Ref: Ro J Infect Dis. 2024;27(2)
DOI: 10.37897/RJID.2024.2.14

Anti-mycotic trial therapy for neonatal septicemia caused a drop in the mortality rate

Salman Khalid Salman[1], Sawsan Qahtan Taha Al-Quhli[2], Yasir Mufeed Abdulateef[3]

[1]M.Sc. Microbiology University of Anbar, College of Medicine, Department of Microbiology, Iraq
[2]PhD in Medical microbiology, University of Anbar, College of Medicine, Department of Microbiology, Iraq
[3]Head of the Microbiology department, College of Medicine, University of Anbar, Iraq

ABSTRACT

Objective. Neonatal respiratory infections continue to be a significant cause of illness and death in newborn infants. the aim was to determine the association of pneumonia in 60 neonates with septicemia and it is role in the morbidity and mortality of neonates in two Neonatal intensive care units (NICU) in Al- Ramadi Teaching Hospital for Maternity and Children.

Material and Methods. All infants in this study were diagnosed with septicemia and were on empirical antimicrobial therapy. An early morning nasogastric tube (NG tube) was used to collect swallowed sputum by suction for culture and sensitivity.

Outcomes. All neonates were diagnosed with septicemia. The positive bacterial blood culture was 28 (46.7%). The NG-tube culture revealed 100% fungal growth, 49 (81.6%) *Candida albicans*, *Candida tropicalis* 6 (10%) and *Cryptococcus laurentii* 5 (8.3 %). The NG-tube culture revealed 100% bacterial growth *Staphylococcus aureus* 8 (13.3%), *Streptococcus pneumonia* 5 (8.3%), *Klebsiella pneumonia* 25 (41.6%), *Klebsiella oxytoca* 2 (3.3%), *Acinetobacter baumannii* 12 (20%), *Pseudomonas aeruginosa* 3(5%) and *Pseudomonas putida* 2 (3.3%). 42 (70%) of patients were received antifungal drug (fluconazole), 34 (80.9%) of them are showing improvement while 8 (19%) didn't show improvement. From the 18 (30%) pacients who didn't received treatment, 3 (16.6%) of them showed improvement, while 15 (83.3%) didn't exhibit any improvement.

Conclusion. Bacterial pneumonia with mycotic co-infection in neonates with septicemia may lead to an increase in the mortality rate. During this study, using antimycotic medications led to a drop in the mortality rate to zero.

Keywords: Neonatal septicemia, Neonatal pneumonia, Sepsis, Mycotic infection

INTRODUCTION

Neonatal septicemia continues to be the most critical issue in neonatal intensive care, leading to substantial morbidity and mortality [1]. Common pulmonary consequences linked to severe septicemia include acute hypoxic respiratory failure, acute respiratory distress syndrome, and acute lung damage [2]. Respiratory tract infections acquired in nosocomial settings are common and lead to significant demand for medical resources for healthcare systems. The most common illness acquired in an intensive care unit (ICU) is pneumonia [2,3]. The technical challenges in obtaining samples from the lower airways of newborns may make it impossible to identify the causative microorganisms definitively [4] Neonate cough ability is inhibited in the early life of neonate; instead, in the case of pneumonia, sputum Swallowed by neonates and aspiration of the gastric continent after overnight sample can reflect the causative microorganisms of pneumonia [5]. Invasive fungal infections (IFIs) are severe medical conditions that occur with greater frequency in

Corresponding author:
Salman Khalid Salman
E-mail: sal22m0006@uoanbar.edu.iq

Article History:
Received: 24 April 2024
Accepted: 28 June 2024

susceptible populations, including individuals with compromised immune systems and critically ill patients (such as those with hematologic disorders, undergoing transplantation, or in intensive care units), as well as neonates receiving care in neonatal intensive care units [6].

The risk factors for invasive Candida infections in neonatal patients differ from those observed in older children. Congenital pulmonary candidiasis, an apparent infection at birth or shortly after, has also been documented [7].

