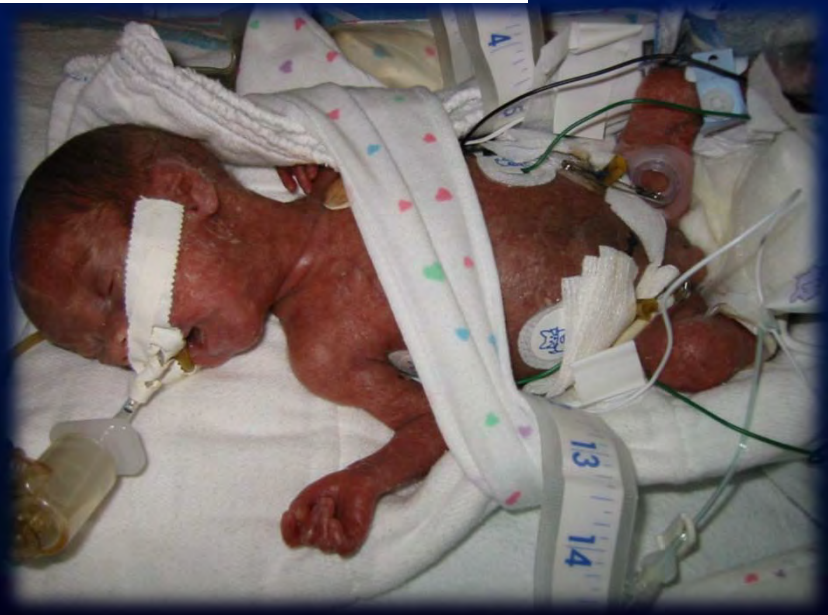
Therapeutic Challenges in Neonates

- 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

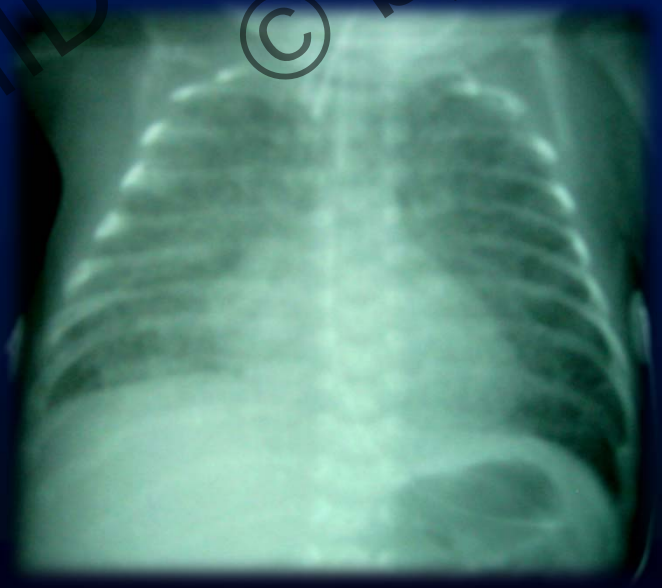
- Neonates are a heterogeneous population!
  - Birthweights of 500 grams are not uncommon (going down to 400 gm now… how low can it go?)
    - LBW, VLBW (< 1.5 kg), ELBW (< 1.0 kg), ?ILBW
  - Organ function (renal, hepatic) matures with gest/chron age
  - Volume of distribution varies with gest/chron 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

