# What is the Potential for Pediatric Master Protocols in Infectious Diseases

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# Disclosures

- Dr. Smith receives grant support from Cempra Pharmaceuticals and Shionogi Inc.  Dr. Smith is a consultant for Astellas Pharma US, Inc. and Abbvie Inc.

# Overview

- 2 examples from the NICHD Pediatric Trials Network
  - PK study – Staph Trio study
  - Safety study – SCAMP study

# Antimicrobials: PK trials

| Rank | Medication | Exposures (/1000 infants) |
|---|---|---|
| 1 | Ampicillin | 681 |
| 2 | Gentamicin | 676 |
| 4 | Vancomycin | 91 |
| 15 | Cefotaxime | 43 |
| 23 | Tobramycin | 24 |
| 27 | Fluconazole | 19 |
| 28 | Clindamycin | 17 |
| 30 | Acyclovir | 16 |
| 38 | Ceftazidime | 12 |
| 41 | Pip/tazo | 11 |
| 43 | Amoxicillin | 11 |
| 44 | Metronidazole | 11 |
| 45 | Oxacillin | 10 |
| 46 | Nafcillin | 9 |
| 47 | Amphotericin B | 9 |
| 48 | Amikacin | 9 |

Hseih, A J Perin, 2014.

# Add-on Therapy Studies - Infants

| Drug | N | Citation |
|---|---|---|
| Micafungin | 12 | PIDJ 2009 |
| Micafungin | 12 | CPT 2010 |
| Fluconazole loading dose | 13 | PIDJ 2011 |
| Fluconazole ECMO | 20 | PIDJ 2012 |
| Daptomycin | 20 | PIDJ 2012 |
| Meropenem | 200 | PIDJ 2013 |
| Acyclovir | 32 | PIDJ 2014 |
| Metronidazole | 24 | AAC 2012 |
| Anidulafungin | 15 | CPT 2011 |
| Cefazolin | 10 | pending |
| Piperacillin-tazobactam | 32 | AAC 2014 |

# Coordinating Center Considerations

- Each trial has:
  - Study documents – protocol, consent form, case report forms, manual of operating procedures, site communications, regulatory documents, statistical analysis plan
  - Study team – project leader, clinical research associate, clinical trials associate, regulatory, safety, statistician, data management, PIs
  - Weekly calls – internal, external

# Staph Trio

- 70% of late-onset sepsis in the NICU is due to gram positive organisms
  - The majority are coagulase-negative *Staphylococcus* and *Staphylococcus aureus*
  - *Staphylococcus aureus* carries up to 40% mortality in this population

**rifampin, clindamycin, and ticarcillin-clavulanate**

**all active against *Staphylococcus***

**rifampin and clindamycin active against MRSA**

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# Study Design Overview

- Multicenter (N=10), open-label, multiple-dose PK study
- Participants: 16-32 infants for each drug
- Study Intervention:  study drug over 2-4 days
- Duration of Participation:
  - 2-4 days of study drug
  - Up to 30 days of safety monitoring
- Outcomes: Pharmacokinetic and Safety

# Study Population

| | | Gestational Age (GA) | Postnatal Age (PNA) |
|---|---|---|---|
| Rifampin | Group 1 | < 32 weeks | < 14 days |
| | Group 2 | < 32 weeks | ≥ 14 days – ≤120 days |
| | Group 3 | ≥ 32 weeks | < 14 days |
| | Group 4 | ≥ 32 weeks | ≥ 14 days – ≤120 days |
| | | | |
| Ticarcillin-clavulanate | Group 1 | < 30 weeks | < 14 days |
| | Group 2 | < 30 weeks | ≥ 14 days – ≤ 45 days |
| | Group 3 | < 30 weeks | > 45 days – ≤90 days |
| | | | |
| Clindamycin | Group 1 | < 30 weeks | < 14 days |
| | Group 2 | < 30 weeks | ≥ 14 days – ≤ 45 days |
| | Group 3 | < 30 weeks | > 45 days – ≤120 days |

## Inclusion criteria

1. GA/PNA
    - Rifampin: <121 days PNA
    - Ticarcillin-clavulanate: <91 days PNA **and** <30 weeks GA
    - Clindamycin: <121 days P  NA **and** <30 weeks GA

