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Identification ofBacterial Resistance Pattern andAntimicrobial Drug Use inNeonatalSepsis in a Tertiary Hospital: An Egyptian Rural Experience.

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Abstract
Background*:In neonates, it is very important to determine different antibiotics used and the antibiotic resistance pattern in each hospital in order to made guidelines used in treatment of different cases of neonate's illness.*
Aim *:Is to correlate between antibiotics really used in treatment of different neonatal illness and the adherence of that with the guidelines provided by ministry of health and population in order to avoid antibiotics resistance.*
Subjects and methods:*Prospective cross sectional observational study was conducted on 80 neonates infants admitted to pediatric intensive care unit in Tertiary Hospital with sepsis , respiratory distress or pneumonia.*
Results*:15% of cases were inconsistent empirical antibiotics used with culture results and 85% of caseswere consistent with culture results .The mostly used empirical antibiotic combination was Vancomycin plus Cefotaxime by a percent of 56.3% with success rate 93.3% and failurein 6.7% of cases .*
Conclusion:*we concluded thatthe antibiotic susceptibility pattern in this study suggested that, initial empirical choice of vancomycin in combination with cefotaxime was the most appropriate as maximum isolates were sensitive to either vancomycin or cefotaxime.*

Keywords: ***Neonate, Antibiotics, Drug Resistant***

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I. Introduction

The bacteria most commonly responsible for early-onset (materno-fetal) infections in neonates are group B streptococci, Enterococci, Enterobacteriaceae and Listeria monocytogenes are the most commonly bacteria responsible for early-onset infections in neonates [1][2]**.**Coagulase-negative staphylococci, particularly Staphylococcus epidermidis, are the main pathogens in late-onset (nosocomial) infections [3]**.**

Combination therapy is recommended for initial empirical treatment ampicillin plus an aminoglycoside. Ampicillin plus a third-generation cephalosporin is also an alternative as empirical therapy. Triple combination therapy (such as Amoxicillin plus Cefotaxime and Aminoglycoside) could also be used for the first 2 to 3 days of life [4]**.**

When antibacterial are used in neonates, accurate determination of dosage is required, particularly for compounds with a low therapeutic index and in patients with renal failure. Very low birthweight infants are also particularly prone to antibacterial-induced toxicity [5]**.**

The duration of therapy relies upon the culture results just as the initial response to therapy. In most of newborn children evaluated for sepsis, culture results will be negative after 48 hours. At that time, if the child appears well and infection was an unlikely cause of original symptoms, antibiotics may be discontinued. However, if the clinical condition of the infant remains unstable and a strong suspicion of sepsis still remains despite negative cultures, a longer course of antibiotics is appropriate. If cultures are initially positive, repeat cultures should be sent after48hours of starting appropriate therapy to assess the response to therapy[6].

Antibiotic resistance pattern is ascending to perilously significant levels in all over the world. New resistance mechanisms are rising and spreading universally, compromising our capacity to treat the common present infections. A developing rundown of contaminations , threatening our ability to treat common infectious diseases. A wide list of infections as pneumonia, blood poisoning ,tuberculosis, gonorrhoeae, and foodborne

diseases are becoming challengeable and in sometimes impossible, to treat as antibiotics become less effective.[7]

The aim of this study is to correlate between antibiotics really used in treatment of different neonatal illness and the guidelines provided by ministry of health and population in order to avoid antibiotics abuse and resistance. Also is to record the rate of bacterial resistance and antibiotics sensitivity in this hospital.

PATIENTS AND METHODS

This prospective cross sectional observational study.The present study was conducted at pediatric intensive care unit of Shobrakheethospital; during a period of from 1/6/2018 to 30/4/2019.80 infants admitted to pediatric intensive care units with sepsis , respiratory distress or pneumonia after 48 hours of hospitalization .Pneumonia was diagnosed by new onset of fever, cough, respiratory distress, leukocytosis, opacity in x ray and positive sputum culture [8]**.**Ethical committee approval obtained from Ethics committee of Faculty of Pharmacy, Damanhour University.

