International Journal of Contemporary Pediatrics
Nagesh HN et al. Int J Contemp Pediatr. 2014 Nov;1(3):142-147
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291
DOI: 10.5455/2349-3291.ijcp20141107

Research Article

Antibiotic usage and auditing of antibiotic sensitivity pattern of culture positive neonatal septicemia in neonatal intensive care unit of a tertiary care hospital: a retrospective study

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Received: 10 September 2014
Accepted: 24 September 2014

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ABSTRACT

Background: Antibiotic resistance is an emerging problem in neonatal intensive care units (NICU) particularly in developing countries. The spectrum of organisms that cause neonatal sepsis changes from time to time and varies from region to region. Hence continuous surveillance for antibiotic susceptibility, rational use of antibiotics and the strategy of antibiotic cycling can provide some answers to it. the present study was undertaken to study the various antibiotics used and to analyze the antibiotic sensitivity and resistance pattern in NICU of tertiary care hospital.
Methods: The clinical files of neonates admitted in the NICU of Cheluvamba Hospital, Mysore from April to September 2012 were revised. The diagnosis, antibiotics used, culture and sensitivity were collected. The data were analyzed using SPSS version 17.0.
Results: A total of 185 blood culture positive reports were analyzed. Most commonly used empirical antibiotic was amikacin (96.2%) followed by cefotaxime (57.3%) and piperacillin-tazobactam (28.1%). Commonly used combination antibiotics were amikacin and cefotaxime (58.6%), followed by amikacin and piperacillin-tazobactam (28.7%). Rarely vancomycin (3.8%) or meropenem (1.7%) were used as first-line antibiotics in severe sepsis. Piperacillin-tazobactam (21.6%) followed by vancomycin (19.5%) were commonly used as second line drugs. Organisms showed maximum resistance against penicillins (91.7%), ceftazidime (96.9%), cefotaxime (85.3%), cefoxitin (75.6%), ceftriaxone (72.4%) and amikacin (55%) and maximum sensitivity to vancomycin (100%), linezolid (100%), imipenem (92.3%), netilmicin (60%) and piperacillin-tazobactum (52.4%).
Conclusions: (1) There is an emerging resistance against cephalosporins (including 3rd generation) and amikacin, (2) vancomycin, linezolid, imipenem are showing maximum sensitivity and hence should be kept in reserve for resistant cases.

Keywords: Neonatal sepsis, Antibiotic sensitivity and resistance, Empirical antibiotics, Combination therapy

INTRODUCTION

Antibiotics are the most frequently used medicines in neonatal intensive care units (NICU). With increasing prevalence of antimicrobial-resistant organisms being reported in many intensive care units (ICU), the assessment of antimicrobial use and determination of need for control measures are important priorities in ICU setting. In NICU, neonatal sepsis is the most common infection to occur, and most of the studies for NICU are targeted to it.[1,2] Septicemia is the major cause of neonatal mortality and morbidity worldwide.[3] It can be defined as "a clinical syndrome characterized by systemic signs and symptoms of bacteremia during the 1st month of life." It is labeled as "early onset (first 72 h of life)" and "late onset" (beyond 72 h) sepsis.[4] Emerging high rate of antibiotic resistance against commonest bacterial pathogen has worsened the situation. In suspected septicemia, 2 or 3 days empirical

antibiotic therapy should begin immediately after cultures have been sent. Antibiotics should be re-evaluated when the results of the cultures and sensitivity are available.[5]

Multidrug antibiotic resistance is an emerging problem in NICU particularly in developing countries. Moreover, the spectrum of organisms that cause neonatal sepsis changes from time to time and varies from region to region.[6] Continuous surveillance for antibiotic susceptibility, rational use of antibiotics and the strategy of antibiotic cycling can provide some answers to it.[7,8] Timely review of sensitivity pattern locally in each hospital can guide about the development of resistance to first line and higher class of antimicrobials. It helps the clinicians in selecting antimicrobials rationally. Hence, the present study was undertaken with the objective to know the antibiotic sensitivity and resistance pattern of organisms isolated by blood culture in neonatal septicemia in our NICU and also to study the pattern of antibiotic usage in our NICU.