Administering appropriate antifungal therapy and providing supportive care are crucial for successfully treating neonatal candidiasis. Additionally, preventive measures should be implemented to minimize the risk of invasive candidiasis (IC) [8].

The use of prophylaxis is one method for preventing invasive candidiasis. Clinical practice and guidelines both endorse the prophylactic use of systemic antifungal agents in nurseries with a high incidence of invasive candidiasis (>10%) to enhance patient outcomes. Increased utilization of fluconazole is observed in preventing invasive candidiasis in very low birth weight neonates [9].

Infants who are admitted to the neonatal intensive care unit (NICU), especially those born prematurely, exhibit significantly elevated rates of nosocomial [10]. The prevalence of nosocomial infections in the NICU is estimated to be around 30%, contributing to as much as 40% of documented neonatal mortalities in underdeveloped nations [11].

MATERIAL AND METHODS

Samples collected

A retrospective study has been conducted at Al-Ramadi Teaching Hospital for maternity and children on 66 newborns who were admitted to the neonatal intensive care unit (NICU) due to septicemia From November 2023 to March 2024. The parents were requested to grant permission for the research to be carried out on their newborn's investigation without interfering with their care, and they consented. A pediatrician made the diagnosis. The name, age, gender, address, and medical history of each patient were collected.

Due to insufficient data collection, six newborns have been excluded from the study.

Blood samples

A blood sample was drawn for a complete blood count (CBC), C-reactive protein (CRP), serum albumin, and bacterial culture to confirm septicemia. The WBC parameters were determined with a Sysmex XN-350 [12]. The serum levels of CRP and albumin were measured using the COBAS C 111 automated photometric technique.

For optimal culture performance, two samples of five ml of blood were inoculated directly into the BacT/ALERT container using an aseptic manner for aerobic and anaerobic conditions, as described in the reference procedure [13]. Positive growth was cultivated in differential media to examine colony shape, and Gram's stain was employed to distinguish between Gram-positive and Gram-negative organisms. The VITEK 2 system (bioMérieux) was used to identify and confirm susceptibility.

Nasogastric tube (NG) Culture

The feeding NG tubes that were inserted into the neonate's stomach early in the morning were flushed with a 1-ml saline solution prior to feeding. The solution was then cultured to detect bacteria and fungi [5]. The positive culture and sensitivity growth were confirmed by the VITEK 2 system for Identification and susceptibility for bacteria and Identification only for fungi.

Urine culture

Urine samples were collected from neonates to ensure that the agents responsible for septicemia were identified; the results were insignificant according to the criterion for urine culture [14].

Statistical analysis

Data analysis was carried out using the available statistical package of IBM SPSS-29 (IBM Statistical Packages for Social Sciences- version 29, Chicago, IL, USA). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The significance of the difference of different percentages (qualitative data) was tested using the Pearson Chi-square test (x2-test) with the application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P value was equal to or less than 0.05.

RESULTS

All 60 newborns diagnosed with septicemia were immediately admitted to the Neonatal Intensive Care Unit (NICU) upon birth, accounting for 100% of the cases. The nasogastric tube (NG) was the primary way to provide all infants with nutrition. The age mean was (Mean ± SD 9.2±6.2), male 28 (46.7) while female 32 (53.3). the very low birth weight (VLBW) <1500 gm was 9 (15%), >1500 gm 51(85%) (Mean ± SD 2062.5±662.2 gm). The periods of pregnancy were premature <36 weeks 22 (36.7%) while full-term ≥36 weeks 38 (63.3%), the number of positive blood cultures was 28 (46.7%) while the negative blood cul-

ture was 32 (53.3), fungal culture for blood was negative for all samples. The total white blood cell count (WBC) (Mean ± SD 8547.0±5884.5 cell/mm^2), Neutrophil (Mean ± SD 5071.0 ± 4384.9 cell/mm^2), C-reactive protein (CRP) (Mean ± SD 39.3 ± 26.0 mg/l), and Albumin (Mean ± SD 2.9 ± 0.2 g /dl). (Table 1)

