Late-Onset Enterobacter cloacae Sepsis in Very-Low-Birth-Weight Neonates: Experience in a Medical Center

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1. Introduction

Enterobacter cloacae are gram-negative bacilli causing nosocomial infection in the neonatal intensive care unit (NICU). This bacteria can cause fulminant late-onset sepsis, a condition associated with a relatively high mortality and morbidity.¹⁻³ Previous studies have usually included both term and premature neonates.³,⁴ No reports have detailed the clinical manifestations, treatment courses and

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outcomes specific to these infections in very-low-birth-weight (VLBW) neonates.

2. Patients and Methods

We retrospectively reviewed the medical records of VLBW (birth body weight ≤ 1500 g) neonates admitted to the NICU of our hospital from January 1997 to December 2006. Our NICU is a 24-bed tertiary referral center for neonates in central Taiwan. Late-onset sepsis was diagnosed if blood and/or cerebral spinal fluid (CSF) cultures sampled after the neonates were admitted in the NICU over 72 hours and yielded E. cloacae in addition to the presence of clinical symptoms and signs of sepsis. The symptoms and signs of sepsis included fever (> 37.8°C), low-grade fever (≥ 37.8°C and ≤ 37.2°C), hypothermia (< 36°C), apnea (no breathing movement for 20 seconds, or for a shorter duration in the presence of cyanosis), bradycardia (heart rate < 80 bpm), desaturation (oxygen saturation SpO2 < 85%), tachycardia (heart rate > 150 beats per minute), tachypnea (respiratory rate over 50 breaths per minute), significant residual milk (over 30% of the preceding feeding amount), hypoglycemia (whole-blood glucose level lower than 40 mg/dL), hyperglycemia (whole-blood glucose level higher than 125 mg/dL) and thrombocytopenia (platelet count ≤ 100,000/mm³).

Blood culture, complete blood cell count, and C-reactive protein (CRP) were checked on the day that infection was suspected and followed up the following day. All E. cloacae isolates were subjected to antimicrobial susceptibility testing by a standard agar diffusion method (Sensi-Disc, Becton, Dickinson and Company, ML, USA). Lumbar puncture was performed in patients suspected of having meningitis. Blood and CSF cultures were collected and cultured according to standard microbiologic techniques.

3. Results

During the 10-year study period, E. cloacae accounted for 21.7% of all neonatal sepsis and 49.3% of all infections caused by gram-negative aerobic bacteria in our NICU. A total of 28 neonates, 14 boys and 14 girls aged 4 days to 70 days, were included in this retrospective study. The 28 neonates were born before 28 weeks’ gestation and 12 (42.9%) were born at 28 to 32 weeks’ gestation. Sixteen (57.1%) neonates were born with body weights of less than 1000 g. The average days of onset of E. cloacae infection after birth was 9.6 days (range: 4 to 70 days). Twenty-three neonates (79.3%) were under percutaneous central venous catheterization (PCVC) and enteral feeding when infection occurred. Twelve of them were totally or partially fed with breast milk. Five (17.2%) neonates were on mechanical ventilators, and four (13.8%) were on continuous positive airway pressure ventilation.

The symptoms and signs of sepsis included desaturation, tachycardia, apnea, unstable temperature, abdominal distention, decreased activity, tachypnea, bradycardia, abdominal distension, and significant residual milk (Table 1). The infected neonates had an average of 3.9 ± 1.5 kinds (range, 1 to 7 kinds) of symptoms in each sepsis episode. The laboratory tests showed thrombocytopenia in nine (65.5%) neonates, CRP ≥ 1 mg/dL in 16 (55.2%) (normal ≤ 0.5 mg/dL), band-form neutrophils ≥ 5% in 12 (41.4%) neonates and white cell count ≤ 5000/µL in six (20.7%) neonates.

Of the E. cloacae isolate strains, 21.4% were sensitive to piperacillin (or piperacillin and tazobactam), of eight infected neonates. These outbreaks were controlled after cohort nursing and hygienic management without changing antibiotic policy. The other 21 infants were sporadic cases in this study period.

