Academic Journal of
Pediatrics & Neonatology
ISSN 2474-7521

Juniper Publishers
key to the Researchers

Review Article
Volume 5 Issue 1 – June 2017
DOI: 10.19080/AJPN.2017.05.555708

Acad J Ped Neonatol

Newborns Hospitalized Due to Suspected Sepsis, Blood Culture Results and Decisions Made by Pediatricians

Mirta Mesquita*, Viviana Pavlicih, Noemi Zarate, Laura Riveros and Pio Alfieri

Hospital General Pediátrico "Niños de Acosta Ñú", Paraguay

Submission: February 05, 2017; **Published:** June 08, 2017

***Corresponding author:** Mirta Mesquita, Pediatrician Neonatologist, Researcher, Hospital General Pediátrico "Niños de Acosta Ñú", Sucre 1808 y Juan Motta Asunción, Paraguay, Tel: 595-21-604640; Email: mirtanmr@gmail.com

Abstract

Objective: To analyze the blood culture results in neonates with suspected sepsis, the decision made by the emergency department pediatricians and the intra-hospital and post-discharge patient progression.

Methods: We conducted a descriptive longitudinal study of newborns admitted to the Pediatric Emergency Department (PED] due suspected sepsis. We analyzed decisions made by the emergency department pediatricians when blood culture results were negative, days of antibiotic therapy, previous hospitalization (PH], and intra-hospital and post-discharge patient progression. Data were analyzed using SPSS V17.

Results: We included 60 newborns admitted with suspected sepsis, of these 30% had a history of previous hospitalization. Blood culture was negative in 87% and in 79% pediatricians decided on suspension of antibiotic therapy and discharge with favorable post-discharge progression. Of the 60 newborns, 4 died, 3 of sepsis due to multidrug-resistant microorganisms, all with a history of PH.

Conclusion: The usual reaction of emergency department pediatricians to a negative blood culture was suspension of antibiotics and discharge within 72 hs, with favorable post discharge progression.

Keywords: Antibiotics; Blood culture; Newborns; Suspected sepsis.

Introduction

Diagnosis and appropriate treatment of sepsis with antibiotics is fundamental for reducing pediatric mortality, especially in newborns, a greatly vulnerable population [1]. In Latin America and the Caribbean, neonatal deaths make up 53% of mortality in children under age 5 years [2]. One-third of these deaths are due to severe bacterial sepsis [3]. Among factors associated with greater risk of sepsis in newborns in these countries are maternal sepsis, childbirth in non-antiseptic conditions, premature birth, a greater prevalence of intrauterine growth restriction, and inadequate medical care [4].

Identification of symptoms in the neonatal period is difficult due to their lack of specificity and the small percentage that provide positive cultures, especially in developing countries, where scarty of resources for use of diagnostic tools makes identification of life-threatening severe sepsis difficult [5] . Because of its high mortality and risk of neurodevelopment squeal [6], when neonatal sepsis is suspected, culture samples are taken and empirical treatment initiated, generally with broad spectrum antibiotics, while culture results are awaited [7]. When a positive blood culture is returned, antibiotic therapy is adjusted according to the antibiogram.

However, when blood cultures are negative, the decision to continue antibiotic therapy is made based on analysis of the expected benefits versus the risk of adverse effects of prolonged administration, such as development of systemic candidacies due to altered gut flora [8], increased risk of death, increased risk of necrotizing enter colitis, and development of microbial resistance [9]. The emergence of antibiotic-resistant organisms has been associated with the inappropriate and indiscriminate use of antibiotics [10].

In 2002, to meet the increase in antibiotic-resistant bacteria, the Center for Disease Control (CDC) launched a prevention campaign of 12 steps incorporated into 4 primary strategies. One of these is the wise use of antibiotics, constituting steps 5 through

10: controlled use of antibiotics, use of local data, treatment of the sepsis rather than the colonization, knowing when to say 'No' to vancomycin, and suspension of the antibiotic when the sepsis is cured [11].