METHODS

This retrospective, observational study was carried out at NICU, Cheluvamba hospital attached to Mysore Medical College and Research Institute, Mysore during June 2012 to October 2012. Cheluvamba Hospital is a 1200 bedded tertiary care, teaching and referral hospital. It is one of the top most hospitals in around three districts where even the poor have access to advanced medical care. The hospital has a well-functioning 40 bedded NICU which combines advanced technology and trained healthcare professionals to provide specialized care for the critically ill or premature neonates and it has an average of 250 admissions per month (both inborn and outborn). After obtaining clearance from institutional ethics committee the clinical files of neonates admitted in the NICU for a period from June 2012 to October 2012 were reviewed. The pathogens isolated from the blood cultures of in-born and out-born patients were observed. Antibiotics given as empirical antibiotics before obtaining the blood culture and sensitivity reports were taken as first line drugs and the antibiotics changed or added based on clinical non response to first line antibiotics or based on blood culture and sensitivity reports were taken as second line drugs. The sensitivity and resistance pattern of isolated pathogens to various antibiotics were noted.

Inclusion criteria

All neonates with blood culture positive septicemia.

Exclusion criteria

1. Antibiotics used prior to admission to hospital
2. Neonates who died before reports of blood culture sensitivity were available
3. Neonates whose blood culture was reported as probable contaminants.

Sample size

The primary objective of this study was to know sensitivity and resistance pattern of bacteria in neonatal sepsis. Highest percentage antibiotic susceptibility of most prevalent organism was taken as a parameter for deciding sample size. Amikacin percentage susceptibility in *Klebsiella* was taken as "*p*" and sample size was calculated using the formula below:-

$$N = Z^2_{(1-\alpha/2)} \times p \times q/d^2$$

Where,

n = sample size
p = expected prevalence = 88.46%
q = 1-p = 11.54%
$Z = z$ statistic for the 95% level of confidence = 1.96
d = precision = 5%

The total sample size calculated by the above formula was 160. With design effect (W) of 1.25, final sample size worked out to be 185.

Statistical analysis

Data were entered into Microsoft excel and analyzed using SPSS version 17.0. (SPSS Inc. 233 South Wacker Drive. 11th Floor. Chicago, USA). Descriptive statistics was calculated for each independent variable in the study. For continuous variables, mean and standard deviation were calculated and for discrete variables percentages were calculated.

RESULTS

A total of 185 (M:F = 1.7:1) neonates with positive blood culture for various bacteria were included for the study. Empirical therapy was started in all neonates due to symptoms and signs suggestive of sepsis before the blood culture susceptibility report. Baseline data of neonates included for the study is shown in Table 1. Majority of neonates (82.2%) were aged ≤7 days of age and were term neonates (62.7%). Half of the neonates included were low birth weight neonates. Among the culture positive reports, Gram-positive organisms such as *Staphylococcus aureus* (35.9%), and methicillin-resistant *S. aureus* (MRSA) (20%) were most commonly reported pathogens followed by Gram-negative organisms such as *Klebsiella* (15.1%) and non-fermenting Gram-negative bacilli (7.6%) as shown in Table 2. Most commonly used first line antibiotic was amikacin (96.2%) followed by cefotaxime (57.3%) and piperacillin-tazobactam (28.1%) as shown in Table 3. vancomycin (3.8%) and meropenem (1.7%) were rarely used as first-line antibiotics in severe sepsis. Based on the clinical non-response and culture reports most commonly used second-line drug was piperacillin-tazobactam (21.6%) followed by vancomycin (19.5%). In combination, amikacin and cefotaxime (58.6%) were commonly used followed by amikacin and piperacillin-tazobactam (28.7%) as shown in Figure 1. Organisms showed maximum resistance against penicillins, cephalosporins and amikacin, maximum

Table 1: Baseline data of neonates (*n*=185).

Characteristics	Number	Percentage
Age (in days)		
≤7	152	82.2
8-28	33	17.8
Mean±SD	4.1±6.3 days	
Gender		
Male	116	62.7
Female	69	37.3
Gestational age		
Term	116	62.7
Preterm	69	37.3
Birth weight (in kg)		
<2.5	94	50.8
≥2.5	91	49.2
Mean±SD	2.27±0.67 kg	

SD: Standard deviation

Table 2: Common micro-organisms causing sepsis in neonates (*n*=185).

