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## Original Article

# Enterobacteria vaginal colonization among patients with preterm premature rupture of membranes from 24 to 34 weeks of gestation and neonatal infection risk



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## ABSTRACT

**Aim:** Premature rupture of membranes (PROM) increases the neonatal morbidity and mortality, because of its association with a high risk of prematurity and infection. The group B streptococcus (GBS) prophylaxis using amoxicillin doesn't seem to be adapted to the emergence of new bacteria found in vaginal samples (VS). Our study aim was to assess, for PROM occurring at 23–34 weeks' gestation (WG), if the presence of ampicillin-resistant enterobacteria in the vaginal microbiome is predictive of an increased risk of early-onset neonatal infection.

**Material and Methods:** We conducted a prospective, observational, single-center study at the Nice Academic Hospital (level 3 maternity ward), between March 16, 2014 and May 3, 2015, that evaluated patients with preterm PROM (24–34 WG). Two groups were constituted according to the VS bacteria isolates and the amoxicillin-resistant enterobacteria found. Two groups of newborns were constituted depending on the suspicion of perinatal maternal-fetal bacterial infection (MFI). An intent-to-treat analysis was performed.

**Results:** Among the 67 patients included, 12 newborns presented a strong MFI suspicion, 83% of which were associated to the group of patients with untreated or amoxicillin-resistant enterobacteria VS isolates.

**Conclusion:** Our study showed that vaginal colonization of untreated or amoxicillin-resistant enterobacteria constitutes a major risk factor of neonatal infection.

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## Introduction

Premature rupture of membranes (PROM), before 37 weeks' gestation (WG), occurs in 2–3% of pregnancies. It is responsible for approximately one third of all preterm births and is associated with 20% of perinatal mortality [1]. Infection seems to play an important part, both as a consequence and as a cause, and can lead to chorioamnionitis [2]. Indeed, for 50% of PROM before 37 WG,

there's evidence of a subclinical inflammation of the amniotic fluid [3]. PROM is consistently associated to prematurity and infection is the major risk that will influence prognosis [4]. For PROM occurring between 24 and 34 WG, management relies on antibiotic prophylaxis associated to tocolysis and antenatal corticosteroids, as recommended by the French Agency for Accreditation and Evaluation in Health (Agence Nationale d'Accréditation et d'Evaluation en Santé - ANAES) [5], the American Congress of Obstetricians and Gynaecologists (ACOG) in the US [6] and the Royal College of Obstetricians and Gynaecologists (RCOG) in the United Kingdom [7]. Antibiotic treatment aims at decreasing the infection-related neonatal mortality. Amoxicillin is the first-intention treatment prescribed, in the absence of penicillin allergy, until the vaginal samples (VS) results are received. Depending on the bacteria isolates and the clinical signs of maternal or fetal

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infection, the antibiotherapy can be interrupted or adapted to the identified bacteria strains [5]. In case of allergy, a cephalosporin or a macrolide can be prescribed.

However, the 15-year-old ANAES recommendations seem today outdated and incomplete regarding antibiotherapy. Indeed, amoxicillin as a first-line treatment targets *Streptococcus agalactiae*, but this course of action is often inadequate, notably when enterobacteria such as *Escherichia coli* are present, as 35%–65% of *E. coli* strains are amoxicillin-resistant [8]. Other strains of enterobacteria found in VS are naturally resistant to amoxicillin (*Klebsiella sp.*, *Enterobacter sp.*). Furthermore, adapting the antibiotherapy to the VS bacteria isolates is conditioned by the presence of clinical signs of maternal or fetal infection. Yet, an asymptomatic *E. coli* vaginal colonization can be observed in 24%–31% of cases [9], close to what has been reported for *S. agalactiae* vaginal colonization [10]. Moreover, *E. coli* alone is responsible for 80% of neonatal infections in preterm children [11]. Couteau showed that there is a multitude of antibiotherapy protocols among the different maternity wards in France [12].

Faced with this reality, we decided to investigate the microbiological characteristics of VS for preterm PROM (24–34 WG) to determine if the presence of amoxicillin-resistant enterobacteria within the vaginal microbiome is predictive of an early-onset neonatal infection risk.

## Materials and methods

### Study design

Prospective, observational, single-center study performed in the Nice Academic Hospital (level 3 maternity ward) between March 16, 2014 and May 3, 2015. Patients were included in the delivery room, either during an unplanned consultation triggered by a suspicion of PROM or during the patient's admission following a transfer organized through the Perinatal Care Regional Network in case of verified PROM. Data was collected through the analysis of medical files (paper and electronic) for the deliveries performed in the Nice Academic Hospital, and through phone survey for deliveries performed in maternity wards belonging to the Perinatal Care Regional Network.

