Late-onset group B streptococcus infections and severe bronchopulmonary dysplasia in an extremely preterm born infant

Suffolk, Raymond; Agertoft, Lone; Johansen, Malene; Zachariassen, Gitte

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Late-onset group B streptococcus infections and severe bronchopulmonary dysplasia in an extremely preterm born infant

SUMMARY
This case is about a boy born extremely preterm at gestational age of 24 weeks and extremely low birth weight, developing severe bronchopulmonary dysplasia (BPD) and in need of mechanical ventilation for 155 days. He also had five recurrent infections with group B streptococcus (GBS) within 4 months from birth, and his respiratory condition clearly deteriorated with every GBS infection. It was difficult to wean him from mechanical ventilation. He was finally extubated 7 months old and kept out of mechanical ventilation after receiving high-dose methylprednisolone given according to international recommendations. After GBS was cultured for the fifth time, he received oral rifampicin along with intravenous penicillin and after this treatment, GBS did not occur again.
At the age of 22 months, the boy is no longer in need of any respiratory support and he is about 6 months late in his neurological development.

BACKGROUND
Through this case report, we wish to bring out the importance of repeated doses of pulse steroids, in managing a patient with severe bronchopulmonary dysplasia (BPD) from mechanical ventilation after several months, in combination with treatment of five late-onset Group B streptococcus (GBS) infections.

BPD is the most common chronic lung disease affecting very and extremely preterm infants. Its incidence is inversely related to gestational age.[1,2] BPD is characterized by disrupted lung development with inhibited alveolar growth and impaired vascular development.[3-5] The pathogenesis of BPD is complex and influenced primarily by immaturity, infections, supplementary oxygen and mechanical ventilation.[6-9] Early weaning from mechanical ventilation with successful extubation may reduce the risk of these complications.[10] However, recurrent infection is associated with increasing risk of re-intubation and prolonged periods on mechanical ventilation, increasing the risk of BPD. BPD, intraventricular haemorrhage and retinopathy of prematurity are all thought to be aggravated by bacterial infection causing systemic inflammation.[8,9,11,12] GBS is a well-known cause of neonatal sepsis. It is more common in the early neonatal period due to maternal genital tract transmission and less in the late neonatal period due to intestinal colonisation or horizontal transmission.[13]

CASE PRESENTATION
The case is about a boy born extremely premature with a gestational age of 24 weeks and 2 days and a birth weight of 528 gram. The mother was admitted to the hospital since gestational week 20 due to vaginal bleeding and suspicion of premature rupture of membranes. Treatment with corticosteroid for lung maturation was administered twice according to guidelines.
The birth was a spontaneous vaginal delivery. APGAR 6/1 and 10/5. Based on high oxygen requirement (60%), surfactant was given twice during the first 24 hours. Afterwards, the boy was stable with nasal continuous positive airway pressure (nCPAP) for a week.
See table 1 for an overview of infections with GBS, respiratory support and medical treatment. The reported inflammatory parameter in the table is C-reactive protein (CRP).

Day 106, oral rifampicin was added to the penicillin treatment, trying to eradicate GBS from the mucous membranes. After this treatment GBS was not cultured again.

A few days after extubation on day 203, the oxygen requirement rose to 80%, and it was agreed to initiate high-dose methylprednisolone treatment. After initiation of high-dose methylprednisolone, there has been no further need for mechanical ventilation.

The boy was transferred from a level III to II NICU on day 243 and discharged home on day 307.

### INVESTIGATIONS

Other clinical and paraclinical investigations not presented or described in details in table 1.

The mother’s urine was screened for bacteria pre-birth, and no GBS was found. The breast milk was examined for bacteria twice (day 26 and 27). We performed no rectal or vaginal swab of the mother. We cultured only coagulase-negative staphylococcus in mothers own milk.

X-ray taken on day 8 showed alterations corresponding to respiratory distress syndrome (RDS). Ongoing x-rays showed increasing signs of BPD. (See figure 1)

Echocardiography (Echo) showed a patent ductus arteriosus (PDA), which was treated with Ibuprofen for 5 days with treatment initiated on day 13. Two weeks after treatment, the PDA was closed and remained closed. From day 59, Echo revealed signs of pulmonary hypertension. Echos were performed on a regular basis and did never show signs of endocarditis.