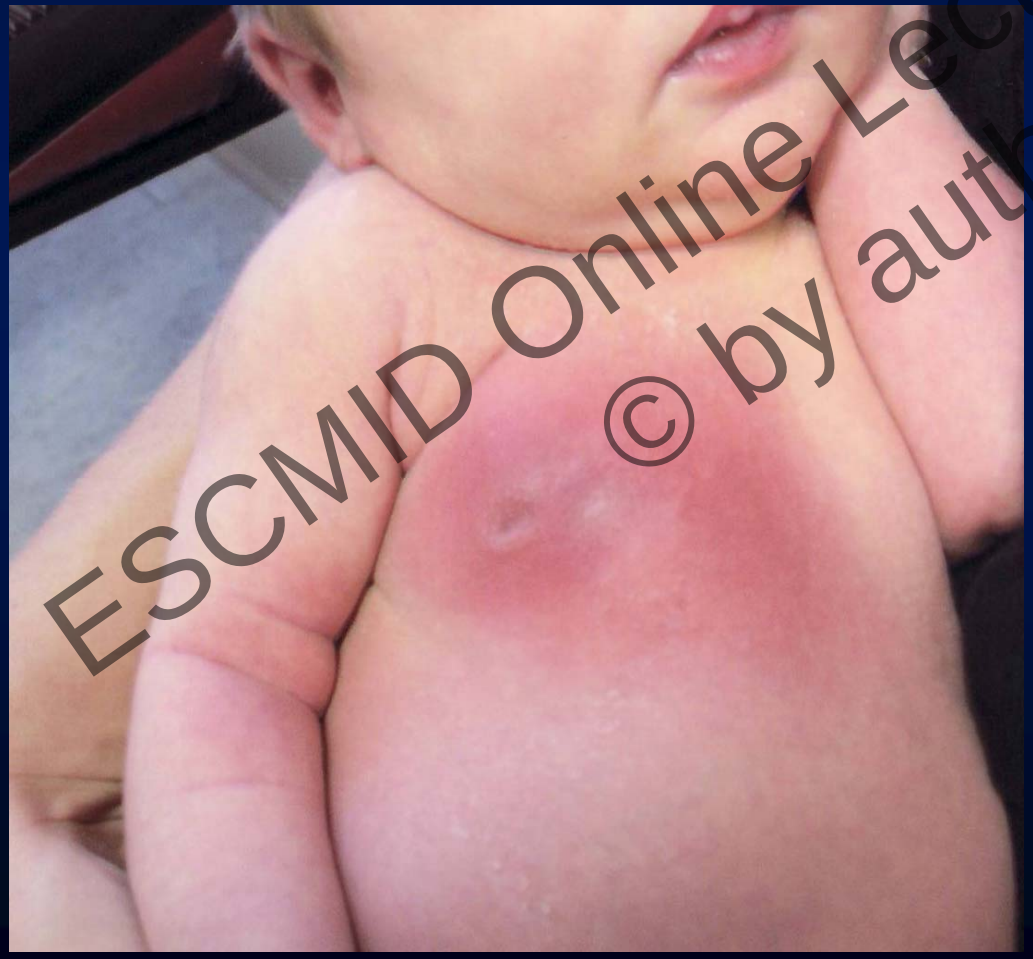
Differences Between Neonates and Adults

- 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?



