



16 December 2010
EMA/477725/2010

Report on the Expert Meeting on Neonatal and Paediatric Sepsis

8 June 2010, EMA London

Role	Name
Chair/Vice-chair	Paolo Rossi, Radu Botgros
Participants:	<p>External experts: Shane Tibby (UK), Simon Nadel (UK), Paolo Manzoni (IT), Sara Arenas-Lopez (UK), Uwe Ewald (SE), Christoph Härtel (DE), Ursula Trafojer (IT), Francesca Calo Carducci (IT), Laura Folgori (IT), Maia de Luca (IT)</p> <p>PDCO Members: Paolo Rossi (IT), Hugo Devlieger (BE), Jean-Pierre Aboulker (FR), Irja Lutsar (EE), Francesca Rocchi (IT), Marianne Orholm (DK), Agnes Gyurasics (HU)</p> <p>FDA (via teleconference) Tom Smith</p> <p>EMA: Paolo Tomasi, Ralf Herold, Radu Botgros, Maria Sala Soriano, Irmgard Eichler, Ralph Bax, Eric Pelfrene</p>
Apologies:	Erik Normann (SE), Susanna Esposito (IT), Adolf Valls-i-Soler (ES), Jan A Hazelzet (NL)

1. Introduction

Sepsis is a severe condition associating infection and the systemic inflammatory response of the organism to the infection. It remains a major cause of morbidity and mortality in the paediatric population, despite progresses encountered in the last decades. Medicinal products targeting neonatal and paediatric sepsis continue to be developed and evaluated.

The Paediatric Committee (PDCO) of the European Medicines Agency (EMA) has assessed several Paediatric Investigation Plans (PIPs) targeting sepsis in the neonatal and paediatric population. Lack of consensus on the requirements for conducting clinical trials in severe sepsis makes the assessment



procedure of these applications difficult. In addition there are no authorised medicinal products for the treatment of sepsis in children, which points to a currently unmet therapeutic need for the paediatric population.

An expert meeting on neonatal and paediatric sepsis was organised on 8 June 2010 at the EMA in an effort to address a number of issues with regard to conducting clinical trials in neonatal and paediatric severe sepsis.

2. Conclusions of the panel

- a. The Experts agreed on the following operational definitions for sepsis: 1. early onset sepsis (onset in the first 72 hours after birth inclusive) and late onset sepsis (onset more than or equal to 72 hours after birth) and agreed for the neonatal population up to 44 weeks of corrected age on the following criteria to be used to include patients in clinical trials:

“Presence of at least two clinical symptoms and at least two laboratory signs (from the table below) in presence of or as a result of suspected or proven infection (positive culture, microscopy or polymerase chain reaction)”

Clinical signs	Laboratory signs
<p>Modified body temperature:</p> <ul style="list-style-type: none"> core temperature greater than 38,5 °C or less than 36 °C AND/OR temperature instability <p>Cardiovascular Instability:</p> <ul style="list-style-type: none"> Bradycardia (mean HR less than the 10th percentile for age in the absence of external vagal stimulus, beta-blockers or congenital heart disease OR otherwise unexplained persistent depression over a 0.5 h time period) OR tachycardia (mean HR greater than 2 SD above normal for age in the absence of external stimulus, chronic drugs and painful stimuli OR otherwise unexplained persistent elevation over a 0,5 h to 4 h time period) AND/OR rhythm instability reduced urinary output (less than 1 mL/kg/h), hypotension (mean arterial pressure less than the 5th percentile for age), mottled skin, impaired peripheral perfusion <p>Skin and subcutaneous lesions:</p> <ul style="list-style-type: none"> petechial rash sclerema 	<ul style="list-style-type: none"> WBC count <ul style="list-style-type: none"> <4000 x10⁹ cells/L OR >20000 x10⁹ cells/L Immature to total neutrophil ratio (I/T) <ul style="list-style-type: none"> greater than 0.2 Platelet count <ul style="list-style-type: none"> <100000 x10⁹ cells/L C reactive protein > 15mg/L OR procalcitonin ≥ 2¹ ng/ml. <ul style="list-style-type: none"> Glucose intolerance confirmed at least 2 times <ul style="list-style-type: none"> hyperglycaemia (blood glucose >180mg/dL or 10 mMol/L) OR hypoglycaemia (glycaemia < 45 mg/dL or 2.5mMol/L) <p>when receiving age specific normal range glucose amounts</p> <ul style="list-style-type: none"> Metabolic acidosis: <ul style="list-style-type: none"> Base excess (BE) <-10 mEq/L OR Serum lactate > 2mMol/L

¹ The cut-off for procalcitonin in neonatal sepsis has not been clearly defined, as the currently available published data are still controversial.

