WHEN TO START ANTIBIOTICS IN PREMIES BELOW 32 WEEKS

Sinno Simons
Erasmus MC – Sophia Children’s Hospital Rotterdam, the Netherlands

s.simons@erasusmc.nl
WHEN TO START ANTIBIOTICS IN PRETERM INFANTS?
From protected and well nourished before birth
The host defence in neonates is not optimal yet.
Infection

MORBIDITY
SEPSIS
INFLAMMATION
DAMAGE

Use of antibiotics

Resistance
Side-effects
Microbioma
IV

Erasmus MC
NEONATUS 2018
## LARGE DIFFERENCES IN NEONATAL DRUG USE BETWEEN NICUS ARE COMMON PRACTICE: TIME FOR CONSENSUS?

<table>
<thead>
<tr>
<th>Classification of drugs</th>
<th>Patient days</th>
<th>Prescriptions</th>
<th>Off-label for neonates</th>
<th>Unlicensed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobial drugs</strong></td>
<td>51,470</td>
<td>10,858</td>
<td>761 (7%)</td>
<td>143 (1%)</td>
</tr>
<tr>
<td><strong>CNS drugs</strong></td>
<td>37,796</td>
<td>5,100</td>
<td>4,720 (93%)</td>
<td>339 (7%)</td>
</tr>
<tr>
<td><strong>Hemodynamic drugs</strong></td>
<td>49,571</td>
<td>3,970</td>
<td>1,505 (38%)</td>
<td>1,375 (35%)</td>
</tr>
<tr>
<td><strong>Respiratory drugs</strong></td>
<td>43,596</td>
<td>3,434</td>
<td>608 (18%)</td>
<td>270 (8%)</td>
</tr>
<tr>
<td><strong>Endocrinological drugs</strong></td>
<td>4,215</td>
<td>243</td>
<td>162 (67%)</td>
<td>55 (23%)</td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td>8,369</td>
<td>1,293</td>
<td>190 (15%)</td>
<td>61 (5%)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>195,004</td>
<td>24,903</td>
<td>7,948 (32%)</td>
<td>1,932 (8%)</td>
</tr>
</tbody>
</table>
Data 4 NICUs in the Netherlands
Most frequently prescribed drugs of a total of 10,985 prescriptions for 1,491 patients.

