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Escherichia Coli Early Onset Sepsis in Term Newborns: What's New

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Abstract

Introduction: Neonatal sepsis is currently one of the most serious and feared problems affecting infants ≤ 28 days of life due to its severity, morbidity and mortality among term and preterm newborns. Group B Streptococcus (GBS) is globally the main etiologic agent of Early Onset Sepsis (EOS) in neonates; *Escherichia coli (E. coli)* is actually estimated as the second cause of EOS in term infants and the main in preterms. *E. coli* is also associated with severe invasive infections and meningitis, and it is estimated as the main cause of sepsis related mortality in very low birth weight newborns. Moreover, newborns with *E. coli* sepsis have an higher risk to develop adverse outcomes, for example neurologic disabilities.

Methods: In a 4 years prospective observational study, all term newborns affected by sepsis with positive blood culture have been enrolled. Data on pre-delivery risk factors, birth, clinical presentation, blood culture, blood test, neonatal treatment, follow-up and outcome have been collected.

Results: *E. coli* resulted the main bacteria found as cause of EOS in our neonatal unit, affecting only term newborns. The calculated incidence of positive blood culture to *E. coli* in the first three days of life in term newborns was 0.69/1000 live births. An immediate recognition of septic signs and symptoms, diagnosis and prompt antibiotic treatment were essential for a positive outcome.

Background

Neonatal sepsis is currently one of the most serious and feared problems affecting infants ≤ 28 days of life, due to its severity, morbidity and mortality among term and preterm newborns [1-6]. Early Onset Neonatal Sepsis (EOS) is defined by the onset of systemic signs and symptoms within 3 days of life [7-10], and it's usually consequence of vertical transmission. The onset after 7 days of life is attributed of horizontal transmission, generally acquired postnatally, and called Late Onset Sepsis (LOS). Main risk factors for neonatal sepsis are prematurity, low and very low birth weight, chorioamniositis, prolonged rupture of maternal membranes, GBS colonization and maternal fever [11-12].

Group B Streptococcus (GBS) is globally the main etiologic agent of EOS in neonates; *Escherichia coli* (*E. coli*) is actually estimated as the second cause of EOS in term infants and the main in preterms [1,12-15]. *E. coli* is also a pathogen associated with severe and complicated infections and meningitis, and it is estimated as the main cause of sepsis related mortality in very low birth weight newborns [1,16]. The sepsis-related mortality is higher in *E. coli* infections compared to gram positive [14,17], in particular when *E. coli* is ampicillin resistant [14].

Moreover, *E. coli* septic patients who survive have an higher risk of adverse outcome, as neurologic disabilities, compared to other bacteria [18].

Objectives

The aim of this study was to evaluate characteristics of EOS in a secondary level neonatal department, focusing on term newborns with positive blood culture to *E. coli*.

Patients and Methods

In a 4 years prospective observational study (2013–2016) all data on newborns with systemic infection and blood culture positive were collected. In this study, to make data uniform, only newborns with onset in the first three days of life were enrolled. In our neonatal department, newborns with a physiologic course are usually admitted for three days, and then discharged. All patients early discharged or transferred to other hospitals were excluded.

On each patient enrolled were collected data about: birth (gestational age, gender, birth weight, type of delivery), infectious diseases risk factors (prolonged rupture of membrane, history recurrent urinary tract infection during gestation, vaginal swab for GBS, pre-partum antibiotic treatment if recommended, chorioamniositis, maternal fever during delivery), clinical presentation, microbiology (blood culture, included eventual germs resistances), blood tests (C reactive protein), neonatal antibiotic treatment and follow-up.

Results

During the four year period 2013–2016, five newborns developed early onset sepsis with positive blood culture in the first 72 hour of life. Four of them had a blood culture positive to *E. coli*, and one to GBS. In this study only *E. coli* infections are described: the characteristics of each newborn enrolled are summarized in table 1.

