A multicentre, single-blind, randomised, controlled trial of prophylactic granulocyte macrophage colony stimulating factor (GM-CSF) to reduce sepsis in preterm neonates
FUNDED BY

- Action Medical Research
  Primary trial and administration
- NHS Executive South East
  Economic evaluation
- Guy’s & St Thomas’ Charitable Foundation
  Laboratory cytokine studies
- The Wellcome Trust
  Follow-up assessments
INVESTIGATORS

• Neena Modi  Imperial College London
• Robert Carr  Guy’s & St Thomas’ Hospital
• Peter Brocklehurst  NPEU, Oxford
HYPOTHESIS

Prophylactic GM-CSF, administered for a limited period after birth to preterm neonates at high risk of sepsis, will lead to a clinically significant reduction in systemic infection, mortality and later disability.
CONTENTS

• Background
• Evidence so far
• G-CSF or GM-CSF for sepsis prophylaxis
• Trial Design
• Practicalities
Neonatal Sepsis

- Published rates in preterms are high and range from 25-50%.
- Mortality rates have remained constant for two decades.
- Damages - both directly and indirectly.
Neonatal Sepsis

...increasingly implicated in the genesis of preterm white matter damage and other brain injury, including cerebral palsy ...

Nelson et al 1998
Damman & Leviton 1998
Major risk factors for sepsis

- **Extremely preterm birth**
- **Neutropenia** – frequent in infants born $\leq 31$ weeks gestation, in small for gestational age infants and in infants born to mothers with pregnancy hypertension
Immaturity of Neonatal Immune System

- Hypogammaglobulinaemia
- Reduced neutrophil cell mass
- Poor phagocyte function
- Altered balance of pro/anti-inflammatory cytokines
Immaturity of Neonatal Phagocyte Immune System

• Reduced neutrophil cell mass

  Sepsis associated neutropenia associated with high mortality

• Immaturity of function

  Pattern of bacterial infection characteristic of neutropenia
EVIDENCE SO FAR

Intravenous immunoglobulin
Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates.


Reduction in mortality

- clinically suspected infection
  
  (n = 318); RR 0.63 (95% CI; 0.40, 1.00)

- subsequently proved infection
  
  (n = 262); RR 0.55 (95% CI; 0.31, 0.98); NNT=11

- 5000 infants in 19 studies
- **reduction** in sepsis, RR 0.85 (95% CI 0.74, 0.98); p = 0.02; NNT 33
- **reduction** in serious infection, RR 0.82 (95% CI 0.74, 0.92); NNT 25
- *no statistically significant differences for mortality from all causes or mortality from infection*
EVIDENCE SO FAR

for the use of CSFs to prevent or treat neonatal infection
The Haemopoietic Growth Factors

- G-CSF
  Granulocyte Colony Stimulating Factor

- GM-CSF
  Granulocyte-Macrophage Colony Stimulating Factor
What is the most effective use of CSFs in neonates?

- Intervention rescue therapy in sepsis associated with neutropenia?
- Early postnatal prophylaxis to prevent neutropenia and sepsis?
Reviewed in

“G-CSF and GM-CSF for Treating and Preventing Neonatal Infections”

Carr R, Modi N, Doré C

Cochrane Library 2003
Treatment trials
All cause mortality to 14 days from start of treatment:

n= 257 recruited to randomised studies

Relative Risk = 0.71
(95% CI, 0.38 - 1.31)

p = 0.3
What is the most effective use of CSFs in neonates?

- Intervention rescue therapy in sepsis associated with neutropenia?
- Early postnatal prophylaxis to prevent neutropenia and sepsis?

