Thieme

Possible Rates of Detection of Neonatal Sepsis Pathogens in the Context of Microbiological Diagnostics in Mothers – Real World Data

Möglichkeiten der Detektionsrate neonataler Sepsiserreger im Rahmen mikrobiologischer Diagnostik bei den Müttern – Real World Data

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ABSTRACT

Objective The aim of this study was to identify the rate of detection of neonatal sepsis pathogens in maternal microbiological smears.

Study Design This is a retrospective study conducted at a Level 1 perinatal center in the context of routine care from 2014 to 2019. For all premature infants and neonates with neonatal sepsis, the neonatal and maternal microbiological findings were examined to see if there was a match.

Results During the study period, a total of 948 premature or newborn infants were identified as having a neonatal infection. Among all of the premature or newborn infants, 209 (22%) met the diagnostic criteria for neonatal sepsis; of these, 157 were premature births and 52 were full-term births. We evaluated the microbiological findings for these 209 mother and child pairs. No pathogens were detected in 27 out of 157 mothers of premature infants (17.1%) and in 31 out of 52 mothers of full-term infants (59.6%). In the premature infant group there were pairs with matching pathogens in 30 out of 130 cases (23.1%, 95% CI: 16.1–31.3), and in the full-term infant group there was a match in 4 out of 21 cases (19%, 95% CI: 5.4–41.9). The number needed to test to have a 90% probability of success for pathogen detection varies between 9 and 11 in the most favorable case and 26 and 32 in the least favorable case, depending on the evaluation method.

Conclusion In cases of neonatal sepsis, the sepsis-causing pathogen was successfully detected through prior analysis of a maternal smear in 7 % of full-term infants and in 19 % of premature infants. The number needed to test was relatively high in all groups. The value of maternal smears for identifying neonatal sepsis-causing pathogens needs to be critically questioned.

ZUSAMMENFASSUNG

Ziel Das Ziel dieser Studie war, die Detektionsrate neonataler Sepsiserreger in mikrobiologischen Abstrichen der Mütter zu identifizieren.

Studiendesign Es handelt sich um eine retrospektive Studie an einem Perinatalzentrum Level 1 im Zeitraum 2014 bis 2019 im Rahmen der Routineversorgung. Bei allen Früh- und Neugeborenen mit neonataler Sepsis wurden die mikrobiologischen Befunde der Neonaten und der Mütter auf Übereinstimmung untersucht.

Ergebnisse Im Untersuchungszeitraum wurden insgesamt 948 Früh- oder Neugeborene mit einer neonatalen Infektion identifiziert. 209 (22 %) der Früh- oder Neugeborenen erfüllten die Diagnosekriterien einer neonatalen Sepsis, davon waren 157 Frühgeborene und 52 Reifgeborene. Von diesen 209 Mutter-Kind-Paaren wurden die mikrobiologischen Befunde ausgewertet. Bei 27 von 157 Müttern von Frühgeborenen (17,1 %) und bei 31 von 52 Müttern von Reifgeborenen (59,6 %) konnten keine Keime nachgewiesen werden. Paare mit Keimübereinstimmung gab es in der Gruppe der Frühgeborenen bei 30 von 130 (23,1 %, 95 %-KI: 16,1–31,3) und in der Gruppe der Reifgeborenen bei 4 von 21 (19 %, 95 %-KI: 5,4–41,9). Die Number Needed to Test, um eine 90 %-Erfolgswahrscheinlichkeit für die Detektion des Erregers zu haben, schwankt je nach Auswertungsmodus zwischen 9 und 11 im günstigsten Fall und 26 und 32 im ungünstigsten Fall.

Schlussfolgerung Bei neonataler Sepsis gelang die Detektion des Sepsiserregers durch vorherige Abstrichuntersuchung der Mutter in 7 % bei Reifgeborenen und in 19 % bei Frühgeborenen. Die Number Needed to Test waren in allen Gruppen relativ hoch. Die Wertigkeit des mütterlichen Abstriches zur Identifikation neonataler Sepsiserreger muss kritisch hinterfragt werden.

Abbreviations

AIS	Amniotic infection syndrome
CNS	Coagulase-negative staphylococci
CRP	C-reactive protein
EOS	Early-onset sepsis
GBS	Group B streptococci
GW	Gestational week
LOS	Late-onset sepsis
PCT	Procalcitonin
PROM	Premature rupture of membranes
SIRS	Systemic inflammatory response syndrome

Introduction

Neonatal sepsis continues to represent a serious clinical picture in neonatal medicine. The definition of (neonatal) sepsis has changed over time, and pediatric sepsis, especially in neonates, differs to sepsis in adults [1]. There are still no screening methods or markers that can reliably predict or exclude neonatal sepsis [2].

In the case of neonatal sepsis, in contrast to sepsis in adults, a distinction must be made between early-onset sepsis (EOS) and late-onset sepsis (LOS); early-onset refers to cases that become clinically conspicuous within the first 72 hours after birth, usually within the first 24 hours, and late-onset refers to onset after the first 72 hours of life [2, 3]. In the meantime, pathogen detection in blood culture is no longer mandatory for the diagnosis of sepsis; the unconditional presence of a "systemic inflammatory response syndrome" as a mandatory component of the diagnostic criteria has also been abandoned, as this can also arise in other scenarios, for example due to severe trauma and other diseases. Serious sequelae of neonatal sepsis include septic shock with a high rate of fatality and organ failure, as well as long-term sequelae due to impaired neurological development of the newborn infant [4].