Respiratory instability:

- apnoea episodes **OR**
- tachypnoea episodes (mean respiratory rate (RR) over 2 SD above normal for age) **OR**
- increased oxygen requirements **OR**
- requirement for ventilation support

Gastrointestinal:

- feeding intolerance,
- poor sucking
- abdominal distention

Non-specific:

- irritability,
- lethargy and
- hypotonia

- b. Experts agreed that the International Paediatric Sepsis Consensus Conference sepsis definition (1,4) should be used for enrolling children from 44 weeks of corrected age onwards in therapeutic clinical trials targeting sepsis (see below):

Definition of sepsis in paediatrics (1)**Infection**

A suspected or proven (by positive culture, tissue stain or PCR test) infection caused by any pathogen **OR** a clinical syndrome associated with a high probability of infection.

Evidence of infection includes positive findings on clinical exam, imaging or laboratory tests (eg WBC in a normally sterile blood fluid, perforated viscus, chest Rx consistent with pneumonia, petechial or purpuric rash or purpura fulminans).

SIRS

The presence of **at least two of the following four criteria, one of which MUST BE abnormal temperature or leukocyte count:**

- core temperature greater than 38,5 Celsius or less than 36 Celsius
- tachycardia (mean HR greater than 2 SD above normal for age in the absence of external stimulus, chronic drugs and painful stimuli **OR** otherwise unexplained persistent elevation over a 0,5 h to 4 h time period) **OR** bradycardia-for children less than 1 year old (defined as mean HR less than the 10th percentile for age in the absence of external vagal stimulus, beta-blockers or congenital heart disease **OR** otherwise unexplained persistent depression over a 0.5 h time period)
- mean respiratory rate (RR) over 2 SD above normal for age **OR** mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anaesthesia.
- Leukocyte count elevated **OR** depressed for age (not secondary to chemotherapy-induced leucopenia) **OR** more than 10% immature neutrophils

Sepsis

SIRS in the presence or as a result of suspected or proven infection

- c. Experts agreed that the following paediatric age groups should be delineated for the purpose of including paediatric patients in clinical trials:

Group	Age
Neonates	birth to less than 1 month
Infants	1 month to less than 2 years
Toddlers and preschool children	2 years to less than 6 years
School age children	6 years to less than 12 years
Adolescents	12 years to less than 18 years

- d. The expert panel agreed that both sepsis without and with proven infection (sepsis in the presence of proven infection- by culture, stain or polymerase chain reaction) should be included in clinical trials. Patients with genetic disease, immune deficiency as well as post surgical patients should not be excluded from the trials. Justification for excluding those patients from clinical trials should be provided. Patients with life expectancy below 3 months could not be included into sepsis clinical trials.
- e. The group agreed that the all-cause short-term (28 days) mortality is not feasible as a primary efficacy endpoint, because of the low mortality rate in neonates. The use of composite outcomes such as organ failure free days, (which incorporate mortality if that occurs (scored as zero free days)) as a primary endpoint is encouraged. A list of possible primary endpoints is presented in the table below:

Possible primary endpoints to be assessed on a case-by-case basis
Clinical cure (resolution of sepsis clinical signs and symptoms) AND/OR organ failure resolution (ICU free days and organ failure free days)
Development of septic shock or organ failure
Microbiological eradication (for antibiotics)
Modification of assigned treatment because of treatment failure
Mortality recorded until the primary evaluation visit

- f. It was agreed that following essential secondary endpoints for paediatric sepsis trials should be collected and reported, in addition to those mentioned above (in the putative endpoints table):

Essential secondary endpoints
All cause short term (28 day) mortality
Neuro-developmental outcome (follow-up for 18 months up to 24 months)
Adverse events
Complications of sepsis (including sepsis sequelae, e.g. ischaemic lesions)
Emergence of infection and/or colonisation with antibiotic-resistant organisms subsequent to treatment
Duration of hospitalisation

Experts agreed that other product- and trial-specific secondary endpoints may also be acceptable.