On day 43, a sign of an abscess over the left clavicle was observed, and intubation was needed as part of surgical clearing of the abscess. During surgery, no sign of abscess was found, but cellulitis-adenitis syndrome was diagnosed.

On day 58, inhaled NO (iNO) was initiated due to an oxygen demand of 100% in high-pressure ventilation. After iNO administration, it was possible gradually to reduce p-mean from 22 to 10-14 cm H₂O. iNO was reduced within 8 days and gradually replaced with Sildenafil in treating pulmonary hypertension and the ventilation/perfusion mismatch.

On day 121, the T-B-NK-cells were evaluated due to suspicion of immune incompetence, but the result was normal.

On day 139, a bronchoscopy was performed due to recurrent infections and x-rays showing continuous infiltration in the right upper lobe. Normal conditions were found including normal vocal cords and no laryngeal oedema.

On day 192, a high-resolution CT (HRCT) of the chest showed 25-30% normal lung tissue and several infiltrative changes. Signs of fibrosis and ground glass image compatible with severe BPD were observed (see figure 2).
Brain ultrasounds were performed several times and were without any intraventricular haemorrhages or periventricular leukomalacia at any time. There were no signs of retinopathy of prematurity at any times.

All reported positive bacterial cultures were significant otherwise not reported. The endotracheal tube (ET) secretion for cultures was obtained. All bacterial strains that were isolated from the child were checked for sensitivities. No genotyping of any strains of bacteria was unfortunately performed.

**DIFFERENTIAL DIAGNOSIS**

Immune deficiency

**TREATMENT**

Table 1. Age in days since birth, GBS infections, cultures and medical treatment, respiratory support and medical treatment with steroids

<table>
<thead>
<tr>
<th>Age in days since birth</th>
<th>Infection, bacterial culture and highest CRP (mg/L) (on day)</th>
<th>Treatment of GBS (and other infections with antibiotics)</th>
<th>Respiratory support</th>
<th>Number of days on mechanical ventilation</th>
<th>Treatment with steroids (and other medications for circulatory and respiratory support)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-</td>
<td>(Ampicillin and aminoglycoside (i.v.) for 3 days due to premature rupture of membranes and need of surfactant)</td>
<td>nCPAP INSURE for surfactant</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td><strong>GBS in blood culture (day 8)</strong></td>
<td>Cephalosporin* (i.v.) and aminoglycocide# (i.v.), change to penicillin (i.v.) for 10 days after verification of culture LP without meningitis</td>
<td>SIPPV</td>
<td>20</td>
<td>(Ibuprofen, 10mg/kg day 1, 5mg/kg day 2-5 for closing patent ductus arteriosus) Dexamethasone, 0.1mg/kg/day, tapering down daily for 10 days</td>
</tr>
<tr>
<td>20</td>
<td><strong>CRP 53 (day 10)</strong></td>
<td></td>
<td>nCPAP for 24 hours</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>GBS in blood and ET secretion cultures (day 22)</td>
<td>Cephalosporin (i.v.) and aminoglycocide (i.v.), change to ampicillin (i.v.) for 2 weeks after verification of culture</td>
<td>nCPAP</td>
<td>-</td>
<td>Dexamethasone, 0.1mg/kg/day, tapering down daily for 10 days</td>
</tr>
<tr>
<td>29</td>
<td><strong>CRP 107 (day 22)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>Case Description</td>
<td>Treatment</td>
<td>Notes</td>
<td></td>
<td></td>
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<tr>
<td>-----</td>
<td>-----------------</td>
<td>-----------</td>
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<td></td>
</tr>
<tr>
<td>43</td>
<td>GBS in blood culture and cellulitis-adenitis syndrome (day 43)</td>
<td>Cephalosporin (i.v.) and aminoglycocide (i.v.), change to penicillin (i.v.) for 3 weeks in combination with aminoglycocide (i.v) for 2 weeks. LP without meningitis. The mother received 10 days of oral penicillin.</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>CRP 126 (day 44)</td>
<td>HFOV 82</td>
<td>Dexamethasone, 0.1mg/kg/day, tapering down daily for 13 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>59</td>
<td>CRP 126 (day 44)</td>
<td>iNO from day 58 to 66 and 75 to 91</td>
<td>(Sildenafil orally until day 369 due to pulmonary hypertension)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>62</td>
<td></td>
<td></td>
<td>Dexamethasone, 0.2mg/kg/day, tapering down daily for 10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65</td>
<td></td>
<td></td>
<td>(Dobutamine from day 76 to 94 and Dopamine from day 77 to 90). (Sedation with Midazolam and Fentanil was necessary for shorter periods of time during the period with HFOV and iNO treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>GBS in ET secretion culture (day 75)</td>
<td>Cephalosporin (i.v.) and aminoglycocide (i.v.), change to penicillin (i.v.) after positive tracheal culture. Treatment period was 4 weeks (until day 103)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>CRP 60 (day 76)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>Negative GBS culture in ETbe secretion</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>106</td>
<td>GBS in ET secretion culture (day 106)</td>
<td>Penicillin (i.v.) for 3 weeks supplemented with oral Rifampicin added after 1 week and continued for another 2 weeks</td>
<td>SIPPV 1, nCPAP -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>CRP 5.4 (day 114)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>131</td>
<td>Negative GBS culture in ET secretion and blood (day 131)</td>
<td>SIPPV 9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>140</td>
<td></td>
<td>nCPAP</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### OUTCOME AND FOLLOW-UP