### Patients inclusion and data collection

Adult patients, with PROM between 24 and 34 WG confirmed by a test Actim<sup>®</sup> PROM, were included (singleton and multiple pregnancies). PROM before 24 WG and after 34 WG constituted a non-inclusion criterion, as the management at these stages differs on several points. Data was collected during the patients' admission and the delivery, and was as follows: gravidity, parity, prior preterm birth history (and associated gestational age), pregnancy type (singleton or multiple), gestational age at PROM diagnosis (weeks), gestational age at delivery (weeks), latency (time from PROM diagnosis to delivery) expressed in days, delivery route, maternity ward where the delivery was performed, maternal infection screening (C-reactive protein - CRP levels) and white blood cells (WBC) count.

### Neonatal infection screening

Data was collected during the 72 h following birth, and was as follows: gestational age at delivery (weeks), newborn sex, transfer or not to the Neonatal Care Unit, suspicion of maternal-fetal infection (MFI) based on the infant's symptomatology [5] (according to the major and minor anamnestic criteria from the September 2001 recommendations and evocative clinical signs) and the early-onset infection screening, infant's viability at 72 h after delivery.

The early-onset neonatal infection screening included a gastric aspiration at birth with direct assessment and culture, and depending on the infant's symptomatology, CRP levels 12 h after birth were assessed (positivity threshold >30 mg/L) and/or blood culture was performed. The diagnosis of neonatal infection suspicion, which will be our main evaluation criterion, is thus a composite clinical-biological criterion.

### Newborns' group setup based on the suspicion of maternal-fetal bacterial infection (MFI)

The study performed was an intent-to-treat study. Two groups of newborns were constituted: one group with a strong MFI suspicion including the verified and probable infections, and for which all the newborns received antibiotics; a second group with a low MFI suspicion including the possible infections and contaminations in which, all newborn received the same antibiotic treatment. The practitioner was free in the choice of the antibiotic.

### Bacteriological analysis of vaginal, endocervical and amniotic samples

The notion of PROM was indicated in the patients' file and on the VS request forms sent to the bacteriology service, using a dedicated label. In our obstetrics department, the VS was performed during the patient's admission when the PROM occurred (VSa), to screen for high MFI risk-associated bacteria: *S. agalactiae*, *E. coli*, *Haemophilus influenzae* and *Staphylococcus aureus* [5]. Then, throughout the hospitalization, endocervical or amniotic fluid samples were collected every week (LSa), following the department's protocol. Amniotic fluid collection was performed during the speculum examination by the midwife, if the amniotic fluid leaked from the cervical canal it could be directly collected in the vagina, otherwise an endocervical sample was collected. According to the VSa and the LSa results, the patients were distributed in 2 groups. The first group (G1) included the patients for which the VSa and LSa were never enterobacteria-positive and the patients for which the VSa was positive for amoxicillin-sensitive enterobacteria. The second group (G2) included the patients for which the VSa were positive for amoxicillin-resistant enterobacteria and the patients for which the VSa were enterobacteria-negative but for which the LSa were enterobacteria-positive. During hospitalization, amoxicillin (1 g, 3 times per day, per os) was given until the VS results were known (48 h to 72 h after sample collection). According to the VSa results, the amoxicillin treatment was either continued or stopped. If the VSa was positive for *S. agalactiae* or an amoxicillin-sensitive enterobacteria, the amoxicillin treatment was continued for a total duration of 7 days. Otherwise, amoxicillin was discontinued, without any treatment adjustment regardless of the bacteria culture results.

### Bacteriological analysis

Wet mount microscopy and Gram stain were performed on all vaginal, endocervical and amniotic fluid samples. Wet mount microscopy allows for a semi-quantitative evaluation of white blood cells, red blood cells and epithelial cells, as well as screening for yeasts and *Trichomonas vaginalis*. Gram stain allows a semi-quantitative evaluation of the bacteria from the sample, and to evaluate, for the VS, the Nugent score, that establishes a vaginal microbiome profile (from "normal" to "vaginosis") depending on the relative quantity of lactobacilli, *Gardnerella vaginalis* and *Mobiluncus sp.* VS were cultured on sheep blood agar plates (Oxoid, Dardilly, France), incubated 48 h at 37 °C in aerobic conditions; on Polyvitex chocolate agar plates (Oxoid), allowing the growth of bacteria such as *H. influenzae*, incubated 48 h at 37 °C in CO<sub>2</sub>-enriched