In the PED, newborns make up from 1.5-2% of patients seen, and although most have lesser complaints, suspected sepsis is a common cause of admission, especially in developing countries [12,13]. The objective of our study is to analyze the blood culture results and the decision made by the emergency department pediatricians in neonates with suspected sepsis, the intra-hospital and post-discharge patient progression.

Methodology

We conducted a longitudinal, descriptive, observational study of newborns admitted for suspected sepsis to the PED of a reference pediatric hospital and with 2 blood cultures taken prior to initiation of antibiotics, with follow up performed by telephone contact in the 10 days following discharge. Variables analyzed were post-natal age, gender, birth weight, type of birth, history of maternal infection during pregnancy, prior hospitalization of the newborn, blood culture results and decision made by the emergency department pediatrician, consultation with infectious disease specialists, days of antibiotic therapy, and intra-hospital and post-discharge patient progression.

Samples for blood cultures were 1mL of blood taken from each of 2 sites using BACTEC 9120 BD Ped Plus/R test bottles with a resin media that allows neutralization of antibiotics present in the sample. Fluorescence-sensing processing equipment was used to detect CO_2 generated by microorganisms.

Detection of bacterial growth is faster using the method, and is signaled by an alarm beginning at 6 hours of incubation. Positive samples were removed from the device and cultivated in 3 solid media (chocolate agar, blood agar, and MacConkey agar). Results were available within 36 to 48 hours of sampling. Data were processed using SPSS version 17, while qualitative variables were expressed as percentages and correlated using the Chi squared test and the Yates test or Fisher test as appropriate. Quantitative variables were expressed as means with a standard deviation if of normal distribution, or if otherwise as medians with ranges. An Alpha error of less than 5% deemed acceptable. The study protocol was approved by the hospital institutional review board in Approval No. 0033, and informed consent was obtained from the patients' parents. Confidentiality of data was ensured.

Results

In the period of December 15th 2013 to April 1st 2014, the PED treated 488 newborns, of whom, 107(22%) were hospitalized, with suspected sepsis in 76(71%). Of this latter population, 60 newborns met the inclusion criteria, with the 16 excluded including 6 for improperly performed blood cultures, 3 transferred from another facility due to suspected sepsis, and 7 transferred to another hospital within 24 hs of admission. Chief complaints are shown in (Table 1), and patient characteristics and perinatal history in (Table 2). Mothers with infection during pregnancy had been treated with antibiotics for urinary tract infection or leukorrhoea. Antibiotics were administered to most (16 of 18) newborns hospitalized in the neonatal period.

Table 1: Chief complaint for newborns admitted to the PEDfor suspected sepsis (n=60)

	No.	%
Fever	31	51.7
Respiratory failure	8	13.3
Skin lesions	5	8.4
Refusal to feed	3	5
Tumefaction	3	5
Vomiting	2	3.3
Other	8	13.3
Total	60	100

Table 2: Characteristics and perinatal history of the study population (n=60).

	Mean SD	Range
Postnatal age (days)	13. 5±8.5	1–28
Birth weight (grams)	3322±722	1070–4230
Gestational age (weeks)	38.8±2	30–42
Preterm	4	6.6
Female	31	51
Maternal infection	23	38
Prior neonatal hospitalization	18	30
Home birth	2	3.3

