ORIGINAL ARTICLE

OUTCOME OF CURRENT ANTIBIOTIC REGIMENS USED FOR NEONATAL SEPSIS IN A TERTIARY HOSPITAL

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

ABSTRACT

Objective: This paper looked into the outcome of currently used antibiotic regimens for neonatal sepsis in a tertiary hospital.
Methods: This retrospective study reviewed all cases of culture positive neonatal sepsis delivered in a tertiary hospital between January 1, 2000 to December 31, 2015. Demographic profile, stratification as to early-onset and late-onset sepsis, clinical manifestations, culture and antimicrobial susceptibility results, and outcomes were analyzed.
Results: There were 28 cases of culture positive neonatal sepsis reported during the study period, and prematurity and low birth weight were the major risk factors identified. Of these, 8 were early-onset sepsis and 20 were late-onset sepsis cases. Respiratory symptoms were the most common presenting manifestations. Sepsis isolates were evenly distributed between gram-negative bacilli and gram-positive cocci with no ESBL *E. coli* or *Klebsiella pneumoniae* identified. The institution's current empiric antibiotic regimen of cefuroxime and amikacin for early-onset neonatal sepsis was shifted to another drug in 57% of cases. Piperacillin-tazobactam or carbapenem was given for late-onset sepsis. The addition of vancomycin for late-onset sepsis was done where Staphylococcus was considered. Sepsis due to gram-negative bacilli had a high mortality rate.
Conclusion: Our institution's empiric antibiotic regimen which consists of cefuroxime and amikacin for early onset sepsis is effective in 43% of cases. A carbapenem or piperacillin-tazobactam, even without amikacin, proved to be effective for late-onset sepsis. Vancomycin, should be considered for late-onset sepsis, if staphyloccoccal disease is suspected.

KEYWORDS: *neonatal sepsis, antibiotic, neonate, low birth weight*

INTRODUCTION

Neonatal sepsis remains to be a leading cause of morbidity and mortality especially among those delivered in developing countries. An increasing concern in the management of neonatal sepsis is the growing problem of antibiotic resistance in the treatment of these infections. As organisms evolve and acquire resistance to commmonly used antimicrobials, it is important to assess if current empiric antibiotic regimens are still effective against organisms encountered in a particular setting.[1]

At the tertiary hospital studied, Cefuroxime and amikacin have been used since the year 2000 for empiric treatment of early-onset sepsis, and piperacillin-tazobactam for late-onset sepsis. This recommendation was made after analysis of institution-specific blood pathogens showing that group B streptococcus or *Streptococcus agalactiae* was a rare pathogen for early-onset sepsis, contrary to western literature reports. On the other hand, gram negative bacilli, notably *Enterobacter cloacae* and *Klebsiella pneumoniae*, were commonly isolated.[1]

This study looked into the efficacy and outcome of current empiric antibiotic regimens used for neonatal sepsis at a tertiary hospital. Risk factors, presenting symptoms, culture and antimicrobial susceptibility results, and outcomes were likewise analyzed.

MATERIALS AND METHODS

Study Design

This was a retrospective study which looked into cases of neonatal sepsis in a private tertiary hospital, and where bacteremia and/or candidemia were documented by blood culture between January 1, 2000 to December 31, 2015.

Population and Sample Size

Inclusion Criteria

All neonates delivered whose blood culture yielded an isolate interpreted to be a true pathogen, were included. Early-onset sepsis was defined as culture-proven infection occurring in the first seven days of life, while late-onset sepsis referred to cases which occurred on the eighth up to the ninetieth day of life. For very low birth weight (VLBW) neonates (weight < 1500 grams), late-onset sepsis was defined as that which occurred at or more than 72 hours of life.[2]

Exclusion Criteria

Neonates who were admitted but delivered outside the hospital studied (outborn cases), and those with clinical signs of sepsis but whose blood cultures showed no growth, were excluded. Excluded also were cases of sepsis transferred to another hospital, and culture positive cases where blood cultures were positive but isolates were interpreted as contaminants. In cases where blood isolates were positive on two separate occasions, the organisms and antimicrobial susceptibilities were noted.

