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A REVIEW ON ANTIMICROBIAL RESISTANCE IN INDIAN NEONATAL AND PEDIATRIC BLOOD STREAM

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ABSTRACT

Introduction: Antimicrobial resistance is the capability of a microbe to resist the effects of medication that once could successfully treat the microbe. Recently, the increasing trend in drug resistant infections in infants and children has gone relatively unrecognised. The reason for the resistance in microbes being at the forefront of medicine over the past seventy years. It is the selective pressure created by the broad use of antibiotics in agriculture, livestock, veterinary and human medical practices. This result has been an expression of multi drug-resistant organism(MDRS) on a global level in all people (including neonates and children). **Aim and Objective:** Aim of the review is to determine the patterns of antimicrobial resistance in isolates of blood stream of infants and children in India. As a result of this, ten pathogenic bacterial isolates from the paediatric population in India is studied. **Methodology:**

- Nucleic acid amplification method (PCR technique)
- Agglutination assays
- DNA micro array technology
- Blood culture positivity test
- Data collection from paper and electronic medical records

Conclusion: This study identify that antimicrobial resistance is mainly caused by gram positive and negative bacterias. It may results in to divergent epidemiology, severe infections

in child soft tissue and upper respiratory tract, allergies, dissemination alternation in porins and efflux pumps of clonal strains etc. As per recognition of this as global health threat. We can find appropriate choices for empiric antibiotic therapy and may contribute to the improvement of infection control, enhance public health education, maternal colonisation and enforcement of regulations.

INTRODUCTION

Antimicrobial resistance is one of the major public health problems mainly in developing countries like India, where relatively easy availability and higher consumption of medicines have lead to disproportionately higher rate of inappropriate use of antibiotics and large levels of resistance seen in developed countries. Indian Council of medical research advised 20 tertiary care hospitals in South India at April 2017 to put a strict control on the use carbapenems and polymixins and labelled them as great need or prevent use antibiotics.

Antimicrobial resistance patterns are significantly differ in adult and pediatrics. It is estimated that India has the highest neonatal mortality due to neonatal blood stream infection caused by bacteria resistant to first line antibiotics. Approximately one fifth of neonates with the infection die in the hospital, and then the mortality increases to 50% for those culture proven sepsis. From one million neonatal deaths in India, neonatal for 0.27million, and birth asphyxia, birth trauma for 0.19 million. Developing countries like India, Nigeria, Democratic Republic of the Congo, Pakistan and China account for half (2.440 million) of the global death from infections in under five children. Significant changes have taken in care of the sick and of immature new borns over the last decade. The study used to prevalence of early and late onset sepsis, and frequency of antimicrobial resistance in a major referral Neonatal Intensive Care Unit(NICU). Pathogens encountered in neonatal sepsis vary wold wide, reports from India more commonly shows gram negative organisms, although gram positive organisms also reportedl.[1] A recent study highlighted on importance of justifying antibiotic use to end antibiotic resistance in India.

Antimicrobial resistance result in problems which controlling the disease in community and ineffective delivery of health care services.[2]

METHODS

The systematic literature search was undertaken relevant published clinical evidences. Mainly included search terms are 'anti-bacterial agents, antibiotics, sepsis and bacteraemia. 'A

hospital based observationl study was conducted from April 2016 to May 2017. A total of 303 neonates with blood stream infection were included.[4]

Blood cultures are gold standard test for diagnosis of sepsis and should be performed in all cases of suspected sepsis prior to administering an antibiotics. 1ml sample of blood was drawn from a veni punctuure site and mixed to a bottle containing 5-10ml of blood agar culture media.[3] Antimicrobial sensitivity testing was done by Kirby Bauer diffusion method using Mueller Hinton agar with incubation of 24 hour at 37 degree celsius.

