Original Research

Relationship between antibiotic consumption pattern and antibiotic resistance in neonatal sepsis

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Abstract

Background and aim. Inappropriate use of antibiotics may increase antimicrobial resistance (AMR) among different microorganisms and may lead to treatment failure in neonatal septicemia. The aim of this study was to recognize the most common microorganisms responsible for neonatal sepsis and to evaluate the trend of change of resistance pattern among microorganisms.

Methods. This study was done retrospectively on 344 cases diagnosed with neonatal sepsis, including both early and late onset cases, admitted to the tertiary care teaching hospital of southern India from January 2012 to July 2017. Accordingly, 231 culture positive neonatal sepsis cases were collected from hospital data base and analyzed. Culture positive cases within 72 hours of life were termed as early onset while after 72 hours were late onset. Antibiotics utilization during the period was calculated using WHO AMC tool and reported as (DDD)/100 bed days.

Results. *Klebsiella pneumoniae* with 56 (21.8%) and *Coagulase negative Staphylococcus* with 52 (20.2%) cases were the most frequent isolated organisms which were responsible for 55.8% and 14.6% of deaths among the study subjects respectively. Amikacin (86.7%), vancomycin (52.3%) and ampicillin (40.6%) were the most used antibiotics in terms of DDD/100 bed days.

Conclusion. The results obtained from our study have brought substantial information on the antibiotic resistance pattern among microorganisms causing neonatal sepsis. Moreover, results obtained from this study can be used for designing antibiotic stewardship policies to prevent the emergence of resistance and to improve the treatment outcome.

Keywords: neonatal sepsis, culture positive, antibiotic, defined daily dose (DDD), microbial drug resistance

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Introduction

Neonatal sepsis is a serious global health issue, which leads to more than 2.6 million neonatal deaths annually in developing countries [1]. According to the National Neonatal Perinatal Database (NNPD-2002-3), the incidence of neonatal septicemia contributes to 30/1000 live births annually in India, which represents 19% of all neonatal deaths [2].

Neonatal sepsis is defined based on the number of laboratory and clinical criteria [3]. World Health Organization defines neonatal sepsis as a clinical syndrome with signs and symptoms of infection, with or without accompanying bacteremia. Various systemic infections such as meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections are encompassed by this definition. However, superficial infections like oral thrush and conjunctivitis are not included under neonatal sepsis [4].

Management of sepsis is a critical task which requires immediate

intervention. Mortality rate from untreated neonatal sepsis might be as high as 50% and culture result takes at least 48-72 hours to be reported, thus physicians are compelled to start empirical therapy [5]. Knowledge of common microorganisms involved in neonatal sepsis locally and their antimicrobial susceptibility is essential to select appropriate antimicrobial therapy [6]. Microorganism causing neonatal sepsis and their sensitivity/resistance pattern differ from region to region and depends on the pattern of antibiotics use [7]. To quantify the pattern of antibiotic use, WHO ATC (anatomical therapeutic chemical) classification and the concepts of defined daily dose (DDD) was used. DDD is a measurement unit, which will help to calculate the average use of drug in different populations irrespective to the price or formulation of drug. DDD/100 bed-days give us an estimate of drug use among hospital in-patients [8].

We anticipate that our study will yield substantial information on antibiotic resistance pattern among microorganisms causing neonatal sepsis. Measurement and display of antibiotic consumption information will help in designing strategies both at the level of physicians and at the level of administrators for careful antibiotic care and policy decisions respectively.

Study objectives

This study was aimed to study the prevalence, the trend of change of resistance pattern against various antibiotics and outcome of *Klebsiella pneumoniae (K. pneumoniae)* and *Coagulase negative Staphylococcus (CoNS)* in culture positive neonatal sepsis patients.

Methods

This is a hospital based retrospective observational study, conducted in a tertiary care teaching hospital, during January 2012 to July 2017, after obtaining Institutional Ethics Committee (IEC) approval (No. IEC 497/2017).

