Neonatal Sepsis: A Two-Year Review of the Antibiograms of Clinical Isolates from the Neonatal Unit

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Background: Neonatal Sepsis is one of the leading causes of morbidity and mortality in Neonatal Intensive Care Units. Identifying the most common organisms and their susceptibility patterns improve the management of infections.

Objective: To evaluate the incidence of Neonatal Sepsis and to identify the most common organisms, their sensitivity patterns to antimicrobials and to formulate future empiric therapy for patients.

Design: A Retrospective Study.

Setting: NICU, King Hamad University Hospital, Bahrain.

Method: Patients admitted to the NICU from 1 July 2013 to 30 September 2015 were reviewed. Sixty-seven patients with positive blood cultures were suspected to have sepsis. Early Sepsis, 18 (26.9%) and late Sepsis, 49 (73.1%), were included in the study. Patients with contaminated blood cultures, cultures with mixed growth and those have been referred from other hospitals with external blood culture reports were excluded.

The following data were documented: culture and sensitivity, antibiotics used, neonatal and maternal risk factors and severity of sepsis and the outcome.

Result: Sixty-seven neonates were included in the study, 34 (50.7%) were males. The incidence of early onset neonatal sepsis compared to late onset neonatal sepsis was 26.8% and 73.1%, respectively. The most common pathogenic organism was Coagulase-Negative Staphylococci (CONS) in 32 (47.7%) neonates, followed by gram-negative bacilli in 17 (25.4%) neonates.

Coagulase Negative Staphylococci species were susceptible to Tazocin and Linezolid. The gram-negative bacilli were mainly sensitive to Amikacin and Imipenem along with Tazocin. All Group B Streptococcus cultures were sensitive to Ampicillin compared to approximately 57 (85%) only being sensitive to Vancomycin, Linezolid and Penicillin.

Conclusion: This is the first study in our NICU. The study revealed the organisms seen in the unit, their sensitivity patterns and the antibiotics used compared to what should be used. This study provides a foundation to improve the standard of care for neonatal Sepsis.

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Sepsis is stressful for a neonatologist. It is the leading cause of neonatal deaths and morbidity and contributes to nearly 50% of the neonatal mortality in developing countries[1,2,3]. The neonatal sepsis pathogens and their antimicrobial susceptibility patterns vary between different units and it changes over time. Therefore, the choice of empiric antibiotic therapy, which is a lifesaving treatment in critical cases, should be guided by the local epidemiology. Safe prescription practices will optimize the treatment, reduce antibiotic toxicity and the emergence of resistant organisms[1,2,3,4].

Retrospective studies reviewed the microbiological spectrums of neonatal intensive care units (NICU) and presented the antibiogram unique to those clinical settings. These studies have examined body samples, such as blood, CSF, urine, respiratory secretion, skin swabs and stool; they included both early and late onset neonatal sepsis cases[1,2,3,4].

Multiple reviews recommended strategies for safe antimicrobial practices specific to the neonatal critical care settings; the aim was to enhance the therapy and clinical prognosis while reducing the complications of drug toxicity and microbial resistance[5-13].

In Bahrain, there is a lack of evidence nationally and regionally (GCC countries) regarding the neonatal sepsis and reports of

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antibiotics resistance and sensitivities. This gap of knowledge forms an obstacle to neonatologists faced with empiric antimicrobial decisions.

The aim of the study is to evaluate the microbiological profile of the suspected neonatal sepsis cases and their antibiogram in the NICU.

METHOD

Sixty-seven neonates who were admitted to the NICU from 1 July 2013 to 31 September 2015 and who have had a positive blood culture were included in the study. Neonates with contaminated blood cultures that showed mixed growth of organisms with no clinical evidence of sepsis and neonates who were referred from other hospitals with external reports of blood cultures were excluded from the study.

The data was compiled on Microsoft Excel and analyzed using the SPSS software.