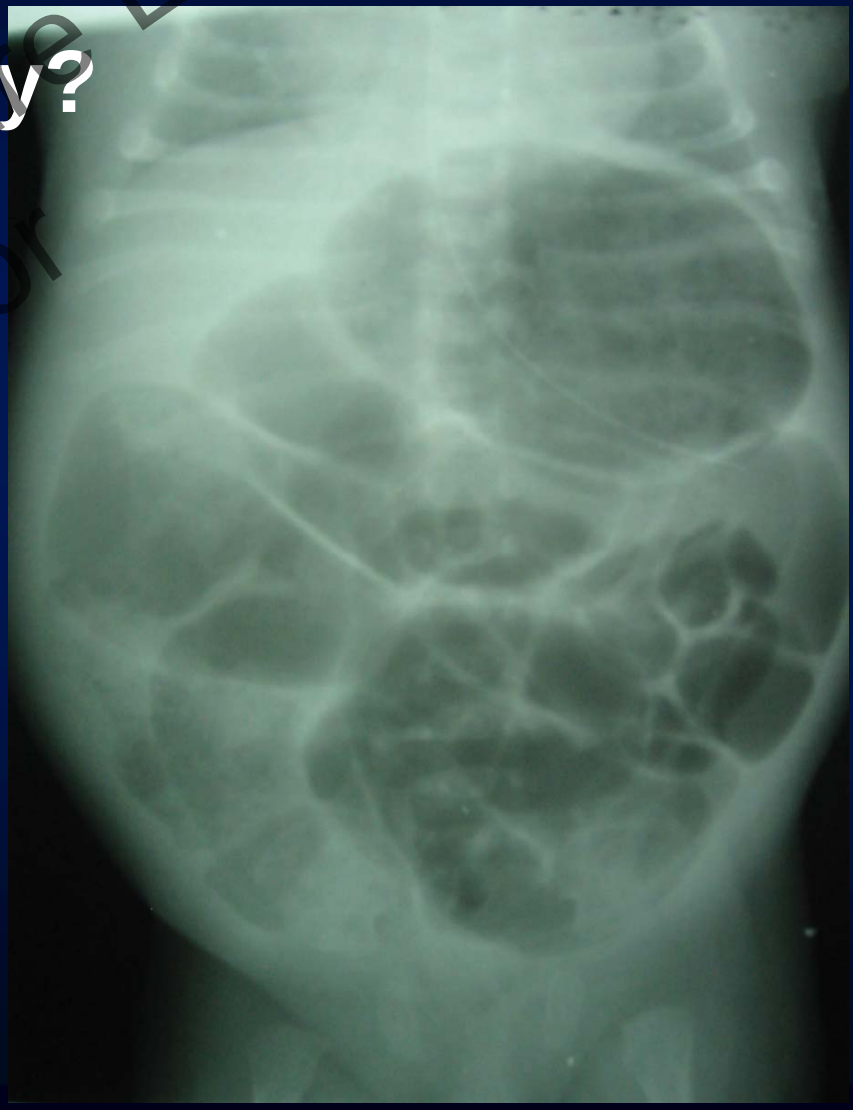
MRSA breast abscess

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?



Clinical Trial Design in Neonates

- 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

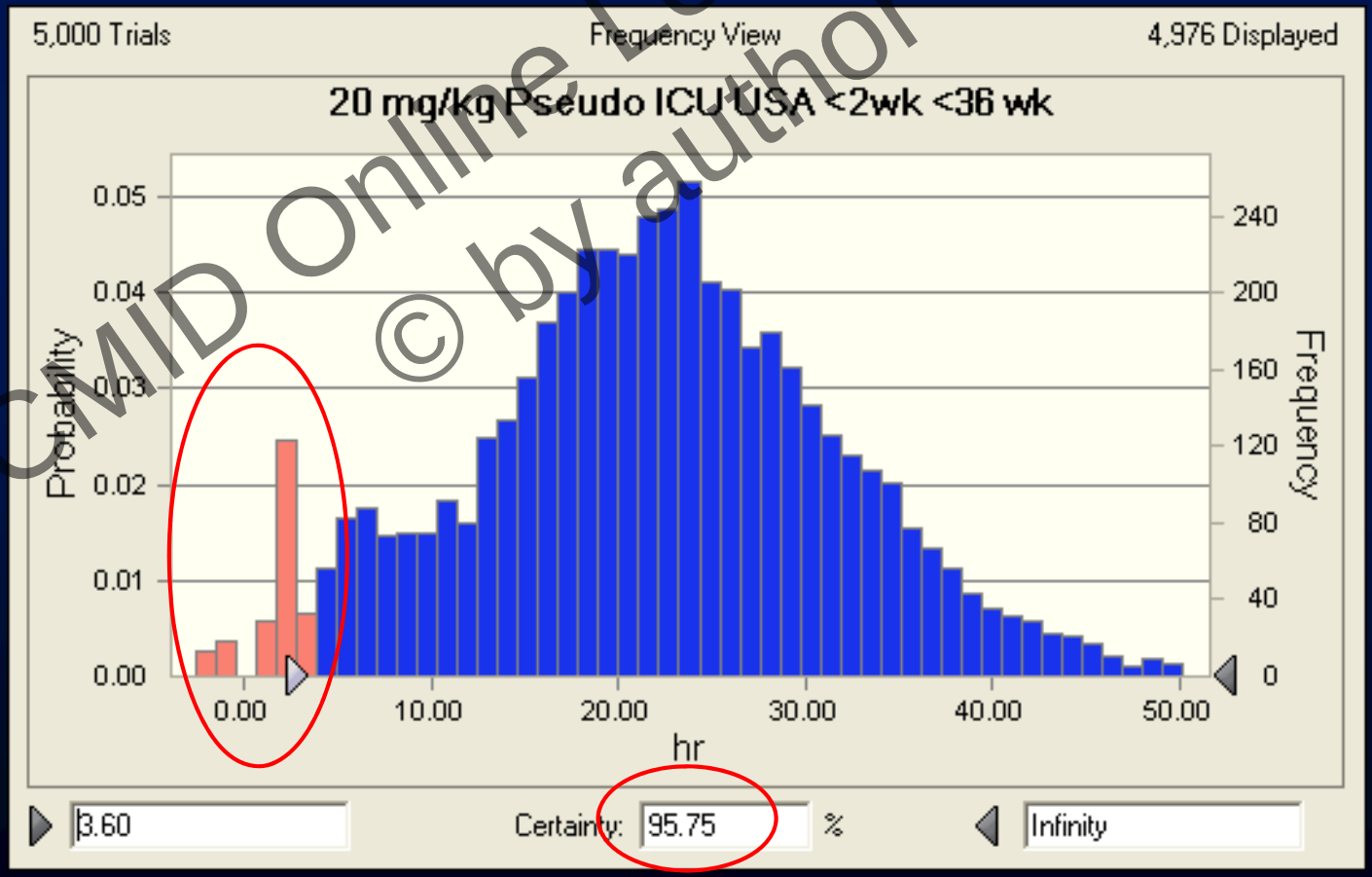
- Obtaining consent from the parents to participate in a study? Both parents?
- Parents are worried sick about their baby, and you are asking them to take on more RISK by using a new antibiotic that may not work as well as Standard of Care!
- You are required to share a long list of possible adverse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