Table 1 Symptoms and signs of E. cloacae sepsis in neonates

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Desaturation SpO2 &lt; 85%</td>
<td>17 (58.6)</td>
</tr>
<tr>
<td>Tachycardia &gt; 150 beats per minute (bpm)</td>
<td>17 (58.6)</td>
</tr>
<tr>
<td>Apnea</td>
<td>16 (55.2)</td>
</tr>
<tr>
<td>Unstable temperature*</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>Low-grade fever ≤ 37.8°C and ≤ 37.2°C</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Fever &gt; 37.8°C</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>Hypothermia ≤ 36°C</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Decreased activity</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>Tachypnea &gt; 50 bpm</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>Bradycardia &lt; 80 bpm</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>Residual milk &gt; 30% preceding amount</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Hyperglycemia &gt; 125 mg/dL</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Hypoglycemia &lt; 40 mg/dL</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Hypotension &lt; 40 mmHg systolic</td>
<td>1 (3.6)</td>
</tr>
</tbody>
</table>

*Low grade fever, fever or hypothermia.

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27.9% were sensitive to third-generation cephalosporins, 31.0% were sensitive to aminoglycosides, and 100% were sensitive to imipenem and ciprofloxacin. Extended-spectrum β-lactamase (ESBL) tests were not performed regularly at that period.

Empirical intravenous antibiotics comprising piperacillin (or piperacillin and tazobactam) and gentamicin (or amikacin) were prescribed when symptoms and signs of sepsis were suspected. Vancomycin or teicoplanin were empirically added to the regimens in 11 neonates. These regimens were successful in stabilizing vital signs and controlling infection in 24 of the 25 neonates who survived. Antibiotics were shifted to imipenem in 12 patients according to the susceptibility testing results. Antibiotics were given to neonates with sepsis for a period of 2 weeks and to neonates with meningitis for a period of at least 4 weeks.

The mortality rate of these VLBW infants was 21.4% (n = 6). Three neonates (10.7%) died due to *E. cloacae* sepsis. The *E. cloacae* cultured from those three neonates were multiresistant strains and sensitive to ciprofloxacin and imipenem only. They were ventilated and had body weights less than 800 g; one died 1 day after the onset of infection and two died 6 days later after 3 and 4 days of imipenem and supportive treatment. The other three patients died due to fungal sepsis, chyllothorax, and *Staphylococcus aureus* respectively, after having recovered from *E. cloacae* sepsis. Only 10 of the 28 neonates received lumbar puncture during sepsis; the others were considered too sick to tolerate the procedure. Four of the ten had meningitis, with sequelae of seizure and development delay. Two of these four neonates had brain abscesses but there was no significant risk factor associated with the brain abscesses noticed. Brain ultrasound, computed tomography (CT), and/or brain magnetic resonance imaging (MRI) were performed on the 22 surviving neonates before discharge from the hospital. The final outcomes are shown in Table 2.

### Table 2 Outcomes of 28 neonates with *E. cloacae* sepsis

<table>
<thead>
<tr>
<th>Morbidity and mortality</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Mortality due to <em>E. cloacae</em> sepsis</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Seizure</td>
<td>9 (32.1)</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Meningitis and/or brain abscess</td>
<td>4 (14.7)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Periventricular leucomalacia</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage ≥ grade III</td>
<td>2 (7.1)</td>
</tr>
</tbody>
</table>

4. Discussion

The risk factors of *E. cloacae* infection in neonates include being small for gestational age, having low birth weight, ongoing parenteral nutrition, understaffing, over-crowding, poor hygienic practices, contaminated thermometers, presence of *E. cloacae* in the stool carriage and exposure to personnel with contaminated hands.

The incidence of *E. cloacae* nosocomial infection in VLBW neonates ranges from 2.5% to 19.2%. In our NICU, *E. cloacae* was the leading microorganism in neonatal gram-negative bacilli sepsis as in some other reports. The higher rate (21.7%) of *E. cloacae* sepsis may be partly related to the three outbreaks in the study period and partly related to the specific environmental factors of our NICU.

The relative late onset of *E. cloacae* infection (median, 27.4 days) after birth in our series may be associated with the fact that 57.1% of our neonates had birth weights of less than 1000g requiring them to stay longer in the NICU. *E. cloacae* infection may occur later in stable and well-fed VLBW neonates as it is a common organism in the intestinal tract of neonates in the NICU.

*Enterobacter* species can colonize the gut of neonates, the risk increases with the duration of hospitalization; 60% after 15 days and 91% after 30 days. It may arise endogenously and increase the infection risk among premature infants. Prevention strategies should focus more on the control of endogenous neonatal flora or environmental sources.