The limited evidence so far suggests this strategy may be the more effective...
A Randomized, Double-Masked, Placebo-Controlled Trial of Recombinant Granulocyte Colony-Stimulating Factor Administration to Preterm Infants with the Clinical Diagnosis of Early-Onset sepsis

Miura E et al, Pediatrics 2001; 1078:30-35

Administration of G-CSF daily for 3 days to neonates <37 weeks and <2000g birth weight, with a clinical diagnosis of sepsis did not improve mortality,

*but was associated with fewer infections over the subsequent 2 weeks.*
Prophylactic strategies are more effective than treatment (post bacterial inoculum) strategies in animal models of infection.
G-CSF or GM-CSF for sepsis prophylaxis?
• GM-CSF has a greater effect on neutrophil and monocyte function
• Neonatal neutrophil dysfunction is secondary to reduced IFN$\gamma$ & IL-12.
• GM-CSF increases IFN$\gamma$ & IL-12
• G-CSF rapidly raises the circulating neutrophil count. Too florid a response may make it an inappropriate agent for prophylaxis in the absence of neutropenia.
An RCT of Prophylactic GM-CSF in Human Newborns less than 32 weeks gestation

Robert Carr, Neena Modi, Caroline Doré, Rim El-Rifai, Dwight Lindo

Hammersmith and Queen Charlotte’s Hospitals
Guy’s and St Thomas’ Hospital

*Pediatrics* 1999, 103:796-802
Aims of pilot prophylactic GM-CSF study

**Primary**
- Effect on full blood count
- Toxicity

**Secondary**
- Sepsis incidence
# Neutropenia*: Day 1-14

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriately Grown</td>
<td>0 (25)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>Small for Gestation</td>
<td>0 (11)</td>
<td>10 (14)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>0 (36)</td>
<td>16 (39)</td>
</tr>
</tbody>
</table>

p<0.001

*≤1.7 x 10⁹/l  *Manroe 1979 - *J Pediatr* 95:89
### Blood Culture Positive Systemic Infection: Day 1 - 14

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriately Grown</td>
<td>9 (25)</td>
<td>11 (25)</td>
</tr>
<tr>
<td>Small for Gestation</td>
<td>2 (11)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Overall</td>
<td>11 (46%)</td>
<td>18 (31%)</td>
</tr>
</tbody>
</table>

(odds ratio 0.51, 95%CI 0.20, 1.31)
Definitions of Culture Positive Systemic Infection

Positive blood culture

plus

Acute onset of at least 3 clinical signs
Pilot Study Conclusions I

Prophylactic GM-CSF for 5 days after birth:

• Completely abolishes postnatal neutropenia, including sepsis-related neutropenia

• Is apparently free from adverse effects

• May lead to a clinically useful reduction in sepsis, in high risk neonates
Pilot Study Conclusions II

Prophylactic GM-CSF for 5 days after birth:

• The maximum benefit appears to be in infants at highest risk of early postnatal neutropenia

• There is currently inadequate evidence to justify the use of G- or GM-CSF in neonates outside a clinical trial
PROGRAMS
TRIAL DESIGN
The study is a single-blind, multicentre, randomised controlled trial, comparing the effect of once daily, short term (5 day) prophylactic GM-CSF in a dose of 10µg/kg/day vs no GM-CSF treatment in preterm neonates at high risk of sepsis.
Control infants do NOT receive placebo

• Placebo would not achieve blinding because of induced neutrophil leucocytosis

• But - sepsis as an outcome is therefore ascertained blind to treatment allocation
Eligibility Criteria

- Preterm neonates in whom it is considered appropriate to continue intensive care
- SGA (<10th centile for birth weight)
- ≤ 31 completed weeks gestational age
- Within 72 hours of birth
- Written informed parental consent
Exclusion criteria

• Immediately life threatening congenital abnormality

• Evidence of early onset sepsis as evidenced by maternal pyrexia exceeding 38°C on 2 consecutive occasions during labour
Consent

• If a baby is eligible discuss trial with parent(s)
• Give patient information leaflet
• Seek consent
Randomisation

- 24 hour telephone randomisation service
- Minimisation (centre, gestational age and birth weight)
- Baby allocated to:
  - GM-CSF
  - no GM-CSF
Intervention (1)

- If allocated GM-CSF (Leukine®)
  - give first injection at time of randomisation
- GM-CSF concentration 10µg in 0.1ml
  - (i.e. a 1000g infant will receive a volume of 0.1ml for each injection)
- SC once daily for 5 days
Intervention (2)

• Stop GM-CSF if total white cell count exceeds $50 \times 10^9/l$ (after correction for NRBCs)

• If any unexpected adverse events occur, complete an Adverse Event Report Form
Intervention (3)

Practical issues

Reconstituted vials of Leukine (GM-CSF) may be kept at 4°C for a maximum of 6 hours.