During the study period, in the neonatal department were admitted 6162 newborns (Table 2): 5845 terms, 312 pre-terms (< 37 weeks of gestational age) and 5 post-term newborns (≥ 42 weeks of gestational age). Considering only patients admitted for at least 72 hours (excluding early voluntary discharges and patients transferred to tertiary level intensive care units), the incidence of sepsis with positive blood culture was 0.82/1000 live births (0.82‰): 0.66‰ for *E. coli* and 0.16‰ for GBS infections. This percentage increases to 0.86‰ (0.69‰ for E. coli and 0.17‰ for GBS infections) considering as denominator only term newborns.

Three of the four patients enrolled had a pre-delivery infectious risk factor (patients 2, 3 and 4): two pregnant with prolonged ruptures of membranes (> 18 hours) without a complete antibiotic prophylaxis for GBS (patients 2 and 4), and one with a vaginal swab positive to GBS and no antibiotic prophylaxis (patient 3). A pre-partum prophylaxis for GBS was considered complete when an adequate antibiotic dose was administered at least four hours before delivery. Any problem was reported from each pregnant in the past medical history, and in particular no history of *E. coli* urinary tract infection during pregnancies. None of them had signs of chorioamniositis at delivery.

Three newborns (patients 1, 2 and 3) had a physiologic course immediately after birth with an APGAR score of 08-09-09 at 1 minute and 09-10-10 at five minutes of life respectively. Only one of them (patient 4) necessitated respiratory assistance immediately after birth, with an APGAR score of 05 at 1 minute and 08 after five minutes of life.

Two of the four patients (1 and 4) did the blood tests (CRP and blood culture) after the insurgence of symptoms suspected for a disseminated infection (poor feeding, suffering aspect and respiratory distress symptoms): the first developed these symptoms during the second day of life (patient 1), and the second (patient 4) few hours after birth. The other two patients (2 and 3) did not develop any clinical symptom: blood tests were performed to the presence of pre-delivery infectious risk factor in anamnesis. They started the antibiotic treatment due to the serum CRP increase. We found a particular abnormal CRP increase in patients 1 and 4, when clinical septic symptoms were present at time of blood tests, compared with patients 2 and 3 (Figure 1).

Table 3 shows the microbiological data collected from positive blood cultures: *Escherichia coli* was sensible to all antibiotics in three of the four patients (1-3), and resistant to ampicillin in one (patient 4). This is the only microbiologic data available, since in none of the newborns enrolled was done the lumbar puncture to collect the cerebrospinal fluid.

Table 1: Characteristics of patients with sepsis and blood culture positive to *E. coli*.

	Gender	WGA	BW (grams)	ID risk	Pregnancy	Delivery	APGAR (1-5 minutes)	Clinical signs and symptoms	Time at onset	Antibiotic treatment (days)	Lenght of admission	*E. coli* microbiology data
Patient 1 (2014)	Male	41	3700	No	Normal course	Dystocic	08 - 09	Poor Feeding, Acrocyanosis, Suffering Aspect	2 Days of Life	Ampicillin + sulbactam (14) + Netilmicin (5)	16 days	Sensitive to all antibiotics tested
Patient 2 (2014)	Female	39+5	2700	Yes (prolonged rupture of membranes with uncompleted antibiotic prophylaxis for GBS*)	Normal course	Normal	09 - 10	Normal	1 Day of Life	Ampicillin + sulbactam (10) + Netilmicin (3)	11 days	Sensitive to all antibiotics tested
Patient 3 (2015)	Male	40+3	2640	Yes (vaginal swab positive to GBS and uncompleted antibiotic prophylaxis for GBS*)	Normal course	Normal	09 - 10	Normal	1 Day of Life	Ampicillin + sulbactam (10)	10 days	Sensitive to all antibiotics tested
Patient 4 (2016)	Male	39+4	3700	Yes (prolonged rupture of membranes with uncompleted antibiotic prophylaxis for GBS*)	Normal course	Normal	05 - 10	Respiratory distress, oxygen administration	Few hours after birth	Ampicillin + sulbactam (18) + Netilmicin (9)	18 days	Resistance to ampicillin

WGA: Weeks of Gestational Age; BW: Birth Weight; ID: Infectious Disease.
*A pre-partum antibiotic prophylaxis for GBS was considered complete when an adequate dose of penicillin was administered at least 4 hours before delivery. Membrane's rupture was considered prolonged when > 18 hours.