Testing was done in antibiotics like Ampicillin(10mg), Cloxacillin(5mg), Gentamycin(10mg), Amikacin(30mg), chloramphrnicol(30mg), ceftriaxone(3 0mg), Ciprofloxacin(2mg), vancomyci n(30mg), clindamycin (2mg and Erythromycin(15mg).[9]

The data was entered in to EPI-INFO version 3.5-1 and is exported to SPSS version 21. For describe study population in relation to relevant variables they use frequencies, proportion and summary statics.[14]

Studies were included if minimum of IU pathogenic bacterial isolates from blood stream within a pediatric population in India were reported in original articles, and studies were excluded if the reported studies done. Published and gray literature on antibiotic resistance in children was searched using "google scholar", "Scopus", and "pubmed "data bases between January 2000 and July 2015.Total number of blood culture in this varied markedly between the studies, proportions and ranges for pathogens were weighted by total sample size of blood culture weighted by total sample size of blood culture and it is given as weighted median of proportions and inter quartile changes.[19]

The method described blood culture derived bacterial isolates from children from birth to 18 years, with the determination of antimicrobial succeptibility patterns. Studies conducted during out breaks or epidemics were also excluded. Gram positive and gram negative bacterial isolates were reviewed include Staphylococcus (CONS) Entercoccus fecalis, Klebsiella pneumonia, E. coli, Salmonella typho etc.[18]

Data was obtained from records records of Pediatric Intensive Care Unit (PICU) and medical microbiology laboratory of patients with positive blood culture after 48 hours of admission to Patient Intensive Care Unit over three time periods.[19]

Patients: Bacterial isolates of infants accompanied by non microbiological laboratory values suggestive of infections. Abnormal leucocyte cout,abnormal total neutrophils count(PMN), increased immature PMN ratio 0.3,platelets count 150,000/mm.[11]

Infectious control management: Infants were considered to have blood stream infection if they had at least one positive blood culture cause to bacteria.

Microbiological sampling: 1ml of blood sample obtained from peripheral vein incubated in blood culture incubator.[19]

Sample processing: Inoculated blood isolates incubated at 37 degree celsius examined for growth 24-28 hours. Antibiotic disc used represented the antibiotics which are from different groups. Inhibition zones were measured.[12,6]

A retrospective case study of Extended-spectrum Beta-Lactamase (ESBL) colonised infants verses controls (matched by date of birth and gestational age).[4] Unvariable and multivariable methods were used to assess association between ESBL colonization and possible clinical risk factors.[14,8]

In this review data were obtained from Google search engine, medline and others. It is mainly used for search the relevant information in Indian context yielded 41 references out of which 29 references were included for analysis the year 2006 till 2011.[17,16]

The study conducted among children in an urban community in Nagpur, India with aureus strains constituted 4.1% of methicillin resistant staphylococci.[5,13] The drug resistance patterns like multi drug resistant extended - spectrum beta lactamase producing klebsiella pneumonia, ciprofloxacin resistant salmonella enteric serovar typhi, emergence of vancomycin intermediate staphylococci, fluoroquinolone resistance among salmonella enteric serovar paratyphiA, pseudomonas aeroginosa and Acinetobacter baumannii resistant to ceftazidime, ceftazidime, cefepime and ciprofloxacin are the highlighted studies in South India.[10,16,7,15]

Importance of microbial resistant staphylococci antibiotics discussed related to its epidemiological aspects, clinical presentations, diagnostic modalities, therapeutic options, contributing factors, growing cost and other pertinent elements.

This will leads to stick and soft tissue infection among young and healthy individuals in the community which further causes severe infections like septic shock and necrotizing pneumonia.[15]

