

The Clinical and Bacteriological Spectrum of Neonatal Sepsis in a Tertiary Hospital in Yaounde, Cameroon

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Abstract

Objective: Sepsis is an important cause of morbidity and mortality in neonates especially in developing countries where identification of the germs and treatment is often unsatisfactory. The aim of the study was to assess the clinical presentation, and bacteriological profile of neonatal infections, and the sensitivity of the causative germs to antibiotics.

Methods: We carried out a prospective analytic study in the Yaounde Gynaeco-Obstetric and Pediatric Hospital in Cameroon over a 6 months period from 18th November 2008 to 18th May 2009. On the basis of history and/or clinical findings and paraclinical investigations, 218 neonates out of a total of 628 admissions were investigated and managed for neonatal infection.

Findings: The most frequent symptoms were fever (44.95%), refusal to feed/irritability (32.11%), and respiratory distress/cough (28.90%). Premature birth and prolonged rupture of membranes were the most frequent risk factors. *Klebsiella spp*, *Escherichia coli* and *Enterobacter spp* were the most frequent germs identified in respectively 28.6%, 21.4% and 14.3% of the positive samples. Overall sensitivity of the cultures to ampicillin, netilmicin and gentamycin was poor at 29.4%, 31.4% and 18.9% respectively, whereas imipenem, ofloxacin, ciprofloxacin and ceftazidime had the best sensitivities in 91.7%, 90%, 85.3% and 69.4% of the cultures respectively. The mortality rate was 22%, and low birth weight, premature birth and septicemia were significant risk factors for death.

Conclusion: Mortality from neonatal sepsis in this context is still high and there is an upsurge of multi-resistant germs to currently used antibiotics, calling for the need for rational use of antibiotics in the management of these infections.

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Introduction

In 2006, the World Health Organization (WHO) reported that out of the 130 million live births every year, 4 million die within the first four weeks of life [1]. Of these deaths, 99% occur in developing countries (approximately half following difficult deliveries at home) against 1% in developed countries [2]. Most of these deaths (30-40%) are due to neonatal infections [3]. According to the 2004 Demographic Health Survey in Cameroon, neonatal infections are responsible for 25% of neonatal deaths, thus constituting a major public health problem [4]. In Cameroon and in most developing countries, a combination of three parenteral antibiotics - ampicillin, aminoside and a third generation cephalosporin - which cover a broad spectrum of germs, is instituted to treat neonatal infections while awaiting culture and sensitivity tests. Yet neonatal infections still claim the lives of many children in this setting.

This study was aimed at determining the incidence and risk factors of neonatal bacterial infections, the clinical and bacteriological profile and sensitivity to antibiotics used, and the clinical outcomes in a referral mother and child hospital.

Subjects and Methods

The study was a prospective study in the neonatology unit of the Yaounde Gynaeco-Obstetric and Pediatric Hospital, from the 18th November 2008 to 18th May 2009. The study population consisted of all symptomatic neonates (0 to 28 days) with a maternal history suggestive of infection admitted in this unit within the study period.

Patient selection

Patient selection was done in two phases:

- **Phase 1:** all the neonates, in-borns or out-borns with at least one of the following anamnestic or clinical criteria as developed by the French National Agency for Accreditation and Health [5].

Anamnestic criteria: Unexplained prematurity with gestational age ≤ 35 weeks, prolonged rupture of membranes (≥ 12 hours), stained or purulent amniotic fluid, untreated recurrent urogenital

infections in the last trimester of pregnancy, maternal fever of $\geq 38^\circ\text{C}$ during labor, delivery at home, apparently healthy twin with other symptomatic.

2. *Clinical criteria:* Fever (temperature $>38^\circ\text{C}$) or hypothermia (temperature $<35^\circ\text{C}$), respiratory signs (apnoea, respiratory distress), neurologic signs (hypotonia, weak reflexes, perturbation of consciousness, convulsions, coma, irritability), digestive signs (refusal to suck, vomiting, diarrhea), jaundice (early [<24 hours after birth] or prolonged),

- **Phase 2:** included all neonates retained after the criteria in Phase 1. Samples for complete blood count (CBC), C-reactive protein (CRP), urine, blood and cerebrospinal fluid (CSF) cultures were taken and sent to the laboratory. Chest x-rays were done on those who presented with respiratory symptoms.

