ETIOLOGY OF NEONATAL SEPSIS IN FIVE URBAN HOSPITALS IN THE PHILIPPINES

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ABSTRACT

The most frequent cause of mortality in neonates is infections which include sepsis, meningitis, pneumonia, diarrhea and tetanus. Approximately 1.6 million deaths due to neonatal infections occur annually in developing countries. The causes of sepsis vary from one geographic area to another. Thus, it is important to create a database for the Philippines regarding the etiologies of neonatal sepsis.

Objectives: The study was undertaken to determine the most common bacterial pathogens of neonatal sepsis in the Philippines and the antibiotic sensitivity patterns of these pathogens.

Methods: A multicenter surveillance and chart review was conducted in five hospital sites for a period of six months- from July to December 2006. All neonates less than or equal to 28 days who had positive cultures from a sterile site and or had fulfilled the SIRS criteria as defined by the International Pediatric Sepsis Consensus Conference in the presence of suspected or proven infection were included in the study.

Results: A total of 289 neonates fulfilled the criteria of sepsis. More than 61% of the patients had early onset neonatal sepsis. The most common site of infection was the lungs, (57%), followed by sepsis without an obvious site of infection (35%).

In 50% of patients, an organism was identified; gram-negative bacteria were the dominant bacteria found (Pseudomonas, Burkholderia, Klebsiella) which comprised 94% of the bacteria isolated. Resistance patterns varied among the different urban study centers. The Pseudomonas and Burkholderia isolates from the Philippine General Hospital (PGH) were sensitive to ceftazidime. All Klebsiella isolates from St. Louis University (SLU) were resistant to third generation cephalosporins. In contrast, Klebsiella isolates from PGH and Davao were sensitive to third generation cephalosporins but resistant to piperacillin-tazobactam. The overall mortality rate was 11%. Ampicillin and an aminoglycoside were the most common regimens used but were only successful in less than 50% of cases.

Conclusion: Gram-negative organisms comprised the majority of the neonatal infections, with Pseudomonas and Burkholderia being the most prevalent. Resistance patterns differed among the different centers. Continuing surveillance of infections is still needed in order choose the most appropriate empiric therapy for each center.

INTRODUCTION

The most frequent cause of mortality in neonates is infections which include sepsis, meningitis, pneumonia, diarrhea and tetanus. [1] Approximately 1.6 million deaths due to neonatal infections occur annually in developing countries. Neonates are a vulnerable population due to their immature immune system. Other factors, such as being premature, being low birth weight, presence of respiratory problems, maternal infection, and delivery room manipulations further put neonates at risk for developing sepsis. The incidence of neonatal sepsis ranges from 7.1 to 38 cases/1000 live births in Asia in contrast to 1.5-3.5 cases/1000 live births in the United States[1]. The causes of sepsis vary from one geographic area to another. Thus, it is important to create a data base for the Philippines regarding the etiologies of neonatal sepsis. Since antibiotic resistance is a national, as well as, a global problem, it is also necessary to have information on the susceptibility patterns of these bacteria. This has implications with regard the choice of empiric therapy in suspected or proven cases thus giving optimal medical treatment from the start of therapy.

The three most common bacterial pathogens of the neonatal period listed in foreign literature are of Group B beta-hemolytic streptococci, *Escherichia coli,* and *Listeria monocytogenes*[2] but to date, no cases were published for group B streptococci in the Philippines. This supports data that group B streptococci are reported more frequently as a cause of neonatal sepsis in developed countries than in developing areas.[2] Previous Philippine studies on neonatal sepsis showed predominant pathogens were that of gram-negative bacilli with *Enterobacter spp.* and *Klebsiella pneumoniae* being the most common organisms isolated.[3,4,5,6,7] *Pseudomonas spp., Acinetobacter spp. a*nd *Candida spp.* were also seen but with lesser incidences.

The International Pediatric Sepsis Consensus Conference[8] revised the definitions of severe sepsis and septic shock for the pediatric population with the objective of facilitating the performance of successful clinical studies in children with sepsis. These new definitions shall be utilized in this study in order to conform to international standards and to differentiate patients suspected of sepsis from those who are truly symptomatic. Only symptomatic cases shall be included in this study.