2. Sufficient intravascular access

3. Suspected systemic infection OR receiving drug per standard of care

**Exclusion Criteria**

1. Allergic reaction to drug of interest
2. Urine output <0.5 mL/hr/kg
3. Serum creatinine >1.7 mg/dL

# Enrollment

| Clindamycin | | | |
|---|---|---|---|
| GA <30 weeks, PNA <14 days | GA <30 weeks, PNA >=14–45 days | GA <30 weeks, PNA >45–120 days | **Total** |
| 6 | 9 | 6 | **21** |

| Rifampin | | | | |
|---|---|---|---|---|
| GA <32 weeks, PNA <14 days | GA <32 weeks, PNA >=14–120 days | GA >=32 weeks, PNA <14 days | GA >=32 weeks, PNA >=14–120 days | **Total** |
| 12 | 10 | 4 | 1 | **27** |

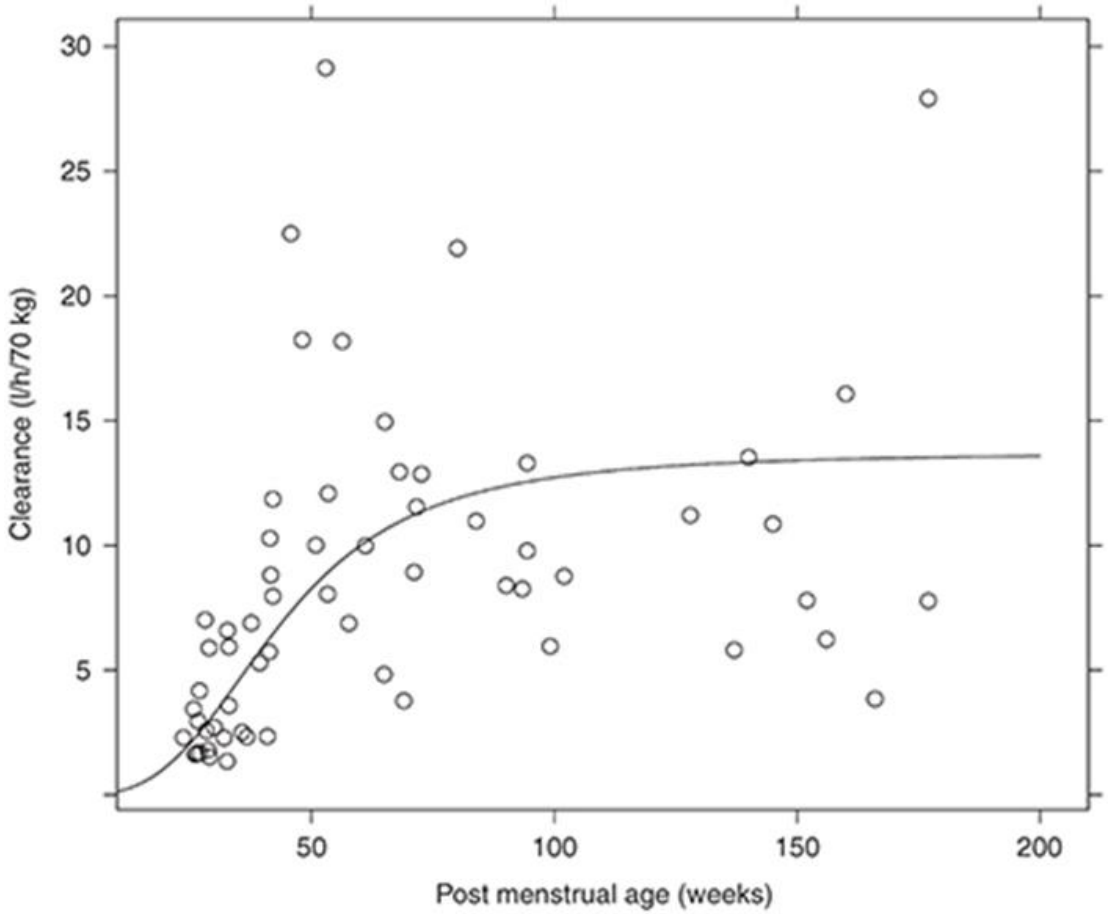
| Ticarcillin-clavulanate | | | |
|---|---|---|---|
| GA <30 weeks, PNA <14 days | GA <30 weeks, PNA >=14–45 days | GA <30 weeks, PNA >45–90 days | **Total** |
| 5 | 10 | 0 | **15** |

