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Early-Onset Neonatal Sepsis: A Retrospective Study among 1,119 Moroccan Newborns Admitted to the National Reference Center in Neonatology and Nutrition, Rabat, Morocco

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ABSTRACT

Background: Early-onset neonatal sepsis is recognized as a common and serious problem for neonates. The clinical manifestations of neonatal sepsis are nonspecific and have varied clinical features. Therefore, their diagnosis is based on a combination of clinical presentation, the use of biological tests, and anamnestic arguments. The present study aimed to describe the infection risk factors, as well as clinical, paraclinical, and evolutionary characteristics of newborns with suspected early-onset neonatal sepsis and highlight the importance of C-reactive protein(CRP) to diagnose neonatal sepsis.

Methods: This retrospective analytical study was conducted at the National Reference Center for Neonatology and Nutrition at Children's Hospital, University Hospital Centre IbnSina of Rabat, from January 1 to December 31, 2016.

Results: During the study period, 1,199 newborns met the inclusion criteria. Upon admission, 52% of cases were under the age of one day. Symptomatic newborns represented 67.4% of the cases. The hospitalized cases with one or more infection risk factors were represented 80.3% of cases. The CRP was positive (> 20 mg/L) in 698 (58%) newborns. Univariate analysis pointed out that CRP value was significantly associated with age groups (P<0.001), presence of at least one infectious risk factor (P<0.001), as well as the presence of respiratory (P<0.001), cutaneous (P<0.001), circulatory (P=0.02), and neurological (P=0.008) symptoms. The diagnosis of early-onset neonatal infection with a meningeal, pulmonary, or ocular location was retained in 5%, 2%, and 0.2% of cases, respectively. The mortality rate was reported as 7%.

Conclusion: Screening, management, and reduction of early-onset neonatal infection remain a crucial challenge, requiring coordination between pediatricians and obstetricians to obtain reliable data and identify newborns at risk.

Keywords: C-reactive protein (CRP), Neonatal sepsis, Newborn, Risk factors

Introduction

Neonatal sepsis is a systemic condition of bacterial, viral, or fungal origin associated with hemodynamic changes and other clinical manifestations. It is recognized as one of the leading causes of morbidity and mortality in term and preterm neonates (1, 2). Neonatal sepsis is classified as either early-onset or late-onset depending on the age of onset and timing of the sepsis episode (3). Early-onset neonatal sepsis (EONS) occurring in the first three days of life is

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transmitted vertically from mother to neonate before or during delivery (4). *Streptococcus agalactiae* (GBS) and *Escherichia coli* (E. coli) are the most common organisms associated with EONS (5). According to the National Survey of Population and Family Health carried out by the Ministry of Health in Morocco in 2004, EONS was the third leading cause of death, followed by birth asphyxia and prematurity (6). The EONS is responsible for 30%-40% of neonatal deaths in developing countries (7).

In Morocco, EONS is recognized as a major public health problem and a constant concern in neonatology units due to its frequency and severity. It results from newborns' immature immune systems and increases the risk of mortality (8). Due to the non-specificity of clinical signs of EONS, diagnosis is based on a range of clinical and biological arguments (9, 10) and remains challenging. Blood culture is considered the "gold standard" for the diagnosis of neonatal infections; nonetheless, blood cultures may come back negative in case of meningeal, pulmonary, ocular, or urinary tract infections. Other biological tests, such as the assay of biomarkers, have long attracted the interest of neonatologists for neonatal sepsis diagnosis, making it possible to identify the newborns at risk of infection instead of just those who are actually infected. The use of inflammatory markers, such as C-reactive protein (CRP), limits the overuse of antibiotics and reduces hospital stays (11,12).

In light of the aforementioned issues, the present study aimed to describe infection risk factors, as well as clinical, paraclinical, and evolutionary characteristics, of newborns with suspected EONS admitted to the National Reference Centre for Neonatology and Nutrition at Children's Hospital of Rabat, and highlight the importance of CRP in the diagnosis of neonatal sepsis.