Once samples were taken, the neonates were placed on triple antibiotherapy (ampicillin, cefotaxime, and gentamycin). In those with positive cultures, antibiotherapy was re-adjusted according to sensitivity results.

After the results of the investigations were obtained, 218 neonates were retained in the study on the basis of the following criteria: symptomatic neonates in Phase 1, positive cultures, abnormalities in the CBC (white blood cells $>25,000/\text{mm}^3$ or $<5,000/\text{mm}^3$ or platelets $<150,000/\text{mm}^3$), raised CRP ($>6\text{mg/l}$), or abnormal chest x-ray.

Ethical clearance was obtained from the ethical committee of the hospital, and all the mothers provided informed consent before inclusion in the study.

Urine cultures were done on Mac Conkey and Cled culture media in an incubator at 37°C for 18 to 24 hours. Identification was on API 20E (Analytical Profile Index 20 Enterobacteria) for enterobacteria; API or typing for streptococci; catalase, coagulase and DNase for staphylococci. For blood cultures, samples were taken in the ward and put directly in the culture medium and incubated in the laboratory till bacterial growth for up to 10 days. In case of growth a Gram stain was done to orientate the diagnosis, and then inoculated in Chapman's culture medium or plain agar for staphylococcus, Mc Conkey or Hektoen enteric agar for enterobacteria, and blood agar

and chocolate agar for streptococcus. Cerebrospinal fluid was first inoculated in chocolate and blood agar and then incubated in carbon dioxide at 37°C for 24-48 hours. Blood for cultures, CBC and CRP was collected from the femoral vein; urine by supra-pubic taps and lumbar taps all done by one of the investigators (A.C. and M.D.).

Sensitivity was done by diffusion with an equivalent bacterial suspension of 0.5 Mc Farland in Mueller-Hinton agar medium with 16 sensitivity discs of commonly used and locally available antibiotics (β lactamines, aminosides, sulfonamides and quinolones). For streptococcus, 5% of sheep blood was added to the Mueller-Hinton agar medium. Sensitivity was interpreted after 18-24 hours incubation at 37°C with a caliper to measure the diameter of inhibition.

Data analysis

Data was entered in Epi Info 2000 and analyzed with the Statistical Package for Social Sciences version 11.0 (SPSS 11.0) software. The Chi-squared test was used to test for associations between risk factors and neonatal infection and secondly between risk factors and mortality. We assumed a statistical significance of $\alpha=0.05$. Our results are presented with 95% confidence intervals.

Findings

Study population:

We enrolled 115 (52.7%) males and 103 (47.3%) females giving a sex ratio of 1.11. Approximately

half (51.45%) of the population were premature (less than 37 weeks gestation) and two-thirds (66.1%) had low birth weights (less than 2500g). Neonatal infection was associated with low gestational age and low birth weight ($P=0.009$). The incidence of neonatal infection was 34.7% out of the 628 neonates admitted within the study period. Of the 218 neonates, 197 (87.6%) were received in the first 7 days of life and 27 (12.4%) from 8th to 28 days of life, with 127 (56.3) inborn, 48 (22%) from other health facilities and 43 (19.7%) home deliveries. There was no statistically significant difference of neonatal sepsis with respect to where the neonate came from.

Mothers' obstetrical and pregnancy past history

Of all the risk factors for neonatal sepsis, unexplained prematurity (with gestational age <35 weeks), and prolonged rupture of membranes (PROM) (≥ 12 hours) were the most frequent in 51 (23.4%) and 46 (21.1%) and a statistically significant P value of 0.02 and 0.04 respectively. (Table 1)

Symptoms on admission

Fever and behavioural disorders (refusal to suck and irritability) were the most frequent symptoms for admission in respectively 98 (44.9%) and 70 (32.1%) of the neonates. (Table 2)

Clinical signs on admission

The most frequent clinical findings were thermal dysregulation and respiratory signs in 167 (76.6%) and 68 (31.2%) respectively. (Table 3)