OBJECTIVES

This study was undertaken to determine the most common bacterial pathogens of neonatal sepsis in the Philippines, the site of infection, based on clinical presentation and laboratory findings and the antibiotic sensitivity patterns of these pathogens.

MATERIALS AND METHODS

A multicenter surveillance and chart review were conducted in five hospital sites for a period of six months- from July to December 2006. The study was conducted at the Philippine General Hospital (PGH) in Manila, Philippine Children's Medical Center (PCMC) in Quezon City, St. Louis University-Hospital of the Sacred Heart (SLU) in Baguio, Davao Doctors' Hospital (DDH) in Davao City and Chong Hua Hospital (CHH) in Cebu City. A mix of private and public hospitals was chosen to obtain data from patients across all socioeconomic levels. Permission from the administration and research committees from each hospital was obtained prior to the study.

All neonates less than or equal to 28 days who had positive cultures from a sterile site and/ or had fulfilled the SIRS criteria as defined by the International Pediatric Sepsis Consensus Conference[8] in the presence of or as a result of suspected or proven infection were diagnosed to have neonatal sepsis and were included in the study.

Definitions

Systemic inflammatory response syndrome (SIRS)

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

a) Core temperature of >38.5°C or <36°C.

b) Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5 to 4 hr time period OR for children <1 yr old bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.

c) Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.

d) Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils.

Infection

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

A standardized surveillance form was used and the same was accomplished by all investigators as each patient with a diagnosis of neonatal sepsis was identified. Data including place of birth, age of gestation, site of infection, bacteria isolated and specimen from which it was isolated, susceptibility pattern, antibiotic used, and outcome of the patient were also included.

Blood cultures were performed routinely on most neonates suspected of sepsis. Cultures from other sites (endotracheal tube, cerebrospinal fluid, urine) were performed depending on the presenting signs and symptoms of the patients and were not routine for all patients. Blood was cultured using brain heart infusion broth according to standard methods. The isolates were identified by standard biochemical tests. Antibiotic resistance of the isolates was performed using the disk diffusion technique (Kirby-Bauer method) and susceptibility of the isolates was interpreted according to the National Committee for Clinical Laboratory Standards (NCCLS).

The antibiotics used for each patient were included as one of the items in the surveillance forms. First line antibiotics are defined as being the initial antibiotics given for at least 48 hours, while the Final antibiotics are defined as being the last antibiotics shifted to if the first-line antibiotics were changed. An antibiotic course was deemed successful if the patient was not shifted to another antibiotic and the patient survived.

RESULTS

Demographic Data

From July to December 2006, a total of 289 neonates admitted at the different study centers fulfilled the criteria of sepsis. Fifty-five per cent of the patients were recorded at PGH, while the least number of patients came from CHH in Cebu. More than half of the total patients were male (59%) and this male predominance was consistently seen among all study centers. Approximately 90% were born in a medical facility, 75% of which in a hospital, the rest in a lying in-clinic.

A great majority of the neonates included in the study were of low birth weight (CHH-78%, SLU-69%, PGH-69%, DDH-55%, PCMC-64%). A large number of the neonates with symptoms of sepsis were premature (PCMC-51%, Davao-65%, Cebu-56%). For PGH, only 29% of the neonates were of premature while in SLU it was 48%.

Table 1. Demographic data of neonatal sepsis patients.

Study Center	No. of Patients (%)	Sex		Place of Birth		
		Male (%)	Female (%)	Home (%)	Lying in (%)	Hospital (%)
SLH	21 (7.2)	11 (52)	10 (48)	0	0	21(100)
CHH	18 (6.2)	14 (78)	4 (22)	1(6)	2(11)	15(83)
DDH	23 (7.9)	15 (65)	8(35)	1(5)	0	22(95)
PCMC	67 (23.1)	38(57)	29(43)			
PGH	160 (55.3)	93(58)	67(42)	23(14)	9(6)	128(80)
Total	289 (100)	171(59)	118 (41)			

Table 2. Onset of infection neonatal sepsis in five urban hospitals in the Philippines.