Positive bacterial blood culture

28 (46.7%) were confirmed by positive blood culture The pathogens responsible for septicemia included *Staphylococcus aureus* 8 (28.6%), *Staphylococcus hemolyticus* 1 (3.6%), *Klebsiella pneumonia* 13 (46.4%), *Klebsiella oxytoca* 1(3.6%), and Acinetobacter *bumannii* complex 5 (17.9%).

NG culture results

The findings of the NG tube culture for all 60 samples (100%) revealed the presence of different types of bacterial species. Among them, 21.6% were Gram-positive and 78.4% were Gram-negative *Acinetobacter baumannii* 12 (20%), *Staphylococcus aureus* 8 (13.3%), *Streptococcus pneumoniae* 5 (8.3%), *Klebsiella pneumonia* 25 (41.6), *Klebsiella oxytoca* 2 (3.3), *Enterobacter aerogenes* 3 (5%), *Pseudomonas aeruginosa* 3(5%) and *Pseudomonas putida* 2(3.3) for fungal culture of NG tube 60 (100%) show positive growth also *Candida albicans* 49(81.7%), *Candida tropicalis* 6 (10%) and *Cryptococcus laurentii* 5 (8.4%). (Table 2)

Resistance pattern of bacteria isolated from blood

All bacterial species isolated were sensitive to Colistin, ciprofloxacin, and trimethoprim-sulfamethoxazole. while resistant to Ampicillin, Piperacillin/Tazobactam, Cefazolin, Cefoxitin, Ceftazidime, Ceftriaxone, Cefepime, Imipenem, Amikacin, and Gentamicin, Levofloxacin, Tigecycline, Nitrofurantoin,

Resistance pattern of bacteria isolated from NG-Tube

All bacterial species isolated were sensitive to Colistin, ciprofloxacin, and trimethoprim-sulfamethoxazole. while resistant to Ampicillin, Piperacillin/Tazobactam, Cefazolin, Cefoxitin, Ceftazidime, Ceftriaxone, Cefepime, Imipenem, Amikacin, and Gentamicin, Levofloxacin, Tigecycline, Nitrofurantoin.

DISCUSSION

In August and September, there was a rise in the mortality rate of newborns diagnosed with septicemia at Ramadi Teaching Hospital for Maternity and Children (9 patients died from a total of 20) despite the administration of antibiotics that were compatible with the results of the susceptibility test conducted using the VITEK2 (bioMérieux) device. Ciprofloxacin and Colistin are recommended in case of antimicrobial resistance bacteria (AMR) infections [15]. The purpose of the investigation was to determine whether or not a bacterial cause of septicemia contributed to mortality.

Out of the 60 patients included in this study, 28(46.7%) were confirmed diagnosed with septicemia by positive blood culture, while fungi cultures

TABLE 1. Demographics and microbiology relating of early- and late-onset sepsis

		Age(day)		Total	P Value
		1-3 n(%)	4-29 n(%)		
Gender	Male	13(52)	15(42.8)	28	0.484
	Female	12(48)	20(57)	32	
Weight	≤ 1500 gm	4(16)	5(14.2)	9	0.855
	≥ 1500 gm	21(84)	30(85.7)	51	
NICU	General NICU	19(76)	14(40)	33	0.006
	Inborn NICU	6(24)	21(60)	27	
Pregnancy periods	full term ≥36 weeks	14(56)	24(68.5)	38	0.319
	premature < 36 weeks	11(44)	11(31.4)	22	

*Significant difference between percentages using Pearson Chi-square test (x2-test) at 0.05 level

TABLE 2. The association between the use of Fluconazole and the improvement of patient

		Improvement after therapy		Total	P Value
		Yes n (%)	No n (%)		
Fluconazole use	Yes	34(91.8)	8(34.7)	42	0.000*
	No	3(8.8)	15(65.2)	18	

*Significant difference between percentages using Pearson Chi-square test (x2-test) at 0.05 level

were negative. These results agree with a study performed in Iraq [16]. The susceptibility test showed that Ciprofloxacin, trimethoprim-sulfamethoxazole, and Colistin.