Organisms	*N* (%)	*N* (%)	
		Early onset sepsis (*n*=152)	Late onset sepsis (*n*=33)
S. aureus	65 (35.9)	52 (34.2)	13 (39.4)
MRSA	37 (20.0)	28 (18.4)	9 (27.3)
Klebsiella	28 (15.1)	24 (15.8)	4 (12.1)
Non-fermenting Gram-negative bacilli	14 (7.6)	13 (8.6)	1 (3.0)
Coagulase negative *S. aureus*	9 (4.9)	7 (4.6)	2 (6.1)
E. coli	8 (4.3)	6 (3.9)	2 (6.1)
Acinetobacter	8 (4.3)	8 (5.3)	-
Enterobacter	7 (3.8)	6 (3.9)	1 (3.0)
Pseudomonas	4 (2.2)	3 (1.9)	1 (3.0)
Citrobacter	2 (1.1)	2 (1.3)	-
Enterococci	2 (1.1)	2 (1.3)	-
H. streptococci	1 (0.6)	1 (0.7)	-

MRSA: Methicillin resistance *S. aureus, S. aureus: Staphylococcus aureus, H. streptococci: Haemolytic streptococci, E. coli: Escherichia coli*

sensitivity to vancomycin, linezolid, imipenem, netilmicin and piperacillin-tazobactum as shown in Table 4. Antibiotic sensitivity and resistance of *S. aureus* showed maximum resistance against ampicillin (100%), penicillin (86.9%), cefotaxime (81.6%), ceftriaxone (60%) followed by amikacin (57.2%), ciprofloxacin (55%) and showed more sensitivity to vancomycin, linezolid, tigecycline, netilmicin, azithromycin and pipercillin-tazobactum. MRSA showed

Table 3: Antibiotic usage pattern in septicaemia in neonates (*n*=185).

Characteristics	*N* (%)
First line therapy	
Amikacin	178 (96.2)
Cefotaxime	106 (57.3)
Pipercillin-tazobactam	52 (28.1)
Ceftriaxone	14 (7.6)
Vancomycin	7 (3.8)
Netilmicin	3 (1.6)
Ciprofloxacin	3 (1.6)
Meropenem	3 (1.6)
Second line therapy	
Pipercillin-tazobactam	40 (21.6)
Vancomycin	36 (19.5)
Meropenem	10 (5.4)
Netilmicin	1 (0.5)

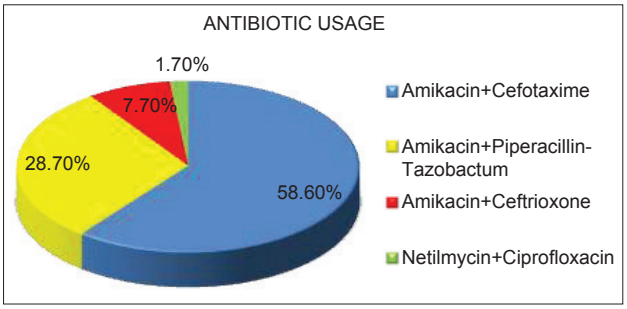

Figure 1: Antibiotic combinations used in septicaemia.

maximum resistance against cefoxitin (100%), ceftazidime (100%), ceftriaxone (100%), ciprofloxacin (97.3%), penicillin (96.9%), gentamicin (86.1%), cefotaxime (78.6%) and amikacin (53.8%) and showed sensitivity to netilmycin, imipenem, linezolid and erythromycin.

DISCUSSION

Neonates are more susceptible to sepsis and nosocomial infections, so antibiotics are being prescribed more frequently in NICU. The emergence of antibiotic resistance in NICU affects the management of sepsis. It affects the initial choice of empirical antibiotics and also leads to multiple antibiotic prescriptions. Multiple antibiotics may increase the chances of drug interactions, adverse drug reactions and reduce the future choice of antibiotics by promoting resistance. It also prolongs the intensive care stay and increases the cost of treatment. So auditing of antibiotic sensitivity pattern guides about the development of early resistance and also helps in selecting appropriate antimicrobials.