Data Collection

This study was conducted in accordance with the ethical principles based on the Declaration of Helsinski, WHO guidelines, International Harmonization – Good Clinical Practice, and National Ethics Guidelines for Health Research and approved by the Institutional Review Board (I.R.B.).

The following data were obtained: sex, gestational age, birth weight, manner of delivery, and onset of sepsis defined as the day of the earliest symptom attributable to sepsis.

Risk factors were analyzed which included maternal and neonatal co-morbidities and contraptions present throughout the hospital stay.

Clinical and culture information were collected from the medical records ArchiveOne database, neonatal intensive care unit (N.I.C.U.) census of septic babies, N.I.C.U. audits, and neonatologist and infectious disease specialists' records.

The presence or absence of specific clinical findings were noted. Laboratory findings were recorded before, and on the day that a positive growth was obtained. If a significant isolate was identified, the organism's antimicrobial susceptibilities were recorded. A blood culture growth was considered to be a contaminant if it grew coagulase-negative Staphylococcus (CoNS) and the blood was drawn during the first three days of hospital stay in a neonate with no indwelling intravascular catheter. Specific antibiotic regimens and outcomes of treatment were recorded. A case report form was utilized to organize the data gathered from each case.

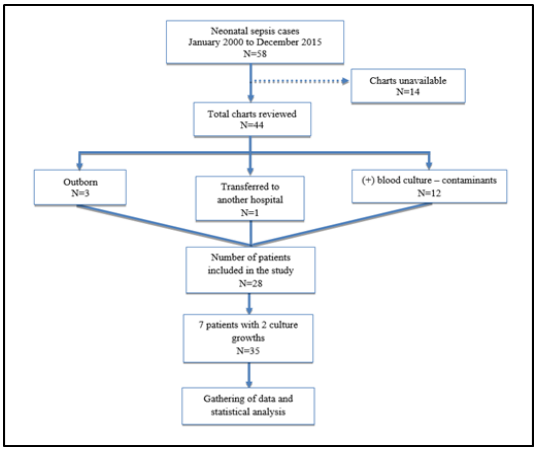

Figure 1. *Methodology Flowchart*

Statistical Analysis

Descriptive statistics using frequencies and percentages were used to analyze the data.

III. RESULTS

There were 58 infants evaluated for sepsis where blood culture grew an organism between January 1, 2000 to December 21, 2015. Fourteen charts (24%) were unavailable or lost in the ArchiveOne database. Among 44 available charts, further exclusions were: outborn (N=3), transferred to another hospital (N=1), and cases where cultures were considered to be contaminants (N=12), yielding a final total of 28 cases. Seven patients had two blood isolates at different times with a total blood isolate of 35. See Figure 1.

The medical records of 28 infants were further reviewed. Of the total cases, 86% were preterms (N=24). Most cases were extremely low birth weight (ELBW, 39%), and VLBW infants (25%). For neonates weighing more than 1,500 grams, there were equal cases of early-onset and late-onset sepsis, while for neonates under 1,500 grams, late-onset sepsis was seen three times more often. Majority of sepsis cases fell under late-onset sepsis (71%). See Table 1.

Table 1. Demographic Data

	Total Number N = 28	% of total N
Gestational Age		
Preterm	24	86%
Term	4	14%
Sex		
Male	16	57%
Female	12	43%
Birth Weight (kg)		
<1	11	39%
1-1.49	7	25%
1.5-2.49	4	14%
>2.5	6	21%
Manner of Delivery		
Spontaneous vaginal delivery	10	36%
Cesarean Section	18	64%
Size for Gestational Age		
Small for GA	10	36%
Appropriate for GA	14	50%
Large for GA	4	14%
Onset of Sepsis		
Early-Onset	**8**	**29%**
>1500g, 0-7 days	5	18%
<1500g, 0-3 days	3	11%
Late-Onset	**20**	**71%**
>1500g, >7 days	5	18%
<1500g, >3 days	15	54%

Maternal urinary tract infection (21%) was the dominant prenatal risk factor for sepsis in the newborn. Neonatal factors that were present among septic neonates were prematurity (86%) and low birth weight (LBW,78%).

