Antibiotic Usage and Microbial Resistance: Indian Scenario

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Abstract

Most common organisms isolated in neonatal sepsis in India are Klebsiella, E coli and Staphylococcus aureus. Inappropriate use of antibiotics has resulted in the emergence of extended spectrum beta-lactamase producing Gram-negative bacteria, methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, carbepenem-resistant Pseudomonas/Acinetobacter and other multidrug-resistant bacteria. This ever-increasing problem can be encountered with better infection control measures, antibiotic stewardship and formulation of local and national antibiotic guidelines.

Introduction

Antibiotic misuse and microbial resistance is an ever increasing problem in the neonatal intensive care units (NICU) of our country. Over the years, undisciplined use of broad spectrum antibiotics, prolonged courses of antibiotic therapy, overdependence on C-reactive protein for initiating, changing and stopping antibiotics and absence of culture facilities have resulted in increased incidence of extended-spectrum beta-lactamase (ESBL), methicillin-resistant Staphylococci aureus (MRSA), vancomycin-resistant Enterococci, carbepenem-resistant Pseudomonas/Acinetobacter and multi-drug-resistant bacteria.

Neonates with resistant infections are more likely to require prolonged hospitalization and are more likely to die.
**Microbial resistance**

It is now well known that antibiotic use selects for antibiotic resistant bacteria. When penicillin was discovered in 1940, all strains of *Staphylococci* were sensitive to benzyl penicillin. Very soon widespread use of penicillin resulted in disease causing strains of *Staphylococci* that were resistant to penicillin. Broad spectrum antibiotics are potent selectors of antibiotic resistance.\(^2\,^3\) Ampicillin and third generation cephalosporins (cefotaxime, ceftriazone and ceftizidime) select for Gram-negative bacilli that produce extended spectrum beta-lactamases, which render the bacteria resistant to many antibiotics not just beta lactams. *E.coli* and *Klebsiella* acquire antibiotic resistance via the plasmid-mediated extended spectrum beta-lactamase (ESBL) production. Owing to the presence of other resistance conferring genes on these transferable plasmids, such organisms are also resistant to other drugs, including aminoglycoside antibiotics.\(^4\) The carbepenams such as imipenem and meropenem are used in the laboratory to induce expression of beta lactamases in the organisms where these genes are repressed.\(^5\) Therefore extensive use of carbepenems will select for beta-lactamases producing and imipenem/meropenem-resistant organisms. Resistance to antibiotics may also occur due to chromosomal mutations, by the capture of integron of antibiotic resistance genes that are part of discrete mobile cassettes and possibly also by interspecies genetic transformation. Excessive and extended use of broad spectrum antibiotics also increases the risk of fungal infections in neonates.\(^6\) Emergence and spread of microbial resistance is more common in the neonatal intensive care units because of relative immuno-
compromised status of neonates, frequent need of invasive lines and skin-breaking procedures and high frequency of staff-to-patient contact. In addition poor compliance to hand-washing routines, use of broad spectrum antibiotics and non-availability of disposables can increase the emergence and spread of microbial resistance.

**Microbes and Resistance pattern**

From the National Neonatal Perinatal Database (NNPD) 2000, the incidence of neonatal sepsis has been reported to be 38 per 1000 live births in tertiary care institutions.\(^7\) Meningitis was diagnosed in 0.5 per 1000 live births. Among inborn neonates, *Klebsiella* was the most frequently isolated pathogen (31.2%), followed by *Staphylococcus aureus* (17.5%), *E.Coli* (10.5%) and *Pseudomonas* (6.8%). Among extramural neonates admitted in tertiary care hospitals, *Klebsiella* was the commonest organism (36.4%), followed by *Staphylococcus aureus* (14.3%) and *Pseudomonas* (13.2%). Most of the *Klebsiella* isolates were resistant to ampicillin (97.2%), gentamicin (88.6%) and cefotaxime (60.6%). However the organism was sensitive to amikacin (64.4%) and ciprofloxacin (73.3%). Similarly *E.Coli* isolates were resistant to ampicillin (86.3%), gentamicin (60%) and cefotaxime (52.3%). Ninety percent of the Staphylococcus isolates were resistant to penicillin and 10% to vancomycin.

In a study from North India, among the 75 cases with Gram-negative septicemia the common isolates were *Klebsiella, E.Coli, Acinetobacter, Proteus* and *Enterobacter* species.\(^1\) Overall 61.5% of Gram-negative isolates and 52.2% of *Klebsiella* isolates were ESBL producers. Most of the isolates were resistant
to gentamicin (57.2%) and cefotaxime (68.3%). However majority were sensitive to amikacin (55.6%), piperacillin-tazobactum (92.1%) and meropenem (96.8%).

In year 2008 and 2009, the incidence of neonatal sepsis in our unit (a tertiary care maternal hospital with only inborn admissions) was 16.5 per 1000 live births. Of the 139 isolates 56% were Gram-negative and 40% were Gram-positive. Common Gram-negative isolates were *Klebsiella* (30%), *Pseudomonas* (9%), *E.coli* (8%) and *Enterobacter* species. Coagulase-negative *Staphylococcus* (19%) and *Staphylococcus aureus* (9%) were the common Gram-positive isolates. Half of the *Klebsiella* isolates was resistant to cephalosporin, 36% to amikacin, 24% to pipericillin-tazobactum and 17% to meropenem. Three-fourth of the *Staphylococcus aureus* isolates were resistant to methicillin and none to vancomycin.