Premature rupture of membranes should be mentioned as the most prominent prenatal risk factor for EOS, affecting approximately 1–5 per 1000 live births [5], especially in the context of the immature immune system in potential premature births [6]. This reduces the physical barrier between the fetus and the environment, making it easier for microbial ascension to occur. Transplacental or transuterine infection is also possible, although this is less common [7]. Thus, amniotic infection syndrome, now referred to as triple I (intrauterine infection, inflammation, or both), must also be considered a risk to the fetus, in addition to general maternal infections. In the majority of cases of newborns exposed to amniotic infection syndrome, there are no cases of EOS confirmed by blood culture [8]; however, completely asymptomatic cases with microbial colonization confirmed by blood culture can also occur [9]. In the vast majority of cases, the site of origin of the pathogens is the maternal anogenital tract; this explains the increased occurrence of group B streptococci and Escherichia coli as the pathogens that cause neonatal sepsis [10, 11], with Escherichia coli in particular associated with higher mortality in EOS [12, 13]. Especially in the case of EOS, it is assumed that there is vertical transmission from mother to child [14]; in the case of LOS, in addition to vertical transmission, there is also horizontal transmission through the environment, for example through (central) venous access or by hospital personnel [2].

Preventive measures that have already been established include GBS screening between GW 35 and 37 for the prevention of neonatal infections; this is also universally recommended in other countries such as the USA [11]. Considering the predominance of this pathogen in the context of neonatal sepsis, it is important to

continue to advocate for the consistent implementation of this screening procedure. While screening certainly leads to a reduction in the number of GBS-positive neonatal sepsis cases, the situation with regard to Escherichia coli as a pathogen remained constant, so that an absolute increase in Escherichia coli as a pathogen causing neonatal sepsis, due to GBS prevention, could be disproved [15]. Empirical antibiotic treatment is recommended in mothers with suspected triple I. However, although increased antibiotic use reduces the number of GBS-positive EOS cases [16], the rate of postpartum complications such as necrotizing enterocolitis was higher in newborns exposed to this antibiotic treatment than in untreated children [7, 17]. Alternative approaches are also sometimes taken – in such cases, clinically inconspicuous infants and infants born near GW 37 and whose mother suffered from triple I are not automatically treated with antibiotics, but are subject to close clinical monitoring in order to avoid unnecessary antibiotic treatment [17, 18]. The spectrum of pathogens that cause neonatal sepsis, including both EOS and LOS, is now widely known and can therefore also be effectively treated with antibiotics postpartum.

Infections are one of the most common causes of premature births [19], and premature infants are at a particularly high risk from neonatal infections due to the immaturity of their immune system [7, 20]. The value of microbiological diagnosis in the mother in case of imminent premature birth is unclear. Some authors recommend general microbiological diagnostics in risk situations, such as premature rupture of membranes and in the case of premature contractions [14]. In the German guidelines "Full-Term Vaginal Birth – S3 guideline" and "Prevention and Therapy of Preterm Birth – S2k guideline", this diagnostic procedure is not generally recommended [21, 22, 23, 24, 25]; nevertheless, it is largely implemented in clinical practice in Germany. In other guidelines, maternal microbiological diagnostics are not mentioned or do not play a role at all, and only preventive maternal antibiotic administration is recommended [23, 26]. Studies with data on concordance of smear results between mothers and their children in the case of sepsis are rare.

The aim of this study was, therefore, to determine the possible rate at which pathogens causing neonatal sepsis are detected through microbiological vaginal smears taken from the mother in the context of routine care in everyday clinical practice in a level 1 perinatal clinic. For this purpose, we searched for microbial matches in neonates and in their mothers, in samples which were collected as part of routine care prior to birth.

Materials and Methods

We identified all newborn and premature infants born in the maternity unit of the Karlsruhe Municipal Hospital (SKK) who were identified as having a neonatal infection and treated in the pediatric clinic of the SKK during the period from 2014 to 2019. Neonates transferred from outside the SKK were not included. In the case of multiple births, each child of a multiple birth was considered individually.

By examining the medical records, we identified the neonates who met the following definition for neonatal sepsis. The definition of neonatal sepsis was based on the "IQTIG guidelines on neonatal care" (QS specification 2021 version 07), which distinguishes between three different sepsis groups: 1.) clinical sepsis (without pathogen detection), 2.) microbiologically confirmed sepsis with pathogen detection without coagulase-negative staphylococci (CNS), 3.) microbiologically confirmed sepsis with CNS in the pathogen spectrum. We also made use of the AWMF guidelines for bacterial infections in neonates (register no. 024/008, version 4.2); the diagnostic criteria in these guidelines is consistent with those in the guidelines mentioned above [27, 28]. The children who did not meet the diagnostic criteria for neonatal sepsis were excluded from further analysis.

Based on gestational age, a further subdivision was made between full-term births (from GW 37 + 0) and premature births (< GW 37 + 0). The clinical parameters and microbiological smear results were then evaluated on the basis of the mother's medical records.

We identified the mothers for whom smear results were available, and then identified mother-child pairs in which there was a microbial match. Based on the time of onset of the sepsis, the disease was classified as LOS > 72 hours of life; if the sepsis occurred prior to this, it was classified as EOS.