The present study showed *S. aureus* (35.9%) followed by MRSA (20%) and *Klebsiella* (15.1%) as the most commonly isolated microorganisms from blood culture in NICU, which

Table 4: Overall antibiotic sensitivity and resistance pattern in septicaemia in neonates (*n*=185).

Antibiotics	Number observed (%)	*N* (%)		
		Sensitivity	Resistance	Moderately sensitive
Amikacin	109 (58.9)	44 (40.4)	60 (55.0)	5 (4.6)
Cefotaxime	136 (73.5)	19 (14.0)	116 (85.3)	1 (0.7)
Ceftriaxone	29 (15.7)	6 (20.7)	21 (72.4)	2 (6.9)
Vancomycin	11 (5.9)	11 (100.0)	-	-
Piperacillin-tazobactum	42 (22.7)	22 (52.4)	20 (47.6)	-
Netilmycin	30 (16.2)	18 (60.0)	12 (40.0)	-
Ciprofloxacin	177 (95.7)	49 (27.7)	117 (66.1)	11 (6.2)
Gentamycin	182 (98.4)	41 (22.5)	141 (77.5)	-
Penicillin	109 (58.9)	9 (8.3)	100 (91.7)	-
Tetracycline	42 (22.7)	8 (19.0)	32 (76.2)	2 (4.8)
Ampicillin	74 (40.0)	4 (5.4)	70 (94.6)	-
Ceftazidime	64 (34.6)	2 (3.1)	62 (96.9)	-
Cefoxitin	45 (24.3)	11 (24.4)	34 (75.6)	-
Imipenem	39 (21.1)	36 (92.3)	3 (7.7)	-
Erythromycin	78 (42.1)	34 (43.6)	29 (37.2)	15 (19.2)
Azithromycin	30 (16.2)	16 (53.3)	12 (40.0)	2 (6.6)
Ceftrioxone-clav	11 (5.9)	5 (45.5)	6 (54.5)	-
Tigecycline	15 (2.7)	13 (86.7)	2 (13.3)	-
cefoperozone	29 (15.7)	1 (3.4)	28 (96.6)	-
Aztreonam	14 (7.6)	3 (21.4)	11 (78.6)	-
Pristinamycin	11 (5.9)	6 (54.5)	4 (36.6)	1 (9.1)
Coilistin	1 (0.5)	1 (100.0)	-	-
Norfloxacin	1 (0.5)	-	1 (100.0)	-
Amoxyclav	7 (3.8)	1 (14.3)	6 (85.7)	-
Linezolid	16 (8.6)	16 (100.0)	-	-
Clindamycin	11 (5.9)	9 (81.8)	2 (18.2)	-
Cefuroxime	2 (1.1)	-	2 (100.0)	-

is consistent with the studies by Shaw et al.[9] and Kairavi and Saklainhaider.[10] According to the studies by Anwer et al.[11] and Mahmood et al.[4] *Klebsiella pneumoniae* was the most commonly isolated micro-organism.

When usage of antibiotics was considered, our study showed amikacin (96.2%) was the most commonly used empirical antibiotic followed by cefotaxime (57.3%) and piperacillin-tazobactum (28.1%). Based on the clinical assessment they were usually used as part of combination antibiotic therapy, most commonly amikacin and cefotaxime (58.56%) followed by amikacin and piperacillin-tazobactam (28.73%), amikacin and ceftriaxone (7.73%) as empirical therapy. According to Kaushal et al.[12] the most commonly used drugs were cefotaxime (59.09%), amikacin (55.45%), levofloxacin (54.55%) and piperacillin-tazobactam (51.82%). The most commonly used combinations were cefotaxime and amikacin (55.45%) followed by levofloxacin and piperacillin-tazobactam (51.82%) followed by ampicillin and gentamicin (14.55%) followed by meropenem and teicoplanin (10.91%). According to study by Reese and Alan[13] the most commonly used antibiotic was ampicillin (69.3%) followed by gentamicin (57.5%), cefotaxime (18.3%) and vancomycin (9.9%). The study by Schellack and Gous[14] showed that most commonly used antimicrobial was amikacin (69.47%) followed by piperacillin-tazobactam (65.25%), benzylpencillin (50.53%), meropenem (49.47%) and ciprofloxacin (29.47%). So when compared there is a variation in selecting antibiotics from region to region.

