

Early-onset neonatal infection in Lithuania

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Abstract

Aim: The aim of the study was to analyze the etiology of early-onset neonatal infection (EONI), the risk factors, the forms and the time of its manifestation, and the tactics and outcomes of antibacterial treatment.

Methods: During the prospective investigation, cases of newborns with diagnosed EONI and initial treatment in 2011 were analyzed. Four in-patient departments of Lithuania took part in the investigation.

Results: In total, 18,778 newborns were included in the investigation. During the studied period, 209 cases of EONI were diagnosed: unspecified EONI in 168 (80.4%) neonates, pneumonia in 20 (9.6%), and early-onset sepsis (EOS) in 21 (10%) neonates. Group B *Streptococcus* (GBS) was responsible for 40% of microbiologically confirmed cases of sepsis. A negative blood culture was found in 11 newborns (52.4%) treated for sepsis. In all the cases, EONI was empirically treated with penicillin and gentamycin. The duration of antibacterial treatment varied between in-patient departments in Lithuania. During the studied period, 51.7% of women were screened for GBS colonization during pregnancy, and 21% of them had a positive vaginal culture for GBS; 78% of GBS carriers received intrapartum prophylactic antibiotics.

Conclusions: The incidence of culture-confirmed early neonatal sepsis in Lithuania is similar to that indicated in the scientific literature, and is decreasing. Routine antenatal screening for GBS vaginal carriage in pregnant women is not universally performed in Lithuania. The duration of antibacterial treatment for EONI should be standardized in Lithuania.

Keywords

Newborn, early-onset sepsis, early-onset neonatal infection, group B *Streptococcus*, risk factors.

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How to cite

Tameliėnė R, Stonienė D, Russetti L, Kudrevičienė A, Gedvilienė V, Tvarijonavičienė R, Bulaukienė A, Nedzelskien I. Early-onset neonatal infection in Lithuania. *J Pediatr Neonat Individual Med.* 2015;4(1):e040107. doi: 10.7363/040107.

Introduction

Early-onset neonatal infection (EONI) is an infection in newborns that manifests itself within 72 hours after birth [1]. Early-onset neonatal sepsis (EOS) comprises a significant part in the structure of neonatal morbidity. The main causative agents of EONI are group B *Streptococcus* (GBS) and *E. coli*. These microorganisms may be transferred from the mother to the child during pregnancy or birth [2, 3]. About 10-30% of the pregnant women have GBS colonies in the vagina or the rectum. However, a negative vaginal culture is not a sufficient basis for the exclusion of maternal colonization during childbirth, because pregnant women found to be GBS-negative during the examination may become GBS-positive during childbirth. Consequently, even though confirmed GBS colonization of the mother suggests EONI, as much as 60% of neonates with GBS-induced EONI were born to GBS-negative mothers [4]. For this reason, of utmost importance is the earliest possible detection of clinical signs of sepsis after the birth. In the absence of such signs, timely evaluation of the risk factors of infection and blood tests would either rule out or confirm EONI. Even though the incidence of GBS-induced EONI has dropped significantly since the global screening of pregnant women for GBS was initiated several decades ago, total prevention of this neonatal pathology has not yet been achieved, and EOS remains one of the major causes of neonatal mortality [5, 6]. Therefore, it is highly important to monitor the epidemiological situation of EONIs, and to search for ways of further reduction of neonatal morbidity from congenital infections.

The subjects and the methods of the study

Four in-patient healthcare institutions of Lithuania participated in this prospective study: one level III hospital, and three level IIb hospitals. In 2011, 30,268 neonates were born in Lithuania. In

districts serviced by the studied hospitals, 18,778 neonates (62% of the total number of births in Lithuania) were born in 2011. The study showed that in 2011, 209 neonates were diagnosed and treated for EONI. Once the neonate was diagnosed and the treatment was initiated, the neonate's data were included into the research form. The following neonatal infections were included into the study: unspecified EONI, EOS, and pneumonia. Microbiologically confirmed EOS means clinical symptoms of infection and/or laboratory findings in the presence of a positive culture within the first 72 hours after birth. Microbiologically unconfirmed EOS means clinical symptoms of infection and/or a minimum of two laboratory indicators in the presence of a negative culture within the first 72 hours after birth. Unspecified EONI means a condition where clinical and laboratory signs of infection are present, but the available data are insufficient for the diagnosis of sepsis. The risk factors for EONI are the following: preterm delivery, time interval > 18 hours between membrane rupture and birth, maternal urinary tract infection, GBS detected in the vagina or the anus, maternal pyrexia > 38 °C during delivery, and chorionamnionitis.