Design of study

This retrospective analytical study was conducted at the National Reference Center for Neonatology and Nutrition at Children's Hospital of Rabat from 1 January to 31 December 2016. The study concerned hospitalized newborns for the management of suspected EONS.

Inclusion criteria

Symptomatic or asymptomatic newborns hospitalized for clinical management of suspected EONS and/or newborns with infection risk factors (IRF) were included in the study.

The IRF is defined by the presence of at least one of the following elements (11-13):

- Premature rupture of membranes (PROM) before labor exceeding 12h
- Unexplained prematurity
- Maternal fever before or during birth ≥ 38ºC
- Unexplained neonatal hypoxia
- Maternal genital tract infection or urinary tract infection, treated or untreated, for less than 72 h before delivery
- Intrauterine infection (Clinical chorioamnionitis) occurring as a result of ascending bacterial infection. It is an acute inflammation of the membranes and chorion of the placenta and is clinically defined by a maternal fever above 38ºC and at least two of the following signs: maternal tachycardia ≥100 beats per min (BPM), fetal tachycardia ≥ 160 BPM, maternal hyperleukocytosis, inflammatory syndrome, uterine pain, fetid leucorrhea, or infected amniotic fluid.
- Documented positive maternal GBS status without prepartum treatment or with inadequate prepartum treatment.

Exclusion criteria

All newborns whose medical records were not retrieved and newborns with non-bacterial neonatal infections were excluded from this study.

Data collection

The data collection was carried out by a documentary technique consisting of consulting the medical records of each neonate. All data were entered using an information sheet containing the following sections:

- Epidemiological data
- Maternal and obstetrical characteristics
- Clinical characteristics of the newborn
- Paraclinical characteristics
- Clinical evaluation of the patient

Definitions of used terms

The following definitions were used:

- Primigravida: a woman pregnant for the first time
- Multigravida: a woman who has had multiple pregnancies
- Primiparous: a woman who has had one birth
- Multiparous: a woman who has had multiple births
- Multiple pregnancies: a pregnancy with more than one fetus
- PROM: is a rupture of membranes before labor begins
- Well monitored pregnancy: a pregnancy is

considered well monitored if the woman has had at least three antenatal visits and one obstetrical ultrasound.
- Hyperleukocytosis: Laboratory abnormality is defined as increased production of leukocytes up to 30,000 cells / mm3 in the newborn's bloodstream.
- Leukopenia: A decrease in the number of leukocytes unless 10 000 elements/mm^3 in the newborn's bloodstream
- Thrombocytopenia: abnormally low levels of platelets. Normal newborn platelet count ranges from 200 x 10^9/L to 350 x 10^9/L.
- Meningitis: The inflammation of the meninges most often caused by viral or bacterial invasion of cerebrospinal fluid (CSF)
- Cranial ultrasonography (cUS): This is the preferred modality to image neonatal brains. It is an excellent tool to detect brain abnormalities and follow brain maturation (14).

Statistical analysis

Data were analyzed in SPSS software (version 19). Firstly, a descriptive analysis was performed, and the qualitative variables were expressed as frequency and percentages. Thereafter, the data were analyzed using the Chi-square (χ^2) test. A p-value of less than 0.05 was considered statistically significant.

Results

Maternal and Obstetric Characteristics

A total of 1,186 mothers were included in the current study, 58 of whom gave birth to twins, resulting in the birth of 1,199 newborns. The mean maternal age was 28±6 years. The majority of women (63%) were in the age range of 19-30 years. Multiparous women represented 41% of cases. The pregnancies of 916 (77%) women were well-monitored, with at least three antenatal care visits and one obstetrical ultrasound. The medicalization of childbirth was documented in 1167 (98%) mothers. Vaginal delivery was the predominant mode with a distribution of 60% (Table 1).

