**Supplemental Information**

**Supplemental Table 1** Clinical characteristics of VLBW infants enrolled in GNN stratified into subgroups discharged in the time periods before and after outbreak reports in the public media (0-3 and 4-6 months before outbreak; 0-3 and 4-6 months after outbreak).

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Clinical characteristics** | **Before**  **Outbr 1**  **Feb-April 2010** | **Before**  **Outbr 1**  **May-July**  **2010** | **Outbr 1**  **reported**  **Aug-Oct**  **2010** | **After**  **Outbr 1**  **Nov 2010-Jan 2011** | **Before**  **Outbr 2**  **May-July**  **2011** | **Before**  **Outbr 2**  **Aug-Oct**  **2011** | **Outbr 2**  **reported**  **Nov 2011-Jan 2012** | **After**  **Outbr 2**  **Feb-April 15th 2012** | **Before**  **Outbr 3**  **April 16th-June 2012** | **Before**  **Outbr 3**  **July-Sept**  **2012** | **Outbr 3**  **reported**  **Oct 2012-Dec 2012** | **After**  **Outbr 3**  **Jan 2013-Mar 2013** |
| No. of infants | 300 | 402 | 342 | 381 | 369 | 381 | 478 | 365 | 464 | 512 | 494 | 448 |
| Gestational age (weeks), mean (SD) | 28.9  (2.7) | 28.6  (2.8) | 28.7  (2.7) | 28.7  (2.5) | 28.7  (2.7) | 28.6  (2.8) | 28.6  (2.8) | 28.8  (2.7) | 28.9  (2.8) | 28.6  (2.6) | 28.5  (2.7) | 28.6  (2.8) |
| Birth weight (grams), Mean (SD) | 1075 (304) | 1061 (318) | 1061 (307) | 1059 (291) | 1040 (306) | 1066 (303) | 1055 (312) | 1042 (303) | 1072 (315) | 1050 (308) | 1031 (303) | 1043 (304) |
| Clinical sepsis (%) | 36.3 | 33.8 | 36.0 | 31.8 | 35.5 | 33.3 | 32.8 | 29.9 | 27.2 | 26.2 | 30.6 | 25.3 |
| Culture proven sepsis (%)  Gram-negative sepsis (%)  Late-onset sepsis (%) | 12.3  3.0  11.3 | 11.2  1.2  10.7 | 12.6  3.2  12.4 | 12.3  2.1  11.8 | 14.6  4.1  14.4 | 14.7  3.7  14.2 | 17.6  2.7  17.4 | 11.5  0.8  11.2 | 10.0  1.9  9.5 | 9.8  2.0  8.6 | 12.8  4.1  11.4 | 13.6  1.6  12.7 |
| NEC or FIP (%) | 5.3 | 3.5 | 4.4 | 4.7 | 6.5 | 3.7 | 4.8 | 4.4 | 4.3 | 3.1 | 2.9 | 3.2 |
| Antibiotics (%) | 82.0 | 82.5 | 81.6 | 84.9 | 85.7 | 84.4 | 86.8 | 86.5 | 87.6 | 86.8 | 87.6 | 85.7 |
| Carbapenems (%)  Third-line antibiotics (%) | 15.3  17.3 | 15.2  15.7 | 17.8  18.7 | 17.6  15.4 | 22.5  23.0 | 18.1  20.5 | 22.8  23.4 | 23.6  25.2 | 19.6  20.9 | 17.6  18.6 | 22.7  25.3 | 20.9  22.5 |

The time periods started at the first day of month if not otherwise declared.