<table>
<thead>
<tr>
<th>#</th>
<th>All drugs</th>
<th>Prescriptions</th>
<th>#</th>
<th>Off-label drugs for neonatal age</th>
<th>Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phytomenadione</td>
<td>996</td>
<td>1</td>
<td>Benzylpenicillin</td>
<td>428</td>
</tr>
<tr>
<td>2</td>
<td>Cholecalciferol</td>
<td>777</td>
<td>2</td>
<td>Paracetamol</td>
<td>407</td>
</tr>
<tr>
<td>3</td>
<td>Caffeine</td>
<td>715</td>
<td>3</td>
<td>Heparin</td>
<td>326</td>
</tr>
<tr>
<td>4</td>
<td>Amoxicillin</td>
<td>559</td>
<td>4</td>
<td>Fentanyl</td>
<td>288</td>
</tr>
<tr>
<td>5</td>
<td>Gentamicin</td>
<td>559</td>
<td>5</td>
<td>Propofol</td>
<td>174</td>
</tr>
<tr>
<td>6</td>
<td>Tobramycin</td>
<td>451</td>
<td>6</td>
<td>Dopamine</td>
<td>163</td>
</tr>
<tr>
<td>7</td>
<td>Benzylpenicillin</td>
<td>428</td>
<td>7</td>
<td>Phenobarbital</td>
<td>136</td>
</tr>
<tr>
<td>8</td>
<td>Paracetamol</td>
<td>407</td>
<td>8</td>
<td>Hydrocortisone</td>
<td>118</td>
</tr>
<tr>
<td>9</td>
<td>Surfactant (Colfosceril®)</td>
<td>374</td>
<td>9</td>
<td>Xylometazoline</td>
<td>101</td>
</tr>
<tr>
<td>10</td>
<td>Morphine</td>
<td>369</td>
<td>10</td>
<td>Miconazole</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>Heparin</td>
<td>326</td>
<td>11</td>
<td>Phenylephrine/Tropicamide</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td>Fentanyl</td>
<td>288</td>
<td>12</td>
<td>Noradrenaline</td>
<td>79</td>
</tr>
<tr>
<td>13</td>
<td>Amoxicillin/clavulanic acid</td>
<td>246</td>
<td>13</td>
<td>Meropenem</td>
<td>64</td>
</tr>
<tr>
<td>14</td>
<td>Midazolam</td>
<td>220</td>
<td>14</td>
<td>Dexamethasone</td>
<td>63</td>
</tr>
<tr>
<td>15</td>
<td>Atropine</td>
<td>205</td>
<td>15</td>
<td>Doxapram</td>
<td>62</td>
</tr>
<tr>
<td>16</td>
<td>Flucloxacillin</td>
<td>199</td>
<td>16</td>
<td>Phenylephrine</td>
<td>56</td>
</tr>
<tr>
<td>17</td>
<td>Rocuronium</td>
<td>198</td>
<td>17</td>
<td>Chloral hydrate</td>
<td>44</td>
</tr>
<tr>
<td>18</td>
<td>Vancomycin</td>
<td>197</td>
<td>18</td>
<td>Ranitidine</td>
<td>40</td>
</tr>
<tr>
<td>19</td>
<td>Furosemide</td>
<td>194</td>
<td>19</td>
<td>Levetiracetam</td>
<td>38</td>
</tr>
<tr>
<td>20</td>
<td>Propofol</td>
<td>174</td>
<td>20</td>
<td>Cefazolin</td>
<td>23</td>
</tr>
<tr>
<td>21</td>
<td>Dopamine</td>
<td>163</td>
<td>21</td>
<td>Cisatracurium</td>
<td>23</td>
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<tr>
<td>22</td>
<td>Ceftazidime</td>
<td>142</td>
<td>22</td>
<td>Antithrombine</td>
<td>21</td>
</tr>
<tr>
<td>23</td>
<td>Phenobarbital</td>
<td>136</td>
<td>23</td>
<td>Esketamine</td>
<td>21</td>
</tr>
</tbody>
</table>
WHEN TO START ANTIBIOTICS IN PRETERM INFANTS?

Early onset sepsis

Late onset sepsis

How to use and dose antibiotics?
Prolonged initial empirical antibiotic treatment is associated with adverse outcome

Table II. Initial empirical antibiotics, total antibiotic exposure, and select adverse outcomes

<table>
<thead>
<tr>
<th>Description</th>
<th>Initial empirical antibiotic therapy, n = infants (% of total study infants)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 Days, n = 60 (16.4%)</td>
<td>1-4 Days, n = 175 (48%)</td>
</tr>
<tr>
<td>Total days treated with antibiotics during hospital course, median (range) [interquartile range]</td>
<td>0 (0-21) [0-0]</td>
<td>3 (1-55) [3-8]</td>
</tr>
<tr>
<td>Composite, no. (%)</td>
<td>7 (11.7)</td>
<td>31 (17.7)</td>
</tr>
<tr>
<td>Late onset sepsis, no. (%)</td>
<td>7 (11.7)</td>
<td>23 (13.1)</td>
</tr>
<tr>
<td>NEC, no. (%)</td>
<td>0</td>
<td>8 (4.6)</td>
</tr>
<tr>
<td>Death, no. (%)</td>
<td>0</td>
<td>8 (4.6)</td>
</tr>
</tbody>
</table>

*Any outcome of death, sepsis, or NEC after 7 days of life.
Duration of antibiotic treatment is associated with NEC/death

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Duration of Initial Empirical Antibiotic Treatment (Odds per Day)</th>
<th>P</th>
<th>Prolonged Initial Empirical Antibiotic Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC or death (total, N = 3883; with outcome, n = 884)</td>
<td>1.04 (1.02–1.06)</td>
<td>&lt;.01</td>
<td>1.30 (1.10–1.54)</td>
</tr>
<tr>
<td>NEC (total, N = 3899; with outcome, n = 427)</td>
<td>1.07 (1.04–1.10)</td>
<td>&lt;.001</td>
<td>1.21 (0.98–1.51)</td>
</tr>
<tr>
<td>Death (total, N = 3882; with outcome, n = 631)</td>
<td>1.16 (1.08–1.24)</td>
<td>&lt;.001</td>
<td>1.46 (1.19–1.78)</td>
</tr>
</tbody>
</table>