Participants

Neonates diagnosed with neonatal sepsis (both early and late onset) and admitted to NICU from 1st January 2012 to 31st July 2017 and in compliance with the inclusion and exclusion criteria were included in the study. The subjects were identified using the ICD 10 Code: P36.0-9from Medical Record Department (MRD) files. Data on the demographics, details of prescribed antibiotics and therapeutic outcome were collected from patient medical record. Data on blood culture reports and sensitivity/resistance of antibiotics for each patient were collected from online microbiology laboratory reports. The WHO Anatomical Therapeutic Chemical (ATC) classification of antibiotics was used to categorize the antibiotics. For each ATC code and a special route of administration, one DDD is assigned.

Inclusion criteria

• All the cases that were categorized as neonatal sepsis patients (early/late onset) according to the NICHD and WHO definition of neonatal septicemia. Cases with culture positive report within 72 hours of life were considered as early onset while after 72 hours of life were termed as late onset sepsis.

Exclusion criteria

• Patients whose records were missing.

Statistical analysis

Cumulative sensitivity and resistance patterns of isolated microorganisms against various antibiotics were calculated from the culture sensitivity report. Resistance pattern data of the most common antibiotics was reported as a percentage. Based on the following formula antibiotic consumption was calculated yearly i.e., 2012-2017 using the antimicrobial consumption tool version 1.9.0 [10] and the data is depicted as DDD/100 bed days.

$$\text{DDD/100 bed days} = \frac{\text{No. of grams of antibiotic used*} \times 100}{\text{WHO DDD Units (g)} \times \text{ No. of bed days**}}$$

* No. of grams of antibiotic used= strength of unit dosage[a] (g)×No. of unit doses per package[b]×No. of packages used

** No. of bed-days=No. of beds in the hospital×Occupancy index×No. of days (during the study period)

Occupancy index= Percentage of beds occupied during study period (0.79 or 79% was occupied)

[a] Package corresponds to, for example a strip of 10 tablets, a bag of 500 tablets or a box of 12 vials etc.

[b] A bed-day corresponds to one occupied hospital bed for one day

DDD of antibiotics used and resistance pattern of the previous year's hospital data was considered for establishing a relationship between the duration of antibiotics use and increased resistance towards them. Change in the resistance trends for *Klebsiella pneumoniae* and Coagulase negative *Staphylococcus* with most common antibiotics were depicted using a graph, where the "X-axis" represents "year" and "Y-axis" denotes "percentage resistance".

Results

General demographic features

A total of 344 cases of neonatal septicemia (early/late onset) were identified using MRD files of which 66.7 % (n=229) of the study population were male and the rest were females. Of the total cases included, 160 (53.5%) were found to be preterm (gestational age <37 weeks) while 211 (61.3%) had low birth weight (birth weight< 2.5 kg).

Out of the total 344 cases, 67.1% (n=231) were culture positive with 257 isolates being identified in this population. Analysis of these positive culture reports reveals that the most common microorganisms causing neonatal sepsis were *K. pneumoniae* 56 (21.8%), and *CoNS* with 52 (20.2%) followed by: *Enterobacter species* with 31 (12.1%), *Acinetobacter species* with 19 (7.4%), *Methicillin*

resistant Staphylococcus with 18 (7%), *Escherichia coli* with 14 (5.4%) and *Candida species* with 12 (4.7%) number of cases.

Neonates infected with *Acinetobacter* species (66.7%) were found to have the highest mortality, followed by *K. pneumoniae* (55.8%), while the lowest was among those infected with Coagulase negative Staphylococcus (14.6%).

Antibiotic consumption pattern

Total utilization of the commonly used antibiotics in neonatal sepsis patients was assessed to evaluate the over/normal consumption of the antibiotics, in comparison to that of WHO - ATC/DDD index. Amikacin, Vancomycin and Ampicillin were most frequently administered antibiotics in our hospital regardless of the culture report. Overconsumption of amikacin (6.772), ciprofloxacin (6.863), Vancomycin (2.349) was also observed in our hospital setting and is shown in detail in table I.