Table 2. Factors Associated with Culture-Proven Sepsis in Neonates

	Frequency	Percentage
Prenatal and Perinatal Factors		
Maternal urinary tract infection	6	21%
Meconium-stained amniotic fluid	5	18%
Maternal Fever (≥38)	1	4%
Neonatal Factors		
Prematurity (<37 weeks)	24	86%
Low birth weight	22	79%
Low Apgar score (<6 at 5 min)	1	4%
Contraptions		
N/OGT	20	71%
Umbilical vein catheter	15	54%
Endotracheal tube	12	43%
Intrajugular catheter	1	4%
Chest tube	1	4%

The most common clinical manifestations of septic neonates were tachypnea (68%), desaturation (54%), apnea (43%), and presence of retractions (36%). See Table 3.

Table 3. Clinical Manifestations of Septic Neonates Before Positive Blood Culture

	Frequency	Percentage
Tachypnea	19	68%
Desaturations	15	54%
Apnea	12	43%
Retractions	10	36%
Poor activity	8	29%
Bradycardia	7	25%
Feeding intolerance	6	21%
Poor cry	5	18%
Grunting	3	11%
Blood in nasogastric or orogastric tube aspirate	2	7%
Abdominal distention	1	4%
Abdominal discoloration	1	4%

Table 4 shows that elevated C-reactive protein (CRP,43%) and thrombocytopenia (32%) were the most common laboratory abnormalities identified. Of the nine neonates who had a lumbar tap done, only one had an isolate. Organisms that grew in the endotracheal aspirate were *P. aeruginosa,* CoNS. and *S. aureus* in three cases, which were identical to the bacteria cultured from the blood.

Table 4. Laboratory Abnormalities at Start of Treatment

	Frequency	Percentage
CRP elevation	12	43%
Thrombocytopenia	9	32%
High WBC (above 30)	5	18%
Stool culture positive	5	18%
Endotracheal tube aspirate culture positive	3	11%
Low WBC (below 5)	2	7%
Segmenters>80%	1	4%
CSF culture positive	1	4%

When sepsis cases were divided by timing of onset to early and late-onset, 29% were early, and 71% were late, as seen in Table 5. In early-onset cases, the etiologic organisms were evenly divided between gram-negative bacilli and gram-positive cocci. Among late-onset cases, 52%, 41% and 7% were due to gram-positive cocci, gram-negative bacilli, and candida, respectively.

Table 5. Blood Culture Isolates and Time of Onset

	Early Onset N=8		Late Onset N=27		Total Positive Blood Culture (N=35)	
	Frequency	Percentage	Frequency	Percentage	Total	Percentage
Coagulase-negative Staphylococcus	1	4%	11	41%	12	45%
Staphylococcus aureus	1	4%	3	11%	4	11%
Enterobacter cloacae	0	0%	3	11%	3	9%
Pseudomonas aeruginosa	1	4%	2	7%	3	9%
Serratia marcescens	1	4%	2	7%	3	9%
Candida	0	0%	2	7%	2	6%
Acinetobacter	0	0%	2	7%	2	6%
Klebsiella pneumoniae	1	4%	1	4%	2	6%
Streptococcus viridans	1	4%	0	0%	1	3%
Pseudomonas stutzeri	1	4%	0	0%	1	3%
Streptococcus agalactiae	1	4%	0	0%	1	3%
Enterobacter aerogenes	0	0%	1	4%	1	3%

Among the gram-negative bacilli isolated, only 75% was susceptible to meropenem and 60%

were susceptible to cefuroxime; 100% were susceptible to piperacillin-tazobactam and amikacin, but these two drugs were tested in only six out of fourteen bacterial isolates. All gram-positive bacilli were susceptible to vancomycin. See Table 6.

