

Changing trends of antibiotic resistance in neonatal sepsis in a tertiary care hospital

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ABSTRACT

Background: Sepsis and other infections cause 15% neonatal deaths in India. The present study is to determine the resistance pattern of pathogens causing neonatal sepsis and to provide antibiogram to pediatricians for better patient management.

Methods: Positive Blood culture reports of neonatal sepsis cases detected during the years 2014 and 2015 were studied. The antibiotic resistance of the organisms found during the years 2014 and 2015 were compared by calculating the probability (p value) using the standard formula.

Results: Coagulase negative staphylococci (CONS) was the most common organism in 2014 whereas pseudomonas was predominant in 2015. Resistance of CONS to amoxicillin and ceftriaxone has significantly increased in 2015. Also resistance of CONS to vancomycin was noted. Resistance of Pseudomonas to cefuroxime, ceftazidime and amoxicillin/clavulanic acid combination were increased but not significantly. There was also emerging resistance of pseudomonas to gentamicin and amikacin. Resistance of acinetobacter to cefuroxime, ceftriaxone and gentamicin has increased in 2015 but not significantly. Citrobacter showed a significant increase in resistance to amoxicillin/clavulanic acid combination (p=0.006).

Conclusions: Bacterial spectrum causing neonatal sepsis varies in different regions, varies in the same site during different time periods, also their antibiotic resistance pattern varies in different regions and changes constantly. Increase in resistance to commonly used antibiotics stress the need of rational use of antibiotics.

Keywords: Antibiotic resistance, Neonatal sepsis, Retrospective study, Tertiary care hospital

INTRODUCTION

Neonatal sepsis or sepsis neonatorum is a clinical syndrome resulting from systemic infection and bacteremia in the first month of life.¹ Sepsis and other infections cause 15% neonatal deaths in India.² Indiscriminate use of broad spectrum antibiotics without appropriate blood cultures and the practice of not stopping their use when no infection is documented has resulted in high antibiotic resistance rate among organisms isolated in India.³ The present study is to determine the resistance pattern of pathogens causing

neonatal sepsis and to provide antibiogram to Pediatricians for better patient management.

METHODS

This is a retrospective study of antibiotic resistance patterns in positive Blood culture reports of neonatal sepsis cases detected during the years 2014 (1st January to 30th December) and 2015 (1st January to 30th December). After obtaining the approval from the ethical committee, the blood culture reports of neonatal sepsis cases were obtained from the Department of microbiology and screened. The incidence and antibiotic resistance of both the Gram positive and Gram negative microorganisms

were found by calculating their percentages. The antibiotic resistance of the commonly occurring organisms during the years 2014 and 2015 was compared by calculating the probability (p value) using the standard formula. The 'p' value less than 0.05 was defined significant.

RESULTS

In the year 2014, the most common Gram positive organism was CONS (43%) followed by *staphylococcus aureus* (11%), enterococci (5%) and *streptococci* 1%. In the year 2015, the most common Gram positive organism was again CONS (12%) followed by *enterococci* (6%), *staphylococcus aureus* (5%), and *streptococci* 2%.

Table 1: percentages of Gram positive microorganisms present in the blood cultures collected during the year 2014 and 2015 (from 1st January to 31st December).

Name of the organism	Year 2014	Year 2015
CONS	43%	12%
<i>Staphylococcus aureus</i>	11%	4%
<i>Enterococci</i>	5%	6%
<i>Streptococci</i>	1%	2%

In the year 2014 *Klebsiella spp.* (33%) was the most common Gram negative organism followed by *Acinetobacter spp.* (19%), *Pseudomonas spp.* (14%), *Citrobacter spp.* (11%), *Proteus mirabilis* (4%) and *Escherchia coli* (1%). In 2015, *Pseudomonas spp.* (29%) was the predominant organism followed by *Klebsiella spp* (26%), *Acinetobacter spp* (12%), *Citrobacter spp.* (7%), and *Escherchia coli* (2%).

