Short Communication

Deaths of Early-Onset, Invasive Sepsis in Full-Term Infants in Miyazaki: Nine Cases from a Regional Population-Based Analysis from 1998-2006

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SUMMARY: In a population-based study we investigated the early-onset, invasive sepsis caused by group B streptococcus (GBS) and non-GBS in the era of intrapartum antimicrobial prophylaxis. From 1998 to 2006, we had 387 perinatal deaths in 98,495 deliveries, and 9 full-term infants met the criteria of early-onset, invasive sepsis, in which microorganisms were proven from blood sampling. Of these cases, 4 involved GBS, 2 ampicillin-resistant *Escherichia coli*, 2 methicillin-resistant *Staphylococcus aureus*, and 1 was unidentified. All 4 cases of GBS related death underwent improper procedures contrary to the prophylaxis recommendation. Eighty percent of non-GBS related deaths had septicemia of antibiotic-resistant pathogens. We found in our population-based study that early-onset, fatal sepsis in full-term infants is associated with insufficient adherence to the prophylaxis strategy for GBS and with the emergence of antimicrobial resistant non-GBS bacteria.

Recent advances in perinatal medicine decreased Japan’s perinatal mortality rate in 2006 to the lowest (4.7/1,000) of all developed countries. However, neonatal invasive sepsis is still an important cause of mortality. Intrapartum antimicrobial prophylaxis significantly lowers the incidence of group B streptococcus (GBS) related neonatal deaths (1), while it potentially raises the incidence of non-GBS, antibiotic-resistant, early-onset sepsis (2,3). In the era of antimicrobial prophylaxis, it is uncertain which pathogens are responsible for early-onset fatal sepsis of full-term infants. We describe herein 9 neonatal deaths of fatal sepsis retrieved from a population-based study in Miyazaki to show their clinical manifestations and the involved pathogens.

This study was approved by the institutional review board of our department. Since 1998, we have investigated the causes of perinatal deaths in confidential peer-review audit-conferences (The Miyazaki Perinatal Data Group), the details of which have been described elsewhere (4). From 1998 to 2006, we had 387 perinatal deaths in 98,495 deliveries. All neonatal deaths and stillbirths were reviewed to determine the causative factors or clinically associated factors of deaths. We found 9 full-term infants who met all criteria of early-onset invasive sepsis, that is, onset at ≤72 h after birth, positive bacterial culture from the neonatal blood, and cardiovascular collapse with poor responsiveness to usual resuscitation procedures, which cannot be attributed to other causes than sepsis. These cases occurred at a rate of 0.91 per 10,000 deliveries and accounted for 2.3% of the perinatal deaths.

The most prevalent bacterium identified was GBS (n = 4), followed by *Escherichia coli* (n = 2) and methicillin-resistant *Staphylococcus aureus* (MRSA) (n = 2) (Table 1). Both *E. coli* cases were ampicillin-resistant, and one was positive for K-1 antigen. One case of MRSA sepsis (No. 7) resulted in maternal septic death. The remaining case (No. 9) was positive for Gram-positive cocci that could not be further identified. Among the 4 GBS women, intrapartum prophylaxis was performed in 2 (50%), but both delivered <4 h of the initial administration. One woman had been negative for GBS at 37 weeks of gestation, but had a neonatal death by GBS sepsis. In the 5 non-GBS women, GBS screening was performed in 2 (40%), and the results were negative. Three non-GBS women (No. 5, 6, 7) had prolonged rupture of the membranes for ≥28 h and showed infectious signs (temperature ≥38°C, leukocytosis ≥15,000/mm³ or C-reactive protein ≥1.5 mg/dl). The remaining 2 women had no risk factors for infection or maternal infectious signs (No. 8, 9).

The important strengths of the present study are its population-wide nature with >98,000 pregnancies, the homogeneous population, and the methods of validating the causes of death by the peer-review conference. The most common pathogen to cause early-onset, fatal sepsis in full-term infants was found to be GBS. Its incidence (0.4/10,000) in Japan is consistent with previous studies in developed countries (2,3,5). Among the 4 GBS-related deaths, 3 were attributed to improper implementation of prophylaxis and 1 to inaccurate screening results. Furthermore, 4 of the 9 women were not screened for GBS. Thus, the present results suggest that further clinical efforts are required for more complete adherence to intrapartum GBS prophylaxis. There are, however, concerns that the increased use of antibiotics against GBS transmission potentially increases the incidence of antibiotic-resistant sepsis (2,3). We also found that half of early-onset septic deaths were caused by non-GBS bacteria and that the antibiotic-resistant pathogens were prevailing.