Each culture was categorized as early or late onset sepsis; the antibiogram, the antibiotic used and any modification after culture report, outcome and survival were documented. The following were recorded: age, birth weight, type of milk consumed, total parenteral nutrition and the presence of central line (PICC, UVC, UAC); leukocytosis (white cell count > 15,000), positive C-reactive protein (if > 10 or trending upwards), thrombocytopenia (platelet count < 150) and any correlation with cultures from other sites (urine, CSF, other body fluids); platelet transfusion, glucose disturbance (hypoglycemia or hyperglycemia), fresh frozen plasma or packed red blood cells transfusion, seizures, respiratory support (noninvasive ventilation or invasive ventilation), circulatory compromise (inotropic support, fluid boluses, hydrocortisone); maternal positive cultures, use of antibiotics before delivery, rupture of membranes and fever before delivery.

RESULT

Sixty-seven neonates with positive blood cultures were included in the study. Eighteen (26.8%) patients had early neonatal sepsis (presented at age of <72 hours of age), while 49 (73.1%) patients had late neonatal sepsis (age of >72 hours of age). The gender distribution of the studied sample was nearly equivalent, with 34 (50.7%) females and 33 (49.2%) males. The mode of delivery was spontaneous vaginal birth for 31 (46.2%) cases and cesarean section for 36 (53.7%). The majority of neonates had normal birth weight, 22 (32.8%). Equal proportions of patients were classified as term (> 37 weeks) and very preterm (28-31 weeks); both categories had 21 (31.34%) patients. Most patients survived until discharge from NICU. However, seven (10.4%) neonates died in the unit. Thirty-two (47.8%) cases were coagulase-negative staphylococci and 17 (25.4%) cases had gram-negative rods. Staphylococcus epidermidis and Staphylococcus hemolyticus were the most commonly encountered bacteria in the septic neonates' blood cultures.

All group B Streptococcus (GBS) cultures were sensitive to ampicillin, whereas 57 (85%) were sensitive to Vancomycin, Linezolid and Penicillin. Despite that, our NICU clinicians used Ampicillin and Gentamicin in the majority of GBS cases before the release of the culture reports. Among the gram negative rods, most isolates were sensitive to Amikacin, followed by Imipenem and Tazocin. However, the clinicians' choices were mostly Vancomycin, Meropenem, Amikacin and Cefotaxime.

All of the coagulase-negative staphylococci were sensitive to Tazocin and Linezolid. However, the NICU clinicians used mostly ampicillin and Meropenem (resistant), as well as Vancomycin and Cefotaxime (sensitive). Many coagulase-positive staphylococci were sensitive to Vancomycin, Linezolid and Rifampicin. Finally, the gram-positive cocci had a wide spectrum of sensitivities, mainly for Cefepime and Vancomycin; our clinicians used mostly Ampicillin, Meropenem, and Vancomycin, which were included in the sensitivity list.

Fullterm neonates are more likely to have early neonatal sepsis, whereas those born at <37 weeks gestation are more likely to have late neonatal sepsis. In addition, neonates born with a normal birth weight are more likely to have early neonatal sepsis, while those with low birthweight are more likely to have late neonatal sepsis. The total parenteral nutrition and the presence of paraphernalia are both more likely to occur in late onset sepsis. Neonates who have respiratory or circulatory compromise at the time of sepsis are more likely to have late onset sepsis as well.

Table 1 shows the following factors: culture results, antibiotics used, symptoms of chorioamnionitis and rupture of membranes in both the early and late neonatal sepsis.