atmosphere, and on Drigalski agar plates (Oxoid), selective for Gram-negative bacilli, incubated 24 h at 37 °C in aerobic conditions, in order to easily identify the different enterobacteria. The bacteria isolates were identified by MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization-Time Of Flight) mass spectrometry, using a MicroFlex LT system and the Biotyper v2.3 databank (Bruker Daltonics). On these samples, labeled “PROM”, antibiograms were systematically performed for GBS and enterobacteria. They were done on Mueller-Hinton (MH) media for the enterobacteria and on blood MH media for GBS, using the disk-diffusion agar method, and the critical inhibition parameters were defined.

### Statistical analysis

Data was collected in Excel and analyzed using the IBM® SPSS® Statistics 21 software. The Chi-Square and Student tests were used. Differences were considered statistically significant for  $p < 0.05$ .

## Results

### Patients clinical characteristics

During the study, 76 patients were recruited, including 9 that were later excluded (8 because of a missing VS at admission and 1 because of a suspicion of maternal-fetal herpes virus infection). According to the VSa and LSa results, 29 patients were distributed in the group G1 and 38 in the group G2. The 2 patients' groups were comparable in terms of age, parity, gestational age at the time of PROM, prior preterm birth history, median gestational age at delivery and latency between rupture and delivery (Table 1).

### Bacteriological results for VSa and LSa

At time of admission, the VSa from the 67 included patients showed the presence of MFI-associated bacteria in 31 cases (46.3%): enterobacteria only in 22 cases (71%), *S. agalactiae* only in 4 cases (12.9%), *Staphylococcus aureus* in 1 case (3.2%), and *S. agalactiae* associated to an *Enterobacter sp.* in 4 cases (12.9%). In the 2 patients' groups, *E. coli* was the most commonly found enterobacteria and in more than 75% of the cases, it was amoxicillin-resistant (Table 2).

During hospitalization, the Group 1 patients initially positive for *S. agalactiae*, *S. aureus* or amoxicillin-sensitive enterobacteria were no longer positive after amoxicillin treatment. Similarly, the Group 2 patients initially positive for *S. agalactiae* became negative. In contrast, patients initially positive for an amoxicillin-resistant enterobacteria remained positive during the hospitalization. For the Group 2 patients, the acquisition during hospitalization of a resistant enterobacteria was observed in 20/22 patients (90.9%) and acquisition of a sensitive enterobacteria was observed in 2/22 patients (9.1%). It should be mentioned that 1 patient that had a

**Table 1**  
Characteristics of the two patients' groups.

	Group 1 (n=29)	Group 2 (n=38)	p
Maternal age (years)	32.9 ± 6.3	31.9 ± 5.9	0.88
Primipara	13 (44.8%)	18 (47.4%)	0.836
PROM occurrence (WG)	30.1 ± 2.8	29.1 ± 2.5	0.39
Singleton pregnancy	21 (72.4%)	36 (94.7%)	0.01
Prior preterm birth history	5 (17.2%)	3 (7.9%)	0.242
Duration of latency (days)	101 ± 16.8	17.2 ± 16.9	0.49
Gestational age at delivery (WG)	31.7 ± 3.0	31.6 ± 3.3	0.32

PROM: Premature Rupture of Membranes.  
WG: Weeks of Gestation.

**Table 2**

Identification of maternal-fetal infection risk-associated bacteria in the vaginal samples (VS) collected for the 2 patients' groups on admission, and identification of enterobacteria isolated from samples (endocervix, amniotic fluids) collected during the hospitalization for the group 2 (n = 22).

	Group 1 (n=29)	Group 2 (n=38)	Total (%)
<b>VS on admission (n = 67)</b>			
Enterobacteria	7 (24.1%)	15 (39.5%)	22 (71%)
<i>Streptococcus agalactiae</i>	2 (6.9%)	2 (5.2%)	4 (12.9%)
<i>Staphylococcus aureus</i>	1 (3.5%)	0	1 (3.2%)
≥ 2 strains <sup>a</sup>	0	4 (10.5%)	4 (12.9%)
<b>LSa collected during hospitalization</b>			
Enterobacteria (n=22)		22 (57.8%)	
<i>Escherichia coli</i>		7 (18.4%)	
<i>Klebsiella pneumoniae</i>		9 (23.7%)	
<i>E.coli</i> + <i>K. pneumoniae</i>		5 (13.1%)	
<i>Morganella morganii</i>		1 (2.6%)	

<sup>a</sup> One VS associated *Streptococcus agalactiae* and *Klebsiella pneumoniae*, and 3 VS associated *Streptococcus agalactiae* and *Escherichia coli*.