	Born in hospital Within 72 hrs (%)	Born in hospital, After 72 hrs (%)	Born at home, Within 72 hrs (%)	Born at home > 72 hrs (%)	Total early onset <72 hrs (%)	Total late onset >72 hrs (%)
SLU	21 (100)	0	0	0	21 (100)	0 (0)
CHH	2 (11)	13 (72)	1 (6)	2 (11)	3 (17)	15 (83)
DDH	8 (35)	14 (61)	0 (0)	1 (4)	8 (35)	15 (65)
PCMC	0	1(2)	51(76)	15(22)	51 (76)	16 (24)
PGH	82 (51)	53 (33)	12 (7.5)	13 (8)	94 (59)	66 (41)
Total	113 (39)	81 (28)	63 (22)	31 (11)	177 (61)	112 (39)

Table 3. Site of infection of neonatal sepsis in five urban hospitals in the Philippines.

Study center	Clinical sepsis without focus (%)	Pneumonia	Meningitis	NEC	Cellulitis	Urinary tract	Infective endo-carditis
SLU	4	16	0	0	0	0	0
CHH	11	5	0	0	1	1	0
DDH	12	6	1	1	0	3	1
PCMC	28	39	0	0	0	0	0
PGH	45	98	3	13	1	0	0
Total	100(35%)	164(57%)	4(1%)	14(5%)	2(<1%)	4(1%)	1(<1%)

Table 4. Number of isolates cultures from the different study centers.

Study center	No. of patients tested	No Organism isolated	(+) Organism isolated
SLH	13	7 (54%)	6 (46%)
CH	18	16 (89%)	2 (11%)
DDH	23	15 (65%)	8 (35%)
PCMC	64	63 (98 %)	1 (2%)
PGH	160	38 (24%)	122 (76%)
Total	278	139 (50%)	139 (50%)

Table 5. Organisms isolated in five urban hospitals in the Philippines.

Organism isolated	Baguio	CHH	DDH	PCMC	PGH	Number of isolates	% of total
Acinetobacter spp.					7	7	5%
Aeromonas spp.	1					1	0.7%
Alkaligenes spp.					5	5	3.6%
Burkholderia spp.					30	30	21.6%
Enterobacter spp.	1		3		2	6	4.3%
E. coli		1	1		1	3	2.1%
Haffnia alvei					1	1	0.7%
Klebsiella spp.	3		1		11	15	10.8%
Pseudomonas spp. (non-aeruginosa)	1		2		55	60	43.2%
P. aeruginosa					2	2	1.4%
Salmonella spp.				1		1	0.7%
MRSE		1			5	6	4.3%
Enterococcus spp.					2	2	1.4%
Candida species			1		1	2	1.4%
Total	6	2	8	1	122	139	100%

Table 6. Organisms isolated and sensitivity pattern from pathogens found in St. Louis University Hospital in patients diagnosed with neonatal sepsis.

Organism Isolated	All isolates Sensitive	All isolates Resistant	Variable	No. of Isolates/No. tested
Klebsiella oxytoca	Cefepime	Amikacin, Ampicillin, Ceftriaxone, Piperacillin-Tazobactam, Meropenem, Imipenem, Cotrimoxazole	Ciprofloxacin (50% sens)	3/3
Pseudomonas maltophilia	Amikacin, Ciprofloxacin, Piperacillin-Tazobactam	Cefuroxime, Ceftriaxone, Imipenem		1/1
Enterobacter cloacae	Imipenem	Netilmicin, Amikacin, Ceftriaxone. Ciprofloxacin		1/1
Aeromonas hydrophilia	Netilmicin, Ceftriaxone, Piperacillin-Tazobactam, Imipenem	Ampicillin, Cefuroxime		1/1

Table 7. Organisms isolated and sensitivity pattern from pathogens found in Chong Hua Hospital in patients diagnosed with neonatal sepsis.