All patients were subjected to history taking including age, sex, residence, time of onset of complaint.Clinical examination to detect manifestations of pneumonia as fever, tachypnea and respiratory distress.Auscultation of the chest to detect decreased breath sounds, bronchial breath sounds, crepitation and wheezing.Laboratory investigations include blood sample forculture and sensitivity was obtained.

Statistical analysis:

Analysis of data was done using Statistical Program for Social Science version 20 (SPSSInc., Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation . Qualitative variables were described as number and percent. Qualitative variables were compared using chi-square (X^2) test with Yates correction. P value < 0.05 is considered significant.

II. Results

The mean age of the studied group is (12±1.3) days with range of (1-28) day, males' percent 61.3%and female percent 38.7%. 6.3% of infants had septicemia, 52.5% had pneumonia and 41.2% had respiratory distress (Table 1). That *Staphylococcus aureus* represented 15% of cases, *Klebsiella pneumoniae*represented 13.8%, *Alpha-hemolyticstreptococci* represented 1.3%, *Enterococcus faecalis* represented 5%, *Acinetobacter baumannii*represented 1.3%, *E.coli* represented 1.3% and *Candida species* represented 1.3%. . There is no significant relation between diagnosis and type of organism or the gender . In this study, resistant specimen were present in 27.9% of amikacin, 21.5% of amoxicillin/clavulanic, 31.2% of ampicillin, 20.8% of ampicillin/sulbactam, 9% of azithromycin, 26.6% of cephadroxil, 21.8% of cefepime, 26.9% of Cefoperazone, 22.1% of Cefoperazone/sulbactam, 22.8% of Cefotaxime, 25.3% of Cefoxitin, 24.1% of Ceftazidime, 22.8% of Ceftriaxone, 26.9% of cefuroxime.sod, 29.5% of Ciprofloxacin, 2% of Clarithromycin, 10.5% of Clindamycin, 4.5% of Colistin, 28.9% of Doxycycline, 20.8% of Ertapenem, 10.3% of Erythromycin, 2% of Fosfomycin, 5.6% of fusidic acid, 30.8% of Gentamycin, 16.7% of Imipenem, 16.7% of Levofloxacin, 9% of Lincomycin, 17.7% of Linezolid, 32.1% of Meropenem, 32.1% of Minocycline, 16.7% of Moxifloxacin, 2% of nalidixic acid, 2% of Nitrofurantoin, 2% of Norfloxacin, 21.5% of Ofloxacin, 2% of Polymyxin, 22.8% of Rifampicin, 17.7% of tazobactam/piperacillin, 31.6% of Teicoplanin, 35.9% of Tigecycline, 31.6% of Tobramycin, 28% of trimethoprim/sulfamethoxazole and 18.9% of Vancomycin specimen (Figure 1)

Table 4 shows that 15% of cases were inconsistent empirical with culture and 85% of cases consistent empirical with culture.The mostly used empirical antibiotic combination was Vancomycin +cefotaxime by a percent of 56.3% which achieved success in 93.3% and failure in 6.7% of cases(Table 5).

Table (1) Demographic characters of the studied patients .

Demographics	**No = 80 Patients (%)**
Age (in days)	
Mean ±SD	12±1.3
Range	1-28
Gender	
Male	61.3%
Female	38.7%
Diagnosis	
Septicemia	5 (6.3%)
Pneumonia	42(52.5%)
Respiratory distress	33 (41.2%)