Table 1. Maternal and Obstetric Characteristics (n=1186)

Variable	n	%
Maternal Age (Years old)		
Mean± SD	28±6	4
≤18	46	63
19-30	744	31
31-40	368	2
≥40	28	
Marital status	1156	97.5
Married	28	2.3
Single	2	0.2
Divorced		
Gravidity	642	54
Primigravida	544	46
Multigravida		
Parity	700	59
Primiparous	486	41
Multiparous		
	1128	95
Simple pregnancy	58	5
Multiple pregnancies		
	916	77
Monitoring of pregnancy	80	7
Well monitoring	119	10
Poor monitoring	71	6
Unknown		
	1167	98
Medicalized delivery	20	2
Non-medical delivery		
Delivery method	708	60
Vaginal delivery	478	40
Cesarean section		

SD : Standard deviation

Newborns' Characteristics

During the study period, a total of 2,787 newborns were admitted to our department, 1,253 (45%) of whom were admitted for the management of suspected EONS. The medical records of 1,199 newborns were analyzed (Figure 1), the majority of whom (60%) were male. The gender ratio was 1.51. A number of 52 newborns were admitted within the first 24 h after birth (Table 2). Moreover, 80.3% of hospitalized cases had one or more IRF. The PROM (50.2%), maternal fever (18.7%), and intrauterine infection (17.8%) were the most frequently reported IRF. The distribution of newborns according to the type of IFRs is displayed in Table 3.

Clinical characteristics

Regarding clinical data, symptomatic newborns accounted for 67.4% of cases. The most frequent clinical findings were respiratory distress (58.7%), jaundice (42.5%), and neonatal hypoxia (21.7%). It is noteworthy that other symptoms (respiratory, circulatory, and neurological) were also observed (Table 4).

Paraclinical characteristics

The serum CRP level was measured for all newborns (the CRP positivity threshold is set at 20 mg/L). The CRP was found positive in 698 (58%) newborns. Median CRP value was reported as 39 mg/L. In addition, 32.6% of cases were asymptomatic and diagnosed based on risk factors, and 59% of them had raised CRP levels. Univariate analysis demonstrated that CRP value

was significantly associated with age groups (P<0.001), presence of at least one infectious risk factor (P<0.001), and the presence of respiratory (P<0.001), cutaneous (P<0.001), circulatory (P=0.02), and neurological (P=0.008) symptoms (Table 5).

Lumbar puncture (LP) was performed in 645(54%) cases, 57 (9%) of whom obtained positive results; therefore, it was positive in 5% of all cases. No pathogens were isolated from CSF. Moreover, all blood culture tests came back negative. A complete blood count was carried out in 765 (64%) neonates, 5%, 6%, 14%, and 18% of whom had anemia, hyperleukocytosis, leukopenia, and thrombocytopenia. The cUS was performed for newborns 216(18%), 13% and 6% of whom were abnormal and had intracranial hemorrhage, respectively. Thoraco-abdominal X-ray was performed for 83 (7%) cases, demonstrating pneumonia in 22 cases.

Diagnosis

The diagnosis of neonatal bacterial meningitis was retained in 57 (5%) cases, 91% of whom underwent cUS analysis. It showed complications in 7 cases, 13% of whom had intracranial hemorrhage, one newborn with hydrocephalus, and another had left choroid plexus cystic lesions. Neonatal conjunctivitis due to neonatal bacterial infection was diagnosed in 2 (0.2%) cases, and a computed tomography (CT) scan revealed a right preseptal periorbital cellulitis in the first case. The bacterial pathogen detected in intra-ocular suppuration was *Serratiamarcescens*. The second case of neonatal conjunctivitis showed non-collected bilateral preseptal cellulitis. As a result of clinical and radiological examinations, 22 cases were diagnosed with pulmonary neonatal infection.