The level of C-reactive protein (CRP) was elevated. The level of CRP began to increase 10-12 hours after infection and reached its highest point at 48 hours [17-19]. Elevated C-reactive protein (CRP) levels can also occur in cases of newborn pneumonia caused by fungal and bacterial infections [20,21].

Albumin (Alb) is the primary protein produced by the liver and found in the blood. It is commonly used as an indicator of nutritional condition [22].

However, other investigations have provided evidence that alb. is a reliable marker of inflammation, indicating its presence in a negative manner [23-25].

Studies indicate that a low WBC count frequently characterizes neonatal septicemia [12,26,27]. The calculated WBC mean was (8547±5884.5 cells/mm^2), which indicates that the infections detected were not exclusively septicemia and that the count of CBC levels could be attributed to other causes [28,29].

An NG-tube aspiration in the morning before implanting it for nutrition can reveal sputum swallowed overnight by premature and critically ill infants. Since an NG-tube is an alien object, a nosocomial biofilm may grow after 24 hours [30].

This study showed that all 60 (100%) of the patients' aspiration had a significant presence of bacteria and yeast; a study conducted in Denmark revealed that NG tube aspiration exhibited high bacterial concentrations from the first day of use [5]. The rising prevalence of antimicrobial- resistant bacteria, becoming more commonly linked to hospital-acquired infections [31], substantially strains healthcare systems and carries considerable economic implications worldwide [32].

60 newborns had higher yeast counts in their NG-tube cultures. *C. albicans* is responsible for 70% of fungal infections globally and is the primary cause of mucosal and systemic infections [33]. Candida pneumonia appears to have two types. Primary *Candida pneumonia* after oropharyngeal debris aspiration is rare. Due to pulmonary candidiasis, secondary *Candida pneumonia* is more common [34].

According to the relation between age and site of admission (general NICU and inborn NICU) (P = 0.006), this may be interpreted as the patients in general NICU have already been contaminated with mycotic infections.

Although Ciprofloxacin and Colistin were used as the first line of drugs by the physician, the mortality rate still didn't change, also the sensitivity pattern of bacteria isolated from blood was the same as that isolated from NG-tube, for this reason, antifungal drug was used for trail (Fluconazole) for all patients this lead to drop of mortality during study period [35,36], this reveal that neonatal septicemia may lead to increase severity of fungal infections.

Fluconazole dose was given 3mg\kg intravenously every 48 hr. in combination with suitable antibiotics for 42 neonates. Table 2 shows the relationship between the use of Fluconazole and improvement (P = 0.000); this may interpret the dropping in death during the study period. Many research have examined fluconazole as a prophylaxis. Evaluations showed a lower incidence of colonization, outbreaks, morbidity, and mortality in the NICU [37–40].

3 (16.6%) patients who did not receive fluconazole drug were admitted to inborn NICU showed improvement. This may be due to the typical development of fungal growth in the gastrointestinal tract (GIT).

CONCLUSION

Bacterial pneumonia with mycotic co-infection in neonates with septicemia may lead to an increase in the mortality rate. During this study, using antimycotic medications led toa drop in the mortality rate to zero.

Conflict of interest: none declared
Financial support: none declared

Disclosure: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Ethical Approval:
This study was approved by the Medical Ethics Committee of the University ofAl-Anbar Governorate in Ramadi, Iraq, following the Helsinki Declaration (of 1975, revised in 2013).
All research participants, including patients and their parents, provided signed informed consent

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