Organism Isolated	Sensitive	Resistant	No. of Isolates/No. tested
E. coli	Gentamicin, Netilmicin, Amikacin, Cefuroxime, Ceftazidime, Cefepime, Ciprofloxacin, Piperacillin-Tazobactam, Imipenem,	Cotrimoxazole	1/1
Staphylococcus epidermidis	Vancomycin, Clindamycin	Cefazolin, Cefuroxime, Ciprofloxacin, Oxacillin, Piperacillin-Tazobactam, Erythromycin	1/1

Table 8. Organisms isolated and sensitivity pattern from pathogens found in Davao Doctors Hospital.

Organism Isolated	Sensitive	Resistant	Variable	No. of Isolates/No. tested
Enterobacter cloacae	Ciprofloxacin, Meropenem, Imipenem	Ampicillin, Gentamicin, Amikacin, Cefuroxime, Ceftazidime	Cefepime (66% sens), Chloramphenicol (66% sens), Cotrimoxazole (66% sens)	3/3
Pseudomonas spp.	Ceftazidime, Cefepime, Ciprofloxacin, Piperacillin-Tazobactam, Meropenem, Imipenem, Cotrimoxazole,	Gentamicin, Amikacin, Ampicillin, Cefuroxime,	Chloramphenicol (50% sens)	2/2
Klebsiella ozanae	Ceftazidime, Ciprofloxacin, Chloramphenicol, Meropenem, Imipenem	Gentamicin, Amikacin, Ampicillin, Cefuroxime, Cefepime, Piperacillin, Tazobactam, Cotrimoxazole		1/1
Escherichia coli	Gentamicin, Amikacin, Ampicillin, Cefuroxime, Ceftazidime, Cefepime, Ciprofloxacin, Piperacillin, Tazobactam, Imipenem, Meropenem	None		1/1

Table 9. Organisms isolated and sensitivity pattern from pathogens found in Philippine Children's Medical Center, Quezon City.

Organism Isolated	Sensitive	Resistant	No. of Isolates/ No. tested
Salmonella spp.	Gentamicin, Amikacin, Cefuroxime, Ceftriaxone, Cefepime, Chloramphenicol, Ciprofloxacin, Piperacillin-Tazobactam, Imipenem	Cotrimoxazole	1/1

life) with only 39% developed sepsis after 72hrs. Early onset sepsis was more prevalent in SLU, PCMC and PGH, while for DDH and CHH, late onset infections predominated.

The most common site of infection was the lungs, presenting as pneumonia 57%, followed by sepsis without an obvious site of infection (35%). Other sites were much less frequent which included urinary tract infection, necrotizing enterocolitis, meningitis, cellulitis and infective endocarditis.

Pathogens Isolated

In 50% of patients, an organism was identified, but the isolation rates differed among the centers. The PGH had the highest yield (76%), while PCMC had the lowest with only one culture positive patient among 67 patients. Gram negative bacteria were the dominant bacteria found (Pseudomonas spp, Burkholderia spp., Klebsiella spp.), which comprised 94% of the bacteria isolated. Two isolates of Methicillin-resistant Staphylococcus aureus and two isolates of Enterococcus were the only gram-positive bacteria isolated. These were from neonates admitted at PGH and CHH only.

The study centers also had diverse gram negative organisms which predominated in their area. *Pseudomonas putida* was the most common isolate in PGH. The sole isolate of PCMC grew Salmonella spp.

Antibiotic Resistance

Resistance patterns varied among the different urban study centers. The Pseudomonas and Burkholderia isolates from PGH were fully sensitive to Ceftazidime. All

Klebsiella isolates from SLU were resistant to third generation cephalosporins. In contrast, Klebsiella isolates from PGH and Davao were sensitive to third generation cephalosporins but resistant to piperacillin-tazobactam. Tables 7 to 11 show the details of antibiotic resistance for each study site.

Antibiotic Usage

Antibiotic usage differed slightly from in each institution. In Baguio, Cebu, Davao and PCMC, first line drugs are a combination of Ampicillin (Ampicillin-sulbactam occasionally for Davao) and an aminoglycoside (amikacin or gentamicin). Unfortunately, in approximately half of these patients, their physicians shifted these antibiotics either due to perceived poor responses of the patients or receipt of the culture and sensitivity results changing to a drug which is sensitive.