In addition to the bacteriological results, other clinical and laboratory parameters were collected from the neonates and mothers. The study protocol is set out in ▶ **Fig. 1**. The study protocol was approved by the Ethics Committee of the National Medical Association of Baden-Württemberg (file number F-2020–058).

Clinical management

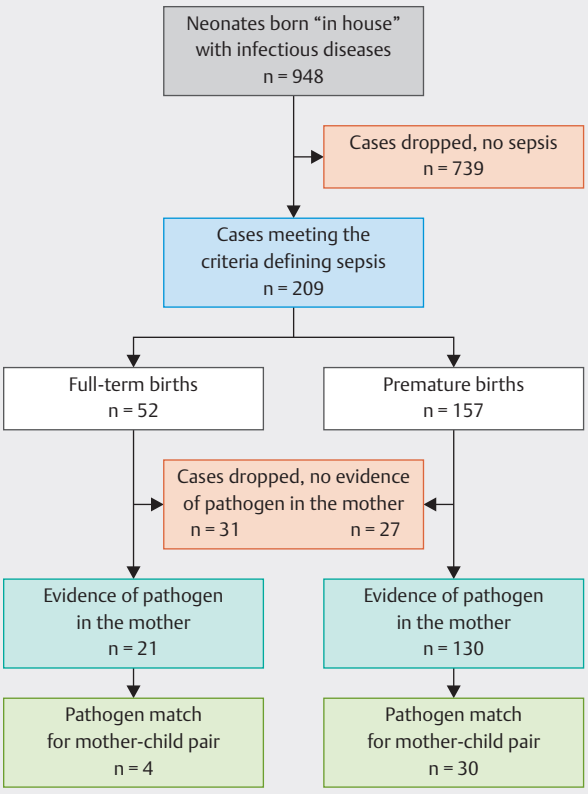
The diagnostic routine during the study period was to perform microbiological diagnostics based on vaginal and cervical smears for all mothers with premature rupture of membranes or premature contractions (GW: < 37 + 0). From the gestational age of 37 weeks + 0 days, microbiological diagnostics were usually not performed for the pregnant women unless there was suspicion of infection, in which case a smear was performed as described above.

During the study period, routine treatment in the case of premature rupture of membranes before GW 37 consisted of prophylactic antibiotic therapy with piperacillin/tazobactam IV for 8 days, while from GW 37 onwards, mothers were given prophylactic treatment with ampicillin or cefuroxime IV. In the case of premature contractions, antibiotic treatment was only given if there was clinical suspicion of infection or when a pathological smear result was obtained. If necessary, antibiotic therapy was adjusted after obtaining the antibiogram. No control smears were performed.

According to the PROMPT trial, mothers from GW 34 + 0 with premature rupture of membranes were given the option of either inducing labor or, in the absence of signs of infection, taking a wait-and-see approach with appropriate monitoring, analogous to the procedure in the PROMPT trial [29].

Statistics

The statistical program "R" was used for statistical analysis of the available data. A confidence interval of 95 % was chosen in all calculations. Because no statistical test was performed, there is no formal significance level; however, the significance level $\alpha = 5\,\%$ is indirectly implied in the 95 % confidence interval (CI) $[(100 - \alpha)\,\% = 95\,\%]$.



▶ **Fig. 1** Flow chart of the study design.

Results

A total of 948 infections in neonates and premature infants were identified during the study period. In 209 cases, the diagnostic criteria for neonatal sepsis were met. Of these, 52 cases (24.9%) were assigned to the full-term birth group, and 157 cases (75.1%) to the premature birth group. In the full-term birth group, no pathogens were detected in 31 mothers (59.6%), and in the premature birth group, no pathogens were detected in 27 mothers (17.2%). These mother-child pairs were excluded from further analysis due to the lack of maternal data. Among the full-term birth group there were 21 mothers for whom microbiological results were available, of which there was a pathogen match in four mother-child pairs. All four of these were EOS cases (95% CI = 39.8–100%). In the premature birth group there were 130 mothers for whom microbiological results were available, of which there was a pathogen match in 30 mother-child pairs, with 11 cases of EOS (36.7%) (95% CI = 19.9–56.1%) and 19 cases of LOS (63.3%) (see flow chart ▶ **Fig. 1**).

▶**Table 1** Rate of detection of neonatal sepsis pathogens based on maternal vaginal smears.

Whole cohort	***Detection rate***
Full-term infants	4 out of 52 (7.7%)
Premature infants	30 out of 157 (19.1%)
Only cases with pathogen detection in the mother	
Full-term infants	4 out of 21 (19.0%)
Premature infants	30 out of 130 (23.1%)
Premature infants, LOS cases excluded	
Whole cohort	11 out of 157 (7.0%)
Pathogen detection in the mother	11 out of 130 (8.5%)

Rates of detection of neonatal sepsis pathogens based on maternal smear result

The detection rate for sepsis pathogens in full-term infants was 4 out of a total of 52 cases (7.7%), and in premature infants it was 30 out of a total of 157 cases (19.1%) (▶ **Table 1**).

The detection rates improve if only cases in which a pathogen was detected in the mother are included in the calculation of the detection rate. This results in a detection rate in full-term infants

▶**Table 2** "Number needed to test" (NNT) based on the results in ▶ **Table 1**.