Statistical analysis of the data was conducted using SPSS® software package (*Statistical Package for Social Sciences® 13.0*). During data analysis, statistical hypotheses about differences between mean values were verified. The mean values were compared by applying Student's t criterion. When verifying statistical hypothesis, the level of significance was set at 0.05.

Results

The study included 18,778 neonates. The majority (94.4%) of them were full-term. EONI was diagnosed in 209 neonates: 40% of cases in level III in-patient healthcare institutions and 60% of cases in level IIb in-patient healthcare units (**Fig. 1**). Boys were significantly more frequently diagnosed with EONI, compared to girls – respectively, 61% and 39% ($p = 0.001$). Full-term neonates comprised the major part of neonates with EONI (76.7%); the percentage of premature neonates with EONI was lower (14.6% of neonates born after 32-36 weeks of gestation, and 8.7% of neonates born before 32 weeks of gestation). The major part of newborns with EONI were born weighting $\geq 2,500$ g (80.9%), compared to 12.4% of neonates with low birth weight and 6.7% of neonates with very low or extremely low birth weight. During the studied period,

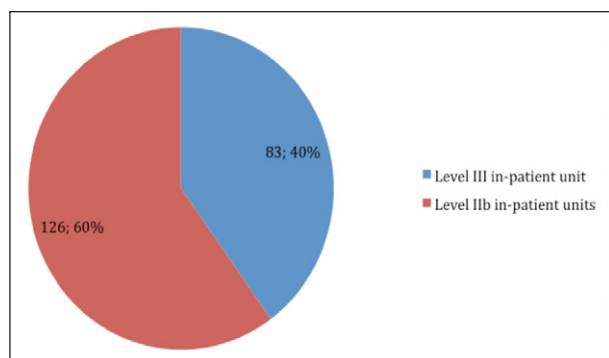


Figure 1. Distribution of neonates with early-onset neonatal infection (EONI) by in-patient healthcare units.

unspecified EONI was diagnosed in 168 (80.4%) neonates, congenital pneumonia was diagnosed in 20 (9.6%) neonates, and EOS in 21 (10%) neonates (**Tab. 1**). EONI was significantly more frequently diagnosed – and treatment was initiated – on the first day of the neonate’s life (87.25%, $p = 0.001$) (**Fig. 2**). The study showed that 50.2% of women whose newborns were diagnosed with EONI had risk factors of neonatal infection (12.9% of women had 2 or more risk factors) (**Tab. 2**). In neonates with risk factors of infection, EONI within the first 12 hours of life was diagnosed more frequently than in neonates without risk factors, $p = 0.035$ (**Fig. 3**). EOS was diagnosed in 21 neonates. In 4 neonates, microbiologically confirmed sepsis was caused by GBS, and in 2 neonates by *L. monocytogenes*, while *E. coli*, coagulase-negative *Staphylococcus*, *S. epidermidis*, and *Corynebacterium spp.* caused EOS in 1 neonate each. Blood culture tests were negative in 11 (52.4%) neonates with EOS (**Fig. 4**). Full-term neonates comprised 60% of cases with microbiologically confirmed and microbiologically unconfirmed EOS, and 75% of cases with GBS-induced EOS. Among mothers whose neonates were diagnosed with EONI, 39.7% had not undergone screening for GBS colonization, while no screening data were found on 8.6% of women. Besides, 51.7% of the women underwent vaginal culture tests for GBS colonization, and in 21% of them the test was positive (**Fig. 5**). Among women with confirmed GBS colonization, 78% were administered preventive antibiotic therapy during labor, and 78% of them received > 2 doses. 91.3% of neonates born from mothers colonized with GBS received antibacterial treatment within the first day of life. Pneumonia was diagnosed in 20 neonates: in 9 (45%), the causative agent was not identified, in 10 (50%) not tested, and in 1 (5%), GBS was identified.

Table 1. Forms of early-onset neonatal infection (EONI).