Outcome

The overall mortality rate was 14% with the highest mortality at PGH (19%) and the lowest at PCMC (7.5%). The mortality rates of neonatal sepsis for the other centers were as follows: DDH-17%, CHH-17% and SLU-9.5%.

DISCUSSION

The large number of patients collected in a six-month period reflects the significance of this disease. The number of patients per center reflects the general economic status of the citizens with large volumes in the public hospitals (PGH), and much fewer admissions in the private hospitals (St. Louis Hospital, and Chong Hua Hospital). The PGH may have an unusually large number because it is a national referral center wherein patients may have been diagnosed with sepsis. Early onset sepsis was also higher in number than late onset sepsis despite narrowing the definition of the latter to the first three days of life.

Prior to the antibiotic era, the mortality from septicemia was more than 90%. In the present times, mortality remains high, between 20%-40%. The mortality rate in this study was 14% which may be due to these hospital having adequate supportive facilities since they are all tertiary hospitals.

transferred from other parts of the country and most deliveries at this hospital were high risk pregnancies. Consistent with previous studies, there were more male patients who were Across all centers, Gram-negative bacteria were the dominant pathogens, although the species were varied. Pseudomonas spp. was the most common bacteria isolated followed by *Burkholderia cepacia*. This is consistent with reports from other countries in Asia and the Middle East. A study from Kashir, Iran showed 72.1% of the bacteria isolated from infants with neonatal sepsis were Gram negative with Pseudomonas and Klebsiella as the most common organisms.[10] In a more recent study from Shiraz, Iran, Early onset sepsis (EOS) was caused by *E. coli*, followed by Klebsiella which was different from Late onset sepsis (LOS) which was due to Coagulase negative Staphylococcus followed by Enterococcus[11].

In the Database of the Aga Khan University Hospital of Pakistan, gram negative organisms accounted for 60% (173 of 292) of all their isolates in their newborn unit; with Klebsiella as the most common one found. [12] In the NICU of MKCG Hospital in Orissa, India 88.4 % (38 of 48) were gram-negative bacilli with *Klebsiella* and *E. coli* being the most common ones.[13] In another study from India, gram negative organisms also predominated (58.5%).[14] In a more recent from Pudcherry, India, the most common etiology of EOS was *Klebsiella pneumoniae*.[15]

Table 10. Top five Organisms isolated and sensitivity pattern from pathogens found in Philippine General Hospital.

Organism Isolated	Sensitive	Resistant	Variable	No. of Isolates/ No. tested
Pseudomonas putida	Ceftazidime	Gentamicin, Amikacin, Ampicillin,	Cefuroxime (43% S), Cefotaxime (50% S), Cefepime (85% S), Ciprofloxacin (35% S), Piperacliin-Tazobactam (82% S), Meropenem (62% S), Imipenem (23% S),Cotrimoxazole (88% S)	55/1-25 depending on antibiotic
Burkholderia mallei	Cefotaxime, Cefepime, Piperacillin-Tazobactam, Cotrimoxazole	Amikacin, Imipenem	Ampicillin (14% S), Ceftazidime (90% S) Ceftriaxone (75% S), Ciprofloxacin (38% S), Meropenem (29% S)	16/3-11 depending on antibiotic
Burkholderia cepacia	Cefuroxime, Ceftriaxone, Ceftazidime, Piperacillin-Tazobactam, Cotrimoxazole	Gentamicin, Amikacin, Ciprofloxacin	Meropenem (75% S), Imipenem (33% S)	8/1-5 depending on antibiotic
Acinetobacter baumanii		Gentamicin, Amikacin, Ciprofloxacin, Imipenem, Cotrimoxazole	Ampicillin (20% S), Cefuroxime 50% S), Ceftazidime (25% S), Ceftriaxone (50% S), Cefepime (25% S), Piperacillin-Tazobactam (40% S), Meropenem (50% S)	7/1-5 depending on antibiotic
Burkholderia pseudomallei	Ceftazidime, Piperacillin-Tazobactam, Meropenem	Gentamicin, Amikacin, Netilmicin, Ceftriaxone,	Cefepime (66% S)	6/1-5 depending on antibiotic

Table 13. First line drugs used and success rates in patients with neonatal sepsis according to hospital.