Antibiotic	*Staphylococcus aureus* 14.7% (7.4%–25.6%) [n = 70]	CONS 10.4% (4.2%–15.9%) [n = 68]	*Enterococcus faecalis* 0.9% (0%–4.4%) [n = 44]
Penicillin	NS	NS	88.5% (41.7%–100.0%) [n = 9]
Ampicillin	NS	NS	100.0% (77.5%–100.0%) [n = 4]
Erythromycin	53.0% (39.5%–65.9%) [n = 31]	43.3% (30.5%–67.1%) [n = 26]	53.2% (44.6%–61.9%) [n = 8]
Cloxacillin	50.0% (31.4%–65.1%) [n = 33]	42.5% (19.1%–66.7%) [n = 24]	NS
Amikacin	25.8% (14.2%–48.7%) [n = 40]	28.6% (0.0%–41.0%) [n = 35]	NS
Gentamicin	44.9% (24.9%–69.7%) [n = 42]	50.0% (29.2%–66.7%) [n = 36]	68.5% (41.7%–77.5%) [n = 13]
Cephelexin	34.3% (27.3%–66.6%) [n = 11]	27.3% (0.0%–51.5%) [n = 10]	NS
Cefotaxime	57.1% (25.0%–66.0%) [n = 23]	35.4% (18.4%–64.1%) [n = 22]	NS
Ceftriaxone	40.0% (21.4%–60.0%) [n = 11]	33.0% (9.0%–47.9%) [n = 9]	NS
Cotrimoxazole	57.7% (30.0%–72.7%) [n = 19]	69.9% (60.6%–87.3%) [n = 16]	75.0% (12.5%–100.0%) [n = 4]
Ciprofloxacin	40.0% (25.0%–59.0%) [n = 39]	38.9% (16.7%–53.6%) [n = 31]	50.0% (0.0%–64.4%) [n = 10]
Amoxiclav	25.0% (16.0%–53.6%) [n = 9]	11.1% (0.0%–40.3%) [n = 11]	20.0% (0.0%–40.0%) [n = 2]
Clindamycin	29.3% (15.9%–40.2%) [n = 14]	27.5% (6.1%–37.1%) [n = 14]	NS
Vancomycin	0.0% (0.0%–0.0%) [n = 37]	0.0% (0.0%–0.0%) [n = 35]	0.0% (0.0%–13.7%) [n = 12]
Linezolid	0.0% (0.0%–12.5%) [n = 19]	0.0% (0.0%–0.0%) [n = 17]	0.0% (0.0%–5.0%) [n = 6]
Teicoplanin	0.0% (0.0%–10.5%) [n = 5]	0.0% (0.0%–0.0%) [n = 5]	0.0% (0.0%–16.6%) [n = 3]
Doxycycline	-NS	-NS	40.0% (40.0%–40.0%) [n = 1]

Abbreviations: CONS, coagulase-negative *Staphylococcus*; IQR, interquartile range; n, number of samples; NS, not studied.
*Data are presented in the following form: median (IQR, Q1–Q3) [number of studies].

RESULT AND DISCUSSION

Among the 89 eligible studies that had given out data about positive blood cultures, 78.7% of data were from neonates, 14.6% were from children older than 1month, and 6.7% studies were done in both neonate and pediatric ages. Studies were spread overall India, with 36% reports from North India, 31.5% from South India, 31.5% from South India, 16-19% from Western India, 12. 4% from the east; and 3.4% from central India. The great majority of studies (78.7%), had been submitted from Neonatal Intensive Care Units (NICUS) and a small percentage <5% had been reported from paediatrics intensive care unit ward, in patient department or their combinations.[18]

Blood culture and isolates were performed on basis of current standards of each centre. Significant blood stream infection caused due to common skin organism was defined as the presence of same organism in 2 separate blood culture sets in 23 (52%) of studies (59% of adult and 38% of Pediatric studies) where as remaining 22 studies gave no criteria for defining the significance of these organisms.[4]

Sixteen manuscripts provided information for nine coutriesly. The median gram positive:

gram negative ratio was 58%:42% ranges from 80%:141% to 32:68% in each individual studies. The median incidence of studies in CNS bacteriemia due to presence of same organism in two consecutive blood culture that did not report this definition.

Few data on bacterial susceptibility causing bacterial means in children haemotolog were studied. Median resistance range were much lower Success of therapy such as organ transplantation, cancer chemo therapy than adults, except for gentamycin resistant gram negative organisms, which were more frequent in children than adult. The observation period recorded in the responses was 4 years ranging from 1-13 years; 14 centers reported data from a one year period. The most frequent pathogens were enterobacteriaceae (30%) followed by CNS (24%) and enterococci species (8%).

Although Antimicrobial resistance is a huge problem, it is related to existing health care delivery system of country. In India, about 5% of GDP is spent on health out of which public health sector contributes to 0.9% and a major portion of remaining is by private health sector.[16] The patient remain sick for a longer period thus requiring continuous treatment usually with expensive and at times toxic drugs which results in increased morbidity and mortality.