ORs were adjusted for study center, gestational age, small-for-gestational age status, gender, black race, 5-minute Apgar score of <5, rupture of membranes for >24 hours, outborn, prenatal steroid treatment, intrapartum antibiotic treatment, maternal hypertension, maternal hemorrhage, and multiple birth. The total numbers of infants shown represent the numbers of infants with nonmissing outcome and covariate data who were included in each model.
WHEN TO START ANTIBIOTICS IN PRETERM INFANTS?

Early onset sepsis:
Early onset sepsis risk factors

- Maternal: invasive group B streptococcal infection in a previous baby, group B streptococcal colonisation, bacteriuria or infection in the current pregnancy
- Prelabour rupture of membranes
- **preterm birth following spontaneous labour** (before 37 weeks’ gestation)
- suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth
- intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis
- parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicaemia) at any time during labour, or in the 24-hour periods before and after the birth (this does not refer to intrapartum antibiotic 10 prophylaxis).
- suspected or confirmed infection in another baby in the case of a multiple pregnancy.

NICE guidelines
WHEN TO START ANTIBIOTICS IN PRETERM INFANTS?

Epidemiology and causes of preterm birth

Robert L Goldenberg et al. The Lancet (January 2008)
WHEN TO START ANTIBIOTICS IN PRETERM INFANTS?

Epidemiology and causes of preterm birth

Robert L. Goldenberg et al. The Lancet (January 2008)
WHEN TO START ANTIBIOTICS IN PRETERM INFANTS < 32 WEEKS AFTER BIRTH?

IN ALL WITH INFECTION AS POTENTIAL REASON FOR PRETERM BIRTH

+ 

IN THOSE WITH SIGNS OF INFECTION AFTER BIRTH
PROCALCITONIN-GUIDED DECISION MAKING FOR DURATION OF ANTIBIOTIC THERAPY IN NEONATES WITH SUSPECTED EARLY-ONSET SEPSIS: A MULTICENTRE, RANDOMISED CONTROLLED TRIAL (NeoPIns)
ANTIBIOTICS IN NEWBORNS AFTER BIRTH

HOW TO STOP?

By the use continuously available physiological data?

doxapram
WHEN TO START ANTIBIOTICS IN PRETERM INFANTS?

Late onset sepsis

Goal is: ZERO infections

PREVENTION
WHEN TO START ANTIBIOTICS IN PRETERM INFANTS? Late Onset Sepsis

BIOMARKERS
HOW TO START ANTIBIOTICS IN PRETERM INFANTS? Late Onset Sepsis

### TABLE 1. Neonatologists’ Usual Choice of Empiric Antimicrobial Therapy for Suspected Late-Onset Sepsis in a 3-Week-Old Infant With a Birth Weight of 900 g Who Develops Apnea/Bradycardia Episodes Requiring Reintubation

<table>
<thead>
<tr>
<th>Empiric Antimicrobial Regimen</th>
<th>Unmodified Clinical Scenario (n = 262)*</th>
<th>Modification: CVC Is Present (n = 220)</th>
<th>Modification: Birth Weight &lt;750 g (n = 216)</th>
<th>Modification: Shock Present (n = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin and Aminoglycoside</td>
<td>23†</td>
<td>4 (P &lt; .0001)‡</td>
<td>14 (P = .026)</td>
<td>9 (P &lt; .0001)</td>
</tr>
<tr>
<td>Cephalosporin§ Oxacillin (or nafcillin) and Aminoglycoside</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>11</td>
<td>13</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Vancomycin and Aminoglycoside</td>
<td>1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>3</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td>40</td>
<td>51 (P = .028)</td>
<td>43</td>
<td>38</td>
</tr>
<tr>
<td>Cephalosporin alone</td>
<td>19</td>
<td>27</td>
<td>21</td>
<td>33 (P &lt; .0007)</td>
</tr>
<tr>
<td>Other¶</td>
<td>&lt;1</td>
<td>0</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
HOW TO USE AND DOSE ANTIBIOTICS?