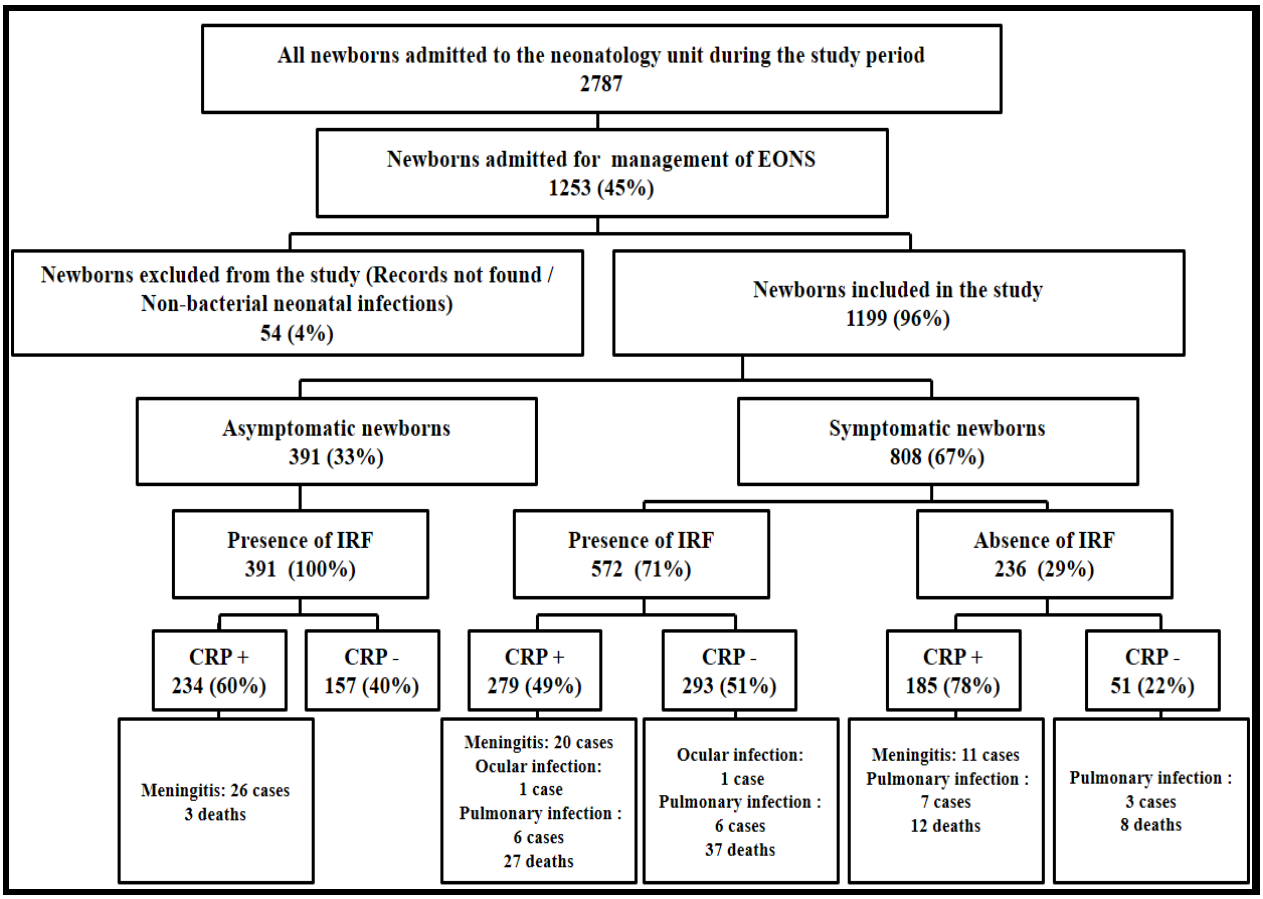

Figure 1. Flow chart of the distribution of study cases depending on the symptomatology, the infection risk factors, the results of the CRP levels, and the diagnosis
EONS: Early-onset neonatal sepsis
IRF: Infection risk factors
CRP+: Positive C-reactive protein level
CRP-: Negative C-reactive protein level

Table 2. Newborns characteristics (n=1199)

Variable	n	%
Gender		
Male	723	60
Female	476	40
Age at hospitalization		
1 HRS- 24 HRS	618	52
1-7 day	581	48
Gestational age		
Full time	794	66
Premature	265	22
Premature <34 WA	43	4
Premature ≥34 WA	222	18
Post-term	140	12
Birth weight		
Hypotrophic (<2500g)	303	25
Eutrophic (2500- 4000g)	798	67
Macrosomia (>4000g)	98	8
Birthplace		
Maternity	1147	95
Birthing center	8	1
Clinic	23	2
Non-medical delivery	21	2
	Mean± SD	Extreme
Birth weight (g)	2999±836	[700-5580]
Height at birth (cm)	48±4	[30-63]
Cranial perimeter (cm)	33±3	[14-50]

