

# Breakout Session #4: Neonatal Sepsis

Danny Benjamin and Catherine Sherwin,  
Moderators

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## International Neonatal Consortium



# Participants of Neonatal Sepsis Breakout

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By Telecon:  
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# Background

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- ▶ “Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life. When pathogenic bacteria gain access into the blood stream, they may cause overwhelming infection without much localization (septicemia) or may get predominantly localized to the lung (pneumonia) or the meninges (meningitis).” [Neonatal sepsis - Newbornwhocc.org - WHO newborn CC]

## Clinical trials in neonatal sepsis

- ▶ “The main obstacle to conducting neonatal antibiotic trials is a lack of consensus on the definition of neonatal sepsis itself and the selection of appropriate endpoints.” [Oeser et al, J. Antimicrob. Chemother. (2013)]

# Background

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- ▶ The vast majority of antibiotic use in neonates is for culture-negative sepsis. Regulatory agencies have been hesitant to give approval for ill-defined clinical sepsis with poorly defined outcomes. The neonatal infectious disease breakout group would like to pursue clinical sepsis in neonates as an indication.

## Response to Breakout Question #1

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For neonatal sepsis, what indication(s) are in most need of effective therapies? Include an estimate of the incidence and severity.

- ▶ **Late-onset clinical sepsis**
- ▶ 0.9% of live births (Isaac 1998) considerably more frequent among premature babies, e.g. 21% of VLBW (Stoll 2002).
- ▶ Associated with prolonged hospital stay (adding USD 10,000 to hospital costs; Johnson 2012), changes on brain MRI (Chau 2012) and adverse neurodevelopment outcomes (e.g. Stoll 2004).

## Response to Breakout Question #2

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- ▶ For **sepsis**, what non-clinical studies need to be carried out prior to designing clinical trials of new and/or existing drugs?
  - ▶ What juvenile animal toxicity studies are needed?
  - ▶ Are animal models available for the indication (e.g. gestational age equivalent)?
  - ▶ Can the non-clinical data be extrapolated to inform clinical development, including initial dosing?
- ▶ a. In most cases knowledge about class effects of drugs can be used to exempt drugs from juvenile animal toxicity studies
- ▶ b. Animal models are not available for the indication
- ▶ c. Yes. Non-clinical data can be used to extrapolate PK and define PK/PD endpoints.

## Response to Breakout Question #3

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- ▶ For **sepsis**, what information would be needed before starting a clinical trial?
  - ▶ Can existing pediatric or adult studies be extrapolated to neonates?
    - ▶ **yes**
  - ▶ Could a master protocol be developed for use when evaluating treatments for this indication?
    - ▶ **Yes. A number of existing protocols can easily be consolidated to generate a Master protocol. Efforts to validate and qualify inclusion criteria are underway already (e.g. NeoMero and NeoGent) and could be extended using routinely collected data (e.g. Modi 2009 )**
  - ▶ Would the use of different drug classes alter the inclusion/exclusion criteria?
    - ▶ **No, but would impact second agent if any**
  - ▶ Do the inclusion criteria drive formulation, mode of administration and/or dose?
    - ▶ **no**
  - ▶ What parameters are needed for constructing a meaningful modelling and simulation tool?
    - ▶ **PK-PD from animal models and older humans**

## Response to Breakout Question #4

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- ▶ Are there impediments to establishing a master protocol (do multiple approaches exist – comparative effectiveness studies) for **sepsis** trials? Is there equipoise?
- ▶ There is willingness to adopt standardised approaches once they have been defined.
  - ▶ Coverage, what do about GNR when you have GPC coverage
  - ▶ Toxicity (small amount oto-tox, nephro-tox but requires monitoring of levels for gent & vanc)
  - ▶ Dosing frequency—double dummy
  - ▶ Equipoise in the community but typically not within a NICU—thus impact on enrollment (e.g., some always add vancomycin, some never add vancomycin)

## Response to Breakout Question #5

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- ▶ What potential biomarkers and clinical trial endpoints could be used?
  - a. Are adequate clinical outcome measures available? If not can they be developed?
  - b. Are any prognostic, predictive, pharmacodynamic, and safety biomarkers available? Are any regulatory ready?
- ▶ a. Clinical outcome measures are available (e.g. resolution of presenting clinical features) and have been included in protocols but need more validation
- ▶ b. A number of biomarkers have been proposed and are used in clinical practice and in extant protocols. However, they need to be refined.