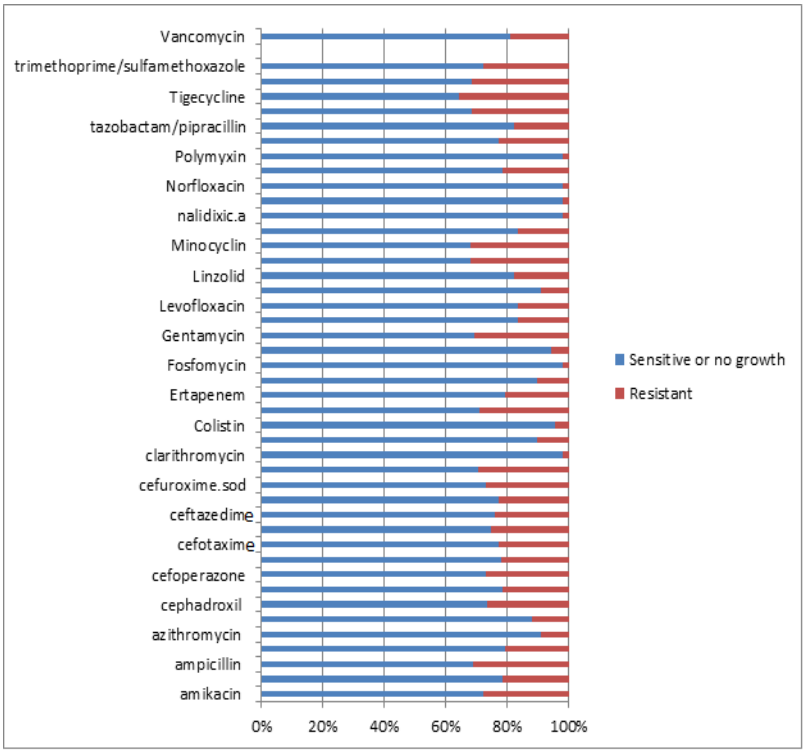

Fig.(1)Antibiotics susceptibility and resistancein this study

Table (2)Relation between diagnosis and type of organism:

The diagnosis / **Type of The organism**	**Pneumonia** N=42		**Septicemia** N=5		**Respiratory distress** N=33		χ^2	**P value**
No growth	27	64.3	3	60	19	57.6	9.45	0.801 (NS)
Staphylococcus aureus	6	14.3	2	40	4	12.1		
klebsiella pneumoniae	4	9.5	0	0	7	21.1		
Alpha-hemolyticstreptococci	1	2.4	0	0	0	0		
Enterococcus faecalis	2	4.8	0	0	2	6.1		
Acinetobacter baumannii	1	2.4	0	0	0	0		
E.coli	1	2.4	0	0	0	0		
Candida species	0	0	0	0	1	3		

Table (3)Relation between diagnosis and gender:

The diagnosis	**Male (N=49)**		**Female (N=31)**		χ^2	**P value**
Septicemia	2	4.1	3	9.7	9.45	
Pneumonia	23	46.9	19	61.3		0.801 (NS)
Respiratory distress	24	49	9	29		

Table (4)Consistency of empirical drugs with culture.

Antibiotics	**No. of cases**	**Outcome**		**X2**	***p* value**
		Success	**Failure**		
Inconsistent empirical with culture -Resistance - Still unstable - Unknown cause	**12(15%)** **9** **2** **1**	5 (41.7 %)	7(58.3%)	19.4456	<0.0001*
Consistent empirical with culture	**68(85%)**	64(94.1%)	4(5.9%)		

Chi-square test with Yates correction
Significant at p <0.05

Table (5)Empirical antibiotics used in this study

Antibiotics	N (%)	Success	Failure	X2	*p*
Vancomycin + Cefotaxime	45(56.3)	42(93.3)	3(6.7)	4.2079	.04*
Vancomycin + Cefepime	2(2.5)	1(50.0)	1(50.0)		
Vancomycin + Meropenem	3(3.75)	3(100.0)	0(0.0)		
Ampicillin/sulbactam + Amikacin	6(7.5)	4(66.7)	2(33.3)		
Ampicillin/sulbactam + Cefotaxime	4(5)	3(75.0)	1(25.0)		
Vancomycin+Meropenem + Ciprofloxacin	11(13.75)	8(72,7)	3(27.3)		
Vancomycin+Meropenem +Cefotaxime + Metronidazole	2(18.2)	2(100.0)	0(0.0)		
Vancomycin+ Meropenem + Ciprofloxacin + Linezolid	1(9.1)	1(100.0)	0(0.0)		
Vancomycin +Azithromycin+ Cefotaxime + Metronidazole	2(18.2)	1(50.0)	1(50.0)		
Vancomycin +Cefotaxime + Ciprofloxacin + Ampicillin/sulbactam	1(9.1)	0(0.0)	1(100.0)		
Vancomycin +Cefaclor	1(9.1)	1(100.0)	0(0.0)		
Ampicillin/sulbactam + Amikacin +Cefotaxime	1(9.1)	1(100.0)	0(0.0)		
Ampicillin/sulbactam +Amikacin +Cefotaxime+ Ciprofloxacin	1(9.1)	0(0.0)	1(100.0)		
Colistin	1(9.0)	1(100.0)	0(0.0)		
Empirical antibiotic and antifungal	9(11.2)	7(77.8)	2(22.2)		
Total	80	68(85.0)	12(15.0)		