Disease	n	%
Unspecified early-onset neonatal infection (EONI)	168	80.4
Pneumonia	20	9.6
Early-onset neonatal sepsis (EOS)	21	10.0
Total	209	100

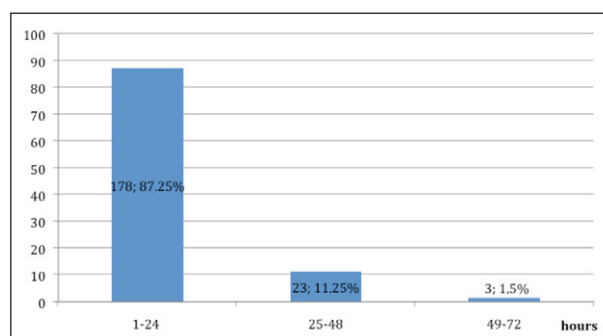


Figure 2. Initiation of antibacterial treatment.

Table 2. Risk factors of infection among pregnant women.

Risk factors	n	%
No risk factors	104	49.8%
1 risk factor	78	37.3%
2 risk factors	17	8.1%
3-4 risk factors	10	4.8%

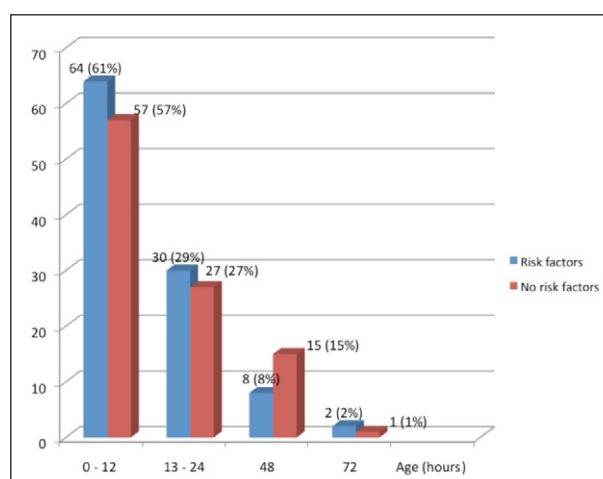


Figure 3. Neonatal risk factors and time of the onset of early-onset neonatal infection (EONI).

Unspecified EONI was diagnosed in 168 neonates. Most (70%) cases of unspecified EONI were diagnosed in level IIb in-patient units. Unspecified EONI in level IIb in-patient units comprised 94%

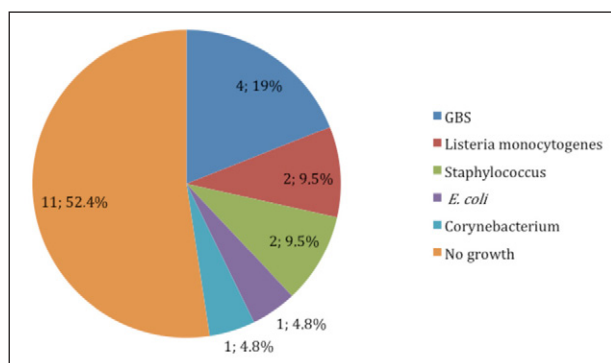


Figure 4. Causative agents of early-onset neonatal sepsis (EOS).

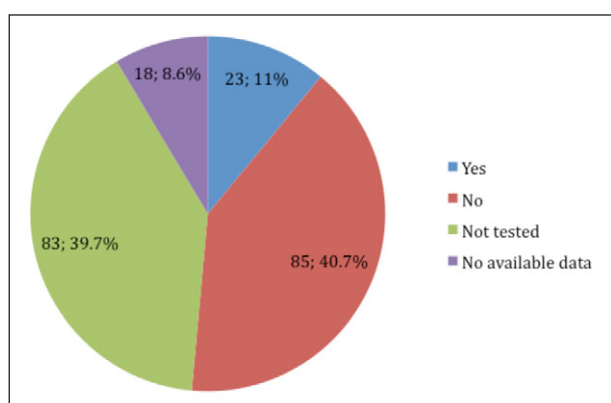


Figure 5. Maternal colonization with GBS during the 35th-37th week of pregnancy.

of all forms of EONI, compared to 60% in the level III hospital. No blood culture tests were performed for 10 (8.5%) neonates who in level IIb in-patient units were diagnosed with unspecified EONI, which raises doubts whether such diagnosis was well-founded. In 100% of cases, empirical treatment of EONI with penicillin and gentamycin was initiated. Of these, in 2.8% of cases, antibacterial treatment was subsequently adjusted following antibiotic sensitivity testing (in 1 case treatment was switched to oxacillin, in 1 case to cefotaxim, vancomycin and fluconazole, in 2 cases to cefotaxim, and in 2 cases to ampicillin). The duration of antibacterial treatment differed between level III and level IIb hospitals. In the level III hospital, 85% of neonates with EONI were treated for 7 days, and the others longer (8-14 days). Meanwhile, the duration of antibacterial treatment in level IIb in-patient units was shorter: in 75% of cases, the treatment for EONI lasted for 6 or fewer days, and in 64% of cases for 5 or fewer days. Two (0.95%) neonates with diagnosed EONI died. Both were twins born at 23 weeks of gestation.