- g. The group extensively discussed the topic of existing organ failure scores, both in neonates and in older children. It was agreed that only outcome organ failure scores (which describe the disease severity by a daily assessment of the organ dysfunctions/failures attributable to sepsis) could theoretically be used as alternative endpoints in clinical trials.
- h. Experts present at the meeting agreed that for the neonates, organ failure scores are not applicable in the late onset sepsis, as opposed to severe sepsis or septic shock, because of the relative lower severity of the former. It was acknowledged that a validated tool that covers the whole neonatal population is lacking at present and therefore no specific recommendation regarding the use of a specific organ failure score can be made for the neonatal population. Further development is needed and could be done by either adapting existing paediatric scores (like MODS, P-MODS, PELOD) or by proposing new sequential organ failure scores targeting the specific aspects of neonatal sepsis (need for ventilatory support, need for inotropic and vasopressor support, need for renal replacement therapy, cholestatic icterus).
- i. Regarding the paediatric organ failure scores, experts agreed to recommend the use of the qualitative Goldstein consensus criteria (1) in clinical trials. Experts discussed the criteria to be met in order to use an organ failure score as a surrogate for mortality. It was agreed that biological plausibility of a causal link between the organ failure and death should exist, the prognostic value of organ failure for mortality should be established after conducting epidemiological studies and there should be evidence from clinical trials that treatment effects on the organ failure score produce similar effects on the main outcome (2). No consensus could be reached towards proposing the use of a particular score. It was acknowledged that a composite score may be useful, but the drawback of most existing scores is the lack of external validation².
- j. Experts present at the meeting agreed that extrapolation of efficacy from adults is generally not possible in neonatal and paediatric severe sepsis clinical trials, because of important differences between adults and children with respect to co-morbidities, organ failure, baseline mortality rate etc. Some experts expressed the opinion that extrapolating efficacy from adults might be possible in older children for antibiotics in the treatment of severe sepsis, provided that PK/PD and safety studies are conducted in children. This opinion was not endorsed by all participants and a consensus could not be reached, as it was acknowledged that such studies in adults are virtually non-existing at present.
- k. The panel discussed possible biomarkers useful for better selecting the trial population. An agreement was reached on the use of C-reactive protein and procalcitonin in neonatal sepsis (see definitions). Use of other biomarkers such as interleukins is not supported at present.
- l. The experts could not agree on specific recommendations with regard to the optimal time to enrol patients in sepsis clinical trials.
- m. The group agreed to encourage the standardisation of the sepsis "standard of care" in the study protocol. Guidelines from learning societies as well as internal guidance may be used. Some experts recommended the use of the clinical practice parameters for haemodynamic support of paediatric and neonatal septic shock, which were recently published (3).
- n. Experts present at the meeting acknowledged that the duration of the post treatment follow-up is highly dependant on the used endpoints, the type of product, the mechanism of action of the medicinal product and on the included age groups. Divergent opinions were expressed. No specific recommendations could be agreed.

² It should be aimed to standardise the collection of information for the purpose of a later validation of at least one score.

3. References

1. Brahm Goldstein, Brett Giroir, and Adrienne Randolph, "International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics," *Pediatric Critical Care Medicine: A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 6, no. 1 (January 2005): 2-8.
2. "ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group," *Statistics in Medicine* 18, no. 15 (August 15, 1999): 1905-1942.
3. Joe Brierley et al, "2007 American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock*," *Critical Care Medicine* (November 28, 2008), <http://www.ncbi.nlm.nih.gov/pubmed/19050601>.
4. Gebara Bassam et al., "Values for systolic blood pressure", *Pediatric Critical Care Medicine: A Journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies* 6, no. 4 (July 2005): 500.
5. Robert Carr et al., "Granulocyte-macrophage colony stimulating factor administered as prophylaxis for reduction of sepsis in extremely preterm, small for gestational age neonates (the PROGRAMS trial): a single-blind, multicentre, randomised controlled trial.", *Lancet*. 2009 Jan 17;373(9659):226-33
6. A M C van Rossum et al, "Procalcitonin as an early marker of infection in neonates and children", *Lancet Infect Dis* 2004; 4: 620-30