Therefore a single vial CANNOT be used for 2 doses to the same baby. Each treated baby will therefore use 5 vials of Leukine.

(However it may be possible to use the same vial for two babies being treated in parallel)
Primary Outcome

• Sepsis-free survival at 14 days from trial entry

The composite endpoint designed to capture:
- reduction in sepsis
- all cause mortality due to: undiagnosed sepsis unidentified toxicity
Secondary Outcomes

• Survival without moderate/severe disability at 2 and 5 years from term

• Sepsis:
  – Culture positive systemic infection, to 14 & 28 days from trial entry
  – “probable” (culture negative) infection, to 14 & 28 days from trial entry

• Survival to discharge
• Clinical morbidity:
  – Chronic lung disease (bronchopulmonary dysplasia)
  – Necrotising enterocolitis
  – Periventricular haemorrhage, periventricular leucomalacia & ventriculomegaly
• Haematological:
  – Sepsis associated neutropenia, to 14 & 28 days from trial entry
Diagnosis of Sepsis

- Positive blood, CSF or suprapubic urine culture, \textit{plus}
- acute onset of at least 3 predefined clinical signs of sepsis, \textit{plus}
- acute rise in CRP \textit{or} fall in platelet count
Diagnosis of “probable sepsis”

- acute onset of at least 3 predefined clinical signs of sepsis, \textit{plus}
- acute rise in CRP \textit{or} fall in platelet count
- \textit{No} positive cultures
Sample size

During the pilot study the following sepsis-free survival was observed at 14 days from trial entry in the subgroup of SGA infants ≤31 weeks:

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>GM-CSF 5 days</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis free survival: n (%)</td>
<td>6/14 (43%)</td>
<td>9/11 (82%)</td>
<td>39%</td>
</tr>
</tbody>
</table>
Sample size

<table>
<thead>
<tr>
<th>Total n</th>
<th>14 day sepsis free survival in control group</th>
<th>14 day sepsis free survival in GM-CSF group</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>43%</td>
<td>67%</td>
<td>24%</td>
</tr>
<tr>
<td>200</td>
<td>43%</td>
<td>63.7%</td>
<td>20.7%</td>
</tr>
<tr>
<td>300</td>
<td>43%</td>
<td>59.1%</td>
<td>16.1%</td>
</tr>
<tr>
<td>400</td>
<td>43%</td>
<td>57%</td>
<td>14%</td>
</tr>
<tr>
<td>600</td>
<td>43%</td>
<td>54.4%</td>
<td>11.4%</td>
</tr>
</tbody>
</table>
Feasibility

- 320 infants
- over 2.5 years
- from 25-30 centres
Analysis

• ‘intention to treat’

• Subgroup analysis:
  – gestational age (23-25, 26-28, 29-31 weeks)
  – neutropenia at trial entry
  – neutropenia risk at trial entry as indicated by maternal hypertension or pre-eclampsia.
Organisation

- Trial Steering Committee
  Make policy decisions regarding trial conduct

- Data Monitoring and Ethics Committee
  Periodically inspect data to confirm that it is ethically appropriate to continue recruitment

- Sepsis Identification Committee
  Use objective data recorded on “daily logs” to diagnose episodes of systemic sepsis, “blind” to the baby’s randomisation
Economic Evaluation

- Funded by NHS Executive South East
- Assessing cost-effectiveness
- Led by Dr Stavros Petrou
PRACTICALITIES
Practical Issues

- GM-CSF is NHS Treatment Cost
- Additional laboratory tests met as Service Support Cost
- Trusts are obliged to meet these costs under terms of agreement with Department of Health
Research Contribution to Unit

£150 per infant recruited
Data Collection

- Trial entry
- Daily for 28 days
- Term
- Discharge or Transfer
Daily FBC with manual differential white cell count

- Daily FBC essential before each GM-CSF dose
- Daily FBC Days 1 - 14, but only at time of other blood tests
- FBC Days 15-28, only as clinically indicated
- Sticker on blood forms requesting manual differential - *talk to haematology laboratory!*
Daily Data Collection... the not so good Daily Log!!