And major surgery would be compromised without effective anti microbials for care and prevention of infections. Now a days growth of global trade and travel was allowed to resistant micro organisms to be spread rapidly to distant countries and continents.[16]

Pathogen-Antibiotic Combination	Neonate	Pediatric	$P^{\dagger}$
Staphylococcus aureus-cloxacillin	53.6% (39.8%–66.2%) [n = 22]	33.3% (29.3%–64.3%) [n = 11]	.08
S aureus-clindamycin	33.0% (20.0%–45.7%) [n = 11]	27.7% (0.0%–30.0%) [n = 3]	ns
S aureus-vancomycin	0.0% (0.0%–0.0%) [n = 30]	0.0% (0.0%–0.0%) [n = 7]	ns
S aureus-linezolid	0.0% (0.0%–12.5%) [n = 14]	0.0% (0.0%–13.2%) [n = 5]	ns
Klebsiella pneumoniae-ampicillin	95.9% (76.2%–100.0%) [n = 42]	93.9% (44.6%–100.0%) [n = 5]	ns
Klebsiella-gentamicin	75.0% (54.8%–86.2%) [n = 56]	83.6% (31.3%–98.5%) [n = 8]	ns
K pneumoniae-cefotaxime	62.6% (42.8%–80.2%) [n = 46]	70.0% (14.3%–89.0%) [n = 7]	ns
K pneumoniae-piperacillin-tazobactam	42.0% (5.1%–62.1%) [n = 20]	25.0% (0.0%–50.0%) [n = 2]	ns
K pneumoniae-imipenem	0.0% (0.0%–8.0%) [n = 27]	0.0% (0.0%–0.0%) [n = 5]	ns
Escherichia coli-ampicillin	92.9% (66.7%–100.0%) [n = 27]	83.3% (62.0%–100.0%) [n = 5]	ns
E coli-gentamicin	55.6% (33.3%–83.3%) [n = 38]	50.0% (0.0%–79.4%) [n = 5]	ns
E coli-amikacin	22.3% (2.3%–40.0%) [n = 38]	38.8% (0.0%–50.0%) [n = 5]	ns
E coli-cefotaxime	47.5% (40.0%–66.3%) [n = 32]	50.0% (45.0%–74.3%) [n = 5]	ns
Pseudomonas-amikacin	39.4% (23.5%–50.0%) [n = 32]	40.0% (25.0%–66.3%) [n = 7]	ns
Pseudomonas-ceftazidime	50.0% (33.3%–73.3%) [n = 19]	67.0% (33.3%–75.0%) [n = 7]	ns
Pseudomonas aeruginosa-ciprofloxacin	43.0% (30.0%–60.0%) [n = 31]	63.0% (40.0%–80.0%) [n = 7]	ns
Enterobacter spp-ampicillin	100.0% (97.4%–100.0%) [n = 17]	97.1% (94.2%–0.0%) [n = 2]	ns
Enterobacter spp-gentamicin	88.0% (61.7%–97.4%) [n = 21]	76.5% (67.6%–83.0%) [n = 4]	ns
Citrobacter spp-ampicillin	95.3% (62.5%–100.0%) [n = 6]	99.0% (87.0%–100.0%) [n = 4]	ns
Citrobacter spp-gentamicin	52.8% (39.8%–80.3%) [n = 12]	0.0% (0.0%–0.0%) [n = 3]	ns
Acinetobacter baumannii-gentamicin	63.6% (45.0%–78.9%) [n = 33]	77.1% (18.8%–94.8%) [n = 4]	ns

Abbreviations: IQR, interquartile range; n, number of samples; ns, not significant.
*Data are presented in the following form: median (IQR, Q1–Q3) [number of samples].
†Significance levels using Mann-Whitney *U* test.

CHALLENGES

- Strengthening the surveillance data.
- Standard operating guidelines.
- Improvement in antimicrobial prescription practices.
- Over counter scale of antibiotics
- Poor sanitation, endemic infections, nutritional deficiency
- Limited public awareness
- Decreased commitment of government
- Low co-ordination and fragmentation of effect.[13]
- Government health policies and health care systems in which they are implemented play a vital role in determining the efficacy of interventions to contain antimicrobial resistance.

In the present condition, national commitment to understand and address the problem and designation of authority and responsibility are the major prerequisites.[7]

CONCLUSION

Over the past decade Gram-negative organisms remained predominant isolates in nosocomial sepsis in our pediatric intensive care unit. Klebsiella species being the commonest. Pseudomonas is uncommon. Staphylococcus aureus is the predominant Gram-positive organism. An increase in resistance to gentamicin cephalosporins, ciprofloxacin and beta lactum with beta-lactamase inhibitor was also observed in it. Currently the combination of carbapenem (imipenam or meropenam) and vancomycin appears as the best choice for empiric antimicrobial therapy for blood stream infection in pediatrics.

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