The resistance of CONS to amoxicillin and ceftriaxone has significantly increased in 2015. Also, CONS showed 10% resistance to vancomycin in 2015. The sensitivity of staphylococcus aureus to amoxicillin did not show any change in both the periods but the resistance to ceftriaxone was raised to 33% in 2015.

Table 2: The percentages of Gram negative microorganisms present in the blood cultures collected during the year 2014 and 2015 (from 1st January to 31st December).

Name of the organism	Year 2014	Year 2015
<i>Acinetobacter</i>	19%	12%
<i>Klebsiella</i>	33%	26%
<i>Pseudomonas</i>	14%	29%
<i>Citrobacter</i>	11%	7%
<i>Proteus</i>	4%	0
<i>Escherichia coli</i>	1%	2%

Klebsiella spp. showed a significant increase in resistance to cefuroxime in 2015. The resistance of *Klebsiella spp.* to amikacin, ceftriaxone/ sulbactam combination and ciprofloxacin was also increased but not significantly.

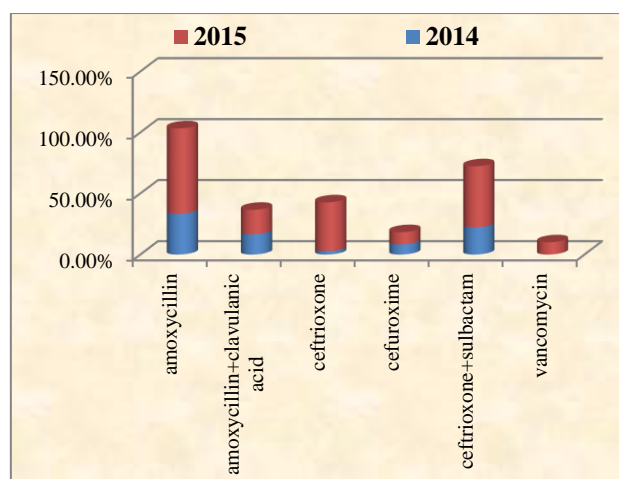


Figure 1: Comparison of antibiotic resistance pattern in Coagulase negative *Staphylococcus aureus* in 2014 and 2015.

The resistance of *Acinetobacter* to cefuroxime, ceftriaxone, ceftazidime and gentamicin has increased in 2015 but not significantly.

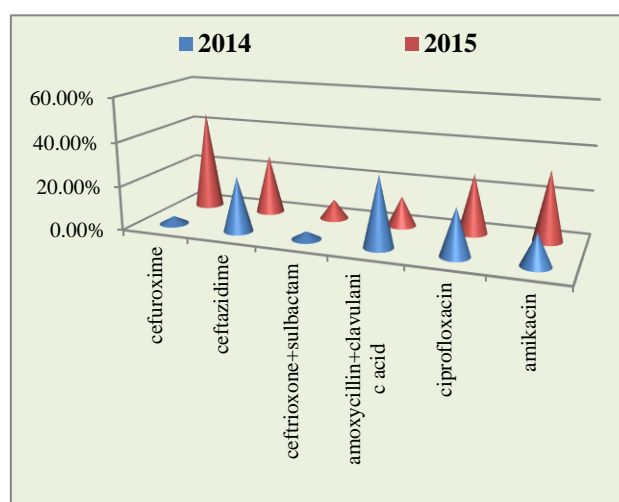


Figure 2: Comparison of antibiotic resistance pattern in *Klebsiella spp.* in 2014 and 2015.

Regarding *Pseudomonas spp.* there was emerging resistance to gentamicin, amikacin whereas the resistance to cefuroxime, ceftazidime and amoxicillin/ clavulanic acid combination was increased in 2015 but not significantly.