Resistance pattern of microorganisms

Trends in the resistance or sensitivity pattern of microorganisms to commonly used antibiotics were evaluated to assess the proper functioning of those antibiotics on the specific organism. We evaluated the sensitivity/resistance pattern of cases infected with *K. pneumoniae* and *CoNS,* as these were the most prominent microorganisms commonly found in our hospital settings. However, evaluation of other micro-organisms sensitivity/resistance patterns was not possible due to the smaller number of patients being infected.

Resistance pattern of *Klebsiella pneumoniae*

K. pneumoniae identified isolates were resistant to Ampicillin/Amoxicillin (49 (100%)), Aztreonam (23 (95.8%)), Cefazolin/Cefadroxil (27 (90%)), Cefuroxime (42 (89.4%)), Netilmicin (18 (62.1%)), Cefotaxime/Ceftriaxone (44 (84.6%)), Cefpirome/Cefepime (31 (77.5%)), Amoxicillin-clavulanic acid (37 (72.5%)), Gentamicin (32 (60.4%)) and Ciprofloxacin/Ofloxacin (25 (48.1)). Comparatively less resistance to Cefoperazone-sulbactam (11 (26.2%)), Amikacin (13 (25%)), Imipenem (11 (26.2%)) and Colistin (1 (10%)) was seen among these isolates. Out of 56 isolates of *K. pneumoniae*, 37 (66.1%) were extended spectrum beta lactamase enzyme (ESBL) producer.

Resistance of *K. pneumoniae* against Amikacin had shown a decreasing trend from 2013 onward; however, its resistance against Amoxicillin-clavulanic acid had peaked in the year 2014. In contrast to that, a decreasing trend was seen during 2015 and 2016 but again picked up in the year 2017. *K. pneumoniae* isolates showed alternative resistance to Cefoperazone-sulbactam from 2012 to 2017. The resistance peaked in 2012, 2014 and 2016. However, resistance to Piperacillin-tazobactam was remarkably decreased from 2014 onwards. This trend of change in the resistance pattern of *K. pneumoniae* to the most common antibiotics was depicted in figure 1.

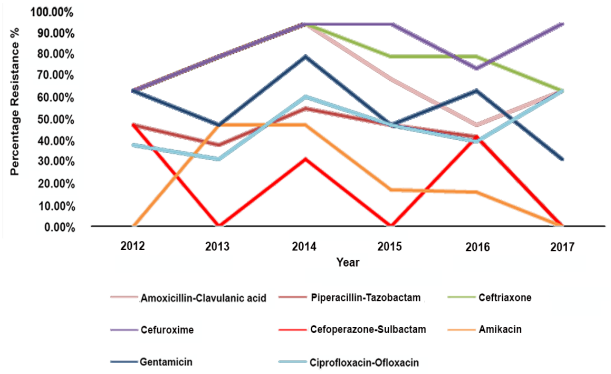

Figure 1. Trend of resistance change in *Klebsiella pneumoniae* identified isolates.

Table I. Antibiotic utilization in neonatal sepsis patients.

Antibiotic	ATC Classification	DDD/100 bed-days						
		2012	2013	2014	2015	2016	2017	TTotal
Ampicillin	J01CA01	9.300	13.355	6.746	5.727	0.024	5.442	40.594
Amikacin	J01GB06	5.449	10.880	9.579	9.943	23.48	27.441	86.772
Piperacillin–tazobactam	J01CR05	3.326	8.843	7.387	2.596	4.619	3.541	30.312
Cefoperazone	J01MA02	0	0	1.131	5.052	5.454	0.180	11.817
Cefuroxime	J01DC02	1.286	0.998	1.988	2.635	0.424	0.697	8.028
Cefoperazone – sulbactam	J01DD62	0.017	0	6.386	0.531	1.082	0	8.016
Amoxicillin – clavulanic acid	J01CR02	0.140	0.180	0.5	0.014	0.714	0.107	1.655
Cefotaxime	J01DD01	2.133	4.229	0.094	1.219	0.171	0.421	8.267
Trimethoprim-sulfamethoxazole	J01EE01	0	11.590	3.896	0	0.195	0.958	16.639
Vancomycin	J01XA01	2.0066	13.379	9.280	11.779	9.786	6.119	52.3496
Ciprofloxacin	J01MA02	6.174	10.430	10.806	4.082	5.240	0.131	36.863
Erythromycin	J01FA01	0	1.993	2.495	0.143	0.419	0.618	5.668
Metronidazole	J01XD01	0.326	1.029	0.324	0.929	0.290	0	2.898