The initial empirical antibiotic regime for the 60 newborns was cefotaximé+ampicillin in 45(75%), ampicillin+gentamicin in 3(5%), and other combinations in 12(20%). Blood culture was positive in 8(13%), with 3 showing coagulase-negative staphylococcus species (CoNS), 2 extended-spectrum beta-lactamase (ESBL) producing Klebsiella pneumoniae , 1 *Escherichia coli*, 1 *Streptococcus agalactiae*, and 1 *Candida albicans*. Treating pediatrician decided on switching antibiotics according to antibiogram results in 7 of the 8, and continued the initial regimen in 1 patient. All these patients were admitted to the pediatric intensive care unit (PICU). Of the 8 patients, 3 died, of which 1 had systemic candidiasis, and 2 sepsis due to ESBL *Klebsiella pneumoniae*. The patient with systemic candidiasis had been preterm, affected by intrauterine growth restriction, administered prolonged antibiotic therapy, and hospitalized from birth until discharged only 4 days prior to admission to the PED. The 2 patients with ESBL *Klebsiella pneumoniae* also had a history of prior hospitalization and had been treated with antibiotics for more than 5 days.

Blood culture was negative in 52(87%) of the 60. The course of action adopted by pediatrician upon a negative blood culture (n:52) can be seen in (Table 3). Follow up of intra-hospital progression of these patients found that those with negative blood

How to cite this article: Mirta M, Viviana P, Noemi Z, Laura R, Pio A. Newborns Hospitalized Due to Suspected Sepsis, Blood Culture Results and Decisions Made by Pediatricians. Acad J Ped Neonatol. 2017; 5(1): 555708. DOI: 10.19080/AJPN.2017.05.555708.

cultures and good clinical progression (n=41) were discharged within 72 hs of admission. Those for whom clinical suspicion of sepsis existed (n=8) received 7-10 days of antibiotics, with those showing poor clinical progress being switched to another antibiotic regimen and transferred to the PICU (n=3). Of these patients, 1 with a congenital defect (annular pancreas) died.

Table 3: Pediatrician treatment choice upon receipt of negative blood culture results at 48 hs (n=52).

	No	%
Discharge to home, Sepsis excluded (no anomalous clinical data and negative blood culture)	41	79
Antibiotic therapy continued (sepsis not excluded at 72 hs)	8	17
Antibiotic switched (possible sepsis suspected due to poor clinical progress)	3	4
Total	**52**	**100**

In comparing patients with a history of prior hospitalization (n=18) and those with none (n=42), during the current hospital stay, those with a history of prior hospitalization had more days of antibiotic therapy 7.6±5 versus 4.3±3 ($p < 0.05$) lower rates of discharge within 72hs, 9/18 (50%) versus 32/42(76%) $p<0.05$.

Consultation with an infectious diseases specialist was done regarding 7(11.7%) of the 60 patients. Parents or custodians of the patients discharged were contacted by telephone within 10 days of discharge, with all reporting the patients to be well, and no patient was readmitted.

Discussion

We found a high rate of prescription of antibiotics for newborns hospitalized at the PED with suspected sepsis.

Some studies report that 1 in 4 patients under age 18 admitted to pediatric emergency departments receive antibiotics, which is one of the most commonly prescribed classes of medications used in pediatric emergency wards [14].

Administration of antibiotics for suspected sepsis is very common in newborns, especially those with very low birth weight (VLBW) or extremely low birth weight (ELBW). In a cohort study conducted at 2 neonatal intensive care units (NICU) in the United States, prescription of antibiotics for suspected sepsis was 8 times more frequent than the antibiotic prescription rate for confirmed sepsis [15]. The evidence indicates that from 30-50% of antibiotic prescriptions in hospitals are unnecessary and inappropriate. The CDC has made recommendations for reducing unnecessary use of antibiotics in hospitals based on creation of programs of hospital administration and monitoring of prescriptions, and although the guidelines are not specific to newborns with sepsis, they can be applied in that group of patients [16].

In our study, predominate pediatrician practice in newborns in the PED with suspected sepsis but a negative blood culture was suspension of antibiotics and discharge within 72 hs with a result of favorable patient progression. In a much smaller percentage of cases it was decided to continue antibiotic therapy based on the clinical diagnosis of sepsis. This pattern of pediatrician practice avoided prolonged exposure of the newborns to broad spectrum antibiotics. It also resulted in fewer days hospitalized and good post-discharge progression.