	Detection rate in the study	**Number of patients required for (at least) one hit**		
		50% success	**80% success**	**90% success**
Whole cohort				
Full-term infants	7.7% (4 out of 52)	9	21	29
Premature infants	19.1% (30 out of 157)	4	8	11
Mothers with pathogen detection				
Full-term infants	19.0% (4 out of 21)	4	8	11
Premature infants	23.1% (30 out of 130)	3	7	9
Premature infants, LOS cases excluded				
Whole cohort	7.0% (11 out of 157)	10	23	32
Pathogen detection in the mother	8.5% (11 out of 130)	8	19	26

of 4 in 21 cases (19.0%) and a detection rate in premature infants of 30 in 130 cases (23.1%) (▶ **Table 1**).

In contrast, the detection rate in premature infants becomes worse if cases with LOS are excluded on the assumption that the infection may also have occurred through horizontal transmission; the rate is 11 out of 157 cases (7%) for all neonates studied, and 11 out of 130 cases (8.5%) if only neonates whose mothers were found to have a pathogen are included (▶ **Table 1**).

Based on the results in ▶ **Table 1**, a number needed to test (NNT) was calculated, analogous to the number needed to treat. This is intended to determine the number of women who would need to be tested in order to then find the probable pathogen causing neonatal sepsis. NNT is presented in ▶ **Table 2** based on probable success rates of 50%, 80%, and 90% (▶ **Table 2**).

General frequency of sepsis pathogens in neonates

Among the full-term infants, 22 neonates (42.3%) were diagnosed with sepsis without pathogen detection (Group 1 in Materials and Methods), and 30 neonates (57.7%) were diagnosed with sepsis with pathogen detection (Group 2 + 3 in Materials and Methods). Among the premature infants, 72 neonates (45.9%) were diagnosed with sepsis without pathogen detection (Group 1 in Materials and Methods), and 85 neonates (54.1%) were diagnosed with sepsis with pathogen detection (Group 2 + 3 in Materials and Methods). In addition, ▶ **Table 3** shows the frequencies of identifiable sepsis pathogens independent of maternal results, broken down by premature and full-term births. The pathogens were either detected in blood cultures or, if the blood cultures did not reveal the presence of pathogens, they were detected in smear results from body surfaces. For the sake of clarity, we have listed no more than 10 of the most common pathogens per group (▶ **Table 3**).

Frequency of pathogens in pathogen matches between mothers and neonates

Four cases of EOS occurred in full-term infants. Three out of four cases showed matching results for group B streptococci and one out of four cases showed a match for Escherichia coli, with these pathogens being detected in both the mother and the neonate. No cases of LOS occurred in full-term infants (▶ **Table 4**).

Among the premature infants, there were 11 cases of EOS with a total of 16 matching results (multiple mentioning was possible). The following frequencies were found: 3 × group B streptococci, 3 × Escherichia coli, 2 × 3 MRGN Escherichia coli, 1 × Enterococcus faecalis, 1 × Enterobacter aerogenes, 1 × Streptococcus mitis, 1 × group A streptococci, 1 × Morganella morganii, 1 × Ureaplasma urealyticum, 1 × Staphylococcus haemolyticus, 1 × coagulase-negative staphylococci (▶ **Table 5**).

Among the premature infants, there were 19 cases of LOS with a total of 31 matching results (multiple mentioning was possible). The following frequencies were found: 6 × Staphylococcus haemolyticus, 6 × Enterococcus faecalis, 4 × coagulase-negative staphylococci, 4 × Escherichia coli, 3 × Staphylococcus epidermidis, 3 × group B Streptococci, 2 × Klebsiella pneumoniae, 2 × Staphylococcus capitis, 1 × Ureaplasma urealyticum (▶ **Table 5**).

▶**Table 3** Frequency of pathogen detection (10 most common pathogens [from blood culture, or from body surface smears if the blood culture was negative]).

	Premature infants *Frequency (n)*
Clinical sepsis (without pathogen detection)	72
Sepsis with pathogen detection	85
	Full-term infants
Clinical sepsis (without pathogen detection)	22
Sepsis with pathogen detection	30
	Premature infants *Frequency (n)*
Staphylococcus epidermidis	31
Staphylococcus haemolyticus	28
Escherichia coli	27
Klebsiella oxytoca	22
Enterococcus faecalis	21
Klebsiella pneumoniae	20
Enterobacter cloacae	19
CNS	19
Bacillus cereus	15
Staphylococcus capitis	13
	Full-term infants *Frequency (n)*
Escherichia coli	11
CNS	4
Staphylococcus epidermidis	4
GBS	3
Bacillus cereus	2
Enterococci	2
Enterococcus faecalis	2
2 MRGN Escherichia coli	2
Miscellaneous pathogens	1 in each case

▶**Table 4** Frequency of microbial matching in mother and child (full-term births).

	EOS *Frequency (n)*
GBS	3
Escherichia coli	1
	LOS *Frequency (n)*
None	None

▶**Table 5** Frequency of microbial matching in mother and child (premature births).