HRS: Hours, SD: Standard deviation, WA: weeks of amenorrhea

Table 3. Infection risk factors (n=1199)

Variable	n	%
Presence of IRF	963	80.3
Absence of IRF	236	19.7
PROM greater than 12h	602	50.2
PROM: >12h - <18h	103	8.2
PROM: ≥18h	499	41.6
Intrauterine infection	214	17.8
Maternal fever ≥38 ° C	224	18 .7
Unexplained prematurity	122	10.2
Urinary tract infection	32	2.7
Unexplained neonatal hypoxia	175	14.6
Positive maternal GBS status	2	0.2

IRF: Infection risk factors, PROM: Premature rupture of membranes, GBS: Group B Streptococcus

Table 4. Clinical symptoms of newborns included in our study (n= 808)

	n	%
Symptomatic newborns	808	67.4
Asymptomatic newborns	391	32.6
General signs		
Hyperthermia	41	5.1
Hypothermia	82	10.1
Neonatal Hypoxia	175	21.7
Dehydration	2	0.2
Refusal to breastfeed	16	2.0
Respiratory symptoms		
Respiratory distress	474	58.7
Polypnea	24	3.0
Apnea	13	1.6
Cyanosis	30	3.7

Table 4. Continued		
Skin symptoms		
Jaundice	343	42.5
Circulatory symptoms		
Greyish tint	2	0.2
Hypotension	3	0.4
Tachycardia	10	1.2
Bradycardia	49	6.1
Neurological symptoms		
Convulsion	36	4.5
Hypotonia	15	1.9

Table 5. Association of C-reactive protein levels with age, infection risk factors, and clinical symptoms (n= 1,199)

Variable	Positive CRP level	Negative CRP level	*P*-value
Age at hospitalization			
1 HRS- 24 HRS	239 (39)	379 (61)	<0.001
1-7 (day)	459 (79)	199 (21)	
IRF			
Presence	513 (53)	450 (47)	<0.001
Absence	185 (78)	51 (22)	
PROM greater than 12 hours	327 (54)	275 (45)	0.004
PROM: >12 HRS - <18 HRS	70 (68)	33 (32)	0.02
PROM: ≥18 HRS	257 (52)	242 (48)	<0.001
Intrauterine infection	100 (47)	114 (53)	<0.001
Maternal fever ≥38°C	104 (46)	120 (54)	<0.001
Asymptomatic newborns	234 (59)	157 (40)	0.2
Symptomatic newborns	464 (57)	344 (43)	
Respiratory symptoms	231 (48)	248 (52)	<0.001
Skin symptoms	227 (66)	116 (34)	<0.001
Circulatory symptoms	41 (48)	45 (52)	0.02
Neurological symptoms	37 (75)	12 (25)	0.008
Hyperthermia	38 (95)	2 (5)	<0.001
Hypothermia	33 (40)	49 (60)	0.001

HRS: Hours, IRF: Infection risk factors, PROM: Premature rupture of membranes
P-value was calculated using the chi-square (χ^2) test

Evolution

The evolution was favorable in 1,081 (90%) cases. A total of 87 (7%) newborns died, with septic shock being the most common cause of death recorded in 43 (49%) cases. The majority of deaths occurred in symptomatic newborns (97%), and the difference between symptomatic and asymptomatic cases was statistically significant (P<0.001). The mortality was significantly associated with the presence of lung abnormalities (P<0.001).

Discussion

The first 48 hours after birth is the most critical time in a newborn's life (15). Neonatal infection is expressed within the neonatal period, as early as day one, in the first week, or in the first four weeks after birth (16). The EONS is expressed during the first week of life, most often in the first three days after birth (17).