Chi-square test with Yates correction to compare between vancomycin + cefotaxime and others
Significant at p 0<0.05

III. Discussion

Sepsis occurs in about 1-2% of all hospitalizations and accounts for more than 25% of intensive care unit (ICU) bed utilization[9]**.**Neonatal **s**epsis continues to be a major problem in the neonatal intensive care unit (NICU) worldwide. Sepsis in preterm infants is an important cause of morbidity and mortality. The risk of sepsis increases with lower gestational age and weight[10] **.**Neonatal sepsis is a dangerous clinical syndrome characterized by both systemic clinical signs of infection and bacteremiawithin the first month of life [11]**.**

Sepsis stays a main source of mortality and morbidity, particularly during the initial five days of life in developing countries [12]**.** Hospital infection also stays a significant reason of death ininfants regardless of progressexperienced in the most recent decades. World health organization (WHO) recommends ampicillin or cloxacillin especially staphylococcal infection is suspected plus gentamicin as empiric treatment of neonates with suspected clinical sepsis when referral is not possible. Once daily gentamicin plus oral amoxicillin can be used. However, in many countries, broader spectrum antibiotics as third generation cephalosporins, were commonly used to treat neonatal sepsis[13].

Against this foundation, concerns are expanding in regards to bacterial pathogens with decreased susceptibility to empiric medication with variations both between and within in developing and low income countries [14]**.**

The WHO tries to give a pediatric point of view on antimicrobials to be included on the list of essential drugs. The potential need to reconsider the current WHO guidelines dependent on new antimicrobial resistance (AMR) information or evidence relating to safety of these drugs in neonates and infants must be assessed. For this reason, various review have been commissioned to address these viewpoints [15].

That is why the study was selected to be conducted to correlate between antibiotics really used in treatment of different neonatal illness and the guidelines provided by ministry of health and population and how to avoid antibiotics abuse and drug resistance the study was conducted at Shobraakheet hospital.

Our ability to perceive the need to start or end the antibiotic use is limited. Results of blood cultures might be negative because of past antibiotic exposure, low colony count sepsis, and difficulty in obtaining a suitable amount of blood requiring for culturing. Without positive culture results, continuation of antibiotics is often based on concern regarding the consequences of inadequate treatment, a careful decision that can easily lead to varied opinions among qualified neonatologists.

Our study shows that Out of the 80 patients, mean age of the studied group is (12±1.3)days with range of (1-28) day. Males percent 61.3% and female percent 38.7% .Also there is insignificant relation between the incidence of neonatal illness and different sex and this are matched with study conducted by **Kabwe et al., 2016 ,** who reported that out of 313; 54% (170/313) of the neonates were male and also found no correlation between sex and the incidence of neonatal sepsis [16]. And this previous results was on the contrary with study of **Verma et al.,(2015)[17]**whoreported thatthe incidence of male :female was 65.27%:34.72%; male: female ratio was 1.87:1. Neonatal septicemia was found to be more common in males. The factors regulating the synthesis of gamma globulin are probably situated on X chromosomes in the male infants thus confers less immunological protection compare to female counterpart [18]**.**

The present study showed that 6.3% of children had septicemia, 52.5% had pneumonia and 42.1% had respiratory distress. Also, regarding causative organism *Staphylococcus aureus*was the most common represented 15% of cases followed by *klebsiella pneumoniae* represented 13.8%, Alpha-hemolytic streptococci

represented 1.3%, *Enterococcus faecalis* represented 5%, *Acinetobacterbaumannii*represented 1.3%, E.coli represented 1.3% and Candida species represented 1.3%.