The major limitation of this study is the small number of individuals included in the study and its retrospective nature. Thus, some useful numbers are lacking, for example, women having positive GBS culture or prophylactic antimicrobial treatments. We also could not perform autopsies in all cases.

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**Members of the Miyazaki Perinatal Data Group are listed in the Appendix.
to exclude causes of death other than sepsis. Despite these limitations, we utilized as much correct information as available regarding the causes of death in full-term infants and showed that GBS-related deaths are associated with insufficient adherence to the prophylaxis strategy. In addition, our data show that non-GBS related deaths are associated with the emergence of antibiotic-resistant pathogens.

APPENDIX

The Miyazaki Perinatal Data Group includes followings as contributors. Chairperson: Tsuyomu Ikenoue.
1. University of Miyazaki; Hiroshi Sameshima, Yuki Kodama, Masatoki Kaneko, Yasuyuki Kasagoe, Shun-ichi Tokunaga, Junji Oonishi, Tomoaki Ikeda, Tsuyomu Ikenoue, Hiroyuki Nunoi, Tooru Sonoda.
2. Miyazaki Prefectural Hospital; Tomihiro Shimamoto, Kei-ichiro Kohno.
3. Nobeoka Prefectural Hospital; Kiminari Terao, Hideki Kawaguchi, Shinji Katsuragi.
4. Nichinan Prefectural Hospital; Yasuhisa Haruyama, Mika Inamori.
5. Miyakonojo National Hospital; Katsuhiko Misawa, Yasushi Takasaki.
6. Miyazaki County Hospital; Seishi Furukawa.
7. Fujimoto-Hayasuzu Hospital; Katsuhide Kai, Hirotoshi Urabe.
8. Koga Hospital; Noriko Takahashi, Takafumi Higo.

REFERENCES

Table 1. Characteristics of the early-onset, invasive, and fatal sepsis in 9 full-term infants from 1998 to 2006

<table>
<thead>
<tr>
<th>No.</th>
<th>Year</th>
<th>Place</th>
<th>GA (w)</th>
<th>BW (g)</th>
<th>Bacteria</th>
<th>Antibiotic</th>
<th>Screening</th>
<th>Fever (≥38°C)</th>
<th>Leukocyte (≥15,000)</th>
<th>CRP (≥1.5 mg/dl)</th>
<th>ROM (h)</th>
<th>Onset (h)</th>
<th>Onset sign</th>
<th>FHR monitor</th>
<th>Mode</th>
<th>UA-pH</th>
<th>Apgar (1 min)</th>
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<td>1</td>
<td>2002</td>
<td>Central</td>
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<td>2,346</td>
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<td>ampicillin</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>0</td>
<td>cyanosis</td>
<td>V</td>
<td>7.30</td>
<td>8</td>
<td></td>
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<tr>
<td>2</td>
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<td>39</td>
<td>3,300</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>10</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>4</td>
<td>hemoptysis</td>
<td>V</td>
<td>7.42</td>
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<td>–</td>
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<td>+</td>
<td>+</td>
<td>40</td>
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<td>28</td>
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<td>West</td>
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<td>4,104</td>
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<td>–</td>
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<td>West</td>
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<td>3,206</td>
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*: Use of antibiotics as intrapartum antimicrobial prophylaxis.

GA, gestational age; BW, birth weight; Leukocyte, leukocyte count; CRP, C-reactive protein; ROM, rupture of the membranes; FHR monitor, fetal heart rate monitor; UA-pH, umbilical arterial blood pH; np, not performed; GBS, group B streptococcus; MRSA, methicillin-resistant Staphylococcus aureus; GPC, Gram-positive coccus; rec LD, recurrent late decelerations; brady, bradycardia; V, vaginal delivery; CS, Cesarean section.