ATC= Anatomical therapeutic chemical; DDD= Defined daily dose.

Resistance pattern of coagulase negative Staphylococcus

Coagulase negative Staphylococcus identified isolates were resistant to Erythromycin (41 (95.5%)), Ampicillin (25 (89.3%)), Cloxacillin (34 (81%)), Cefazolin/Cefadroxil (18 (78.3%)), Amoxicillin-clavulanic acid (23 (76.7%)), Gentamicin (31 (72.1%)), Ciprofloxacin/Ofloxacin (28 (68.3%)), Clindamycin (23 (59%)) and Trimethoprim-sulfamethoxazole (24 (54.5%)). Comparatively less resistance to Tetracycline/Doxycycline (3 (8.8%)), Linezolid (1 (2.9%)) and Rifampicin (1 (2.2%)) was seen among *CoNS* isolates. This organism was 100% sensitive to Vancomycin.

Resistance of *CoNS* isolates against Rifampicin is decreasing from 2014 to 2016. Resistance of the same isolates to the other commonly used antibiotics like Amikacin, Ciprofloxacin/Ofloxacin, Cloxacillin and Trimethoprim-sulfamethoxazole had shown increasing trend from 2014 onward. However, *CoNS* isolates showed less resistance against Gentamicin in 2015 in comparison to 2014 and 2016. Moreover, resistance of *CoNS* isolates could not be presented in 2012 and 2017 due to less sample number. The change in trend of resistant pattern of c*oagulase negative Staphylococcus* to the most common antibiotics was shown in figure 2.

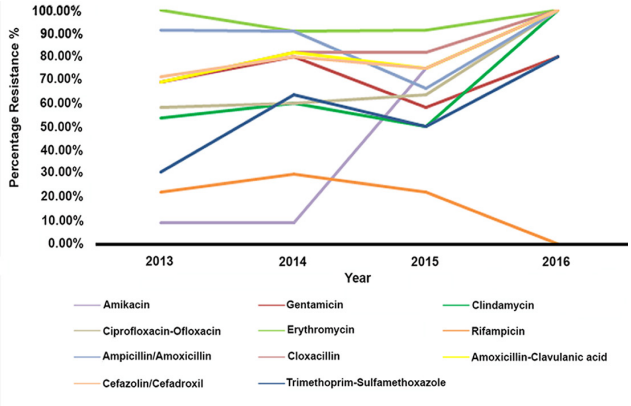

Figure 2. Trend of change of resistance in coagulase negative *Staphylococcus.*

Discussion

Antimicrobial resistance (AMR) is one of the alarming problems emerging in the current scenario. Failure to address this, might lead to a "post antibiotic era" defined by erosion of reserved antibiotics, limited usage of available antibiotics leading to increased strain in the health care system. Proper and judicious use of antibiotics specific to microorganism invaded, is the key to prevent antimicrobial resistance (AMR) in any clinical settings [9]. Thus, keeping this in account, we aimed to study the prevalence, sensitivity/resistance pattern against various antibiotics and outcome of the most common microorganism isolated from neonatal sepsis patients. The current research interpretation is based on three divisions i.e. most common microorganism isolated, resistance/ sensitivity pattern of the microorganism and analysis of change in trend of these organisms from 2012-2017.