The boy has been without GBS since the last positive culture from ET secretion on day 106. He was discharged from the hospital at the chronological age of 10 months (307 days). He required high-flow nasal cannula (HFNC) during part of the night at home and during upper airway infections until day 665. He is about 6 months delayed in motor development and improving at every monthly check. His fine motor development including speech is better than his gross motor development. A physiotherapist treated the boy during hospital stay and at home after discharge. He received all required vaccinations according to the Danish vaccination programme and monoclonal antibody therapy with palivizumab, Synagis from October to March after discharge.

### DISCUSSION

This case illustrates several interesting issues; primarily, the frequent nature and treatment of late-onset GBS infections and, secondly, the outcome of several months of mechanical ventilation, severe BPD and the difficulties associated with weaning a child from mechanical ventilation.

<table>
<thead>
<tr>
<th>Day</th>
<th>Event Description</th>
<th>Medical Treatment</th>
<th>Duration or Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>149</td>
<td>Gastroenteritis</td>
<td>CRP 25 (day 131)</td>
<td>SIPPV and tube-CPAP</td>
</tr>
<tr>
<td>161</td>
<td>CRP &lt;1 (day 149)</td>
<td></td>
<td>nCPAP</td>
</tr>
<tr>
<td>169</td>
<td>Urinary tract infection with enterococcus faecalis (day 149)</td>
<td>CRP 86 (day 169)</td>
<td>SIPPV and tube-CPAP</td>
</tr>
<tr>
<td>171</td>
<td>(Cephalosporin (i.v.) for 2 days and oral Amoxicillin for 7 days)</td>
<td></td>
<td>nCPAP</td>
</tr>
<tr>
<td>203</td>
<td></td>
<td></td>
<td>Oxygen need in nCPAP 80%</td>
</tr>
<tr>
<td>240</td>
<td></td>
<td></td>
<td>Oxygen need in nCPAP 30%</td>
</tr>
<tr>
<td>243</td>
<td>Transferred from level III NICU to another hospital with level II NICU due to closer to parents home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>302</td>
<td>Discharged home at the chronological age of 10 (corrected age of 6) months and still in need of HFNC</td>
<td>HFNC</td>
<td>-</td>
</tr>
<tr>
<td>665</td>
<td>No more HFNC at the chronological age of 22 (corrected age of 18) months of age</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRP; C-reactive protein, GBS; group B streptococcus, LP; lumbar puncture, ET; endotracheal tube, nCPAP; nasal continuous positive airway pressure, INSURE; intubation-surfactant-extubation, SIPPV; synchronised intermittent positive pressure ventilation, HFOV; high-frequency oscillatory ventilation; iNO; inhaled nitric oxide, HFNC; humidified high-flow nasal cannula, NICU; neonatal intensive care unit.