Neonates are not small adults

and

GA and PNA are very important covariates
Body composition

Formula dependent

Hepatic

Renal

Kearns et al, NEJM 2003
Developmental Pharmacology

Critical Illness

Inflammation

Artificial Support Devices

Pharmacokinetics / Pharmacodynamics

Pharmacogenetics

ELBW - Obesity

Whole Body Cooling

Pharmacokinetics

Concentration/time curve:

Cmax
Cmin
Tmax
T1/2
AUC
PK/PD

Minimal Inhibitory Concentration (MIC)
Antibiotic mechanisms

Bacterial Targets for Current Antibiotics Used in the Clinic

Cell wall synthesis
- Cycloserine
- Vancomycin, Teichoplanin
- Bacitracin
- Penicillins
- Cephalosporins
- Monobactams
- Carbapenems

Cell wall
- peptidoglycan

DNA Gyrase
- Quinolones
- DNA-directed RNA polymerase

Folic acid metabolism
- Trimethoprim
- Sulfonamides

DNA
- THFA
- mRNA

Ribosomes
- 50S inhibitors
  - Erythromycin (Macrolides)
  - Chloramphenicol
  - Clindamycin
- 30S inhibitors
  - Tetracycline
  - Spectinomycin
  - Streptomycin
  - Gentamicin, Tobramycin (aminoglycosides)
  - Amikacin

Disruption of Protein Synthesis

Cell Membrane
- PABA
- Polymyxins

Chloramphenicol Transacetylase
Antimicrobial Efficacy

- 2 main patterns of bacterial killing

**Time dependent with no persistent effect**
- Betalactams
- Correlated with Time above MIC (T>MIC)

**Concentration dependent**
- Aminoglycosides, quinolones, macrolides, azalides, clindamycin, tetracyclines, glycopeptides, oxazolidinones
- Correlated with AUC/MIC, Peak/MIC
Aminoglycosides:

aim for a high peak and wait for a low trough level

Aminoglycosides exhibit concentration dependent killing

Single daily (extended time interval) is more effective and less toxic
Aminoglycosides:
aim for a high peak and wait for a low trough level

**Peak/MIC > 8**

ratio of the peak Concentration to MIC (aminoglycosides)

(bacterial killing)

PEAK (effect)

TROUGH (side effect)

(toxicity)

Time
Aminoglycosides:

One characteristic of pharmacodynamics is the post-antibiotic effect (PAE):

→ the delayed regrowth of bacteria following exposure to an antibiotic.
why concentration dependent killing and post antibiotic effects exist

Mature Protein

Growing Polypeptide

5’ AUG 3’

blocked initiation

premature termination

3’

incorporation of wrong amino acid

Disruption of Protein Synthesis

mRNA translation

Amino Glycoside

+ 50S 30S
Clinical practice....

Where can we find the correct antibiotic dosages?
Sources for local guidelines.

- Pediatric and Neonatal Dosage Handbook: 5%
- Published studies: 21%
- Various references: 20%
- Scientific opinions (from pharmacist, infectiologist or other NICU): 17%
- Vidal (French physician’s desk reference): 16%
- Neofax: 13%
- Pediatric Emergency (book edited by Philippe Labruné et al): 10%
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Minimal dosing intervals</th>
<th>Maximal dosing intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survey results (h) (Min–max)</td>
<td>Neofax (h)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>6–8</td>
<td>8</td>
</tr>
<tr>
<td>Amikacin</td>
<td>8–24</td>
<td>24</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>8–24</td>
<td>24</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>8–24</td>
<td>24</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>8–48</td>
<td>24</td>
</tr>
</tbody>
</table>

* NA, not available.
No international consensus yet...

and still room for improved dosages?
PK/PD modeling: vancomycine...

Neonates, PNA=14 days

- ID1: bBW=500 g
- ID2: bBW=650 g
- ID3: bBW=1200 g
- ID4: bBW=2200 g
- ID5: bBW=2800 g

Dutch Pediatric Formulary