	EOS *Frequency (n)*
GBS	3
Escherichia coli	3
2 MRGN Escherichia coli	2
Enterococcus faecalis	1
Enterobacter aerogenes	1
Streptococcus mitis	1
Group A streptococci	1
Morganella morganii	1
Ureaplasma urealyticum	1
Staphylococcus haemolyticus	1
CNS	1
	LOS *Frequency (n)*
Staphylococcus haemolyticus	6
Enterococcus faecalis	6
CNS	4
Escherichia coli	4
Staphylococcus epidermidis	3
GBS	3
Klebsiella pneumoniae	2
Staphylococcus capitis	2
Ureaplasma urealyticum	1

Clinical parameters of mothers and full-term or premature infants with a microbial match

The clinical parameters of mothers and full-term and premature infants are shown in ▶ **Table 6** and ▶ **Table 7**. Among mothers of premature infants with sepsis (n = 157), there was a total of 26 cases of AIS (16.6%), whereas in mothers of full-term infants with sepsis (n = 52), there was only one case of postpartum fever (1.9%). Premature infants with EOS were born at an average gestational age of 31 weeks + 0 days, and premature infants with LOS were born at an average gestational age of 30 weeks + 2 days. Among the full-term infants, there was no difference in the mode of delivery; in the case of premature infants, no statement can be made as only two children from the group of premature infants with LOS were born spontaneously; all other premature infants were born by caesarean section. The maternal CRP and WBC values did not show any clustering of particularly high results; the values appear fairly evenly distributed (▶ **Table 6**).

Full-term infants predominantly showed a good clinical course. There were four deaths among the premature infants with EOS, and one death among the premature infants with LOS. Full-term infants and premature infants with EOS and LOS did not show any clustering of particularly high CRP, WBC, or interleukin-6 levels (▶ **Table 7**).

▶**Table 6** Clinical parameters of mothers in the case of microbial matching between mother-child pairs.

	Premature rupture of membranes *Frequency (n)*
Full-term infants	2/4
Premature infants (EOS)	7/11
Premature infants (LOS)	8/19
	Mode of delivery *Frequency (n)*
Full-term infants	2/4 by vacuum extraction 2/4 by spontaneous delivery
Premature infants (EOS)	6/11 by caesarean section 4/11 by emergency section 1/11 by forceps
Premature infants (LOS)	15/19 by caesarean section 2/19 by emergency section 2/19 by spontaneous delivery
	Average delivery time
Premature infants (EOS)	GW 31 + 0
Premature infants (LOS)	GW 30 + 2
	CRP *Peripartal maximum (mg/dl)*
Full-term infants	2/4 **< 10** 1/4 **10–20** 1/4 **> 20**
Premature infants (EOS)	7/11 **< 10** 1/11 **10–20** 3/11 **> 20**
Premature infants (LOS)	17/19 **< 10** 2/19 **10–20** 0/19 **> 20**
	White blood cells (WBC) *Peripartal maximum (per nl)*
Full-term infants	0/4 **< 20** 3/4 **20–30** 1/4 **> 30**
Premature infants (EOS)	4/11 **< 20** 5/11 **20–30** 2/11 **> 30**
Premature infants (LOS)	12/19 **< 20** 7/19 **20–30** 0/19 **> 30**
	Maternal infections
Mothers of premature infants	26 AIS (16.6%)
Mothers of full-term infants	1 postpartum fever (1.9%)

Discussion

Neonatal sepsis represents a very serious and severe clinical picture that can lead to permanent impairment [1, 4, 22, 23]. Therefore, efforts are made to diagnose and treat the condition as early as possible [27]. For this reason, seeking to identify possible pathogens as early as possible so as to allow a targeted treatment is an understandable approach [14].

▶**Table 7** Clinical parameters of neonates in the case of a microbial match between the mother-child pair.

	Discharge state *Frequency (n)*
Full-term infants	4/4 **clinically unremarkable**
Premature infants (EOS)	4/11 **fatal outcome** 6/11 **clinically unremarkable** 1/11 **Transfer to external clinic, stable, close to home***
Premature infants (LOS)	1/19 **fatal outcome** 14/19 **clinically unremarkable** 1/19 **Transfer to external clinic, stable, close to home***
	CRP *Maximum (mg/dl)*
Full-term infants	3/4 **< 10** 1/4 **10–20**
Premature infants (EOS)	11/11 **< 10**
Premature infants (LOS)	16/19 **< 10** 3/19 **10–20**
	White blood cells (WBC) *Maximum (per nl)*
Full-term infants	2/4 **< 20** 1/4 **20–30** 1/4 **> 30**
Premature infants (EOS)	5/11 **< 20** 2/11 **20–30** 3/11 **> 30**
Premature infants (LOS)	8/19 **< 20** 7/19 **20–30** 4/19 **> 30**
	Interleukin-6 *Maximum (pg/ml)*
Full-term infants	1/4 **< 1000** 1/4 **1000–2000** 2/4 **> 2000**
Premature infants (EOS)	6/11 **< 1000** 4/11 **1000–2000** 1/11 **> 2000**
Premature infants (LOS)	14/19 **< 1000** 4/19 **1000–2000** 1/19 **> 2000**

* Neonates in a stable condition were transferred for further treatment to another pediatric clinic closer to the parents' place of residence.

There is a lack of data on the extent to which the pathogen spectrum in the case of neonatal sepsis matches that of the mother. There is a large and good body of data on the general pathogen spectrum in neonatal sepsis, which is consistent with our results, as well as with the theoretical pathways of transmission [11, 30, 31, 32]. However, to date there has been no data on how often there is a match between the pathogen spectrum of mother and child; we are presenting this kind of data for the first time in this study.

To our knowledge, this is the first study to demonstrate match rates between the pathogen spectrum in neonatal sepsis and in maternal smear results. Overall, the match rates are low, which means the probability of early detection of neonatal sepsis pathogens based on a maternal smear is very low, and the NNT is correspondingly high. In full-term infants, 59% of mothers had no smear result, and in premature infants, 17% of mothers had no smear result. A limiting factor is that the smear result is not always available in a timely manner when the treatment of the neonate needs to be started; in other words, the result comes too late. While this aspect was not considered in this study, it would further reduce the clinical value of the maternal smear.