Their blood culture test was negative, but they had several concomitant pathologies that might have caused the poor outcome.

Discussion

Scientific literature provides different data on the timing of EONI: 0-2, 0-3, or 0-7 days. However, 80-90% of cases of EONI manifest themselves within the first 48 hours of life [7]. For this reason, recent sources more frequently indicate that EONI starts within the first 72 hours of life [1]. The results of our study are concordant with literature data: during the first day of life, EONI was diagnosed in 87.25% of cases, on the second day in 11.25% of cases, and on the third day only in 1.5% of cases.

According to the data from the US, before 1990 when the Center of Disease Control and Prevention started an active screening of pregnant women for GBS colonization and initiated intrapartum antibiotic prevention, the incidence of microbiologically confirmed EOS was 3-4 cases/1,000 liveborn children, and the incidence of GBS-induced EONI was 1.8/1,000 liveborn children. The situation has changed, significant positive results have been achieved over the last two decades. According to the most recent data published in scientific literature, the incidence of microbiologically confirmed EOS was 0.8-1.0 cases/1,000 liveborn children, and the incidence of GBS-induced EONI in the US in 2010 was 0.25/1,000 liveborn children [8, 9]. Our findings are in accordance with those published in scientific literature: our study showed that the incidence of microbiologically confirmed EOS was 0.53/1,000 liveborn children. However, in light of the fact that no blood sampling prior to antibiotic treatment was conducted in 5.9% of cases of unspecified EONI, the estimate of the incidence of microbiologically confirmed EOS is only approximate. In our study the incidence of GBS-induced EONI was 0.26/1,000 liveborn children, meanwhile the incidence of GBS-induced EONI in the group of liveborn preterm neonates was 0.94/1,000. Compared to the findings of a similar study on the incidence of EONI conducted in 2006-2007, a significant reduction was observed in the incidence of microbiologically confirmed EOS (1.5 vs. 0.53/1,000 liveborn children) and GBS-induced EOS (0.63 vs. 0.21/1,000 liveborn children) [10].

The colonization of a pregnant woman with GBS is the main risk factor for EONI. Studies have shown that 10-30% of pregnant women have GBS colonies in the vagina or the rectum

[4]. According to the data of studies conducted in Lithuania, about 15% of pregnant women were GBS-colonized [3, 11]. In global practice, the risk factor-based technique or the general screening of pregnant women for GBS colonization on weeks 35-37 of pregnancy are applied. Based on the results of the studies, in 2002 the US Center of Disease Control and Prevention recommended a general screening technique for GBS colonization and preventive intrapartum antibiotic therapy in pregnant women, which was by 50% more effective [12]. Most Western European countries (France, Italy, Switzerland, and Belgium) conduct general screening of pregnant women for GBS, while others (the UK, Holland, and Denmark) apply the risk factor-based technique [13]. In Lithuania, the risk factor-based technique is more commonly used, although general screening of pregnant women for GBS was introduced on July 11, 2011. However, this technique has only partially been implemented, and so far is not uniform yet [11].

The data of our study showed that only one-half (51.7%) of the mothers of EONI-positive neonates underwent vaginal culture tests for GBS colonization. According to various studies, in the US, 85% of pregnant women are screened, and the statistical data in Europe are similar (86% of pregnant women in Italy, and 90% in France undergo screening for GBS colonization) [4, 14, 15]. Meanwhile, none of the mothers of the 5 neonates with confirmed GBS-induced EONI had undergone vaginal smear testing or preventive antibiotic therapy. Of all the vaginal smears taken, 21% were positive. A similar rate of GBS colonization (15.3%) was found in women who delivered in level III hospital in Kaunas city in 2006-2007. The data obtained in Lithuania approximately corresponds to the incidence of GBS colonization of 10-30% reported in international scientific publications [14-16]. Preventive antibiotic therapy was administered to 78% of GBS-colonized women; 78% of them received > 2 doses. International research data show that the rate of the application of preventive antibiotic therapy in GBS-colonized women is usually higher (87-92%) [4, 14].