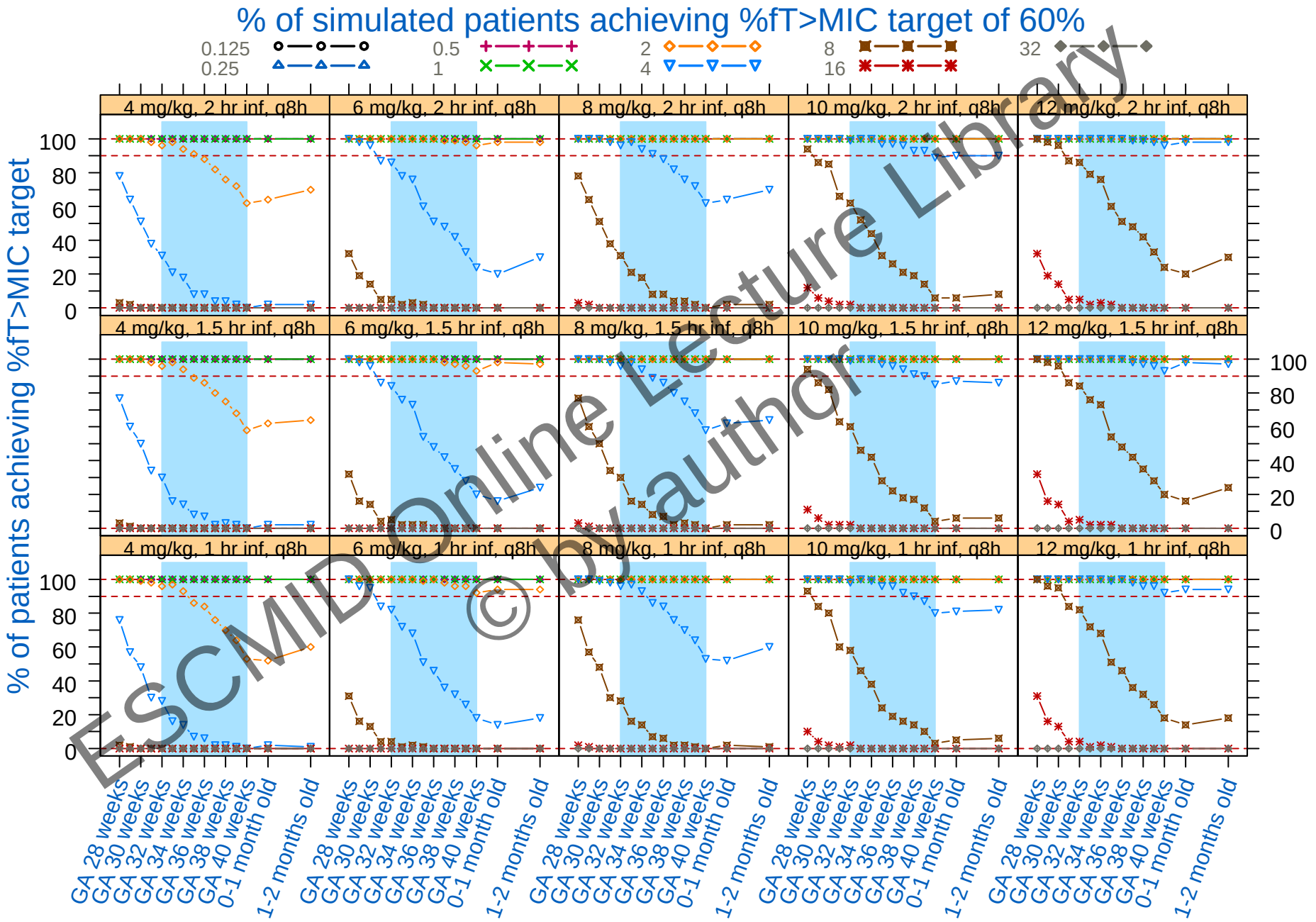
Therapeutic Challenges in Neonates

- 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????