Table 6. Antibiotic Susceptibility of Clinically Significant Organisms Isolated: % Susceptible

Gram-negatives (N=14)	Frequency	Percentage
Ciprofloxacin	10/10	100%
Cefepime	9/9	100%
Gentamycin	7/7	100%
Piperacillin-Tazobactam	6/6	100%
Amikacin	6/6	100%
Imipenem	4/4	100%
Ceftriaxone	4/4	100%
Ceftazidime	3/3	100%
Meropenem	3/4	75%
Cefuroxime	3/5	60%

Gram-positive cocci (N=18)	Frequency	Percentage
Vancomycin	14/14	100%
Linezolid	6/6	100%
Ciprofloxacin	3/3	100%
Gentamycin	2/2	100%
Clindamycin	6/10	60%
Oxacillin	6/16	38%

Figure 2 shows the antibiotics used among eight cases of early-onset sepsis. The first-line antibiotic regimen of cefuroxime and amikacin was used in most (88%) cases. Among those given cefuroxime and amikacin, amikacin was continued up until the end of treatment, but cefuroxime was shifted in 57% of cases. The treatment regimen of one neonate who was started on ampicillin and amikacin, was shifted to meropenem. At the end of treatment for the eight cases of early-onset sepsis, all were on amikacin, three were on cefuroxime, two each were on a carbapenem or a third-generation cephalosporin, and one was on piperacillin-tazobactam.

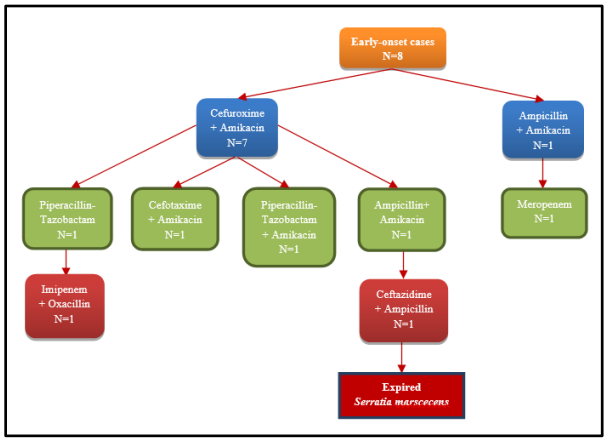

Figure 2. *Initial antibiotic choices and subsequent changes during the course of early-onset sepsis. Orange: Total early-onset cases (N=8); Blue: Antibiotic regimen initiated; Green: First shift of regimen; Red: Second shift of regimen*

Figure 3 shows the antibiotic usage pattern among twenty cases of late-onset sepsis. Initial regimen showed that piperacillin-tazobacatam was used in 70%, amikacin in 65%, and meropenem in 10%. Among the 14 cases started on piperacillin-tazobactam, two (14%) were given the drug up to the end of treatment while in the remaining twelve (86%), piperacillin-tazobacatam was shifted to a carbapenem in 67%. At the end of treatment for 20 cases of late-onset sepsis, 50% were on a carbapenem, 30% on vancomycin, 25% on fluconazole, and 10% on piperacillin-tazobactam.

Figure 3: *Initial antibiotic choices and subsequent changes during the course of late-onset sepsis. Green: Total late-onset cases (N=20); Blue: Antibiotic regimen initiated; Violet: First shift of regimen; Orange: Second shift of regimen; Red: Expired cases.*