Amikacin and netilmicin have the widest spectrum of activity and resistance to bacterial aminoglycoside inactivating enzymes and less chance of cross-resistance and hence were preferred over other aminoglycosides. Combination therapy produces synergistic action and covers both Gram-positive and Gram-negative organisms.

Our result on culture sensitivity pattern of *S. aureus* was similar to the study conducted by Kairavi and Saklainhaider[10] which showed maximum sensitivity with vancomycin (100%) for Gram-positive organisms. Another study by

Shaw et al.[9] reported that the Gram-positive organisms displayed a high degree of resistance to most pencillins and cephalosporins but glycopeptides and monobactams were effective in most cases.

Gram-negative organism, *Klebsiella* showed maximum resistance against ampicillin, penicillin, 2nd and 3rd generation cephalosporins followed by gentamicin and amikacin and sensitivity against imipenem and ceftriaxone-clavulanate. The findings in our study was similar to the study conducted by Movahedian et al.[15] which reported that *K. pneumoniae* showed a high degree resistance to commonly used antibiotics ampicillin as well as third generation cephalosporins. According to the study by Aurangzeb and Hameed,[16] Gram-negative organisms showed high degree of resistance to commonly used antibiotics, ampicillin (79.3%), amoxicillin (74.6%), ceftazidime (71.6%), cefotaxime (55.2%) and comparatively low resistance to gentamicin (43.2%), tobramycin (34.3%), imipenem (23.6%), amikacin (22.3%), ofloxacin and ciprofloxacin (11.9%) respectively.

Organisms acquire resistance to penicillins and cephalosporins by elaboration of β lactamases which destroy specific antibiotics, alteration in target proteins reducing the affinity for the antibiotics and activation of efflux pump so that antibiotic does not reach its site of action. Resistance to aminoglycosides is acquired by aquisition of cell membrane bound inactivating enzymes (plasmid-mediated bacterial transferase enzymes), mutation of the receptor protein on 30S ribosomal unit, which prevent the attachment of the drug and decreased efficiency of the aminoglycoside transporting mechanism. Resistance to fluoroquinolones is due to chromosomal mutation producing a DNA gyrase or topoisomerase IV with reduced affinity or due to reduced permeability/activation of efflux pump.

In the present study overall vancomycin (100%) was found to be most sensitive antibiotic, followed by the imipenem (92.3%) and piperacillin-tazobactam (52.40%). Whereas resistance was more with following drugs - Ceftazidime (96.9%) followed by cefoperzone (96.6%), ampicillin (94.6%), penicillin (91.7%), amoxicillin-clavulanic acid (85.7%), cefotaxime (85.3%), gentamycin (77.5%), ceftriaxone (72.4%), ciprofloxacin (66.1%), cefazolin (53.84%) and cefuroxime (42.3%). Hence, antibiotics must be administered conservatively according to epidemiological studies in the region, with confirmed indications, and cyclical change of antibiotics should be recommended based on culture and sensitivity reports.

CONCLUSION

1. There is an emerging resistance against cephalosporins (including 3rd generation) and amikacin
2. Vancomycin, linezolid, imipenem were showing maximum sensitivity and hence should be kept in reserve for resistant cases.

ACKNOWLEDGMENT

We wish to express our sincere thanks to Dr. Parashivamurthy B.M., Professor and Head, Department of Pharmacology and Dr. Krishnamurthy, Professor and Head, Department of Paediatrics, MMC and RI, Mysore, for providing permission to do this study and their valuable suggestions during the period of this work.

We thank to Dr. Bhanupriya and Dr. Ambika, Postgraduates and medical record section staff for helping us in the collection of data.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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DOI: 10.5455/2349-3291.ijcp20141107
Cite this article as: Nagesh HN, Basavanna PL, Savitha MR. Antibiotic usage and auditing of antibiotic sensitivity pattern of culture positive neonatal septicaemia in neonatal intensive care unit of a tertiary care hospital: a retrospective study. Int J Contemp Pediatr 2014;1:142-7.