Breast feeding and reduced exposure to antibiotics can increase microbial diversity in the feces of extremely low-birth-weight infants. Breast-feeding therefore is highly recommended to reduce the amount of pathogenic bacteria in the intestinal tract of VLBW neonates. But it was reported that a lack of breast feeding was not associated with isolation of gram-negative bacilli from stools. We did not notice significant protection from *E. cloacae* infection due to breast milk in the 12 neonates who were totally or partially fed with breast milk in our study.

Because of the high incidence of mortality and morbidity among VLBW neonates, early identification of sepsis in neonates is important. But in our study, the common symptoms and signs of *E. cloacae* infection in VLBW neonates were nonspecific, including desaturation, tachycardia, apnea, unstable temperature, decreased activity, and tachypnea. It is difficult to identify early the VLBW neonate infected with *E. cloacae* by these nonspecific signs.
Our observation is consistent with the reports that nonspecific clinical and hematological signs of late-onset sepsis are similar across enteric gram-negative bacilli infections.3,18

These infected VLBW neonates had an average of four kinds of symptoms occurring simultaneously early on the first symptomatic day. Further laboratory tests for evidence of thrombocytopenia, leucopenia, band-form neutrophils ≥ 5% and elevated CRP for identification of the severe infection may be needed in these infants.

In our series, PCVC was the most common therapeutic intervention that neonates were undergoing when infection occurred. PCVC was reserved for parenteral nutrition and was usually related to the late-onset infection in NICU neonates.7,11,18−21

It was reported that minimizing the use of central venous catheter and reducing the number of catheter days would decrease the risk of infection.11 But there were studies which reported that the protective effect of appropriate catheter care may be less relevant for the prevention of blood stream infections associated with gram-negative bacteria in VLBW than for the prevention of infection caused by gram-positive cocci.16 This observation is supported by the reports that state that gram-negative-bacilli species isolated from the neonatal blood stream and nurses’ hands vary significantly.16,22

Drug resistance is a major therapeutic problem in treating E. cloacae sepsis. Jean et al reported that 97% of the E. cloacae strains isolated in their study were resistant to multiple antibiotics.23 Jain et al reported that 73.4% of E. cloacae produced ESBL and 74 to 81% of these ESBL producers were resistant to cefotaxime.24 Considering the aggressive nature of sepsis caused by the pathogen, empirical treatment against bacilli producing ESBL is important in VLBW infants.25 Indiscriminate use of third-generation cephalosporins may be responsible for the selection of ESBL-producing strains.24 De Man et al reported the relative risk for colonization with strains resistant to the empirical therapy was 18 times higher for the amoxicillin-cefotaxime regimen compared with the penicillin-tobramycin regimen.26 There was a high incidence (70%) of E. cloacae resistant to the empirical antibiotics regimens in our series. But due to the restriction of laboratory facilities, ESBL testing was unable to be performed in the early stage of the study period and we could not know the incidence of the ESBL rate among these infections. The mortality rate of our series was 10.7% lower than that reported in the literature (6.2%−40%).1,2,11,21,25,27 We suggest that empirical treatment of piperacillin (or piperacillin and tazobactam) with gentamicin (or amikacin) might have some effect for empirical treatment of neonatal sepsis caused by multi-resistant E. cloacae.

Considering the three mortality cases were infected by strains that were resistant to piperacillin and amikacin. The antibiotic regimen should be adjusted immediately according to the susceptibility testing results.

CSF examinations and follow-up sonography, CT or MRI of the brain are recommend in these infected infants.28 The incidence of meningitis in our series may be underestimated because less than half of our patients underwent lumbar puncture examination. All four infants with meningitis and/or brain abscesses survived with mild neurological sequelae. The result is better than other reports on VLBW infants Enterobacter spp. meningitis, in which such neonates had high incidence of morbidity and mortality.5,8 Unlike neonatal Enterobacter sakazaki sepsis, which has high incidence of brain abscess, brain abscesses were rarely reported in previous E. cloacae neonatal sepsis studies.

Our study includes a comprehensive review of the early symptoms and signs, treatment regimens and outcomes of E. cloacae sepsis among VLBW neonates. The limitation of our study is its retrospective nature and relative small sample size.

In summary, the common symptoms and signs of E. cloacae infection in VLBW neonates were nonspecific but multiple kinds occur simultaneously. Early recognition of these symptoms and signs of sepsis followed by laboratory test confirmation with empirical treatment of piperacillin (or piperacillin and tazobactam) and gentamicin (or amikacin), then adjusting the antibiotics by susceptibility test, may be helpful in treatment of late-onset sepsis caused by E. cloacae in VLBW neonates.

References