**Supplemental Table 2** Clinical characteristics of infants born in GNN centers with “low”

and “high” prescription rate of third-line antibiotics before 1st outbreak

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical characteristics** | **Low rate** | **High rate** | **p** |
| **No. of infants** | 5433 | 8342 |  |
| **Gestational age (weeks), mean (SD)** | 28.8 (2.9) | 28.7 (2.9) | 0.1\* |
| **Birth weight (grams), mean (SD)** | 1067 (315) | 1053 (315) | 0.006\* |
| **Gender, male (%)** | 50.8 | 51.5 | 0.4 |
| **Multiples (%)** | 31.7 | 33.1 | 0.1 |
| **Antenatal steroids (%)** | 89.8 | 89.9 | 0.9 |
| **Antenatal antibiotics (%)** | 48.3 | 50.5 | 0.03 |
| **Postnatal antibiotics (%)**  Penicillins  Aminoglycosides  Vancomycin/Teicoplanin  Carbapenems  Third-line antibiotics | 80.3  74.3  62.8  25.8  14.3  14.8 | 85.3  64.1  59.4  40.6  24.7  26.9 | <0.001  <0.001  0.001  <0.001  <0.001  <0.001 |
| **Central venous lines (%)** | 54.7 | 57.4 | 0.01 |
| **Mechanical ventilation (invasive, %)**  Duration of ventilation [mean/median (SD) days]  Duration oxygen supplementation [mean/median (SD) days] | 46.8  5.7/0 (49)  32/15 (40) | 50.0  6.3/6 (92)  34/15/42 | <0.001  <0.001\*  0.1 |
| **Duration until full feeding [150 ml/kg/d; mean/median (SD) days]** | 15/11 (13) | 17/13 (14) | <0.001\* |
| **Clinical sepsis (%)** | 25.8 | 30.9 | <0.001 |
| **Blood culture proven sepsis (%)**  Gram-negative sepsis  Gram-positive sepsis  Gram-positive sepsis without CoNS  Late-onset sepsis | 9.0  2.6  7.7  2.6  9.5 | 12.3  2.6  11.4  2.7  12.7 | <0.001  0.9  <0.001  0.8  <0.001 |
| **NEC or FIP requiring surgery (%)** | 4.7 | 4.4 | 0.5 |
| **Mortality (%)** | 8.8 | 9.9 | 0.04 |

P-values are derived from Fisher´s exact test or Mann-Whitney-U-test if indicated (\*)

**Methods - Definitions**

***Gestational age*** was calculated from the best obstetric estimate based on early prenatal ultrasound and obstetric examination. ***Clinical sepsis*** was defined as condition with at least two signs of systemic inflammatory response (temperature > 38°C or < 36.5°C, tachycardia > 200/min, new onset or increased frequency of bradycardias or apneas, hyperglycemia > 140 mg/dl, base excess < -10 mval/l, changed skin color, increased oxygen requirements), plus one pathologic laboratory sign (platelet count < 100/nl, C-reactive protein > 20 mg/L, immature/total neutrophil ratio > 0.2, white blood cell count < 5/nl) plus the decision of the attending neonatologist to treat with antibiotics for at least 5 days, but without growth of bacteria in blood culture. ***Blood culture proven sepsis*** was defined as clinical sepsis with growth of bacteria in the blood culture. If coagulase-negative staphylococci (CoNS) were isolated as single pathogen in one peripheral blood culture, two clinical signs and one laboratory sign (platelet count < 100/nl, C-reactive protein > 20 mg/L, immature/total neutrophil ratio > 0.2, white blood cell count < 5/nl) were required to fulfill the definition of blood culture confirmed sepsis.

***Early-onset sepsis*** (EOS) was defined as blood-culture confirmed sepsis occurring in the first 72 h of life. ***Late-onset sepsis*** (LOS) was defined as blood-culture confirmed sepsis occurring later than 72 h of life. ***Gram-negative sepsis*** was defined as blood-culture confirmed sepsis with Gram-negative bacteria. ***Gram-positive sepsis*** was defined as blood-culture confirmed sepsis with Gram-positive bacteria.

***Mortality*** was defined as death during the initial hospital stay. ***Cause of death, e.g. proportion of death due to sepsis*** was documented by the attending neonatologist in charge of the patient, and was based on the clinical course, post-mortem pathology and consensus decisions made in neonatal mortality conferences.

***NEC requiring surgery*** was defined as clinical NEC classified as Bell Stage II or Bell Stage III with need for peritoneal drainage, laparotomy with or without resection of necrotic gut, and macroscopic findings by the attending surgeon. ***NEC or focal intestinal perforation (FIP) requiring surgery*** combines the two main causes of abdominal surgery (peritoneal drainage or laparotomy) in the first weeks of life.