Table 1: The Antibiograms of Microorganisms Causing Bacteremia

Sensitivity	Listeria (n=1)	GBS (n=7)	Gram Negative Rods (n=17)	Fungal	CONS (n=32)	Coagulase Positive (S. Aureus and S. Intermedius) (n=3)	Gram Positive Cocci (n=6)
Ampicillin							2 (33.3%)
Amikacin			16 (94.1%)				2 (33.3%)
Cefotaxime		5 (71.4%)	1 (5.8%)		4 (12.5%)	1 (33.3%)	1
Ciprofloxacin	1 (100%)	3 (42.8%)	11 (64.7%)		12 (37.5%)	2(66.6%)	2 (33.3%)
Clindamycin		5 (71.4%)			9 (28.5%)	1(33.3%)	1 (16.6%)
Erythromycin	1 (100%)	4 (57.1%)			2 (6.25%)	1(33.3%)	1 (16.6%)
Gentamicin	1 (100%)		13 (76.4%)		8 (25%)	2(66.6%)	2 (33.3%)
Meropenem			12 (70.5%)		5 (15.6%)		2 (33.3%)
Metronidazole		2 (28.5%)	3 (17.6%)		2 (6.25%)	1(33.3%)	
Levofloxacin		5 (71.4%)	13 (76.4%)		8 (25%)	1(33.3%)	2 (33.3%)
Rifampicin	1 (100%)	1(14.2%)			30 (93.7%)	3 (100%)	
Tazocin			14 (82.3%)		32 (100%)		2 (33.3%)
Vancomycin	1 (100%)	6 (85.7%)				3(100%)	4 (66.6%)
Ceftazidime			10 (58.8%)				2 (33.3%)
Ceftriaxone			8 (47 %)				2 (33.3%)
Imipenem		1 (14.2%)	14 (82.3%)		4 (12.5%)	1(33.3%)	2 (33.3%)
Oxacillin	1 (100%)				3 (9.3%)	1(33.3%)	
Linezolid	1 (100%)	6 (85.7%)			32 (100%)	3(100%)	3 (50%)
Augmentin			6 (35.2%)		4 (12.5%)	1(33.3%)	
Septrin	1 (100%)	1 (14.2%)	8 (47%)		20 (62.5%)	2(66.6%)	2 (33.3%)
Cefepime		5 (71.4%)	10 (58.8%)				3 (50%)
Penicillin	1 (100%)	6 (85.7%)					1 (16.6%)
Amoxicillin		7 (100%)					1 (16.6%)
Cefuroxime			7 (41.1%)				

Table 2: The Antibiotics Used by Clinicians in NICU in Sepsis

Antibiotic	Listeria (n=1)	GBS (n=7)	Gram Negative Rods (n=17)	Fungal	CONS (n=32)	Coagulase positive (S. Aureus and S. Intermedius) (n=3)	Gram Positive Cocci (n=6)
Ampicillin	1 (100%)	7(100%)	5(29.4%)		15(46.8%)	1(33.3%)	5(83.3%)
Amikacin			7(41.1%)		11(34.3%)	1(33.3%)	1(16.6%)
Cefotaxime		3(42.8%)	7(41,1%		15(46.8%)		2(33.3%)
Ciprofloxacin							
Clindamycin							
Erythromycin							
Gentamicin	1(100%)	5(71.4%)	4(23.5%)		9(28.1%)	1(33.3%)	2(33.3%)
Meropenem			7(41.1%)		15(46.8%)	1(33.3%)	3(50%)
Metronidazole			2(11.7%)		2(6.25%)	1(33.3%)	
Levofloxacin							
Rifampicin							
Tazocin							
Vancomycin		1(14.2%)	8(47%)		19(59.3%)	1(33.3%)	3(50%)
Ceftazidime			1(5.8%)		1(3.1%)		1(33.3%)
Ceftriaxone							
Imipenem							
Oxacillin					5(15.6%)		1(33.3%)
Linezolid							
Augmentin							
Septrin							
Cefepime							
Penicillin							
Amoxicillin							
Cefuroxime							
flucloxacillin			4(23.5%)		2(6.25%)	1(33.3%)	
Aminophylline			1(5.8%)		1(3.1%)		1(33.3%)