Drug	SLU		CHH		DDH		PCMC		PGH		All hospitals	
	No.	Succ (%)		Succ (%)	No.	Succ (%)	No.	Succ (%)	No.	Succ (%)	No.	Succ (%)
Ampicillin	4	1 (25)	15	6 (40)	7	2 (29)	62	33(53)	31	15 (48)	119	57 (48)
Ampicillin-Sulbactam	0		0		9	3(33)	0		0		9	3(33)
Gentamicin	19	6 (32)	0		5	2 (40)	62	3(53)	0		86	41 (48)
Amikacin	0		15	7 (47)	15	6 (40)	1	0	158	28(26)	189	82(43)
Cefotaxime	1	0	2	1 (50)	0	0	2	2(100)	0		5	5(100)
Piper-Tazo	0		0		2	1(50)	1	0	106	84(76)	106	29(27)
Meropenem	1	0 (0)	0		0	0	3	3(100)	1	0	5	3 (60)
Ceftazidime	0		1	1(100)	5	1 (20)	0		6	6(100)	11	5(45)
Cefepime	1	1 (100)	0		2	0	0				3	1 (33)
Oxacillin	0		1	0 (0)	0		0				4	3(75)
Metronidazole	0		1	1 (100)	1	1 (100)	0		14	11(79)	13	4(31)
Penicillin	13	4 (31)	0		0		0		1	1(100)	15	5 (36)

Traditionally, *Group B streptococci (GBS)*, *E. coli* and *Listeria monocytogenes* are considered to be most common in the Western countries, but this phenomenon too is changing in certain groups of patients. In the latest data from the National Institute of Child Health (NICH) and human Development Neonatal Research Network VLBW registry, gram-negative organisms already predominate for early onset sepsis (53%) with *E. coli* being the most dominant organism.[16] In the Neonatal Network of Burgundy France, from preterm infants (<35 weeks) with early onset sepsis, gram negative bacilli was the most frequent organism isolated. But for term and near-term infants, GBS followed by *E. coli* was most frequent.[17]

Gram-positive organisms found in other studies include GBS, *S. epidermidis, S. aureus*, Enterococcus and *S. pneumoniae*. In our study, only *S. epidermidis* and Enterococcus were found.

There is also a changing pattern of antimicrobial resistance in many parts of the world. In India, gram negative pathogens isolated from neonates have high rates of resistance to almost all antibiotics (50% for amikacin, 75% for gentamicin, >80% resistance to third generation cephalosporins, about 40% resistance to piperacillin-tazobactam and about 20% resistance to imipenem).[18] In Pakistan, a similar trend is being experienced with Gram-negative bacilli having a resistance of >50% for third generation cephalosporins, >50% resistance to Ampicillin and >80% resistance to gentamicin[19]. In a recent study from Jordan, gram negative bacteria isolated from septic neonates were highly resistant to Ampicillin (82.8-100%), Gentamicin (41.4-79.5%), Ceftazidime (46-50%) and Piperacillin-Tazobactam (21.4-54.3%) [20]. Only Imipenem and Ciprofloxacin showed good sensitivity. In the United States, resistance to ampicillin is the main concern (57%) for the gram negative bacteria that they have isolated[21]. In Iran, Klebsiella isolates from neonates showed 100% resistance to ampicillin, 31% resistance to ceftriaxone, 46% resistance to Amikacin and 27% to gentamicin.[10] Our study shows varying resistance to the different groups of antibiotics among the different hospitals.