In cases of EOS in particular, pathogen transmission from mother to child is assumed, although the route of infection is unclear; while an ascending infection seems likely in the case of premature rupture of membranes, there are also cases of infection in the child in which the mother has intact membranes or lacks other risk factors. In contrast, in cases of LOS, interventions such as ventilation and central venous access must also be considered as possible routes of infection.

The pathogen spectrum found in cases of neonatal sepsis that were not consistent with pathogens found in the mother was largely composed of skin bacteria such as Staphylococcus epidermidis and Staphylococcus haemolyticus. However, as we have included LOS cases here, horizontal colonization cannot be ruled out. If only EOS cases are considered, and if pathogen match between mother and child is taken into a count, a shift can be seen in the bacterial spectrum towards group B streptococci and Escherichia coli and other bacteria of the anogenital region; in these cases, vertical transmission from mother to child therefore appears the most likely scenario.

Overall, rates of detection of neonatal sepsis pathogens based on a maternal smear of approximately 7% in full-term infants and 19% in premature infants can be achieved under routine conditions within the framework of normal care structures; if a pathogen can be detected in the mother, then the rates are slightly higher. However, since it is not always possible to identify a pathogen in the mother, the detection rate in the overall cohort drops to 7.7% and 19.1% respectively for full-term infants and premature infants, and if cases with LOS are excluded, the detection rate drops further to 8.5% and 7% respectively. Again, this seems to argue against the clinical significance of a maternal smear result.

The smear results were not obtained under study conditions, but reflect the care situation in obstetrics in a level 1 perinatal center. Overall, rates of detection of neonatal sepsis pathogens from maternal smears are low, especially when we exclude LOS cases in which horizontal pathogen transmission cannot be excluded. Therefore, the importance of maternal smear diagnostics in pregnancy with regard to early identification of neonatal sepsis pathogens seems questionable, especially considering that unnecessary antibiotic treatment in pregnancy can promote resistance [33]; also, the possibility of transplacental antibiotic therapy having an effect on the fetus cannot be ruled out [7]. Furthermore, according to current studies, pathogen detection is not considered a mandatory diagnostic criterion for neonatal sepsis. A distinction is made between "clinical sepsis" and bacteriologically "confirmed sepsis"; accordingly, it is questionable where there is a need to

start searching for causative pathogens already during pregnancy [5, 26]. Given the severity of the clinical picture, it is also debatable whether broad, empirical antibiotic treatment of the neonate should be abandoned due to questionable findings in the mother during pregnancy. In this context, pretreatment of the mother with the chosen antibiotic regimen plays a role that must not be underestimated; while bacterial selection in the case of a neonatal infection cannot be ruled out in this way, Schilling et al. nevertheless showed that 65% of all pregnant women received antibiotic treatment during pregnancy or birth [17].

To our knowledge, the advantage of this study is that we were able, for the first time, to identify the correspondence between pathogen detection in infants with neonatal sepsis and in maternal vaginal smear findings, and thus to calculate possible rate of detection of neonatal sepsis pathogens from a maternal smear. To date, no other results of this kind have been published in the literature. Our study also included a large case number of 200 infants; moreover, the distinction between EOS and LOS in the data analysis is not always commonly made.

The disadvantage of this study is its retrospective design, and thus the lack of data in some cases. Bacterial detection was not available from all mothers. Also, smears were not taken at precisely defined times, and bacterial determination was performed according to general bacteriological diagnostic criteria and not by genetic testing. Thus, even in the case of a bacterial match, this does not necessarily prove that the maternal bacterium is also the sepsis pathogen in the neonate.

One instrument used for sepsis prophylaxis in neonates is GBS screening in GW 35–37, during which colonization with group B streptococci can be detected by vaginal and rectal smear. The risk of sepsis in the case of maternal colonization is reported to be approximately 1–2/100 births, with an increased risk in the case of premature labor (< GW 37), premature rupture of membranes, or if the mother develops an elevated temperature or fever during birth [11, 33]; however, the infection rate of GBS-positive cases regardless of maternal colonization is estimated to be 2–5/1000 births [34]. In the case of a positive finding, antibiotic prophylaxis is administered; this has been found, at least in studies, to reduce the incidence of EOS [35]. However, it should also be remembered that antibiotic prophylaxis can trigger a disorder of the enteral microbiome, and can thus become the causative agent of serious neonatal diseases such as necrotizing enterocolitis [7, 17, 36]. It remains unclear to what extent this screening process, which is not part of the care mandated by the EU Pregnant Workers Directive, and the treatment given in case of a positive finding, actually leads to a reduction in sepsis cases in real care settings; also, in the cohort studies we conducted, group B streptococci were the most common pathogens causing EOS in both premature and full-term infants [37, 38].

Other risk assessment instruments, such as the "EOS Calculator" used in the USA, which includes not only the risk of infection by group B streptococci but also by other pathogens, should make it possible to calculate the general risk of EOS from a gestational age of 34 weeks + 0 days, thus enabling a reduction in unnecessary antibiotic treatments [39, 40, 41, 42].

Despite all the limitations of the retrospective study design and the fact that we could only include results obtained or available in the context of routine care, we were able to demonstrate, for the first time, matches in pathogen detection between children with neonatal sepsis and pregnant mothers, and calculate possible rates of detection of sepsis pathogens based on maternal smears.