Table 2: Characteristics of patients admitted in Neonatal and Neonatal Pathology Departments of the Hospital G. Fornaroli of Magenta (Milan, Italy).

Years	2013	2014	2015	2016	Total	Yearly mean
Total Newborns	1651	1587	1477	1447	6162	1540,5
Terms (37 to 41+6) wga	1559	1504	1405	1377	5845	1461,25
Prematures < 37 wga	90	82	71	69	312	78
< 25 wga	0	0	0	0	0	0
< 28 wga	0	2	2	2	6	1,5
25 to 31+6 wga	0	3	3	2	8	2
32 - 33+6 wga	21	4	7	9	41	10,25
34 - 36+6 wga	69	75	61	58	263	65,75
Post terms ≥ 42 wga	2	1	1	1	5	1,25
Early discharged (within 72 hours)	16	11	9	10	46	11,5
Voluntary discharges (within 48 hours)	1	1	1	0	3	0,75
Newborns not included	17	12	10	10	49	12,25
Newborns elegible	1634	1575	1467	1437	6113	1528,25
Term newborns not included	8	7	5	4	24	4,8
Term newborns elegilbe	1551	1497	1400	1373	5821	1455,25
Positive blood cultures	1	2	1	1	5	1.25
Positive blood cultures yearly incidence	0.61‰	1.26‰	0.68‰	0.69‰	0.82‰	0.82‰
Positive blood cultures yearly incidence in terms	0.66‰	1.33‰	0.71‰	0.72‰	0.86‰	0.86‰
***E. coli* positive blood cultures**	1	1	1	1	4	1
***E. coli* positive blood cultures yearly incidence**	0.61‰	0.63‰	0.68‰	0.69‰	0.66‰	0.66‰
***E. coli* positive blood cultures yearly incidence in terms**	0.66‰	0.67‰	0.71‰	0.72‰	0.69‰	0.69‰

Table 3: *E. coli* antibiotic sensibilities (S) or resistances (R) on blood cultures isolates.

	Patient 1	Patient 2	Patient 3	Patient 4
Amikacin	S	S	S	S
Amoxicillin + Clavulanate	S	S	S	S
Ampicillin	S	S	S	R
Cefepime	S	S	S	S
Cefotaxime	S	S	S	S
Ceftazidime	S	S	S	S
Ciprofloxacin	S	S	S	S
Ertapenem	S	S	S	S
Gentamycin	S	S	S	S
Imipenem	S	S	S	S
Meropenem	S	S	S	S
Piperacillin + Tazobactam	S	S	S	S
Tigecyclin	S	S	S	S
Tobramycin	S	S	S	S
Trimethoprin + Sulfametoxazole	S	S	S	S

BW: Birth Weight; CRP: C Reactive Protein; *E. Coli*: *Escherichia coli*; EOS: Early Onset Sepsis; GBS: Group B Streptococcus; ID: Infectious Diseases; LOS: Late Onset Sepsis; WGA: Weeks of Gestational Age.

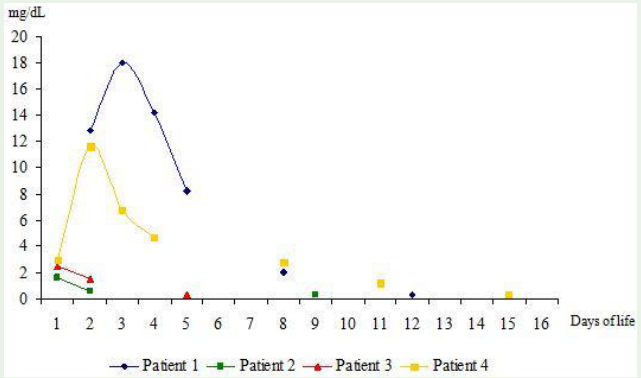

Figure 1: CRP trends during admission (normal CRP value < 0.5 mg/dL).

All patients enrolled were treated with ampicillin + sulbactam for 10-18 days, in association with an amynoglicoside (netilmicin) for 3-9 days.

All of them had a good final outcome, were discharged in good general conditions, and no sequelae were found during the follow-up available until now.

