

Bacterial Confines of Neonatal Sepsis and Anti-Infection Opposition Example in A Dimension III Neonatal Emergency Unit Eastern India: A 4 Years Report

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Abstract— This examination was embraced to explore the appropriation of etiological specialists and antimicrobial opposition design among the blood culture-positive instances of neonatal sepsis admitted to a dimension III neonatal consideration unit in a showing medical clinic Kolkata, Eastern India for the time of 4 years (2014 – 2017). Blood culture was accomplished for all infants conceded with clinical sepsis or with positive sepsis screen via mechanized BACTEC 9050 framework. In positive cases, distinguishing proof of creature was done trailed by antimicrobial affectability testing by Kirby Bauer plate dissemination strategy utilizing Clinical Research Center Standard Organization Rules. Multi-sedate obstruction (MDR) was characterized as the nearness of protection from at any rate three of the five anti-microbial gatherings if there should arise an occurrence of gram-negative microscopic organisms. Chi-squared test was performed to test the relationship between various gatherings. Out of 4781 instances of clinical neonatal sepsis, 415 (8.68%) were culture positive. In 240 (69%) cases, the pathogens had a place with the family Enterobacteriaceae. Gram-positive cocci represent 38 (11%) instances of positive blood culture cases. Klebsiella is the preeminent irresistible operator with positive in 187(54%) of all bacterial segregates. Enterobacteriaceae positive children had 90 (36.9%) passing which is fundamentally higher than that related with others. Klebsiella best the rundown of MDR creatures with the most elevated mortality. Gram-negative pathogens and all the more explicitly Klebsiella represent a considerable malady weight of neonatal sepsis as anti-infection opposition, multidrug obstruction, and mortality in a neonatal emergency unit.

Keywords— Enterobacteriaceae, Multi-sedate obstruction, Neonatal sepsis, anti-toxin stewardship

1. Introduction

Neonatal sepsis remains the significant reason for mortality and grimness among neonates worldwide despite extraordinary advances in neonatal consideration. South Asia alone records for 3.5 million cases out of 6.9 million instances of neonatal sepsis every year. In India, the occurrence of neonatal sepsis is 30/1000 live births. 1,2 Considering the way that 27 million birth each year in this nation, which is one-fifth of worldwide live births, India asserts a tremendous weight of neonatal sepsis cases in the worldwide situation. More than one-fourth of neonatal passing happen in India and neonatal sepsis alone adds to 19% of every single neonatal demise here is really. 3 Absence of antenatal consideration, unhygienic and risky conveyance practices, rashness and low birth weight add to the high bleakness and mortality in neonatal sepsis. 4 Consequently this theme truly merits principal importance. Diseases are routinely treated with antimicrobial operators, the viability of which relies upon the affectability of the causal living beings. In any case, as of late the rising protection from the antimicrobial operators in creating nations including India is proclaiming a developing therapeutic emergency that necessities dire consideration. 5 It is evaluated that India has the most elevated neonatal mortality because of neonatal sepsis brought about by microscopic organisms impervious to first-line anti-infection agents. Around one-fifth of neonates with sepsis bite the dust in the medical clinic and the mortality ascend to half for those with culture-demonstrated sepsis. 6 Abuse of numerous and wide range anti-infection agents experimentally without appropriate blood culture office, obliviousness on the overall verdure and nonappearance of adherence to exacting anti-microbial convention in neonatal escalated care units have

expanded the frequency of anti-toxin opposition and even multidrug obstruction. In an ongoing multi-focus Indian partner ponder from North India, life forms demonstrated a high level of antimicrobial protection from the top of the line anti-toxins like broadened range cephalosporins and carbapenems. 7 Of an assorted nation like India with high birth rate, occasional microbial disconnects at neonatal serious consideration units and their antimicrobial affectability may dependably vary not just in connection to better places and populace yet in addition intermittently in a solitary spot. Be that as it may, in all actuality, there is a deficiency of this observation information here in this nation where most of neonatal passing because of sepsis happen. In this setting this examination was attempted to explore the conveyance of etiological specialists and antimicrobial weakness designs among the blood culture-positive instances of neonatal sepsis from a dimension III neonatology unit of a huge tertiary-care showing emergency clinic in Kolkata, Eastern India, over a time of 4 years so as to assemble important data with respect to rising enemy of microbial opposition (AMR) design among causative life forms of neonatal sepsis in eastern India. This will define an anti-microbial stewardship program with appropriate information of winning bacterial vegetation which can be the main response to this rising issue of antimicrobial opposition even in an infant.