# Response to Breakout Question #5

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- ▶ What potential biomarkers and clinical trial endpoints could be used for **sepsis**?
  - ▶ Are adequate clinical outcome measures available? If not can they be developed?
  - ▶ Are any prognostic, predictive, pharmacodynamic, and safety biomarkers available? Are any regulatory ready?
- ▶ **I. Clinical Criteria (at least 2):**
  - ▶ Hypothermia ( $< 36^{\circ}\text{C}$ ) OR fever ( $> 38.5^{\circ}\text{C}$ )
  - ▶ Bradycardia OR tachycardia OR rhythm instability
  - ▶ Urine output 0.5 to 1 mL/kg/h OR hypotension OR mottled skin OR impaired peripheral perfusion
  - ▶ Petechial rash OR sclerema neonatorum
  - ▶ New onset or worsening of apnea episodes OR tachypnea episodes OR increased oxygen requirements OR requirement for ventilation support
  - ▶ Feeding intolerance OR poor sucking OR abdominal distention
  - ▶ Irritability
  - ▶ Lethargy
  - ▶ Hypotonia
- ▶ **II. Laboratory Criteria (at least 2):**
  - ▶ White blood cell count  $\leq 4,000 \times 10^9/\text{L}$  OR  $\geq 20,000 \times 10^9/\text{L}$
  - ▶ Immature to total neutrophil ratio  $> 0.2$
  - ▶ Platelet count  $\leq 100,000 \times 10^9/\text{L}$
  - ▶ C-reactive protein  $> 15 \text{ mg/L}$  OR procalcitonin  $\geq 2 \text{ ng/mL}$
  - ▶ Hyperglycemia OR Hypoglycemia
  - ▶ Metabolic acidosis

## Response to Breakout Question #6

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- ▶ What long-term outcome measures are available to assess the safety and efficacy of therapies for **sepsis**?
  - ▶ 2 year NDI extremely difficult and probably not worth pursuing because of sample size
  - ▶ Interim, cost-effective, web-based parent reported outcomes are worth pursuing
  - ▶ Targeted surveillance for specific adverse events could be done using case-control or case-cohort studies based on routine data collection. Hypotheses about specific AEs could be based on knowledge from class effects (e.g. ototoxicity) or emerging concerns.
  - ▶ This would benefit from good ascertainment of exposures and covariates during the neonatal period and strong record linkage beyond the neonatal period.

## Response to Breakout Question #7

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- ▶ In light of your responses to Questions 1-6, where are the gaps in knowledge and how would you prioritize the studies needed to approach the neonatal **sepsis**?

### Goals of group:

- a) a) Work toward sepsis as an indication, or basis for inclusion in trials, in neonates
- b) Define inclusion exclusion criteria
- c) Define comparator agents
- d) Define endpoints and outcomes
- e) Move toward a master protocol for Late Onset Sepsis under regulatory guidance

Recognize the approach of using babies with late onset sepsis in PK/PD-driven trials for specific infections (rather than efficacy for each culture-positive infection)

In light of your responses to Questions 1-6, where are the gaps in knowledge and how would you prioritize the studies needed to approach this indication?

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- ▶ Validity of inclusion criteria
- ▶ Validity of biomarkers used to recognize treatment success or failure: clinical and PK/PD
- ▶ Proposed studies:
- ▶ 1. Cohort study or integrated series of database-specific cohort studies or individual patient data meta-analysis of the relationship between presenting features of sepsis and outcome, taking account of the time-course of the onset of sepsis. Output: validated criteria to guide enrolment in trials of anti-infectives during late onset sepsis including when to randomise and when to start study treatment.
- ▶ Learning and validation datasets required.
- ▶ 2. Cohort study or integrated series of database-specific cohort studies or individual patient data meta-analysis of the relationship between clinical findings during the resolution of sepsis and eventual outcome. Output: validated criteria to define treatment success or failure in trials of anti-infectives during late onset sepsis.
- ▶ Learning and validation datasets required.
- ▶ Studies 1 and 2 could be combined.
- ▶ NeoMero is a pilot for study 1 and NeoGent serves as a pilot study for study 2.
- ▶ 3. Validation of predictions from modelling and simulation approaches to dose-selection (is already underway to some extent through GRIP WP6).