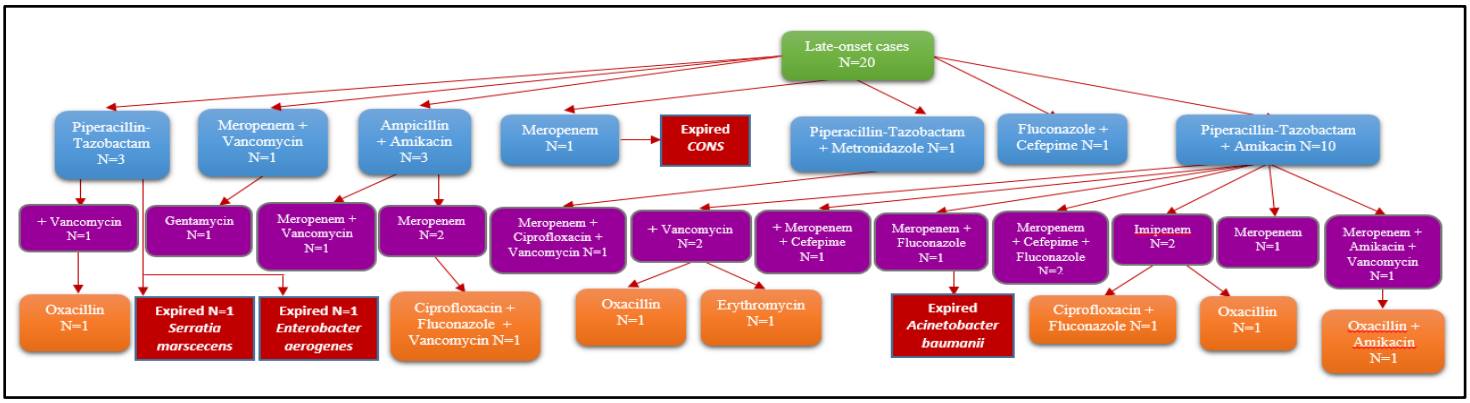

Table 7 shows that 20% of gram-negative bacterial infections and 6% of gram positive sepsis died. Two cases with candidemia survived.

There were six mortalities, with five due to gram-negative bacilli septicemia. One infant with late-onset CoNS died due to severe hyaline membrane disease.

Table 7. Summary Table of Outcomes

	Length of Stay (days)	Length of Treatment (days)	Pneumonia	Low platelet count	Bleed	NEC	Meningitis	Osteomyelitis	Septic Arthritis	Well	Died
Gram-Negative	60.2	13.4	7%	27%	7%	7%	7%	0	0	80%	20%
Gram-Positive	58.1	14.7	17%	6%	0	0	0	6%	6%	94%	6%
Candida	91.5	18.5	0	0	50%	50%	0	0	0	100%	0

IV. DISCUSSION

This study found that 86% of sepsis cases were in preterm neonates of which 25% were VLBW and 39% were ELBW This supports a similar study done which looked into five-hospitals in Manila, Cebu, Baguio and Davao and cases of neonatal sepsis with blood culture growths where 29-65% were preterms.[3] At Philippine General Hospital (PGH), a study on 103 neonates with blood culture growths, found that 66% were premature, 36% were L.B.W., and 7% were ELBW.[4]

In another study in PGH involving 17 culture-proven cases, 65% were preterms.[5] Presence of VLBW is a known independent risk for neonatal sepsis.[6]

The most common clinical manifestations were respiratory in nature. Mayuga reported that among 17 neonatal sepsis cases at PGH, 71% showed respiratory manifestations.[5] Among 63 neonates with *Serratia marcescens* bacteremia at Baguio General Hospital, presenting signs and symptoms were respiratory distress (51%), poor suck (25%) and bleeding (22%).[7]

The most common laboratory abnormalities seen at the start of treatment were an elevated CRP (43%) and thrombocytopenia (32%). Such indicators of bacteremia are of value while awaiting blood culture results since not all patients will present with frank signs of sepsis. In a study in PGH, bacteremic neonates had an odds ratio of 4.7 to be thrombocytopenic; sensitivity of thrombocytopenia for bacteremia was low at 35%, and negative predictive value (NPV) was 87%.[8] In a review of various quantitative CRP tests used in neonatal sepsis, Da Silva found that CRP is probably the best diagnostic test to evaluate neonatal sepsis; sensitivity was 58-100%, and NPV was 86-100%.[9]

Of nine neonates where a lumbar tap was done, only one had a growth. Among 103 septic neonates at PGH where 93% grew gram-negative bacilli in the blood, there was no documented case of meningitis.[5] Among 289 blood culture-positive neonates from five local hospitals, only 1.4% had meningitis.[5] These data indicate low rates of meningitis occurring with bacteremia.