2. Materials and Methods

It was a review investigation of the examination of all blood societies positive sepsis cases got from neonates admitted to the dimension III Neonatal emergency unit a tertiary consideration showing clinic in Kolkata, eastern India, over a time of 4 years, from July 2014 to December 2017. This dimension III Neonatal Emergency unit (NICU) was a referral unit with a high confirmation rate of 1600-1800 infants every year including both intramural and extramural children. All the infant who was admitted to the said neonatal unit during the investigation time frame and got treatment for sepsis were incorporated into the examination. Children with deadly inherent abnormalities and distortions, analyzed instances of innate blunders of digestion and infants with careful crises were prohibited according to the examination convention.

Educated assent was acquired from both the guardians or the lawful watchmen when each child was enlisted with the determination of clinical sepsis. Blood culture was performed for all neonates with suspected clinical sepsis. Clinical sepsis was suspected when the infant gave a lot of clinical signs according to the Youthful Newborn Child Study Calculation. 6 Then again clinical sepsis was additionally associated even in nonappearance with clinical manifestations yet within the sight of perinatal hazard factors with positive sepsis screen. A positive septic screen again was characterized as the nearness of two of the five parameters: all out leucocytic tally $<5,000/\text{cmm}$, juvenile neutrophil to add up to neutrophil (I/T) proportion >0.2 , total neutrophil tally $<1,800/\text{cmm}$ or according to Monroe diagram for term and Mourinho's outline for low birth weight babies, smaller scale ESR >15 mm first h, C-receptive protein ($>1\text{mg/dL}$). The sentiment of two free clinicians was taken for affirming the case as clinical sepsis by the clinical manifestations suggestive of sepsis or the sepsis screen being certain if there should arise an occurrence of essence of hazard factors as it were. Clinical sepsis with perinatal hazard variables and positive sepsis screen was important for just early beginning sepsis, the i.e event of sepsis at or before 72 hours of life. Clinical sepsis characterized by the nearness of clinical side effects was applicable for both early and late beginning sepsis i.e event of sepsis following 72 hours of life. Segregation of a perceived pathogen from blood, in instances of neonatal clinical sepsis based on clinical highlights or perinatal hazard factors, alongside treatment with suitable kind and length of anti-toxin treatment was known as blood culture positive sepsis.

The examination unit was following an anti-microbial strategy which was in effect intermittently inspected according to the rule of the unit disease - control group including one microbiologist, one neonatologist and one medical attendant professional. During the examination time frame, as per the convention, anti-toxins

were utilized at first exactly if there should be an occurrence of clinical sepsis. For experimental use, the principal line of anti-toxins utilized was Inj piperacillin-tazobactam and aminoglycoside blend, the second line of anti-toxins being a mix of a fluoroquinolone - aminoglycoside and the third line being carbapenem for the board of clinical sepsis in the unit. The selection of anti-infection agents and its heightening in the event of clinical crumbling was chosen by the advisor specialist available to come back to work. After the beginning of anti-toxins, the future course was chosen by the accessibility of blood culture results and clinical course. Be that as it may, if the blood culture was certain, the anti-microbials were picked according to the affectability design. The scientists routinely recorded subtleties of the anti-infection agents managed and the clinical course of the child to be specific the survival or mortality and bacteriological report of the blood culture.

Microbiological Strategies: 1ml blood for culture was drawn from a fringe vein and Mechanized BACTEC 9050 framework utilizing Peds in addition to Vial was utilized for blood culture. After the blood culture was discovered positive, Gram stain was performed and subculture was done on fitting media dependent on the Gram recolor, similar to Macintosh Conkey agar and 5% sheep blood agar (Biomerieux, la balme les Grottes, France) for Gram-negative and positive creatures individually. Contains were hatched in the framework for to 7 days, toward the finish of which all the negative jugs were subcultured once on blood agar before disposing of. Distinguishing proof was finished by regular strategies and affirmed by scaled down Programming interface analyzer utilizing ID32E unit for Enterobacteriaceae, ID32GN for non-fermenters, ID32 Staph and Fast ID32 Strep for Gram-positive living beings (BioMérieux, Marcy l'Etoile, France). Antimicrobial defenselessness testing was finished by Kirby Bauer circle dissemination technique and determination of anti-infection agents for vulnerability testing for each secluded microbes was finished utilizing Clinical and Research Center Standard Establishment (CLSI) rules 8 for understanding as safe (R), middle of the road delicate (IS) and touchy (S). In the Kirby-Bauer strategy, little circles containing various anti-microbials or impregnated paper plates were dropped in various zones of the way of life plate, bringing about zones of bacterial lysis as per the helplessness. The width of the lysis zone in millimeter for every anti-microbial circle has been changed over to Least Inhibitory Focus (MIC) in $\mu\text{g/ml}$, in view of realized direct relapse bends. Protection from a gathering of anti-infection was characterized as non-vulnerability ("R" or "IS" report on plate dissemination test).