The Infectious Diseases and Tropical Medicine Section of the Department of Pediatrics of the PGH has an ongoing surveillance since the mid 1990's of nosocomial infections of which many of the neonates born at their institution are also included. There has been an increasing trend of multi-drug resistant gram negative bacilli in the neonatal intensive care unit. This is the reason that for certain subsets of patients (low birth weight neonates born at PGH), piperacillin-tazobactam plus an aminoglycoside had been the first line regimen. But due to this practice and other factors, such as improved infection control, the pattern seems to be changing for the better because the gram negative bacteria now are more susceptible to third generation cephalosporins. These regimens is has to is undergoing re-evaluation undergo reevaluation periodically to give the most effective treatment depending on the changes which occur.

Dr. Darmstadt has recommended the following first line therapy in facility settings: for early and late sepsis: ampicillin and gentamicin; for early-onset meningitis: ampicillin plus gentamicin; and for late onset meningitis: ampicillin, gentamicin (or amikacin), and/or cefotaxime.[22] In Iran, some experts advocate using a third generation cephalosporin for treating *E. coli* and *Klebsiella* infections, and Vancomycin for Staphylococcal infections.[11]

Ampicillin and an aminoglycoside are still being used as first line drugs in most hospitals in the Philippines. These antibiotics seem to be less useful in the hospitals studied based on resistance rates and antibiotic outcomes seen. Although the mortality was not high, the hospital stays of these patients were presumed to be longer because of the initial non-response to the regimen. This combination may still be given to patients with risk factors of sepsis (PROM, maternal fever, etc) but with no signs and symptoms and are still awaiting results of blood cultures or other laboratory indicators for sepsis. For symptomatic patients (those who strictly fulfill the criteria of neonatal sepsis as defined in this study) the use of a third generation cephalosporin plus amikacin may be more cost-effective, although clinical trials may be needed to confirm this. Once culture and sensitivity results are available, antibiotics should be adjusted according to this new information, while taking into consideration the clinical response of the patient.

The reason why there is a reluctance to promote third generation cephalosporins as first line drugs is that although they are poor inducers of beta-lactamase expression, they are sensitive to these enzymes and are significantly associated with repressor mutations. The importance of limiting its use only to symptomatic patients (fulfilling the criteria of sepsis as defined in this study) should be emphasized and duration of therapy must be

well-defined. Potentially septic patients who are asymptomatic may be started with Ampicillin and an Aminoglycoside. In treatment protocols such as in France, antibiotic therapy is discontinued as soon as clinical infection is resolved and blood CRP concentration is <10 mg/L. Their treatment duration is usually seven days for septicemia, 14 days for GBS meningitis and 21 days for gram negative bacillary meningitis.

CONCLUSIONS

Neonatal sepsis is still an important cause of morbidity and mortality in our country. The most common site of infections is the lungs, presenting as pneumonia, followed by clinical sepsis without a focus. A changing pattern of bacteria isolated as well as their resistance has been observed. Gram negative bacteria were the dominant bacteria found (Pseudomonas spp, Burkholderia spp., Klebsiella spp.) which comprised 94% of the bacteria isolated. Two isolates of Methicillin resistant Staphylococcus aureus and two isolates of Enterococcus were the only gram positive bacteria isolated.

Increasing resistance to commonly used antibiotics is seen. Ampicillin and an aminoglycoside were the most common regimens used but were only successful in less than 50% of cases. A third generation cephalosporin plus an aminoglycoside might be a more cost-effective combination but its use should be limited only to symptomatic patients who fulfill the sepsis criteria.

RECOMMENDATIONS

Surveillance should be continued because changes in pathogens as well as susceptibility patterns are expected. For asymptomatic neonates but with risk factors for sepsis (prolonged rupture of membranes, maternal fever, chorioamnionitis, etc.) ampicillin plus an aminoglycoside may be started and re-evaluate its need in 48-to-72 hours. If the patient is asymptomatic and cultures are negative, antibiotics should be discontinued. If a neonate is symptomatic (fulfills the sepsis criteria), a third generation cephalosporin (ceftazidime, or cefotaxime) plus an aminoglycoside should be started. Reevaluation should again be done in 48-to-72 hours. Adequate supportive measures aside from antibiotics as well as good infection control should not be forgotten. More research is also needed to determine the shortest effective duration of treatment.

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