Citrobacter spp. showed a significant increase in resistance to amoxicillin/clavulanic acid combination (p=0.006). It also showed an increase in resistance to amikacin, cefuroxime, ciprofloxacin, ceftriaxone/ sulbactam combination and other 3rd and 4th generation cephalosporins.

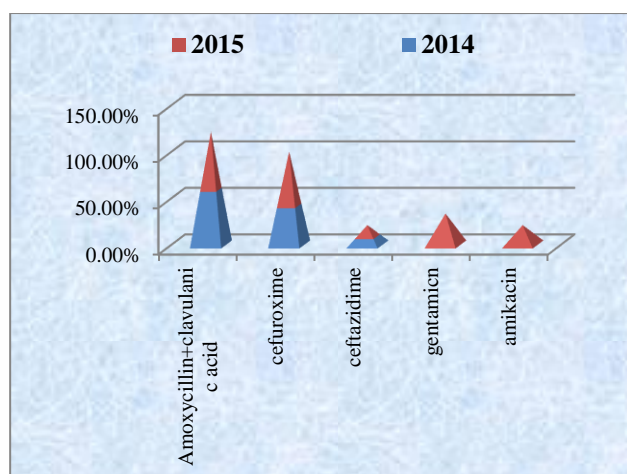


Figure 3: Comparison of antibiotic resistance pattern in *Pseudomonas* spp. in 2014 and 2015.

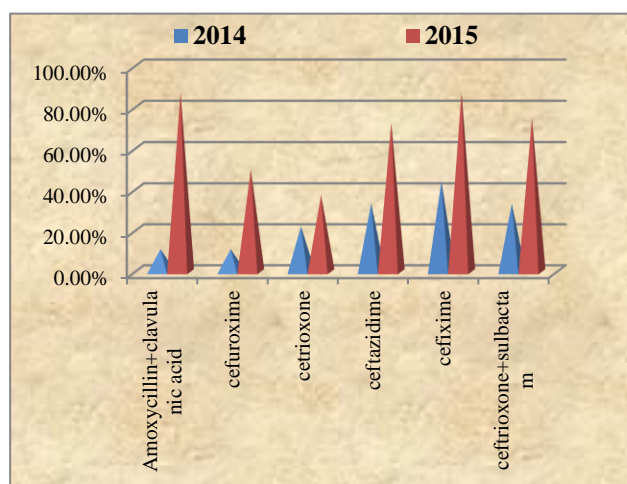


Figure 4: Comparison of antibiotic resistance pattern in *Citrobacter* spp. in 2014 and 2015.

DISCUSSION

In this study, the positive blood culture reports of neonatal septicemia cases detected during the years 2014 (1st January to 30th December) and 2015 (1st January to 30th December) obtained from the Department of microbiology were studied.

In the year 2014 CONS (43%) was the most common organism followed by *Klebsiella* spp. (33%) and *Acinetobacter* spp. (19%). This result was similar to that in the study by Arpita et al where CONS (27%) was the most common organism and also in the Delhi neonatal study CONS (46%) was the commonest organism in one of the sites.^{4,5} Whereas in other studies by Sharma CM et al and Marwah P et al *Staphylococcus aureus* was the commonest.^{6,7} In the year 2015, the status was completely different with *Pseudomonas* spp. (29%) as the commonest followed by *Klebsiella* spp. (20%), *Acinetobacter* spp. (12%) and CONS (12%). whereas in other studies by Viswanathan et al and Al Taiar et al

Klebsiella spp. was the commonest.^{8,9} In the Delhi neonatal study *Acinetobacter* spp. (27%) and *Klebsiella* (25%) were shown to be predominant in two different sites.⁵ This shows that *Pseudomonas* spp. has emerged as the most common organism causing neonatal sepsis. This inference shows that there is a high preponderance of hospital acquired infection. Hospital acquired infection can be minimized by good hand hygiene, promoting provision of Breast milk to sick LBW neonates, good adherence to sepsis protocols and strict antibiotic policy that limits its use when required.³