VSa positive for an amoxicillin-sensitive *E. coli* was successfully treated but later had a *K. pneumoniae*-positive LSa during hospitalization. As for the multibacterial VS, all the enterobacteria (n=4) found were amoxicillin-resistant.

For the positive samples (endocervical or amniotic fluid), the Group 2 patients were in most cases positive for *K. pneumoniae* (9/22=41%), then *E. coli* (7/22=32%) including 2 that were amoxicillin-sensitive, and finally *Morganella morganii* (1/22=4%). For 23% of cases (5/22), there was concomitant positivity for *E. coli* and *K. pneumoniae* (Table 2). Evaluation of antibiotics resistance by the disk-diffusion agar method showed that out of the 35 *E. coli*-positive VS (23 VSa and 12 LSa), 77% (27/35) were resistant to amoxicillin: 96% (26/27) via production of penicillinases and 4% (1/27) via production of extended-spectrum β-lactamases (ESBL).

### Neonatal infection screening

The infection screening was performed on 64 newborns. Two newborns didn't get an infection screening because they were born after 37 WG without symptomatology evocative of MFI, prompting them to be considered negative. The third one was stillborn at 25 WG + 1, in a context of chorioamnionitis suspicion and had been considered positive.

In our intent-to-treat analysis, 17.9% (12/67) of newborns had a strong MFI suspicion, and the gastric fluid culture was positive in 7 cases: 6/7 for enterobacteria and 1/7 for *S. agalactiae*. The gastric fluid culture came back sterile for 2 cases and was not performed in 3 cases. Out of the 12 blood cultures, only 2 were positive: 1 for *S. aureus* and 1 for *S. agalactiae*. The CRP levels 12 h after birth were greater than 30 mg/L for 4 newborns.

In Group 1, 2 newborns (2/12 = 16.6%) presented a strong MFI suspicion, 1 with an enterobacteria-positive gastric fluid sample and the other with high CRP levels.

In Group 2, 10 newborns (10/12 = 83.4%) presented a strong MFI suspicion, including 6 newborns with a positive gastric fluid sample: 4 enterobacteria-positive samples and 2 positive samples (1 enterobacteria and 1 *S. agalactiae*) associated with a positive CRP; and 2 newborns with a positive blood culture: 1 for *S. aureus* only and 1 for *S. agalactiae* associated with a positive CRP. Overall, 10 newborns have a positive bacteriological sample, of whom half were amoxicillin-sensitive (3 *S. agalactiae*, 1 *E. coli* and 1 *S. aureus*).

The analysis of VSa, LSa and neonatal infection screenings showed that the neonatal infection risk was higher in Group 2 (26.3%) than in Group 1 (6.9%) (Chi-Square test,  $p = 0.04$ ) (Table 3). The retrospective files' analysis showed that only 4 newborns presented a probable MFI and 2 presented a verified MFI,

**Table 3**

Comparison of the number of probable neonatal infections in the two patients' groups. Intent-to-treat analysis.

	Group 1 n = 29	Group 2 n = 38	p
Number of viable newborns at 72 hours	29	36	p = NS
Number of "strong MFI suspicion"	2 (6.9%)	10 (26.3%)	p = 0.04
Number of "strong MFI suspicion" enterobacteria infections	1 (3.4%)	5 (13.1%)	p = NS

\*NS: not significant.

representing 50% of the infants (6/12). In our population, bacteria were two-third amoxicillin-sensible (2 *S. agalactiae*, 1 *E. coli* and 1 *S. aureus*) and one-third amoxicillin-resistant (1 *E. coli*, 1 *K. pneumoniae*). All were treated with the appropriate antibiotics. Only 1 newborn belonged to Group 1 (1/6 = 16.7%) and 5 newborns belonged to Group 2 (5/6 = 83.3%).