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Date</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16/2/01</td>
<td>17/2/1</td>
<td>18/2/1</td>
<td>19/2/01</td>
<td>20/2/01</td>
<td>21/2/01</td>
<td>22/2/01</td>
<td></td>
</tr>
<tr>
<td>IV Antibiotics</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Steroids</td>
<td>(agent and total daily dose)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Invasive devices: central lines</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>(record number)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Level of care</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>(1, 2, or 3)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>FBC Data</td>
<td>(Manual differential)</td>
<td>Measure FBC each day during days 1-14</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>g/dl</td>
<td>15.7</td>
<td>15.6</td>
<td>15</td>
<td>14.2</td>
<td>13.4</td>
<td>12.5</td>
<td>13.6</td>
</tr>
<tr>
<td>Total WBC</td>
<td>x 10^9/l</td>
<td>12.4</td>
<td>15.4</td>
<td>15.0</td>
<td>13.8</td>
<td>20.4</td>
<td>13.0</td>
<td>19.8</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>x 10^9/l</td>
<td>6.1</td>
<td>9.5</td>
<td>9.0</td>
<td>6.2</td>
<td>9.5</td>
<td>9.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Monocytes</td>
<td>(including Bands)</td>
<td>6.1</td>
<td>9.5</td>
<td>9.0</td>
<td>6.2</td>
<td>9.5</td>
<td>9.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Platelets</td>
<td>x 10^9/l</td>
<td>164</td>
<td>174</td>
<td>185</td>
<td>191</td>
<td>217</td>
<td>32</td>
<td>284</td>
</tr>
<tr>
<td>Study Day</td>
<td>3</td>
<td>7</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
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<tr>
<td><strong>Cultures Taken</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Cultures (✓ taken)</td>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CSF (✓ taken)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>SPA Urine (✓ taken)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Swab (Specify site of local infection)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Culture Results</strong> (specify under date taken)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Blood Cultures (Organism)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>CSF (Organism)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Suprapubic aspirated urine (Organism)</td>
<td></td>
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<td></td>
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<tr>
<td>Swab (Organism and site)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>CRP (Measure daily, days 1 – 14)</td>
<td>17</td>
<td>19</td>
<td>24</td>
<td>34</td>
<td>27</td>
<td>26</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Indicators of Sepsis</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Increased oxygen requirement or ventilatory support (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Type of support (state daily min/max) (NIPPV: NIPPV, BTPAP, N-CPAP, Ventilation)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Min. appropriate FiO₂ (%)</td>
<td>22.7</td>
<td>22.7</td>
<td>22.7</td>
<td>22.7</td>
<td>31%</td>
<td>31%</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>Max. appropriate FiO₂ (%)</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Clinically relevant increase in apnoea/bad cardiac (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Hypotension (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Lowest BP - record mean (mmHg)</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Volume replacement given (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Intravascular used (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Glucose intolerance (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Highest blood glucose (mmol/L)</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Reduction in glucose delivery (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Insulin given (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Impaired Peripheral Perfusion (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Pallor/ Mottling (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Capillary refill time &gt; 3 secs (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Core-peripheral gap &gt; 2°C (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<td>N</td>
</tr>
</tbody>
</table>
Daily Data Collection... how to get the daily log right!