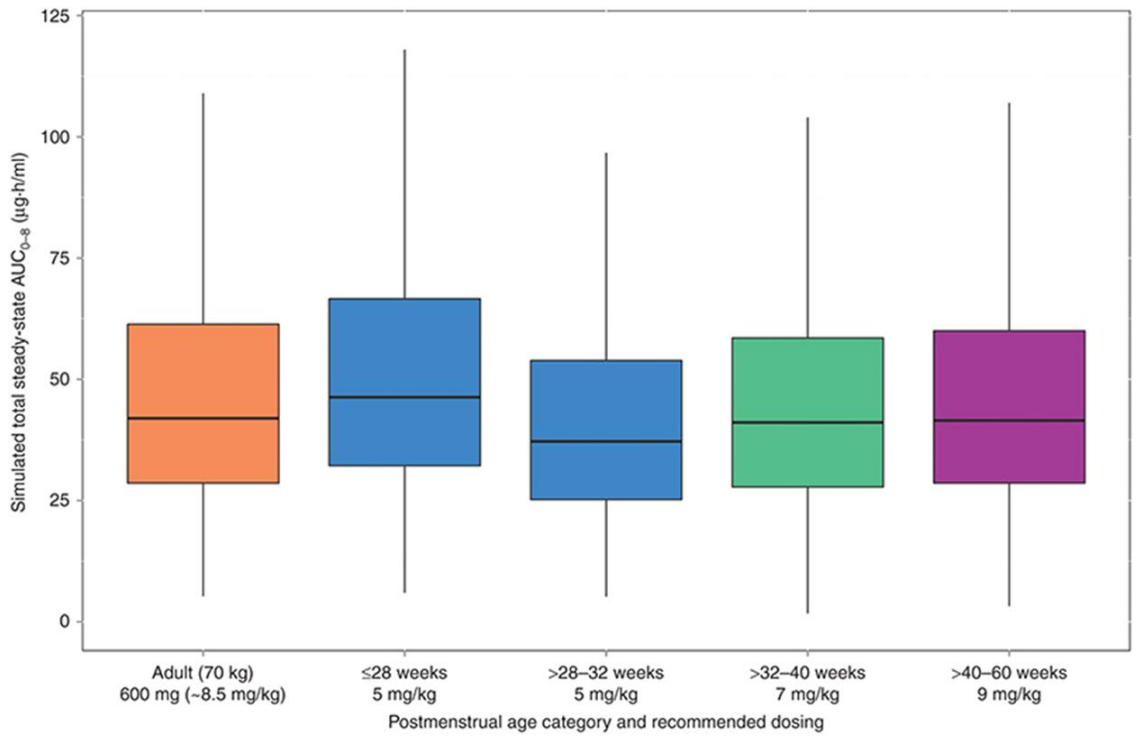
# Clindamycin

- FDA-labeled
  - Infants >1 month to 16 years
  - Sepsis, serious infections
- FDA label dosing
  - 1 month to 16 years 13 mg/kg/dose q8h
  - Full term neonates 7 mg/kg/dose q8h
  - Preemies 5 mg/kg/dose q8h
- POPS study - 125 subjects, preemies to 18 years of age
- Staph trio study - 21 subjects, <30 weeks GA and <120 days of age

Gonzalez, AAC, 2016

# Clearance and Dosing



# Overview of Drug Development

| Drug | Phase I (PK and Dosing) | Phase II (Safety and Efficacy) |
|---|---|---|
| Ampicillin | **PTN (N=28)** | SCAMP |
| Clindamycin | **PTN (N=21)** | SCAMP |
| Metronidazole | **PTN (N=24)** | SCAMP |
| Piperacillin-tazobactam | **CTSA supplement (N=32)** | SCAMP |

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# Protocol: Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections *(SCAMP)*

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# Complicated intra-abdominal infections in premature infants

- High morbidity and mortality
- Antibiotics used in almost all cases
  - No standard of care (SOC)
  - Safety and efficacy of antibiotics is lacking
  - used off-label