Table 3: Maternal Risk Factors

Variable	Early Onset Sepsis	Late Onset Sepsis
Maternal Culture	**HVS**: 18	**HVS**: 45
	Not done: 4	Not Done: 24
	Negative: 4	Negative: 6
	GBS: 8	Unknown: 3 (transferred from other hospitals, unknown history)
	Klebsiella: 0	GBS: 2
	Candida: 2	Enterococcus: 2
	Enterococcus: 1	Klebsiella: 1
	Provendcia Stuartii: 1	ESBL Klebsiella: 1
	Mixed growth out of the above: 2 patients (GBS +Enterococcus and GBS + Candida)	Pseudomonas: 1
		E. Coli: 1
		Candida: 1
		Morgnael Morgagni: 2 (twins)
		Mixed Growth out of the above : 1 (Klebsiella + Pseudomonas)
	Urine: 18	**Urine**: 45
	Not done: 4	Not Done: 24
	Negative: 10	Negative: 13
	Klebsiella: 1	E. Coli: 2
	E. Coli: 1	GBS: 1
	Candida: 1	Candida: 1
	No Mixed Growth	MRSA: 1
		Unknown: 3 (transfer from another hospital with no history)
		Mixed Growth: Nil
Maternal Antibiotic	No Abx: 12	No Abx: 36
	Clindamycin: 3	Clindamycin: 5
	Ampicillin: 2	Cefuroxime: 3
	Cefuroxime: 1	Meropenem: 2
	Metronidazole: 1	Ampicillin: 0
	Gentamicin: 1	Mixed use of Abx: 2 (Clindamycin + Cefuroxime For No C/S done AND Gentamicin + Clindamycin for -ve C/S)
	Mixed use of Abx: 2 (Metronidazole + Cefuroxime for Klebsiella +ve AND Clinda + Genta For GBS +ve)	No Abx: 36
Rupture of Membranes	PPROM: 2	PPROM: 7
	PROM: 3	PROM: 2
	SROM: 2	SROM: 6
	AROM: 2	AROM: 1
	None: 9	None: 28
		Unknown: 1 (transferred without history from another hospital)
Fever/ Chorioamnionitis	Symptoms of Chorioamnionitis: 3	Symptoms of Chorioamnionitis: 3
	Fever Only: 1	No symptoms: 42
	No Symptoms: 14	

DISCUSSION

The majority of our microbiological isolates were coagulase-negative staphylococci; the most common microorganisms were Staphylococcus epidermidis and Staphylococcus hemolyticus; this finding is similar to the microbiological study of Hsu et al[4]. We believe that most of these positive cultures are contaminated blood samples, despite the fact that these neonates were treated with antibiotics; it requires a separate study to differentiate proven sepsis in neonates with positive cultures, similar to the study performed by Osuch et al, where 91% of the positive blood cultures were classified as colonization[1].

The cumulative antibiograms of our clinical isolates were variable and different from those published in other studies. Most of our gram negative rods were sensitive to Amikacin, while most of the Group B Streptococci were sensitive to Ampicillin. The CONS had a high sensitivity to Tazocin and linezolid, but resistant to Meropenem and ampicillin. Low sensitivity of gram-negative rods to amikacin and ampicillin were observed in Ousch et al and Sharma et al[1,11]. Vancomycin and Amikacin were not good choices for CONS and Staphylococcus aureus infection in the cumulative antibiograms of Sharma et al[11].

However, there was clearly a discrepancy in the choices of antibiotics prescribed by our neonatologists and the sensitivity patterns of the microorganisms. Powerful antibiotics, such as Meropenem and Vancomycin were used frequently and unnecessarily in sepsis cases of which the culture results showed resistant microorganisms. The percentage of antibiotic modification following the result of culture (35%) was much lower than the one observed by Hsu et al (81%)[4].

Our study has several limitations. First, the retrospective design of the study can predispose to observer bias. The small study sample questions its validity, especially since its performed in one neonatal unit in a single hospital. In addition, the collection of data for the clinical course, maternal history, and regimen of antimicrobials prescribed was done through the electronic medical records. These were typed by different physicians, and varied in their length and adequacy; hence there were no objective records of what happened around the time of suspected sepsis.

Our study contributes to building a baseline of local data that can be utilized in designing an antimicrobial program. The study would help in refining the empiric antimicrobial prescription practices in the unit, reducing the emergence of resistant microorganisms, and avoiding antibiotic toxicities in the neonates. These policies once implemented would reduce the healthcare expenditure costs of unnecessary prescriptions and the expenses of sepsis complications.

CONCLUSION

Adherence to antibiotics susceptibility reports and safe prescription practices is essential to all physicians. In the future, we aim to conduct studies with narrower focus on specific groups of microorganisms like fungal infections.

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