*Cephalosporine was second-generation (Cefuroxime) and the #aminoglycide was gentamicin.
The boy probably hosted the GBS since there were several negative GBS cultures from both the blood and ET secretion while treating with penicillin, and only one negative GBS culture between the fourth and fifth treatment, and this was just 1 day after penicillin was stopped. At the same time GBS is an unusual contaminant in our NICU. Adding rifampicin to the penicillin treatment though seemed to eradicate GBS form the mucous membranes.

To manage GBS infections in the present case, several long-term antibiotic courses were given based on several culture sensitivities. After the third infection, the mother was treated with oral penicillin, even though we were unable to culture any GBS in the mother’s milk. The effect of treating the mother is uncertain. Furthermore, after the third infection, we tried treatment with immunoglobulin based on the fact that recurrent GBS infections have been associated with hypogamma-globulinaemia.[14] We did though not test the boy’s immunoglobulin status beforehand. The fifth positive culture of GBS was treated with a combination of penicillin for 3 weeks and rifampicin for 2 weeks, and subsequently we did not culture GBS again. This is in line with the approach taken in a previous report of successful eradication of GBS infections with penicillin and oral rifampicin.[15] In the present case, we tried prophylactic treatment of the mother with penicillin; however, it might have been more efficient if both the mother and the child had received oral rifampicin, even though we did not prove that the mother was the host of the GBS. We could also speculate if it would have helped changing the ET at the end of an antibiotic treatment since the ET might as well be colonised with GBS. Prior to the fifth treatment with both penicillin and rifampicin we cultured GBS from ET secretion but the child did not yet have any signs of infection.

Severe BPD is well known among very and extremely premature infants, especially if treated with mechanical ventilation for longer periods. We cannot establish which effects these infections had on the boy’s respiratory status, but it was clear that his respiratory condition deteriorated and his BPD worsened with every infection. The third septicaemia resulted in increasing difficulties in ventilation and increased oxygen requirement to 100% and heightened the need for high PEEP even though this approach involved a high risk of worsening the BPD.[16] Several studies of the administration of postnatal corticosteroids to reduce the risk of BPD in preterm infants have been conducted, and a higher dose has been shown to be more effective compared to a moderate and lower dose of corticosteroids.[17] These studies also show that the use of corticosteroids might be associated with an increased risk of neurodevelopmental impairment especially if corticosteroids are given early during the postnatal period.[17] Steroids are used to improve lung function by decreasing number of pro-inflammatory and inflammatory cells in severe BPD.[18] Given the boy’s deteriorating respiratory conditions from 2 weeks of age to almost 3 months corrected age, we administered repeated low-dose dexamethasone courses in conformity with local guideline,[19] based on the European consensus guideline treating RDS from 2016, [20] even though this approach had well-known risks. According to our guideline, and to decrease the risk of neurological impairment, the patient had to be older than 2 weeks prior to treatment with low-dose dexamethasone. The boy was 20 days old when treated for the first time. Parental consent was obtained every time steroids were used in treating the boy after explaining the risk of using steroids. Usually one or sometimes two courses of low-dose dexamethasone help our premature infants from further development of BPD and facilitates extubation, which was challenged in this case probably due to recurrent GBS infections. In our case, the boy’s respiratory condition improved with every corticosteroid course. After the last extubation at 3 months corrected age, high-dose methylprednisolone reduced his oxygen requirement, and as because of this improvement, he managed without further need of mechanical ventilation. A tracheotomy was discussed as an option if methylprednisolone could not have kept him without mechanical ventilation. Instead, he managed to do without any further need of mechanical ventilation and only in need of nCPAP and HFNC until 22 months of age.
LEARNING POINTS/TAKE HOME MESSAGES

We have learned that oral rifampicin in combination with intravenous penicillin probably eradicated GBS in the present case with 5 recurrent GBS infections.

We have learned that systemic corticosteroid with high-dose Methylprednisolone helped our patient with severe BPD and need of mechanical ventilation for 155 days. The treatment should probably have been initiated earlier and thereby improved lung function and shortened the time with mechanical ventilation.

REFERENCES


19. BPD instriks [Internet]. Available from: http://ekstern.infonet.regionsyddanmark.dk/


FIGURE/VIDEO CAPTIONS

Figure 1
X-ray showing lung affection with BPD

Figure 2
CT thorax showing lung affection with BPD

PATIENT'S PERSPECTIVE

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