Bacteriological findings

Out of 437 samples (189 blood, 180 CSF and 68

Table 1: Distribution of neonates according to the pregnancy and obstetrical past history*

| Past history | Number (%) | P value |
|--|------------|---------|
| Unexplained prematurity (<35 weeks of gestation) | 51 (23.4) | 0.02 |
| Prolonged membrane rupture (>12 hours) | 46 (21.1) | 0.04 |
| Maternal fever | 41 (18.8) | > 0.05 |
| Resuscitation in septic conditions | 31 (14.2) | > 0.05 |
| Uro-genital infections | 20 (9.2) | > 0.05 |
| Delivery at home | 12 (6.0) | > 0.05 |
| Meconial amniotic fluid | 11 (5.0) | > 0.05 |
| Foul-smelling amniotic fluid | 8 (3.7) | > 0.05 |
| Twin with confirmed sepsis | 4 (1.8) | > 0.05 |

*A mother could have had more than one of the above

Table 2: Distribution of neonates according to presenting symptoms *

| Presenting symptoms | | Frequency | Total (%) |
|---|------------------------------|----------------------|-----------|
| Thermal dysregulation | Fever | 98 | 44.9 |
| | Refusal to suck | 41 | 70 (32.1) |
| Behavioural disorders | Irritability | 29 | |
| | Respiratory disorders | Respiratory distress | 61 |
| Cough | | 2 | |
| Neurologic disorders | Convulsions | 31 | 14.22 |
| Skin/mucosa disorders | Jaundice | 17 | 7.80 |
| Others (Vomiting and abdominal distension) | | 11 | 5.05 |

* One child could have had more than one symptom

urine) sent for cultures, a germ was isolated in only 42 samples (9.6%). The germs cultured were *Klebsiella spp*, *Escherichia coli*, *Enterobacter spp*, *Citrobacter spp*, *Acinetobacter baumannii*, *Proteus mirabilis*, *Serratia fonticola*, *Chryeomonas luteola*, Group A, B, and D *streptococcus* and non-Group or B *streptococcus* (Table 4). Gram negative bacteria were responsible for most of the cases of neonatal sepsis. *Klebsiella spp*, *Escherichia coli* and *Enterobacter spp* were the most frequent germs isolated in respectively 28.6%, 21.4% and 14.3% of the neonates.

Septicemia was the most frequent presentation in the early neonatal period with 23 (54.8%) positive cultures, and urinary tract infection most frequent in the late neonatal period with 5 (12%) positive cultures. (Table 4)

We noted poor sensitivity of the germs to ampicillin (29.4%), gentamycin (18.9%) and netilmicin (31.4%). These are the first-line empiric antibiotics used for neonatal infection in this unit.

The best sensitivities were seen to imipenem (91.7%), ofloxacin (90%), ciprofloxacin (85.3%) and ceftazidime (69.4%). (Table 5)

Other investigations

Abnormalities of the CBC were observed in 123 (56.5%) neonates with 124.45% having leucocytosis (WBC >25000/mm³), 10.69% leucopenia (WBC <5000/mm³) and 66.41% thrombopenia (platelets <150000/mm³). The CRP was positive (>6mg/l) in 87 (66.4%) of the neonates. Of 23 chest x rays done in those with respiratory symptoms, 13 were abnormal with 11 pneumonias and 2 bronchopneumonias.

Evolution

Of the 218 neonates included in this study, 163 (74.8%) were successfully treated, and treatment was interrupted in 7 (3.2%) because of financial constraints and 48 (22%) died. Forty six (93.8%) deaths occurred in the early neonatal period

Table 3: Distribution of the neonates according to the clinical findings *

| Clinical findings | | Number (%) |
|------------------------------|--------------------------------|------------|
| Thermal dysregulation | Fever (n=101) | 167 (76.6) |
| | Hypothermia (n=66) | |
| Respiratory disorders | Respiratory distress (62) | 68 (31.2) |
| | Apnea + lung crackles (n=6) | |
| Neurologic disorders | Hypotonia (n=29) | 42 (23.9) |
| | Weak primitive reflexes (n=15) | |
| | Coma (n=8) | |
| Skin/mucosa disorders | Jaundice (n=14) | 17 (7.8) |
| | Skin lesions (n=3) | |
| Digestive disorders | Abundant gastric residue (n=9) | 15 (6.9) |
| | Abdominal distension (n=6) | |
| Hemodynamic disorders | Pallor | 13 (6.0) |

*A child could have had more than one of the above clinical findings.