The SENTRY surveillance programme reported the frequency of *Klebsiella pneumoniae* to be 37% in Latin America as compared to 7% in United States. Frequency of ESBL producing bacteria in the Asia-Pacific region is reported as 5% from Japan, 21.7% from Taiwan, 31% from Philippines, and 38% from Malaysia/Singapore. From the available data, the incidence of resistant bacteria in our country is higher than that reported from neighboring countries and also from resource rich nations.

**Steps to reduce microbial resistance to antibiotics**
1. Infection control measures: Continuous availability of water, ventilation, cleanliness, hand washing, hand rubs, availability of disposables, effective management of diapers, appropriate disposal of medical waste and adequate staff-patient ratio can decrease the spread of antimicrobial resistant bacteria. Improved hand washing has consistently been shown to reduce the incidence of nosocomial infections. Early introduction of enteral feeds, preferably breast milk, allows intravenous access to be removed quicker, reducing the risk of sepsis.6

2. Appropriate use of antibiotics

- Prophylactic antibiotics should not be stated in conditions like severe asphyxia, neonatal jaundice, prematurity, caesarean delivery and exchange transfusion.

- Bacterial colonization do not need antibiotic therapy. Routine culture of tips of endotracheal tubes, central lines and urinary catheter is not helpful.

- Without exception blood culture should be obtained before starting antibiotics. Laboratories should use culture techniques that are highly sensitive such as BacTec® and BacTAlert®. With use of specific techniques sample volume as less as 0.2ml has been observed to be sufficient to isolate the organisms from neonate’s blood.11

- Positive C-reactive protein (CRP), elevated micro-ESR and abnormal blood counts are only markers of inflammation and are not specific for
infections. In a well baby with negative cultures, persisting positive CRP is not a marker of infection.

- If the blood culture is sterile after 48-72 h of incubation, it is almost always safe and appropriate to stop antibiotics. Recommended durations of antibiotics are 5 days for pneumonia, 10 days for culture-positive sepsis and 14-21 days for meningitis.

3. Restrict use of broad spectrum antibiotics

- The best empiric antibiotic for neonate is a penicillin or semisynthetic penicillin (crystalline penicillin, cloxacillin, ticarcillin-clavulanic acid, and pipericillin-tazobactum) together with an aminoglycoside (gentamicin, netilmicin, amikacin, tobramicin). The choice of penicillin will depend on the organism causing sepsis (ampicillin for Listeria, group B streptococcus and cloxacillin for Staphylococcal aureus). In units where Gram-negatives’ resistance to ampicillin or cephalosporin is high, the appropriate antibiotic should be ticarcillin-clavulanic acid or pipericillin-tazobactum. Empiric Vancomycin is not necessary unless MRSA is common. Choice of aminoglycoside should be based on the local data. If colonizing and infecting bacteria in a neonatal unit is resistant to gentamicin, it may become sensitive again, after a prolonged period of using another aminoglycoside such as netilmicin. In a telephonic survey by the author from 25 neonatal units in the country, in 23 the empiric antibiotic is either a cephalosporin or amoxicillin-clavulanic acid or a quinolone along with an aminoglycoside. Only 2 units are using
either a single aminoglycoside or penicillin as an empiric antibiotic. Most of the neonates referred to the neonatal units are already on empiric broad-spectrum antibiotics.

- Use of cephalosporins, quinolones and carbapenems should be restricted to microbes resistant to aminoglycosides or penicillins. In a study done by Lee J, et al. on pediatric patients, the incidence of ESBL producing Gram-negative bacteria decreased from 39.8% to 22.3% with cephalosporin restriction.\(^\text{13}\) Similarly in our experience, cephalosporin restriction reduces the incidence of ESBL producing bacteria from 46.8% to 19.5%.\(^\text{8}\) In a study from Brazil, neonatal health care associated infections were reduced from 32% to 11% after education and restriction of the use of cephalosporins.\(^\text{14}\)

- There should be national and local antibiotic policies to restrict the use of broad spectrum antibiotics. Blood culture facilities should be available near or at all neonatal service centers.

4. Rotation of antibiotics

- Using antibiotics in rotation has been effective in some settings in reducing resistance. In a systematic review on antibiotic cycling (mostly from surgical ICU’s, two from NICU and one from pediatric hospital) reduced microbial resistance to gentamicin was observed.\(^\text{15}\) However the optimal cycle duration, when to start cycling and the antibiotic spectrum needed to cycle are questions yet to be answered in well designed prospective studies.
Conclusions

Antimicrobial resistance has emerged as a major public health issue all over the world, especially in developing countries like India. Current evidence suggests that controlling the use of broad spectrum antibiotics and implementation of infection control measures can result in decreased microbial resistance. Ensuring blood culture facilities, minimizing the use of cephalosporins, quinolones and carbepenems, reducing the duration of antibiotic therapy and formulation of national and local antibiotic policies is the need of the hour to prevent the extinction of available antibiotics.
Reference


8. Murki S, Shravanth J. Role of cephalosporin restriction in reducing the incidence of extended spectrum beta-lactamase producing gram negatives. (personal communication)