Then comparing the antibiotic resistance of the common organisms in the year 2014 and 2015, CONS showed significant increase in resistance to amoxicillin ($p=0.042$) and to ceftriaxone ($p=0.0016$). So, this increase in resistance to the first line antibiotic and also the third-generation cephalosporin may be due to injudicious use of antibiotics when not needed, which could be avoided in future. Increase in resistance to amoxicillin/clavulanic acid combination and cefuroxime was not much significant. But, in the study by Arpita et al⁴ Gram positive organisms showed more resistance to amoxicillin/clavulanic acid combination (55%).⁴ It was alarming to notice that 10% of CONS showed resistance to vancomycin in 2015, but it was 100% sensitive to vancomycin in another study by Madhur Sharma et al.⁶ *Staphylococcus aureus* showed no resistance to ceftiozone in 2014 but it has increased to 33% in 2015. So, judicious use of vancomycin is also a need of the hour.

Klebsiella spp showed significant increase in resistance to cefuroxime ($p=0.0009$) in 2015. It showed no significant increase in resistance to amikacin, ceftiozone/sulbactam combination and ciprofloxacin. Resistance to cephalosporins may be related to the inability of the antibiotic to reach its site of action due to alteration in the penicillin binding proteins (PBPs) that are the targets of the cephalosporins such that the antibiotics bind to bacterial enzymes (β -Lactamases) that can hydrolyze the β -lactam ring and inactivate the cephalosporins.¹⁰ Third generation cephalosporins are susceptible to hydrolysis by inducible chromosomally encoded type I β lactamases.¹⁰

Regarding *Pseudomonas* spp. there was emerging resistance to gentamicin (33%), amikacin (20%), whereas in a study by Sharma CM et al the sensitivity of *Pseudomonas* spp. to amikacin was 100%.⁶ Clinically drug inactivation is the most common mechanism for any microbial resistance. The genes encoding aminoglycoside-modifying enzymes are acquired primarily by conjugation and transfer of resistance plasmids.¹⁰ The resistance *Pseudomonas* to amoxicillin/clavulanic acid combination (62%), cefuroxime (58%), ceftazidime (12%) was increased in 2015 but not significantly. The resistance is mediated by plasmid encoded enzymes (e.g. β -lactamases and acetylating enzymes).¹¹ Neonates infected with

Pseudomonas spp. had the highest case fatality rate.⁵ So, the increasing burden of resistant *Pseudomonas spp.* might pose a formidable threat in the coming years.

Acinetobacter spp. did not show any increase in resistance to amoxicillin/ clavulanic acid combination in 2015. This report is in sharp contrast to that in Delhi neonatal study,⁵ where *Acinetobacter spp.* showed 82% multidrug resistance and 38% resistance to extended spectrum penicillins. *Citrobacter spp.* showed a significant increase in resistance to amoxicillin/clavulanic acid combination ($p=0.006$). This may be due to the fact that there is a frequent use of amoxicillin/clavulanic acid combination in our area. *Citrobacter spp.* occurs in the environment and in the human colon and can cause sepsis in immunocompromised patients.¹¹ It also showed an increase in resistance to amikacin, cefuroxime, ciprofloxacin, ceftrioxone/sulbactam combination and other 3rd and 4th generation cephalosporins. The emergence of antibiotic resistance in pathogens that infect the newborns is of great concern. Antibiotics interfere with colonization of normal flora, thereby facilitating colonization with more virulent pathogens. The rational use of antibiotics in neonates involves using narrow-spectrum drugs when possible, treating infections and not colonization and limiting the duration of therapy.¹²

CONCLUSION

Bacterial spectrum causing neonatal sepsis varies in different regions. It may also vary in the same site during different time periods. Antibiotic resistance also varies and in fact it is increased mostly in 2015 when compared to 2014 in the same site. Surveillance of pathogens and their resistance patterns should be done in regular intervals so that it can help in empirical treatment of neonatal sepsis.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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