This agreement with study conducted by**Sharmaetal.,(2013**)the most common organism isolated was *Staphylococcus aureus* (37.22%) followed by *Klebsiella pneumoniae* (27.01%) and *Escherichia coli* (19.70%). The gram-positive organisms except *Streptococci* displayed a high degree of resistance to most penicillin's and ciprofloxacin but were sensitive to vancomycin, amikacin and cefepime[19].

Most of the studies have found a preponderance of gram-negative organisms like *klebsiella, pseudomonas*, and *Enterobacter species*[20]**.** However, *staphylococcus* was the commonest gram-positive organism to be isolated in most of the studies [21].

In western countries, Group B streptococcus is mainly responsible for neonatal sepsis,CoNS are usually associated with indwelling catheters or central lines[22]..All of them were sensitive to vancomycin only. Similar findings were reported by a study in Nepal [23]**.**

Klebsiella pneumoniae was the most common gram-negative organism (13.8%) and the second most frequent after staphylococcus aureus in the study. This finding is not in accordance with **Rajaratnam et al.,2010** data, where the most common organisms causing neonatal sepsis was klebsiella pneumoniae followed by staphylococcus aureus and pseudomonas[24] .

In this study, Amikacinresistant specimen presented in 27.9% of cases followed by 21.5% of cases were resistant to amoxicillin/clavulanic, 31.2% of ampicillin, 20.8% of ampicillin/sulbactam, 30.8% of Gentamycin, 31.6% of Tobramycin and these results were resistant to the recommendation of WHO first and second line antimicrobials used in neonatal sepsis .

Almost all the isolates in our study were sensitive to vancomycin in combination with cefotaxime and hence a co-prescription of these two antibiotics appear prudent as the initial choice while waiting for the blood culture reports. This combination has given us the best results in our neonatal intensive care unit. This agreement with study conducted by**Sivanandan et al.,2011** who revealed that Vancomycin and third-generation cephalosporinshould be considered for sepsis in a neonate [25].

Also, a similar study of **Cailes et al.,2018** concluded that a combination of vancomycin and cefotaxime displayed coverage of 92% of isolates tested while flucloxacillin and gentamicin covered 89% .Amoxicillin and clavulanic acid provided significantly lower coverage than any other tested combination[26].

Whereas**Sharmaetal.,(2013**) reported that all the isolates were resistant to penicillin. Ampicillin, gentamicin & ciprofloxacin had lowest sensitivity to all bacterial isolates. Highest sensitivity was recorded with meropenem and vancomycin followed by amikacin and cefepime. Vancomycin and meropenem showed sensitivity of 100%[19].

As far as cephalosporins are concerned, moderate sensitivity was observed for third generation cephalosporins i.e., cefotaxime while higher sensitivity was documented for fourth generation cephalosporins i.e. cefepime.

Tallur et al., (2000) concur with us that most isolates were resistant to ampicillin, gentamicin and cotrimoxazole[27].Only very limited reliable data on antimicrobial susceptibility are available from Asia, Latin America and Africa. From existing summaries of the data, it is evident that considerable antibiotic resistance is observed to many commonly used antibiotics with variations both between and within regions[28]**.**

There are several limitations in this study. the sample set was relatively small, and the observation period was short. Further long-term studies with larger sample sizes will be needed for a more accurate result .

In conclusion, Neonatal infection is a leading cause of neonatal admissions, morbidity and mortality in developing countries. Bacterial spectrum for sepsis could be different in different regions. Sensitivity pattern also differs accordingly. The antibiotic susceptibility pattern in our study suggested that, initial empirical choice of vancomycin in combination with cefotaxime was the most appropriate as maximum isolates were sensitive to either vancomycin or cefotaxime.

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Availability of data and materials

Please contact author for any data requests.

Competing interests

The author declares that there are no competing interests

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