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Date</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Day i = date of study entry)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV Antibiotics</td>
<td>(y/n or Ch = changed)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Steroids</td>
<td>(y/n)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>invasive devices: central lines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>record number</td>
<td>peripherical lines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other (include ETT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of care</td>
<td>(1, 2, or 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
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</tbody>
</table>

(See definitions in Data Collection Booklet Part 2)

FBC Data (Manual differential) Measure FBC each day during days 1-14

<table>
<thead>
<tr>
<th>Hb</th>
<th>Total WBC $\times 10^9$</th>
<th>Neutrophils $\times 10^9$ (excluding Bands)</th>
<th>Monocytes $\times 10^9$</th>
<th>Platelets $\times 10^9$</th>
</tr>
</thead>
<tbody>
<tr>
<td>g/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.3</td>
<td>9.0</td>
<td>2.2</td>
<td>1.8</td>
<td>45</td>
</tr>
<tr>
<td>11.5</td>
<td>10.7</td>
<td>0.5</td>
<td>2.4</td>
<td>78</td>
</tr>
<tr>
<td>15.3</td>
<td>12.7</td>
<td>0.5</td>
<td>2.4</td>
<td>96</td>
</tr>
<tr>
<td>16.5</td>
<td>10.8</td>
<td>1.7</td>
<td>2.5</td>
<td>48</td>
</tr>
<tr>
<td>12.9</td>
<td>12.9</td>
<td>1.7</td>
<td>2.5</td>
<td>250</td>
</tr>
<tr>
<td>12.2</td>
<td>12.9</td>
<td>2.7</td>
<td>1.6</td>
<td>328</td>
</tr>
<tr>
<td>11.9</td>
<td>16.2</td>
<td>2.7</td>
<td>2.4</td>
<td>341</td>
</tr>
<tr>
<td>CVP</td>
<td>(Measure daily, days 1 - 14)</td>
<td>24</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td><strong>Clinical Indicators of Sepsis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased oxygen requirement or</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Ventilatory support (Y/N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of support (cont. daily min (hrs))</td>
<td>N - CPAP</td>
<td>N - CPAP</td>
<td>N - CPAP</td>
<td>N - CPAP</td>
</tr>
<tr>
<td>N - CPAP</td>
<td>N - CPAP</td>
<td>N - CPAP</td>
<td>N - CPAP</td>
<td>N - CPAP</td>
</tr>
<tr>
<td>Min. appropriate FiO₂ (%) or est (Y/N)</td>
<td>21%</td>
<td>21%</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>Max. appropriate FiO₂ (%) or est (Y/N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically relevant increase in ...</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Hypotension (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Lowest BP - record mean (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume replacement given (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Inotrope used (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Glucose intolerance (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Highest blood glucose (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in glucose delivery (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Insulin given (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Impaired Peripheral Perfusion (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Palor / Mottling (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Capillary refill time &gt;3 secs (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Core-peripheral gap &gt;2°C (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Fatigue / Tiredness / Poor handling (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Temperature instability (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Ileus</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>(US esoph; abs distension)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Acute increase in bilirubin (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Acute fall in urine output (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Maximum base deficit (mmol)</td>
<td>-2.2</td>
<td>0.3</td>
<td>1.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Anticonvulsant therapy (Y/N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>
Blood Samples for Cytokine Studies

1. At trial entry - before 1st dose GM-CSF
2. 24 hrs after final dose, or day 6 in “controls”
3. During any subsequent acute episode of sepsis
4. Approximately day 28 from trial entry

*This component of the study has additional MREC approval for all centres who might wish to participate*
Training

- CPD accredited training meetings
- Certificate of participation
Current Trial Status

• 15 centres in the UK are participating
• 220 infants recruited between January 2001 & October 2002
• Recruitment halted following disruption to drug supply
• Recruitment recommenced, using Leukine, in December 2004
• Aim to complete recruitment within 12 months
2 Year Follow-up Study

All eligible children have now had a detailed developmental assessment at 2 years corrected age by a PROGRAMS paediatrician.

We aim to see these children again when they start school at age 5 years.
Follow-up paediatricians

We would like to express our thanks to the following paediatricians for their help with the 2 Year Follow-up assessments

Dr Samantha Johnson  
Dr Sajjad Rahman  
Dr Michele Cruwys  
Dr Angela Huertas–Ceballos  
Dr Angela D’Amore  
Dr Nicholas Wood  

Dr Georgina Siggers  
Dr Amanda Cundy  
Dr Huw Jones  
Dr Louise Watson  
Dr Lesley McDonald
Further information

http://www.npeu.ox.ac.uk

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Email:programs@perinat.ox.ac.uk