Most common microorganisms isolated

The current research states that 67.1% (n=231) of the study population were culture positive. However, another study conducted by Zakariya et al., to evaluate the bacteriological profile and antibiotic sensitivity pattern in neonatal sepsis had showed 120 patients, 50 (41.6%) number of the cases to be culture positive [10]. Similarly, another additional study carried out in an Indian tertiary care hospital by Shah et al. had showed 31.57% of the 190 cases of study population as culture positive [11]. The noticeable difference in the percentage of culture proven cases reported in the above two mentioned study and our study can be attributed to the different methods applied for obtaining culture report of microorganisms. Moreover, the differences in diagnostic criteria used by physicians in various settings can be considered as one of the factors for the same as any neonate with signs and symptoms of infection may be diagnosed as neonatal sepsis patient, even though the culture report is negative [10].

Klebsiella pneumoniae (22.4%) and *coagulase negative Staphylococcus* (21.9%) were the most common gram negative and gram-positive organism isolated and identified in infected neonatal sepsis patients respectively. This can be attributed to the fact that *Klebsiella pneumoniae* is highly prevalent in sophisticated intensive care unit settings and is predominantly observed in developing countries like India and Nigeria [10]. Analogous results were shown by another study conducted by Zakariya et al on bacteriological profile and antibiotic sensitivity pattern in neonatal sepsis where, *K. pneumoniae* isolates (66%) and *CoNS* isolates (12%) were the most common identified microorganisms [10]. Likewise, the study conducted in Anand District located in western India reveals that *K. pneumoniae* was the most common isolated organism found both among the early and late onset cases [12].

However, contrary to our study, a study carried out during 2016 in a tertiary care hospital of north India reveals that *CoNS* (17.43%) was the predominant identified isolate followed by, *K. pneumoniae* (16.11%) [13]. Similarly, a study conducted in south Indian, tertiary care neonatal unit found that the most common identified organisms were *S. aureus* (60%) and *K. pneumoniae* (23%), which can be due to prior exposure of the neonates to these pathogens during delivery [10].

Resistance/sensitivity pattern of the microorganism

The current research illustrates that *K. pneumoniae* isolates were resistant against most of the antibiotics which are commonly used in our settings such as piperacillin-tazobactam, ticarcillin-clavulanic acid, gentamicin,

netilmicin and all classes of cephalosporins. However, the identified isolates showed least resistance against colistin, and can therefore be recommended as the "antibiotic of choice" in patients who are infected with this microorganism. Meanwhile, amikacin and imipenem were recommended as the second effective choices as there is remarkable decrease in resistance of *K. pneumoniae* to Amikacin since 2013 to 2017. Furthermore, for the above-mentioned reason, it can be we recommend as drug in empirical therapy of gram-negative organism.

66.1% of *K. pneumoniae* isolates in our study were ESBL producer. Recent studies suggest that beta-lactam beta-lactamase inhibitor combinations (BLBLICs) can be used to treat patients infected by ESBL producer microorganisms. Thus, our study showed that cefoperazone-sulbactam is the most effective choice among BLBLICs against *K. pneumoniae*. Similar results were showed in a study carried by Sakellariou et al, where 27.1% *K. pneumoniae* identified isolates were also extended spectrum beta lactamase producers. But contrary to our study, the same identified *K. pneumoniae* isolates were sensitive to aminoglycosides and ciprofloxacin, which gives a clue regarding routine monitoring of ESBL production in gram negative isolates [14].

K. pneumoniae isolates show alternative resistance to Cefoperazone-Sulbactam from 2012 to 2017. The resistance peaked in 2012, 2014 and 2016 which can be explained by the change in trend of use of this antibiotic where the maximum use was during 2014 (6.386 g) and 2016 (1.082 g).

This study showed that *CoNS* identified isolates were resistant to antibiotics like cloxacillin, trimethoprim-sulfamethoxazole, gentamicin and ciprofloxacin/ofloxacin which were commonly used for treatment of patients infected by this microorganism. However, *CoNS* isolates were 100% sensitive to vancomycin and teicoplanin treatment. Linezolid and rifampicin were recommended as the second effective choice of antibiotics against these isolates. Although *CoNS* isolates show less resistance (8.8%) against tetracycline, it is not recommended, as it might cause permanent teeth discoloration and enamel hypoplasia [15].