In this study, among eight neonates with early-onset sepsis, the etiologic organisms were evenly distributed between gram-negative bacilli and gram-positive cocci. Among 139 neonates with blood culture-positive sepsis from five local hospitals, the most common organisms were Pseudomonas spp. (43%), Burkholderia spp. (22%), Klebsiella spp. (11%), Acinetobacter spp. (5%), and Enterobacter (4%) spp. and *S. epidermidis* (4%); 88% of the isolates came from PGH. For the four other hospitals, there were 17 blood culture growths, and the organisms were Enterobacter spp. (24%), Klebsiella spp. (24%), Pseudomonas spp. (18%), E. coli (12%), and Aeromonas spp., Salmonella spp., *S. epidermidis*, and Candida spp. (6% each). There was not a single growth of *Streptococcus agalactiae* in the study[3] contrary to studies in the U.S. where up to 46% of early-onset sepsis are due to *S. agalactiae*.[10]

Among 108 bacteremic neonates at Cebu Doctors' University Hospital (2005-2008), Staphylococcus spp. (30%), Enterobacter spp. (23%), Klebsiella spp, (13%), Streptococcus spp. (9%), E. coli

(7%), Acinetobacter spp. (6%) and Enterococcus spp. (5%) were the most common isolates.[11]

Among 20 neonates with late-onset sepsis, 52% were due to gram-positive cocci, 41% were due to gram-negative bacilli, while 7% were due to candida. There is no published local study that distinguishes pathogens seen in early-onset vs late-onset sepsis.

Still at the NICU of the study hospital, there were three studies conducted (unpublished) on the most common organisms isolated from blood cultures among neonates evaluated for sepsis. Disregarding the CoNS growths which were generally regarded as contaminants, the top four isolates were Enterobacter spp., Klebsiella spp., Pseudomonas spp. and Acinetobacter spp. *Streptococcus agalactiae* was isolated in three neonates (2%) over the 10-year period.[1 12 13] Together with the local data cited above, it appears that S. agalactiae is an infrequent pathogen in neonatal sepsis in the Philippines.

For the gram-negative bacilli in the study, 75% were susceptible to meropenem and 60% were susceptible to cefuroxime; 100% were susceptible to piperacillin-tazobactam and amikacin. All gram-positive cocci were susceptible to vancomycin. The antibiogram results cannot be generalized however, since testing is automated and the list of antimicrobials tested is specific and limited. For example, *P. aeruginosa* or *B. cepacia* are not inherently susceptible to cefuroxime, hence, testing is not done.

Among early-onset sepsis cases, the first-line antibiotic regimen of cefuroxime and amikacin was used in 88% of cases. This regimen has been used at the tertiary hospital studied since 1999 on the basis of two unpublished studies using blood culture growths from the institution and their antimicrobial susceptibilities.[1 12] In this study, among those given cefuroxime and amikacin, amikacin was continued for all, but cefuroxime was shifted to another antibiotic in 57% of cases. At end of treatment for early-onset sepsis, all eight neonates received 3 to 7 days of amikacin, three were on cefuroxime, two were on a carbapenem, two were on a third-generation cephalosporin, and one was on piperacillin-tazobactam. In a local study involving five-hospitals, four institutions used ampicillin and an aminoglycoside for empiric treatment of neonatal sepsis; however, the success rates of ampicillin and gentamicin were only 48% for the sepsis cases, including those who were culture-negative. The authors suggested that the regimen of ampicillin and aminoglycoside was less useful in the participating hospitals, based on antimicrobial resistance rates and the outcomes seen.[3]

Among twenty cases of late-onset sepsis, the initial regimen consisted of piperacillin-tazobacatam in 70%, amikacin in 65%, and meropenem in 10%. Among 14 patients started on piperacillin-tazobactam, only two (14%) remained on this drug up to the end of treatment; in the other twelve (86%), piperacillin-tazobacatam was replaced with a carbapenem in nine (75%). At the end of treatment for the 20 infants with late-onset sepsis, 50% were on a carbapenem, 30% on vancomycin, 25% on fluconazole and 10% on piperacillin-tazobactam. These results imply that carbapenems may be more effective than piperacillin-tazobactam for the organisms encountered in the unit, but this finding is inconclusive given the retrospective nature of the study.