The issue of the protection of preterm neonates from GBS-induced EONI remains. These neonates are at an increased risk of GBS-induced EONI, and premature labor usually precludes vaginal sampling and the administration of the effective antibiotic therapy of > 2 doses [12]. Our data showed that the mothers of 29 out of 46 (63%) preterm neonates diagnosed with EONI had not been tested for GBS colonization. Only 30% of the

mothers of preterm neonates received effective (> 2 doses) antibiotic therapy – even though preterm delivery is one of the risk factors of EONI.

If no preventive measures against infection were applied, 1% of the neonates of GBS-colonized women would be born with congenital infections [17]. A confirmed maternal GBS colonization suggests EONI [4]. Our study showed that 91.3% of the neonates of GBS-colonized mothers received antibacterial therapy within the first day of life. However, as much as 60% of GBS-induced EONI occur in newborns of GBS-negative mothers [4]. For this reason, a negative culture test of the mother should not reduce the neonatologist's vigilance in diagnosing a congenital infection.

The majority of GBS-induced EONI (which have been registered for decades) occur in full-term neonates, although the prevalence of GBS-induced EONI among preterm neonates is higher, compared to the general population [4, 7]. Our findings corroborate these data: the majority (i.e. 75%) of neonates with GBS-induced EOS were full-term, although the incidence of GBS-induced EONI was higher in the group of preterm neonates (0.94 vs. 0.26/1,000 liveborn children).

Blood culture tests of 11 neonates (52.4%) with EOS were negative. Compared to the data of a similar study conducted during 2006-2007 in Lithuania (27.9%), the incidence of such cases has increased, yet it still does not correspond to that provided in scientific literature, which indicates that the incidence of suspected (microbiologically unconfirmed) EOS is by two to three times higher than that of microbiologically confirmed EOS [10, 18].

The most common form of EONI detected in our study was unspecified EONI (168 cases [80.4%]), which is similar to the incidence indicated in the data of the study conducted in Lithuania in 2006-2007 (76.9%) [10]. A disease under such name is not mentioned in scientific articles. A condition with clinical signs and not less than two laboratory findings confirming an infection should be called possible EOS [1]. Therefore, a part of the cases of EOS in our study could have been misdiagnosed as unspecified EONI.

The study showed that 50.2% of neonates who were diagnosed with EONI had risk factors for an infection. Scientific literature indicates a similar incidence (41%) [19].

The treatment of EONI was in all cases initiated with penicillin and gentamycin, as recommended in scientific literature [20]. The duration of the

treatment differed between level III and level IIb in-patient healthcare institutions: in level III institution, 7 days of treatment were selected in 85% of cases, and longer in the remaining cases, whereas in level IIb institutions, the duration of antibacterial treatment was shorter: 75% of EONI were treated for 6 or fewer days. The international recommendations indicate 7-10 days of treatment in the presence of microbiologically confirmed EOS or strongly clinically suspected unconfirmed EOS. In the presence of a negative blood culture test after 36-48 hours and in the absence of a strong suspicion of clinical EOS, discontinuation of antibacterial therapy should be considered [20, 21]. Scientific literature does not indicate any other duration of treatment, and thus a duration of antibiotic therapy of 5 or 6 days in level IIb in-patient healthcare institutions raises doubts concerning the rationality of antibiotic therapy in such circumstances.

Conclusions

1. Our study showed that the prevalence of microbiologically confirmed EOS in Lithuania was similar to that indicated in scientific literature.
2. From 2006 to 2011, the incidence of microbiologically confirmed EOS decreased from 1.5 to 0.53/1,000 liveborn children, and the incidence of GBS-induced EOS decreased from 0.63 to 0.21/1,000 liveborn children.
3. Unspecified EONI in level IIb in-patient units was diagnosed more frequently than in level III hospitals (94% vs. 60%), which could be the consequence of overdiagnosis. In addition to that, as much as 8.5% of the neonates who in level IIb healthcare units were diagnosed with unspecified EONI did not undergo blood sampling. For this reason, pregnant women with risk factors of an infection should be directed to level III in-patient institutions because they have better capacities for an effective examination and treatment of infected neonates.
4. The study showed that Lithuania does not have a uniform system for the screening of pregnant women for GBS because only one-half of the mothers of neonates with EONI underwent vaginal sampling, which is a significantly lower proportion than that indicated in scientific literature.
5. The duration of the antibacterial treatment for EOS differed between level III and level IIb in-

patient units of Lithuania. The duration of the early antibacterial treatment for EONI should be standardized in Lithuania.

Declaration of interest

The Authors declare that there is no conflict of interest.

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