Deciding the duration of antibiotic therapy in newborns with suspected sepsis and a negative blood culture is a serious challenge due to the need to consider the danger of severe sepsis compared to the adverse effects of prolonged empirical therapy and the antibiotic toxicity.

Few well-designed studies examine the duration of initial antibiotic therapy in newborns with suspected sepsis and a negative blood culture. Although prospective studies are limited, some authors consider the administration of antibiotics for 48-72 hs, until blood culture results are received and assessed, reasonable. While symptoms attributable to sepsis may indicate a false negative, and motivate continued treatment, it should be suspended in patients progressing favorably [17]. In this regard we have not found prior studies in newborns with characteristics similar to those in our study. In one study conducted in ELBW preterm newborns with suspected early-onset neonatal sepsis in an NICU, the percentage of negative blood cultures was 88%, a figure similar to that in our study. Antibiotic therapy was administered to 40% of that cohort for a minimum of 3 days, and those patients had shorter hospital stays (59vs75 days, $p<0.01$) compared to patients administered more than 3 days of antibiotic therapy [18]. In another study in a similar ELBW population, the risk of death, adjusted for other variables, increased 16% for each additional day of antibiotic therapy [9]. Alexander et al. [19] analyzed risk factors for necrotizing enterocolitis in preterm newborns and found that prolonged administration of antibiotics in the absence of sepsis was associated with greater risk.

We found only one randomized clinical study, which included 52 preterm newborns of less than 1000g, that studied suspected sepsis and negative blood cultures. In that study, one group received antibiotics for 48-96 hs, while another group received them for 7 days. The authors found no difference in clinical progress between the groups in the two weeks following end of treatment [20]. Some authors have studied the role of C reactive protein [PCR] as an adjunctive tool for diagnosis and in follow up of neonatal sepsis. While their results indicated that it is not useful in diagnosis due to elevated levels being found in only 35-65% of newborns with confirmed sepsis [21], it did show a negative predictive value on the order of 98-99% [22]. Serial PCR testing has not demonstrated great usefulness in guiding the duration of antibiotic therapy [23,24]. No patient in our study had undergone C reactive protein testing.

The initial empirical treatment regimen was cefotaximé+ampicillin in 75% of our patients. Initial empirical therapy for suspected sepsis with broad spectrum antibiotics such as cefotaximé can induce bacterial resistance and increased risk of death compared to ampicillin+gentamicin [23,24]. However,

How to cite this article: Mirta M, Viviana P, Noemi Z, Laura R, Pio A. Newborns Hospitalized Due to Suspected Sepsis, Blood Culture Results and Decisions Made by Pediatricians. Acad J Ped Neonatol. 2017; 5(1): 555708. DOI: 10.19080/AJPN.2017.05.555708.

recent publications question the inclusion of ampicillin in the initial regimen for newborns in emergency wards due to the high resistance shown to that antibiotic, close to 73% for *Listeria monocytogenes* and *Enterococci* [25]. Initial empirical therapy regimens vary widely by region, with a recent observational study of antibiotic management for late-onset neonatal sepsis in 6 European countries finding 43 different antibiotics used in initial treatment regimens [26].

All patients in our study with positive blood cultures (n:8) represented cases of late-onset neonatal sepsis, with the most common organism found being coagulase-negative staphylococci, a finding similar to those reported in other studies with larger numbers of patients [27]. In patients in our study with a history of prior hospitalization, we found that those patients had been administered antibiotics for more than 5 days during that stay. That group received prolonged antibiotic therapy during re-hospitalization, and lower rate of discharge within 72hrs, compared to those without prior hospitalization.