The management of suspected EONS varies depending on different teams and countries. Therefore, there is a vast variety of inclusion criteria in different studies, making comparison difficult. Consequently, several countries have adopted best-practice recommendations for the management of EONS. According to French publications, the diagnosis of EONS is based on a combination of clinical and/or biological abnormalities. They include symptomatic or asymptomatic newborns and focus on inflammatory markers concentration in the serum. On the other hand, the Anglo-Saxon publications limit the diagnosis of EONS to sepsis documented by the positivity of a blood culture or a CSF culture (18, 19).

Newborns are exposed to infection risk due to perinatal contamination, including both

asymptomatic and symptomatic cases (20). In the present study, the IRF was positive in 73.6% of newborns. It was predominated by PROM (50.2%), maternal fever ≥38°C (18.7%), and intrauterine infection (17.8%). It is worth noting that maternal GBS colonization was documented in two cases. Currently, due to maternal antibiotic prophylaxis, the majority of EONS caused by GBS occurs with negative vaginal culture for GBS. However, this is not realized in some countries, such as Morocco, where systematic screening of maternal GBS colonization is not routinely managed. The IRF, which was positive in 72% of cases according to Chemsi and Benomar, was dominated by PROM and maternal prepartum fever. Nonetheless, it was dominated by PROM and intrauterine infection according to Aseri et al., and PROM and unexplained neonatal hypoxia according to Nouri-Merchaoui et al. (7, 8, 11, 21). Furthermore, maternal prepartum fever and intrauterine infection are the most frequent factors used to identify newborns at risk for EONS (22).

The clinical manifestations of EONS are very heterogeneous and non-specific; however, their early occurrence (in the first 48 hours after birth) should indicate the condition (23). The EONS diagnostic criteria vary from one study to another due to their dependency on practitioners' knowledge and experience. They are most often based on clinical presumption and biological assessment. The bacteria responsible for EONS are rarely isolated from samples, making definitive diagnosis difficult (24, 25, 26). In the current study, clinical symptoms were highly variable and insufficient for the diagnosis of EONS. Therefore, it is necessary to build on a combination of anamnestic, clinical, and paraclinical data, including the CRP assay.

The CRP is a protein of the acute phase of inflammation largely used for EONS diagnosis.

The CRP has been reported in several studies to be of interest in the diagnosis of neonatal infections (8, 23, 27, 28). The serum CRP concentration rises 6-12 h after the onset of infection (greater than 20mg/L); thereafter, it decreases after 24-48 h and normalizes after 4-7 days (29, 30, 31). The sensitivity and specificity of the CRP were reported as 74%-98% and 71%-94% in several studies, respectively (30, 32, 33). In the current study, the CRP level was positive in 58% of cases, compared to 67.3% and 77.8% as reported by Chemsi et al. (8) and Folquet et al., respectively (34).

According to best-practice recommendations of the French Society of Neonatology and the French Society of Pediatrics, the CRP test is not recommended in the first 12 h after birth. The CRP test is performed in suspected cases at the event of antibiotic initiation after 12 h of life. If the blood culture is negative within 48 h, the CRP test will be performed 24 and 48 h after antibiotic administration to stop antibiotic treatment. Therefore, the CRP test is useful for the assessment of antibiotic treatment effectiveness (18, 35). Most of the publications concerning EONS only refer to those confirmed through pathogenic bacteria isolated from newborn's sample (36,37). In the present study, a germ was isolated in a sample of intra-ocular suppuration culture.

According to the study conducted by Chemsi and Benomar at the Casablanca University Hospital Centre, a pathogen germ was isolated in 6.2% of cases by CSF culture and blood culture; moreover, the most predominant pathogens were GBS and *E. coli.* This result is similar to the finding of a study conducted in Tunisia by Ben Hamida Nouaili et al. who reported that GBS and *E. coli* represented 50% and 29 % of the isolated germs, respectively (8, 38). In a similar vein, according to Gaschignard et al., GBS and *E.coli* were isolated in 59% and 28% of neonatal meningitis cases, respectively (39). The most common germs causing EONS, including meningitis, are GBS, *E. coli*, and Enterobacteriaceae (40).