Table 4: Germs cultured in the different samples

| Germs | Blood | | Urine | | CSF | | Total (%) |
|---|-----------|-----------|----------|-----------|----------|-----------|------------------|
| | 0-7 days | 8-28 days | 0-7 days | 8-28 days | 0-7 days | 8-28 days | |
| <i>Klebsiella spp</i> | 7 | 2 | 2 | 1 | - | - | 12 (28.6) |
| <i>E. coli</i> | 5 | - | 1 | 3 | - | - | 9 (21.4) |
| <i>Entérobacter spp</i> | 2 | - | 4 | - | 1 | - | 7 (14.3) |
| <i>Citrobacter spp</i> | 1 | - | 2 | 1 | - | - | 4 (14.3) |
| <i>Acinetobacter baumanii</i> | 1 | 1 | - | - | - | - | 2 (9.5) |
| <i>Proteus mirabilis</i> | 1 | - | - | - | - | - | 1 (2.4) |
| <i>Serratia fonticola</i> | - | - | 1 | - | - | - | 1 (2.4) |
| <i>Chryseomonas luteola</i> | 1 | - | - | - | - | - | 1 (2.4) |
| Total Gram negative bacilli | 18 | 3 | 9 | 5 | 1 | | 36 (85.8) |
| Gram Positive Cocci | | | | | | | |
| <i>Group B streptococcus</i> | 2 | - | - | - | - | 1 | 3 (7.1) |
| <i>Group D streptococcus</i> | 1 | - | - | - | - | - | 1 (2.4) |
| <i>Non Group A or B streptococcus</i> | 1 | - | - | - | - | - | 1 (2.4) |
| <i>Group A streptococcus</i> | 1 | - | - | - | - | - | 1 (2.3) |
| Total Gram positive Cocci | 5 | - | - | - | - | 1 | 6 (14.2) |
| Total Gram negative and positive | 23 | 3 | 9 | 5 | 1 | 1 | 42 (100) |

CSF: cerebrospinal fluid

(within the first week of life). Mortality was associated significantly with premature birth and low birth weight ($P<0.001$, 95 % CI, $P<0.01$).

Discussion

In this study, we noted an incidence of 34.7% indicating that this disorder is very frequent in neonates in the neonatology unit of our hospital. Similar high rates have also been observed in

other developing countries notably 27.5% in Abidjan^[6] and 73.9 % in Burkina Faso^[7], in contrast to the very low rates of neonatal infections seen in developed countries. In France, Aujard and Rambaud found an incidence of 1% for all neonatal infections ^[8,9]. The variations in incidence between developing countries could be due to variations in the technical advancements of the health facilities, study designs and diagnostic criteria. The low incidences in the developed countries reflect higher standards of the health care in these countries, with neonates less exposed to infections.

Table 5: Distribution of the germs according to the global sensitivities

| Antibiotics | Global sensitivities (%) | Gram negative bacilli sensitivities (%) | Gram positive cocci sensitivities (%) |
|----------------------|--------------------------|---|---------------------------------------|
| Ampicillin (n=36) | 29.4 | 19.23 | 62.5 |
| Cefotaxime (n=38) | 58.3 | 55.20 | 71.43 |
| Ceftriaxone (n=39) | 62.2 | 62.10 | 62.50 |
| Ceftazidime (n=38) | 69.4 | 71.43 | 62.50 |
| Gentamycin (n=39) | 18.9 | 20.69 | 12.50 |
| Netilmicin (n=37) | 31.4 | 37.93 | 14.29 |
| Amikacin (n=38) | 58.3 | 55.17 | 71.43 |
| Imipenem (n=38) | 91.7 | 92.86 | 87.50 |
| Ciprofloxacin (n=35) | 85.3 | 88.89 | 71.43 |
| Ofloxacin (n=21) | 90.0 | 94.12 | 66.70 |

The most frequent symptoms were fever, behavioral disorders and respiratory symptoms. Our results reflect those observed in Morocco [10] and Madagascar [11], but differ from those of Shresta et al in Nepal [12], who observed that behavioral (42.7%), thermal (41.7%) and mucocutaneous signs (41.7 %) were most frequent.

The most frequent risk factors found in our study are not different from those described by other authors. We found that the most frequent risk factors for infection were unexplained prematurity with gestational age <35 weeks and PROM. In other studies, the most frequent factors were foul-smelling vaginal discharge and PROM [13], or prematurity and cervico-vaginal infections [14]. In developed countries especially in France, abnormal amniotic fluid and PROM were most frequent [15]. According to the French National Agency for Accreditation and Health [5], PROM, premature gestation and perinatal maternal fever above 38°C are major factors in neonatal infection.