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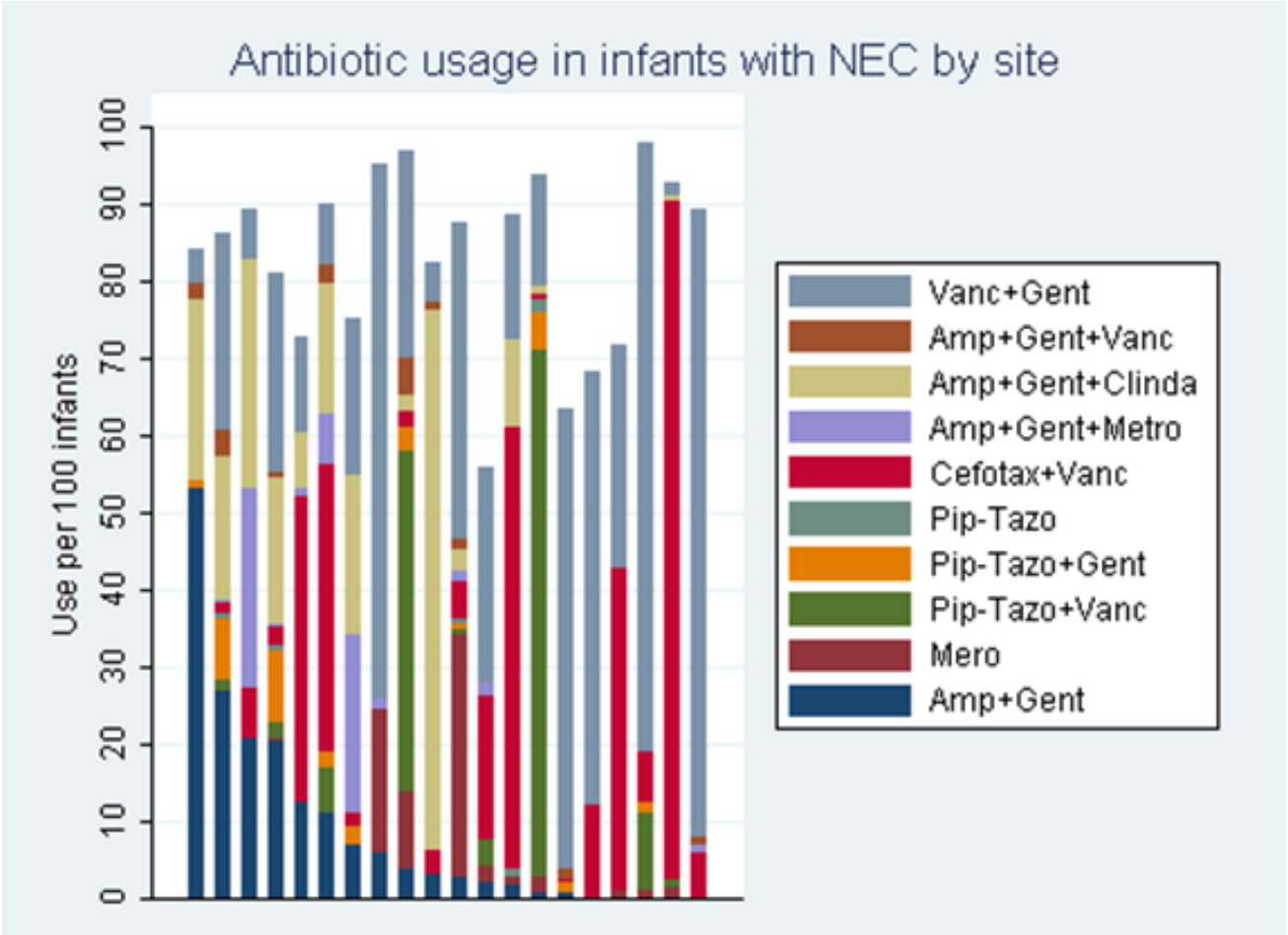
# Empirical Therapy for Necrotizing Enterocolitis

Antibiotic prescribing practices vary by center

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# Study Objectives

Primary:

- Safety of drug regimens used in infants with complicated intra-abdominal infections

Secondary:

  - Efficacy
  - PK
  - Biomarkers - urinary I-FABP, intestinal microbiota
- Polymorphisms in CYP450 and metronidazole and clindamycin exposure
- CSF PK of metronidazole, clindamycin, and piperacillin-tazobactam in infants

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# Study Population

- Phase 2/3 – safety, prospective, open-label, randomized, multi-center
- 210 premature infants (≤33 weeks gestation at birth) randomized 1:1:1 to:
  - Group 1 (N=70): ampicillin, gentamicin, and metronidazole
  - Group 2 (N=70): ampicillin, gentamicin, and clindamycin
  - Group 3 (N=70): piperacillin-tazobactam and gentamicin
- 50 late preterm and term infants (≥34 weeks gestation at birth) will be assigned to Group 4
  - Group 4 (N=50): metronidazole in addition to the antibiotic regimens prescribed per SOC

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# Study Population

Group 5: 24 infants with suspected or confirmed infection for which the study drug may provide therapeutic benefit and CSF is to be collected per SOC will be assigned by site PI to subgroup 5a, 5b, and/or 5c:

- Group 5a (N~8): metronidazole
- Group 5b (N~8): clindamycin
- Group 5c (N~8): piperacillin-tazobactam

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# Study Duration

- Groups 1-4:  up to 100 days (10 therapy + 90 follow up)
- Group 5:  up to 17 days (up to 10 days therapy + 7 days follow up)

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# Inclusion Criteria

- Presenting physical, radiological, and/or bacteriological findings of a complicated intra-abdominal infection within 48 hours prior to the first dose of study drug (Group 1-4)
- Suspected or confirmed infection, therapeutic benefit from study drug, and planned CSF collection per SOC (Group 5)
- ≤33 weeks gestation at birth (Groups 1–3)
- ≥34 weeks gestation at birth (Group 4)
- Postnatal age (PNA) < 121 days

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# Exclusion Criteria

- History of anaphylaxis to study drugs
- Serum creatinine >2 mg/dL
- Known ALT >250 U/L or AST >500 U/L

*Do not apply to Group 5 participants receiving drug per SOC.

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# Study Drug Dosing Schemes

| Drug | PNA days | GA wks | PMA wks | Weight kg | Loading dose mg/kg | Maintenance dose mg/kg | Dosing interval h |
|---|---|---|---|---|---|---|---|
| Ampicillin | ≤28 | ≤29 | | | | 50 | 12 |
| | >28 | ≤29 | | | | 50 | 8 |
| | ≤14 | 30–32 | | | | 50 | 12 |
| | >14 | 30–32 | | | | 50 | 8 |
| Metronidazole | | | <34 | | 15 | 7.5 | 12 |
| | | | 34–40 | | 15 | 7.5 | 8 |
| | | | >40 | | 15 | 7.5 | 6 |
| Clindamycin | ≤7 | | | ≤2 | | 5 | 8 |
| | ≤7 | | | >2 | | 5 | 12 |
| | >7 | | | ≤1.2 | | 5 | 8 |
| | >7 | | | 1.2 - 2 | | 5 | 12 |
| | >7 | | | >2 | | 5 | 8 |
| Piperacillin- tazobactam* | | | ≤30 | | | 100 | 6 |
| | | | >30 | | | 80 | 6 |

PNA = Postnatal Age, GA = Gestational Age, PMA = Postmenstrual Age; *Dosing based on piperacillin component

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# Study Drug Dosing Schemes

- Gentamicin dosing and therapeutic drug monitoring performed per routine medical care.
- Ampicillin - for suspected/confirmed meningitis, dosing may be increased; maximum dose of 300 mg/kg/day.

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# Outcomes of Special Interest

- Gastrointestinal surgeries
- Progression to a higher stage of NEC
- Intestinal strictures
- Intestinal perforation
- Positive blood culture (bacterial or fungal)
- Short bowel syndrome
- Seizures
- Death
- Intraventricular hemorrhage (IVH) grade 3 or 4
- Feeding intolerance

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# Efficacy Assessments

- Gastrointestinal
  - Assessed at 90 days after last dose of study drug
  - Time to first full enteral feed (≥100 mL/kg/day)
- Overall therapeutic success
  - Assessed at 30 days after last dose of study drug
  - Blood culture result closest to (prior to) the 30-day assessment will be used
  - Success = alive, negative culture, clinical cure score >4
  - Failure = death, positive culture, clinical cure score ≤4

| Element | Score |
|---|---|
| $FiO_2$ ≤ baseline $FiO_2$ | 1 |
| Urine output ≥1 mL/kg/h for 24-hour period prior to assessment | 1 |
| Absence of inotropic support at time of assessment | 1 |
| Absence of mechanical ventilation at time of assessment | 1 |
| No seizure in 24-hour period prior to assessment | 1 |
| pH ≥7.25 or not measured in 24 hours prior to assessment | 1 |

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# CSF PK Sampling

- Collection only if performed per routine medical care
- Collection can occur any day of therapy period
- Sources: lumbar puncture, ventriculoperitoneal shunt, or externalized ventricular device
- Group 5:  At least 1 dose of the drug of interest will be administered prior to CSF collection
- One blood PK sample within 1 hour of CSF collection
- Maximum of 5 CSF/blood PK samples per infant

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# Enrollment – PTN SCAMP

- 46 sites
- 215 infants

| Group1 | Group 2 | Group 3 | Group 4 | Group 5 |
|---|---|---|---|---|
| 53 | 44 | 59 | 49 | 20 |

- Eligible participants: 1.2 participants/site/month
- Enrollment: 0.2 participants/site/month = 17% of eligible participants