There were two neonates with candidemia, a known risk with the use of very broad-spectrum antimicrobials. Use of very broad-spectrum antimicrobials like carbapenems and piperacillin-tazobactam is common in the N.I.C.U. due to high resistance rates to third generation cephalosporins. Among 25 neonates with Enterobacter spp. bacteremia at Cebu Doctors' Hospital, 60% of the isolates were resistant to cefotaxime and

ceftazidime.[11] Among 34 neonates treated for sepsis in Baguio (31% of whom were bacteremic) with 70% of bacteremia due to Enterobacter spp., meropenem was used for all, with a favorable outcome in 84% and a mortality rate of 6%.[14] Piperacillin-tazobactam, in combination with an aminoglycoside, was used in PGH among 57 children with culture-proven infections, 63% of whom were neonates. This was done because of high rates of cephalosporin resistance. The favorable response rate was 79%, with no deaths occurring while on piperacillin-tazobactam.[15]

The results showed no sepsis-attributable mortality to CoNS or *Staphylococcus aureus*. The addition of vancomycin should be considered in late-onset sepsis as 50% of early onset sepsis and 52% of late onset sepsis respectively are due to these two organisms.

This study revealed that in spite of over 17 years of empiric use of cefuroxime and amikacin for early onset-sepsis, and a choice of piperacillin-tazobactam or a carbapenem for late-onset sepsis, there was not a single case of extended-spectrum-beta-lactamase-producing (ESBL) *E. coli or K. pneumoniae* among the blood isolates.

Even as data in Figure 2 and Table 6 indicate that the combination of cefuroxime and amikacin will not cover all potential pathogens in cases of early-onset sepsis, it remains to be seen if a stronger empiric first-line regimen (e.g., third generation cephalosporin) will be recommended, because of the risks of the emergence of ESBL strains of gram-negative bacilli. Third-generation cephalosporin use is a known risk for the emergence of ESBL strains in an intensive care unit.[16] At the institution studied, the hospital-wide (year 2015) ESBL rates for *K. pneumoniae* and *E. coli* were 16.8% and 21.5% respectively, but these growths have been mostly confined to the adult service intensive care areas.[17]

Twenty percent of gram-negative sepsis and 6% of gram-positive bacteremia cases died. Among 289 blood culture-positive neonates from five local hospitals, overall mortality was 11%.[3] Among 63 neonates with *Serratia marcescens* bacteremia at Baguio General Hospital, case fatality rate was 29%.[7] Among 25 neonates with Enterobacter spp. bacteremia in Cebu Doctors' Hospital, overall mortality rate was 56%.[3]

Organisms causing neonatal sepsis were roughly evenly divided between gram-negative bacilli and gram-positive cocci, but gram-negative bacilli caused a higher mortality rate (20% vs. 6%). The current antibiotic regimen of cefuroxime and amikacin for early-onset neonatal sepsis was changed in 57% of cases, indicating that a constant re-evaluation of any regimen is necessary to determine if change in the treatment is needed. Although piperacillin-tazobactam has been favored for late-onset sepsis in the studied unit in the last 15 years, more septic neonates ended treatment with a carbapenem. The addition of vancomycin in the treatment of late-onset sepsis should be considered.

V. CONCLUSION

In our tertiary hospital, cefuroxime and amikacin are effective for early-onset sepsis in 43% of cases. For late-onset sepsis, a carbapenem or piperacillin-tazobactam are recommended. There was a mortality rate of 20% and 6% among gram-positive and gram-negative bacteria with the current regimen. The antibiotic of choice should be decided upon by the clinician based on current recommendations, with consideration for maternal and neonatal risk factors, including clinical manifestations and laboratory abnormalities.

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