These data suggest that administration of prolonged antibiotic therapy in the immediate neonatal period may be a risk factor for late-onset neonatal sepsis who seek treatment in PEDs. We found no earlier reporting in similar newborn populations, but did find reporting that administration of antibiotics ≥5 days within 24hs of life in preterm newborns with a gestational age ≥32 weeks in an NICU was associated with greater risk of late-onset neonatal sepsis [28]. Our study has, limitations due to the small number of patients, and because data from 21% of patients admitted with suspected sepsis was excluded due to data being unavailable.

It nonetheless provides information about outcomes for newborns seen at the PED with suspected sepsis, and evidence that decision made by the pediatrician to negative blood cultures and no anomalous clinical data, of suspension of antibiotic therapy and discharge to home within 72hrs was appropriate in view of the favorable clinical progress, lack of readmissions, and the consequent shortened hospital stays and duration of empirical antibiotic therapy. It is also noteworthy that the blood-culture processing technique used made results available quickly. An unexpected finding was that a history of prior hospitalization may be a risk factor for late-onset neonatal sepsis by multiresistant organisms. This hypothesis merits further study in a larger population for the purpose of establishing monitoring systems to govern use of antibiotic therapy in the immediate neonatal period in hospitals treating newborns.

References

1. Darmstadt GL, Bhutta ZA, Cousens S, Adam T, Walker N et al. (2005) Evidence - based ,cost-effective interventions: How many newborn babies can we save?. Lancet 365(9463): 977- 988.
2. http://www.childmortality.org/files_v20/download/Levels%20and%20Trends%20in%20Child%20Mortality%20Report%202012.pdf
3. Liu L, Johnson HL, Cousens S, Perin J, Scott S, (2012) Child Health Epidemiology Reference Group of WHO and UNICEF. Global regional and national causes of child mortaity: an updated asystematic analisys for 2010 with time trends since 2000 Lancet. 379(9832): 2151 - 2161.
4. Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, et al. (2005) Hospital Acquired neonatal infections in developing countries. Lancet 365(9465): 1175-1188.
5. Thaver D, Zaidi AK, (2009) Burden of neonatal infections in developing countries: a review of evidence fron community based- studies. Pediatr Infect Dis J. 28 (1 supply): 3-9.
6. Seale AC, Blencowe H, Zaidi A, Ganatra H, Syed S, et al. (2013) Neonatal severe bacterial infections impairment estimates in south Asia,sub Sahara Africa and Latin America for 2010. Pediatr Research 74(Supply 1): 73- 85.
7. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR, (2006) Empiric use of ampicillin and cefotaxime compared with ampicillin and gentamicin for neonates at risk of sepsis is associated with an increased risk of neonatal death. Pediatrics 117(1): 67-74.
8. Cotten CM, McDonald S, Stoll B, Goldberg RN, Poole K et al. (2006) The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth weight infants.Pediatrics 118(2): 717- 722.
9. Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, et al. (2009) Prolonged duration of inicial empirical antibiotic treatment is associated with increase risk of necrotizing enterocolitis and death for extremely low birth weigth infants.Pediatrics 123(1): 58-66.
10. https://www.cdc.gov/drugresistance/index.html
11. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5115a5.htm
12. Fernandez Ruiz C, Sainz de la Masa T, Curcoy Barcenilla AI, Lasuen del Olmo N,Luaces Cubells C (2006) Asistencia a Neonatos en el servicio de urgencias del un hospital pediatrico terciario. An Pedaitr (Barc) 65: 123-28.
13. Lee AC, Chandran A, Herbert HK, Kozuki N, Markell P, et al. (2014) Treatment of infections in Young infants in low-and middle –income countries: A systematic review and Meta-analysis of frontline health workes,diagnosis and antibiotic acces. PLoS Med 14 (10): 1-21.
14. Novell BC, Hernández-Bou JJ, García G (2013) Grupo de trabajo de la Sociedad Española de Urgencias Pediatricas (SEUP).Prescripcion antibiótica en los pacientes hospitalizados desde Urgencias.Estudio multicentrico.An Pediatr (Barc) 79: 15-20.
15. Wirtschafter DD, Padilla G, Suh O, Wan K, Trupp D, Fayard EE. (2011) Antibiotic use for presumed neonatally acquired infections far exceeds that for central line-associated blood stream infections: an exploratory critique J Perinatol. 31(8): 514-518.
16. https://www.cdc.gov/getsmart/index.html
17. Sivanandan S, Soraisham AS, Swarnam K (2011) Choice and duration of antimicrobial therapy for neonatal sepsis and meningitis. Int J Pediatr 2011: 712150.
18. Cordero LM, Ayers LW (2003) Duration of empiric antibiotic for suspected early -onset sepsis in extremely –low- birth-weigth infants. Infect Control Hosp Epidemiol 24: 662- 666.
19. Alexander VN, Northrup V, Bizzarro MJ (2011) Antibiotic exposure in the newborn intensive care unit and the risk of necrotizing enterocolitis. J Pediatrc 159: 392- 397.
20. Saini SS, Dutta S, Ray P, Narang A (2011) Short course versus 7-days course of intravenous antibiotics for probable neonatal septicemia: a pilot, open –label, randomized controlled trial. Indian Pediatr 48(12): 19-24.
21. Benitz WE, Han MY, Madan A, Ramachandra P (1998) Serial serum C–reactive protein levels in the diagnosis of neonatal infection. Pediatrics 102(4): 4-e41.