Multi-Medication Opposition Further the gram-negative pathogens were ordered dependent on their protection from different anti-toxin classes. Multi-sedate obstruction was determined dependent on the technique adjusted from Sievert et al because of the nonappearance of generally acknowledged criteria. 9 Multidrug oppositions were characterized for as protection from any three of five anti-toxin classes like Aminoglycoside (Gentamicin, Amikacin, Netilmicin), a carbapenem (Imipenem, Meropenem), expanded range cephalosporins (Cefotaxime, Ceftriaxone, Ceftazidime), fluoroquinolones (Ciprofloxacin, Levofloxacin, Ofloxacin), (Piperacillin, Piperacillin-Tazobactam).

Factual Examination: For measurable investigation information were gone into a Microsoft Excel spreadsheet and after that broke down by SPSS 20.0.1 and Chart Cushion Crystal adaptation. Chi-squared test was performed to test the relationship between mortality with a rate of anti-toxin obstruction. P-esteem ≤ 0.05 was considered for measurably critical.

3. Outcomes

During the examination time frame, 4781 children with clinical sepsis were dealt with and blood culture was drawn for them. Positive blood culture was found in 415(8.68%) cases and of which 348 cases (7.21%) were observed to be bacterial sepsis. Blood culture for contagious sepsis was certain for 7 cases. The parasitic

sepsis cases were not viewed as further in this examination.

There was a strength of gram-negative microbes causing neonatal sepsis in babies in this inside. The quantity of different detaches alongside recurrence, the rate of death among culture positive cases were portrayed in table 1. In excess of two third of the pathogens had a place with the family Enterobacteriaceae (Klebsiella spp, Escherichiacoli, Enterobacter spp, and Serratia spp) representing 241 (69.2%) instances of every single bacterial contamination. Gram-positive cocci represent just 38 cases, i.e., 11 % of the absolute bacterial diseases. Klebsiella spp was the principal irresistible specialist with 187 (53.7%) of the complete culture-positive bacterial diseases pursued by E. coli spp in 48 (13.7%), Acinetobacter spp in 40 (11.5%) and Pseudomonas spp in 29 (8.3 %) cases. Aside from bacterial pathogens, 67 cases were seen to be tainted with Candida (information not appeared).

In this investigation complete, 113 children passed on among 348 blood culture positive cases, the case casualty rate is 32.4%. Enterobacteriaceae bunch alone represented an aggregate of 90(79.6%) demise. Klebsiella spp prevailed the neonatal sepsis contaminations and caused the most astounding number of passings, as high as 72 (63.7%) pursued by 17(15.0%) demise by E.coli. Acinetobacter represented 11(9.7%) passings while for 08(7.07%) passings Pseudomonas was the causal living being. Gram-positive pathogens (Staphylococcus aureus and Enterococcus sp.) were in charge of just 4(3.5%) of absolute passings. Candida has represented 15 cases, however, are excluded in our investigation. The case casualty rate of sepsis because of various life forms has been additionally portrayed in table 1 which demonstrated Klebsiella spp and Escherichia coli sepsis conveyed practically equivalent high case casualty rate of 35-39% pursued by Acinetobacter spp and Pseudomonas spp (27.5% each). The case casualty rate of Staphylococcus spp was as low as 8% where Enterococcus had a higher case casualty rate of 25%.

The anti-microbial obstruction example of gram-positive living beings like Staphylococcus spp and Enterococcus spp has appeared while the opposition example of different gram-negative life forms like Klebsiella spp, Escherichia coli, Serratia spp, Enterobacter spp, Pseudomonas spp, and Acinetobacter spp has been portrayed in table 3. Gram-positive cocci displayed 100% affectability to amikacin, netilmicin, vancomycin, and linezolid. In any case, over 90% of these life forms were impervious to ampicillin and roughly 80% of them were impervious to fluoroquinolones. A fourth of them were impervious to carbapenems and over 65% were impervious to cephalosporin.