A prolonged treatment (ampicillin + sulbactam for 18 days and netilmicin for 9) was necessary in patient 4, with ampicillin resistant *E. coli* infection, who had a very slow CRP decrease during the

admission and antibiotic administration. This patient necessitated respiratory resuscitation at delivery (APGAR score 5 at one minute) and developed septic symptoms few hours after birth.

Discussion

Currently, GBS and *E. coli* account for 70% of all the cases of neonatal sepsis (EOS and LOS) considering the whole neonatal period [1,19,20]. Despite GBS still remains the leading cause for neonatal sepsis (globally for both EOS and LOS), in the last years the role of Gram negative germs, in particular in EOS and in very low birth weight newborns, has progressively increased [7,13,18,21-23].

E. coli is actually estimated as the second leading cause of EOS in neonates, and the main pathogen causing EOS in preterms, accounting 24% of all EOS episodes, with 81% in preterm infants [1,7,13,24].

It's frequently associated with severe infections and meningitis, with high mortality rate, and it's estimated as the main cause of EOS mortality in very low birth weight newborns [1,18,20]. The outcome of *E. coli* infections in frequently poor, with a high rate of adverse complications, in particular neurologic and long term disabilities [18].

The widespread use of pre partum chemoprophylaxis in at-risk pregnants has dramatically reduced the rate of GBS-EOS [4,7,13,15,23,25,26], and is considered necessary where non realized [27]. However, this treatment could be associate to an alteration of the vaginal flora, with selections of antibiotic resistant pathogens potentially cause for neonatal sepsis [18,23,28-33].

Some studies revealed an high rate of amoxicillin resistant *E. coli* as cause of EOS [8,21] as a possible consequence of pre partum antibiotic use, in particular in the preterm population [20,23,31-33]. Gram negative resistance to aminoglycosides is relatively uncommon but to be considered in patients with deterioration despite initiation of empiric antibiotic treatment [12,18,21,34]. Multi drug resistant *E. coli* has also been associated with lethal neonatal meningoencephalitis [35].

In our clinical records, during the 4 years survey *E. coli* was the main cause of EOS revealed through blood culture among newborns admitted in the first three days of life. An immediate recognition of septic signs and symptoms was very important for an early diagnosis and a good outcome. In the patients described a prompt recognition of clinical septic symptoms and an accurate evaluation of infection diseases risk factors leaded to an immediate antibiotic treatment, necessary for a good prognosis. An adequate gestational age, birth weight and the *E. coli* sensibility to both the antibiotics started played a favorable role in the cases we managed. An antibiotic association with penicillin + aminoglycoside is always recommended until the antibiotic sensibility culture result is available, due to the increasing rate of amoxicillin resistant germs and a possible role of a pre-partum prophylaxis on the microbial selection. In the clinical cases we described, only one patient (number 4), with ampicillin resistant *E. coli*, necessitated a prolonged antibiotic administration with a very slow serum CRP decrease during the treatment. In another patient (number 3) the treatment was carried on with only penicillin due to the good general conditions, the absence of sings/symptoms of sepsis at onset and the rapid CRP decrease after antibiotic start; in this patient, when the microbiology department communicated the blood culture positivity, the very good clinical status of the newborn leaded us to carry on without an aminoglycoside association until the antibiotic sensitivity test was available.

Increased CRP levels and a prolonged length of admission and an higher duration of antibiotic treatment were recorded in patients with clinical signs/symptoms of sepsis.

Comparing our own data with literature, *E. coli* was surprisingly found as main cause of sepsis with positive blood cultures in the first 72 hours of life in term newborns. It's well known that the main cause of sepsis in this category of patients is GBS, followed by *E. coli*. We did not found any *E. coli* infection in preterm newborns (where *E. coli* is estimated as the main cause of bloodstream infections).

Despite *E. coli* sepsis in newborns is usually described with more dangerousness and at higher risk of sequela, in particular in preterm newborns and very low birth weight, all our patients had a very good clinical course with positive outcome. None of them showed any sequela or sepsis related disability during the follow-up. As reported in the literature, the only patient we managed with ampicillin resistant *E. coli* infection had a more prolonged clinical course in our neonatal unit, with a slower recovery and the necessity of a prolonged antibiotic treatment and admission.

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