How to cite this article: Mirta M, Viviana P, Noemi Z, Laura R, Pio A. Newborns Hospitalized Due to Suspected Sepsis, Blood Culture Results and Decisions Made by Pediatricians. Acad J Ped Neonatol. 2017; 5(1): 555708. DOI: 10.19080/AJPN.2017.05.555708.

22. Sola A (2009) Tiene o no tiene infección este recién nacido? En Sola A edit Diálogos en Neonatologia. Aprendiendo de las preguntas. (Does this newborn have or do not have an infection? In Sola To edit Dialogues in Neonatologia. Learning of the questions) Buenos Aires: Edimed, pp. 131-154.

23. Bomela HN, Ballot DE, Cory BJ, Cooper PA (2000) Use of C-reactive protein to guide of empirical antibiotic therapy in suspected early neonatal sepsis. Pediatr Infect Dis J 19(5): 531-35.

24. Al- Zwaini EJ (2009) C- reactive protein: a useful marker for guiding duration of antibiotic therapy in suspected neonatal septicaemia? East Mediterr Heath J 15(2): 269-275.

25. Hassoun A, Stankovic C, Rogers A, Duffy E, Zidan M, et al. (2014) Listeria and enterococcal infections in neonates 28 days of age and younger: is empiric parenteral ampicillin still indicated? Pediatr Emerg Care. 30(4): 40-43.

25. Lutsar I, Chazallon C, Carducci FI, Trafojer U, Abdelkader B, et al. (2014) Current management of lateonsetneonatal bacterial sepsis in five European countries. Eur J Pediatr 173(8): 997-1004.

26. Muller-Pebody B, Johnson AP, Heath PT, Gilbert RE, Henderson KL, et al. (2011) iCAP Group (Improving Antibiotic Prescribing in Primary Care). Empirical treatment of neonatal sepsis : are the current guidelines adequate? Arch Dis Child Fetal Neonatal Ed 96(1): F4-8.

27. Kuppala VS, Meinzen- Derr J, Morrow A (2011) Prolonged initial empirical antibiotic treatment is associated with adverse outcome in premature infants. J Pediatr 159(5): 720-725.

DOI: 10.19080/AJPN.2017.05.555708

How to cite this article: Mirta M, Viviana P, Noemi Z, Laura R, Pio A. Newborns Hospitalized Due to Suspected Sepsis, Blood Culture Results and Decisions Made by Pediatricians. Acad J Ped Neonatol. 2017; 5(1): 555708. DOI: 10.19080/AJPN.2017.05.555708.