Early-onset neonatal sepsis was by far the most frequent clinical presentation in 87.61% of the neonates, and is comparable to the rates from other African studies [16,17] and developing countries studies [8]. This finding could imply that contamination occurred before or during delivery therefore highlighting the importance of good antenatal and perinatal care in order to prevent neonatal infections.

The bacterial ecology was dominated by gram negative bacilli in both the early and late neonatal periods, although we had only 42 neonates with positive cultures. From all the germs isolated *Klebsiella spp*, *Escherichia coli*, and *enterobacter spp* were the most frequent. This high prevalence of gram negative bacteria compared to gram positive has also been found in many other studies in other developing countries [14,18,19]. The pathogens implicated in neonatal sepsis in developing countries differ from those in developed countries. Overall, Gram negative pathogens are more common and Group streptococcus, is generally rare [20].

The small number of positive cultures reflects the difficulties neonatologists encounter when investigating babies with patent clinical signs and symptoms of neonatal infection in our setting. This makes it difficult to know the exact bacterial

profile in our units and should draw our attention to the urgent need for the knowledge on the spectrum of germs responsible for neonatal infection so that treatment can be initiated early in the absence of culture and sensitivity

A major finding in our study was the resistance of germs especially enterobacteria to commonly used antibiotics like ampicillin, gentamycin and netilmicin. This resistance of isolated bacteria to commonly used antibiotics has also been observed in other developing countries [20,21]. Gangoué et al, in Yaounde [22], had a similar observation of low sensitivity (35%) of *Klebsiella spp*. to ampicillin. Cissé et al in Dakar [23], and Hossein et al [18], in Iran noted 100% resistance of *Klebsiella spp* to ampicillin whereas there was a 33% resistance to gentamycin in Dakar [23]. WHO recommended in 1999 [3], and in 2002 [24], the empirical association of ampicillin and gentamycin despite the resistance of enterobacteria to these antibiotics and their high frequency as causative germs of neonatal sepsis in developing countries.

Sensitivity of isolates was best with imipenems, ofloxacin and ciprofloxacin which are not frequently used and are considerably expensive in a low-resource setting. However, the fact that these resistant germs were isolated in our study does not imply that they were the most common causes of neonatal infections since only less than 10% of the cultures gave a positive yield.

Concerning outcome, 48 (22%) babies died, mostly within the few days of admission. Low birth weight, prematurity and septicemia were the most frequent risk factors for death. According to the WHO, low birth weight neonates have 20 times more risk of dying than those of normal weight [25]. Aboussad et al in Morocco [10], observed that prematurity was a risk factor for death, whereas in France [9], prematurity was observed to be a criterion denoting severity of neonatal infection. *Escherichia coli*, *Klebsiella spp* and *Enterobacter spp* were the most frequent germs responsible for the deaths. These findings are similar to those of Cisse et al in the Dakar University Teaching hospital [23]. This study and others, demonstrate that the germs usually responsible for mortality are those which are most resistant to empirical treatment. We think new guidelines need to be drawn, coupled with larger more recent bodies of evidence to combat neonatal infections and reduce

neonatal death in settings with limited diagnostic resources.

Strengths and limitations: This study is the first prospective study of its kind in this setting which is a mother and child referral hospital in the capital Yaounde, the capital city of Cameroon. The results obtained will serve as baseline data for future larger prospective studies.

The fact that infection was confirmed bacteriologically in only 42 neonates is a major limitation of our study. Some of the neonates had been through other health facilities where antibiotherapy was administered before being referred to the hospital, coupled with the fact that some parents could not pay for laboratory tests, and the small sample size. This however emphasizes the need for up to date knowledge on the management of neonatal infections in the absence of laboratory confirmation especially in low resource settings.

Conclusion

We conclude that neonatal sepsis is a major cause of morbidity and mortality in neonates in Cameroon despite recent improvements in the health care system. Clinical manifestations are non specific and varied. The emergence of resistant bacterial strains to commonly used antibiotics in this low resource setting is a serious problem.

We thus recommend the rational use of first line antibiotics in the management of neonatal sepsis with periodic evaluation of the bacterial ecology and sensitivity to antibiotics.

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Conflict of Interest: None

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