Considering the severity of the clinical picture for neonatal sepsis, a detection rate of approximately 20% in premature infants may be an argument for continuing to perform routine smears; however, if cases of LOS are excluded, the detection rate falls below 10%, and the risk/benefit ratio then needs to be critically discussed, as well as the potential risk arising from unnecessary antibiotic treatment.

Conclusion

The causes of neonatal sepsis cannot always be clearly determined. However, due to the severity of the clinical picture, early diagnosis and treatment are important. Nevertheless, starting diagnostics already during pregnancy by taking vaginal smears from the mother seems very questionable, since the rate of detection of neonatal sepsis pathogens by this method is very low. The value of the maternal smear for identifying neonatal sepsis pathogens must be critically questioned. It is likely that it makes more sense to start the diagnostic procedure in neonates, and focus on these examination results.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References/Literatur

[1] Wynn JL. Defining neonatal sepsis. Curr Opin Pediatr 2016; 28: 135–140. doi:10.1097/MOP.0000000000000315

[2] Sharma D, Farahbakhsh N, Shastri S et al. Biomarkers for diagnosis of neonatal sepsis: a literature review. J Matern Fetal Neonatal Med 2018; 31: 1646–1659. doi:10.1080/14767058.2017.1322060

[3] Puopolo KM, Lynfield R, Cummings JJ et al. Management of Infants at Risk for Group B Streptococcal Disease. Pediatrics 2019; 144: e20191881. doi:10.1542/peds.2019-1881

[4] Buhimschi IA, Nayeri UA, Laky CA et al. Advances in medical diagnosis of intra-amniotic infection. Expert Opin Med Diagn 2013; 7: 5–16. doi:10.1517/17530059.2012.709232

[5] Odabasi IO, Bulbul A. Neonatal Sepsis. Sisli Etfal Hastan Tip Bul 2020; 54: 142–158. doi:10.14744/SEMB.2020.00236

[6] Rathore H, Rahman AJ, Salman M et al. Frequency of early-onset neonatal sepsis following prolonged rupture of membranes. Cureus 2020; 12: e6864. doi:10.7759/cureus.6864

[7] Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet 2017; 390: 1770–1780. doi:10.1016/S0140-6736(17)31002-4

[8] Randis TM, Rice MM, Myatt L et al. Incidence of early-onset sepsis in infants born to women with clinical chorioamnionitis. J Perinat Med 2018; 46: 926–933. doi:10.1515/jpm-2017-0192

[9] Wortham JM, Hansen NI, Schrag SJ et al. Chorioamnionitis and culture-confirmed, early-onset neonatal infections. Pediatrics 2016; 137: e20152323. doi:10.1542/peds.2015-2323

[10] Hanna M, Noor A. Streptococcus group B. StatPearls Treasure Island (FL): StatPearls Publishing; 2022.

[11] Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease. 2010. Accessed June 12, 2022 at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5910a1.htm

[12] Glaser MA, Hughes LM, Jnah A et al. Neonatal sepsis: A review of pathophysiology and current management strategies. Adv Neonatal Care 2021; 21: 49–60. doi:10.1097/ANC.0000000000000769

[13] Simonsen KA, Anderson-Berry AL, Delair SF et al. Early-Onset Neonatal Sepsis. Clin Microbiol Rev 2014; 27: 21–47. doi:10.1128/CMR.00031-13

[14] Anonymous. Prevention of group B streptococcal early-onset disease in newborns: ACOG Committee Opinion, Number 797. Obstet Gynecol 2020; 135: e51. doi:10.1097/AOG.0000000000003668

[15] Schrag SJ, Farley MM, Petit S et al. Epidemiology of invasive early-onset neonatal sepsis, 2005 to 2014. Pediatrics 2016; 138: e20162013. doi:10.1542/peds.2016-2013

[16] Boyer KM, Gotoff SP. Prevention of early-onset meonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. N Engl J Med 1986; 314: 1665–1669. doi:10.1056/NEJM198606263142603

[17] Schilling AL, Rody A, Bossung V. Antibiotic use during pregnancy and childbirth: prospective observational study on prevalence, indications, and prescribing patterns in a German tertiary center. Geburtshilfe Frauenheilkd 2022; 83: 192–200. doi:10.1055/a-1934-1761

[18] Randis TM, Polin RA, Saade G. Chorioamnionitis: time for a new approach. Curr Opin Pediatr 2017; 29: 159–164. doi:10.1097/MOP.0000000000000466

[19] Goldenberg RL, Culhane JF, Iams JD et al. Epidemiology and causes of preterm birth. Lancet 2008; 371: 75–84. doi:10.1016/S0140-6736(08)60074-4

[20] Klein LL, Gibbs RS. Infection and Preterm Birth. Obstet Gynecol Clin North Am 2005; 32: 397–410. doi:10.1016/j.ogc.2005.03.001

[21] Abou-Dakn M, Schäfers R, Peterwerth N et al. Vaginal birth at term – Part 1. Guideline of the DGGG, OEGGG and SGGG (S3-Level, AWMF Registry No. 015/083, December 2020). Geburtshilfe Frauenheilkd 2022; 82: 1143–1193. doi:10.1055/a-1904-6546