Analysis of change in trend of microorganisms from 2012-2017

Utilization pattern of antibiotics plays a pivotal role in knowing the change of trend of susceptibility pattern of microorganisms against various antibiotics. Utilization of antibiotics was calculated using WHO-AMC tool and reported as DDD/100 bed days. amikacin (86.7), vancomycin (52.3) and ampicillin (40.6) were the most used antibiotics in terms of DDD/100 bed days.

Analysis of the shif of trend of resistance of *K. pneumoniae* to various antibiotics from January 2012 to the end of July 2017 revealed that resistance to amikacin, ceftriaxone and piperacillin-tazobactam was decreasing, while that of cefuroxime was increasing. Research by Willemsen et al. suggested that increase or decrease in resistance rate of different identified isolates against various antibiotics in different years can be accounted for by the change in consumption pattern of these antibiotics over time. Thus, according to the above-mentioned statement, increase in resistance rate of *K. pneumoniae* against cefuroxime from 2012 to 2015 can be due to increase in consumption of this antibiotic. Similarly, decreasing consumption of this antibiotic during 2016 resulted in decreased rate of resistance of *K. pneumoniae* against it. Decrease in trend of resistance of *K. pneumoniae* against Piperacillin-tazobactam may be due to decrease in consumption of this antibiotic since 2013. Increase in consumption of Amikacin since 2012 did not influence the decrease in rate of resistance of *K. pneumoniae* against it. Resistance of this isolate against Amoxicillin-clavulanic acid peaked in 2014 decreased during 2015 and 2016 and again increased in 2017. This can be explained by change in trend of use of this antibiotic which increased during 2014 (0.5 g) and 2016 (0.714g) compared to 2012 (0.140 g), 2013 (0.180 g) and 2015 (0.107 g).

Analysis of the trend of resistance change of *CoNS* to various antibiotics from 2013 to 2016 reveals resistance to rifampicin was decreasing while resistance to cloxacillin, amoxicillin-clavulanic acid, cefazolin/cefadroxil, trimethoprim-sulfamethoxazole, ciprofloxacin/ofloxacin and amikacin was increasing. Increased resistance of *CoNS* against amoxicillin-clavulanic acid, ciprofloxacin, and trimethoprim-sulfamethoxazole from 2012 to 2014 can be due to the increased rate of consumption. Decreased consumption of these antibiotics during 2015 resulted in decreased rate of resistance of *CoNS* against them in the same year. Dramatic increase in resistance of *CoNS* against amikacin might be due to increased rate of consumption from 2012 onward.

Thus, results from our research clearly state that proper use of these antibiotics pertaining to the microorganism isolates is crucial in decreasing the growing antimicrobial resistance in the current scenario. Study and interpretation of changing trends of these microbes is the key to the selection of appropriate antibiotics thus, ensuring reducing burden to the health care system and community by availing proper and legitimate treatments and framing antibiotic stewardship guidelines.

Conclusion

Results obtained from our study have brought substantial information on antibiotic resistance pattern among microorganisms causing neonatal sepsis. Outcomes from this study assert that resistance to Amikacin by *K. pneumoniae* has decreased from 2013 onward, thus it is recommended to be used in empirical therapy against gram negatives. Isolates of *K. pneumoniae* showed least resistance against colistin and can therefore be recommended as the

"antibiotic of choice" in patients who are infected with this microorganism. However, *CoNS* identified isolates showed decreased resistance against rifampicin and thus itcan be recommended to be used in empirical therapy of gram positives, even though it is not the most effective antibiotic against *CoNS.* Meanwhile, vancomycin and teicoplanin can be mediated as choice of antibiotics for *CoNS* infected patients. However, linezolid and rifampicin were recommended as second effective choices for treatment of *CoNS*. Thus, results obtained from this study can be utilized for designing antibiotic stewardship policy to prevent the emergence of resistance and to improve the treatment outcome.

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