## Discussion

This study allowed us to describe the composition of the MFI risk-associated microbiome found in vaginal, endocervical and amniotic fluid samples from patients with PROM between 24 and 34 WG and hospitalized in our department. The study of the repartition of the different enterobacteria highlighted a strong predominance of *E. coli*, as *E. coli* represented 60.3% (35/58) of bacteria isolates. The literature has described an increase of enterobacteria resistance to  $\beta$ -lactam antibiotics over the past 15 years, and the antibiotics resistance spectrum we observed during our study correlates with the current French epidemiology. According to the French National Observatory for Epidemiology of Bacterial Resistance to Antimicrobials (Observatoire National de l'Epidémiologie de la Résistance Bactérienne aux Antibiotiques – ONERBA), the amoxicillin-resistant *E. coli* strains associated with bacteremia increased from 48% to 57% between 2000 and 2013, with a major increase of ESBL production from 0.6% in 2000 to 8.5% in 2013 [13]. However, amoxicillin, targeting the group B streptococcus (GBS) and ineffective against the majority of enterobacteria, is still the first choice in PROM prophylactic protocols in France, as was confirmed by Couteau [12] in his 2012 study, where amoxicillin was prescribed as first-line therapy in 82% of maternal wards. This GBS prophylactic therapy for near-term pregnancies follows recommendations on MFI management established in France by the 1999 Clinical Practice Recommendations [14] and the 2001 ANAES recommendations [5]. This prophylactic therapy is justified by the frequency of GBS vaginal colonization (10% in France) [5,10] and GBS major role in neonatal sepsis, associated to frequent morbidity/mortality [5,8,15]. However, since these recommendations, the MFI epidemiology has been modified and, even though it is still a controversial hypothesis, the increase of MFI (notably *E. coli*-associated) frequency might be promoted by the selective pressure associated to the probabilistic amoxicillin therapy. Indeed, Towers et al. showed in 2 studies that the incidence of amoxicillin-resistant neonatal sepsis was associated to maternal amoxicillin therapy [16,17]. The challenge of initiating amoxicillin therapy is thus highlighted by the increase of resistant bacteria. However, the statistical analysis of our data showed that the vaginal colonization by amoxicillin-resistant enterobacteria during PROM or the colonization by an enterobacteria during hospitalization exposed the newborn to an increased risk of early-onset neonatal infection. It then seems reasonable to account for these bacteria when devising a therapeutic strategy. The association between *E. coli* vaginal colonization and increased risk of prematurity and MFI is still controversial in the literature. Nevertheless, Krohn et al. showed

that *E. coli* vaginal colonization was statistically more frequently associated to prematurity below 34 WG (RR = 1.7 IC 95% 1.3–2.3), to hypotrophy (RR = 1.9 IC 95% 1.3–2.7) and that the risk was proportional to the colonization density [18]. It has also been reported that *Enterobacter* neonatal sepsis, and notably *E. coli* ones, are associated to increased levels of mortality and morbidity when compared to *S. agalactiae* sepsis [15]. Even though an *S. agalactiae* coverage seems necessary in PROM perinatal prophylaxis, the treatment duration and the subpopulation that could benefit from a broader antibiotic spectrum still need to be defined [19]. The need for a more adapted maternal PROM antibiotherapy to decrease the incidence of neonatal sepsis has to be weighted against the risk of emergence of multi-resistant bacteria in the microbiome, that would be even harder to treat.

One of the limitations of our study was its low statistical power. Indeed, the neonatal sepsis incidence is 1–4 for 1000 live births and the incidence of probable sepsis and infections is 3–8 for 1000 births [5]. Due to this low incidence of early-onset MFI, performing a high statistical power clinical study is challenging because it is necessary to have a large population in order to show the presence of a verified MFI, as well as the potential superiority of a PROM prevention strategy by antibiotherapy for patients with PROM occurring before 34 WG. It will thus be necessary to perform a multicenter study as a next step.

Another limitation was the recent change of MFI diagnostic tools, with the less systematic use of gastric fluid analysis and the emergence of procalcitonin (PCT) measured in cord blood as a discriminating marker of early-onset MFI.

It will thus be necessary, in our next study, to account for these diagnostic tool changes to refine our MFI diagnosis and the following newborn therapeutic management.

## Conclusion

This single-center study, led over a 14 month-period, included a total of 67 patients, PROM being a rare event. To confirm the observed tendencies, we envision to perform a multi-center study over an extended time period. However, these first results, that showed that amoxicillin-resistant enterobacteria vaginal colonization is a risk factor of neonatal infection, lead us to question the current ANAES recommendations. In the light of these results, it seems necessary to assess the balance benefits/risks for neonatal infections and the diffusion of enterobacteria resistance, and to propose a possible therapeutic adaptation depending on the VS bacteria isolate and its antibiogram.

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