[22] Abou-Dakn M, Schäfers R, Peterwerth N et al. Vaginal birth at term – Part 2. Guideline of the DGGG, OEGGG and SGGG (S3-Level, AWMF Registry No. 015/083, December 2020). Geburtshilfe Frauenheilkd 2022; 82: 1194–1248. doi:10.1055/a-1904-6769

[23] Berger R, Abele H, Bahlmann F et al. Prevention and Therapy of Preterm Birth. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry Number 015/025, September 2022) – Part 1 with Recommendations on the Epidemiology, Etiology, Prediction, Primary and Secondary Prevention of Preterm Birth. Geburtshilfe Frauenheilkd 2023; 83: 547–568. doi:10.1055/a-2044-0203

[24] Berger R, Abele H, Bahlmann F et al. Prevention and Therapy of Preterm Birth. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry Number 015/025, September 2022) – Part 2 with Recommendations on the Tertiary Prevention of Preterm Birth and on the Management of Preterm Premature Rupture of Membranes. Geburtshilfe Frauenheilkd 2023; 83: 569–601. doi:10.1055/a-2044-0345

[25] Thomson A, The Royal College of Obstetricians and Gynaecologists. Care of women presenting with suspected preterm prelabour rupture of membranes from 24+0 weeks of gestation. BJOG 2019; 126: e152–e166. doi:10.1111/1471-0528.15803

[26] Di Renzo GC, Melin P, Berardi A et al. Intrapartum GBS screening and antibiotic prophylaxis: a European consensus conference. J Matern Fetal Neonatal Med 2015; 28: 766–782. doi:10.3109/14767058.2014.934804

[27] Eschborn S, Weitkamp J-H. Procalcitonin versus C-reactive protein: review of kinetics and performance for diagnosis of neonatal sepsis. J Perinatol 2019; 39: 893–903. doi:10.1038/s41372-019-0363-4

[28] Keij FM, Kornelisse RF, Tramper-Stranders GA et al. Improved pathogen detection in neonatal sepsis to boost antibiotic stewardship. Future Microbiol 2020; 15: 461–464. doi:10.2217/fmb-2019-0334

[29] Morris JM, Roberts CL, Bowen JR et al. Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial. Lancet 2016; 387: 444–452. doi:10.1016/S0140-6736(15)00724-2

[30] Özenci V, Schubert U. Earlier and more targeted treatment of neonatal sepsis. Acta Paediatr 2019; 108: 169–170. doi:10.1111/apa.14597

[31] Giannon E, Agyeman PKA, Stocker M et al. Neonatal sepsis of early onset, and hospital-acquired and community-acquired late onset: a prospective population-based cohort study. J Pediatr 2018; 201: 106–114.e4. doi:10.1016/j.jpeds.2018.05.048

[32] Stoll BJ, Puopolo KM, Hansen NI et al. Early-onset neonatal sepsis 2015 to 2017, the rise of escherichia coli, and the need for novel prevention strategies. JAMA Pediatr 2020; 174: e200593. doi:10.1001/jamapediatrics.2020.0593

[33] Iroh Tam P-Y, Bendel CM. Diagnostics for neonatal sepsis: current approaches and future directions. Pediatr Res 2017; 82: 574–583. doi:10.1038/pr.2017.134

[34] Franz A, Härtel C, Herting E et al. Prophylaxe der Neugeborenensepsis – frühe Form – durch Streptokokken der Gruppe B. Leitlinie des BVF, BVDfK, der DGGG, DGHM, DGPI, DGPM und GNPI. (S2k-Level, AWMF-Registernummer 024/020, März 2016). Z Geburtshilfe Neonatol 2017; 221: 122–129. doi:10.1055/s-0043-105207

[35] Polin RA, Papile L-A et al. the Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics 2012; 129: 1006–1015. doi:10.1542/peds.2012-0541

[36] Bennett PR, Brown RG, MacIntyre DA. Vaginal microbiome in preterm rupture of membranes. Obstet Gynecol Clin North Am 2020; 47: 503–521. doi:10.1016/j.ogc.2020.08.001

[37] Brown AP, Denison FC. Selective or universal screening for GBS in pregnancy (review). Early Hum Dev 2018; 126: 18–22. doi:10.1016/j.earlhumdev.2018.09.002

[38] Ramesh Babu S, McDermott R, Farooq I et al. Screening for group B Streptococcus (GBS) at labour onset using PCR: accuracy and potential impact – a pilot study. J Obstet Gynaecol 2018; 38: 49–54. doi:10.1080/01443615.2017.1328490

[39] Benitz WE, Achten NB. Technical assessment of the neonatal early-onset sepsis risk calculator. Lancet Infect Dis 2021; 21: e134–e140. doi:10.1016/S1473-3099(20)30490-4

[40] Achten NB, Klingenberg C, Benitz WE et al. Association of Use of the Neonatal Early-Onset Sepsis Calculator With Reduction in Antibiotic Therapy and Safety. JAMA Pediatr 2019; 173: 1032–1040. doi:10.1001/jamapediatrics.2019.2825

[41] Kuzniewicz MW, Walsh EM, Li S et al. Development and implementation of an early-onset sepsis calculator to guide antibiotic management in late preterm and term neonates. Jt Comm J Qual Patient Saf 2016; 42: 232–239. doi:10.1016/S1553-7250(16)42030-1

[42] Escobar GJ, Puopolo KM, Wi S et al. Stratification of risk of early-onset sepsis in newborns ≥ 34 weeks' gestation. Pediatrics 2014; 133: 30–36. doi:10.1542/peds.2013-1689