In the present study, neonatal bacterial meningitis was diagnosed in 5% of cases. It occurs when the pathogenic bacteria invade the blood-meningeal barrier at the level of the brain capillaries and/or choroidal plexuses (41). The absence of meningism in newborns can make diagnosis challenging. It is recommended to perform an LP in the event of positive blood culture and general health deterioration with the presence of neurological symptoms (35, 42, 43, 44, 45, 46). The LP must be performed before or immediately after taking antibiotics to avoid skewing the bacterial analysis results. Nevertheless, if the newborn's state does not allow performing LP, antibiotic therapy should not be delayed (47, 48). Gastric aspirate and superficial bacteriological samples are not recommended in the management of EONS (35).

The suspected cases of EONS should receive antibiotic treatment immediately after performing infectious screening tests. The antibiotherapy must be adapted to the pathogens which are more frequently involved in EONS, such as GBS and *E. coli*. Antibiotic resistance of those germs varies with each study; for instance, according to the

general literature, 20%-70% of *E. coli* strains are resistant to ampicillin, while according to Sutkin et al., 63% of *E. coli* cultures were resistant to ampicillin, and all *E. coli* cultures were sensitive to gentamicin and cefotaxime. In the same study, among 14 GBS cultures, only one was resistant to clindamycin, while none of them was resistant to penicillin, ampicillin, and erythromycin (30, 49). Multiple studies have assessed GBS resistance to antibiotics; for instance, Sahnoun et al. reported an increase in GBS strains with high-level resistance to kanamycin and gentamicin (50). Therefore, the resistance of GBS to aminoglycosides (e.g., gentamicin, kanamycin, and amikacin), which are frequently used to treat EONS, should be continuously monitored. In their study, Hays et al. reported a sensitivity of all GBS cultures to penicillin G, amoxicillin, and vancomycin. High-level resistance to amikacin was higher (8.8%), compared to resistance to gentamicin (0.3%). It is therefore recommended to use gentamicin in the treatment of EONS caused by GBS (51). It is reported that GBS resistance to macrolides, aminoglycosides, and fluoroquinolones is higher among adults, as compared to neonatal infections. Although GBS resistance to clindamycin has been widely reported in pregnant women, it is not well documented among newborns (52, 53, 54, 55).

If there is no bacteriological guidance, a combination of antibiotics is recommended to cover all the germs implicated in EONS. In the setting of the present research, the management of symptomatic newborns started by combining third-generation cephalosporins, aminoglycosides, and ampicillin, while associating ampicillin and aminoside is used for the treatment of asymptomatic newborns. The duration of antibiotic therapy is based on the symptomatology, as well as bacteriological and inflammatory test results. If bacteriological and inflammatory tests are negative and a newborn has no symptoms, the treatment will be interrupted within 48 h. If the newborn has symptoms and/or a positive bacterial culture test and/or positive inflammatory tests, the length of the antibiotic treatment ranges from 5-21 days. In the following phases of patient management, any antibiotic therapy must be re-evaluated.

The results of the present study pointed to the limited contribution of bacteriology to the diagnosis of EONS. The CRP helped to confirm or remove the suspicion of EONS, and therefore stop treatment. Other Inflammatory biomarkers, such as interleukin 6, are also detected in the sera of infected newborns within the first hours of infection (56). Umbilical cord blood procalcitonin (PCT) has a good predictive value in the detection of bacterial infection. Therefore, PCT assays have higher sensitivity and specificity, compared to CRP (57, 58, 59).

Conclusion

As evidenced by the obtained results, the frequency of EONS in Morocco is worrisome, presenting a serious public health problem. Diagnosis and management of EONS are critical in preventing severe and life-threatening complications. Diagnosis of EONS remains a major challenge due to nonspecific clinical presentation; therefore, it requires coordination among a team of pediatricians, obstetricians, and biologists. Furthermore, the optimization of diagnostic criteria can decrease the use of antibiotics and limit the length of treatment.

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None.

Conflicts of interest

The authors declare that they have no conflict of interest.

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