Gram-negative living beings all in all were discovered impervious to ampicillin in 82.9% of cases, cefotaxime in 55% of cases, piperacillin-tazobactam to 42% of cases, aminoglycosides to 39-42 % of cases and fluoroquinolones aside from ofloxacin to 45 % of cases. Gram-negative living beings indicated less obstruction and better helplessness design for ofloxacin (27.8%), carbapenems (20-21%), colistin (1.9%) and cefoxitin (1.3%)

The investigation has likewise noticed the nearness of multidrug obstruction on account of a gram-negative life form. Klebsiella spp beat the rundown of MDR living beings with 88 cases pursued by Acinetobacter spp with 20 cases, Escherichia coli with 14 cases and Pseudomonas spp with 7 cases (Table 4). We have additionally watched more passing on account of MDR life forms. Fifty children kicked the bucket among 129 infants who were sure for MDR gram-negative microscopic organisms with and the case casualty rate was 38.7 %. In comparison, 58 babies kicked the bucket among 175 babies positive for non-MDR gram-negative microorganisms case casualty rate being 33.1%. In spite of the fact that not measurably huge, we have discovered this expanding pattern of mortality among MDR positive life forms. ($p=0.31$). We have discovered the case casualty has been expanded in the MDR bunch in contrast with the general case fatality in instance of Acinetobacter spp and Pseudomonas spp. The rate of MDR was most noteworthy in Acinetobacter spp (half) trailed by Klebsiella spp (47%), Escherichia coli (29%) and Pseudomonas spp (

24%). Generally, 129 segregates indicated MDR among 304 gram-negative culture-positive cases, the rate being 42.4%.

4. Discussion

The range of microbial etiology of neonatal sepsis changes from area to locale, shifts in various clinics of a similar district. The similar examination of bacterial detachments announced from various parts of the nation has been portrayed in Table 5. While examinations from Chennai and Rajasthan, detailed pre-predominance of *Klebsiella* spp. as the causal life form as likewise found in the present investigation, think about from Delhi. Detailed *Acinetobacter* spp. Curiously, reports from Punjab, Himachal Pradesh, and Karnataka, 11,14,15 demonstrated *Staphylococcus aureus* as the primary pathogen which is less basic in our examination. Our examination uncovered individuals from Enterobacteriaceae as the most pervasive gathering of creatures with *Klebsiella* spp. as the lead causal life form. Methodical investigation by Le Doare and associates included outcomes from eleven neonatal units: three in Africa, one in the Center East, one in South East Asia, and six in Asia. In all zones, *Klebsiella* spp. was the overwhelming pathogen, representing 49.8% of all gram-negative bacilli, trailed by other Enterobacteriaceae which confirms our finding.

Two prior reports from a similar unit from 2007 to 2014 had demonstrated *Acinetobacter* spp. as the most well-known causal life form. The creators found that Non-aging gram-negative microscopic organisms (NFGNB) ruled the neonatal sepsis diseases including certain uncommon life forms. In the present examination, *Acinetobacter* spp. (12%) has been dwarfed by *Klebsiella* spp. and *Escherichia Coli* which record for 67% of every single bacterial disease. Both *Acinetobacter* spp. and *Pseudomonas* spp. (NFGNB) have been found related with 20% of the bacterial neonatal sepsis cases in the present examination when contrasted with 23.6% as detailed by Vishwanathan et al. in 2014 [18]. One life form or gathering of living beings might be supplanted over some undefined time frame in basic zones like neonatal serious consideration units (NICU) which has been additionally reflected in past examinations like by Roy et al. That is the reason progressing observation and survey of the anti-microbial approach is required for avoidance of rise of antimicrobial opposition.

As indicated by our investigation mortality related with Enterobacteriaceae is essentially higher than the equivalent related with different gatherings. Inside this gathering, *Klebsiella* spp. was observed to be most deadly causing demise in around 38 % cases tainted with it. (Table 1). *Klebsiella* spp. is intently trailed by *Escherichia coli* as far as lethality with 35.4% death rate, however it is put lower in MDR list. This is predictable with prior perceptions and this mortality has been credited to K1 capsular antigen present in a few strains. [18] K1 antigen is a polysialic corrosive that debilitates opsonophagocytic slaughtering. They report that children tainted with K1 antigenic strains have expanded dreariness and mortality contrasted with infants contaminated with different strains. Other destructiveness components connected to neonatal sepsis incorporate supplement opposition interceded by O-lipopolysaccharide and a gathering of surface proteins which help in official and intrusion of cerebrum endothelium. [20]

We have discovered a few contrasts in commonest disengagements in NICU which might be owing to variety of the microbial range from district to area and in various medical clinics of a similar locale and frequently one life form or gathering of living beings might be supplanted by others over some undefined time frame. Without an exacting anti-microbial arrangement for neonatal sepsis, utilization of various anti-toxins at various focuses may offer ascent to the rise of isolated safe vegetation at different focuses.

Fundamentally, *Klebsiella* spp has indicated pre-ponderance in multidrug obstruction in this investigation pursued by *Acinetobacter* spp and *Pseudomonas* spp. The ascent of MDR Gram-negative microscopic organisms (GNB) is of most prominent worry in the neonatal populace and with very restricted helpful choices. [19] A positive relationship among's MDR and mortality was watched. Antimicrobial obstruction among the Enterobacteriaceae speaks to a noteworthy issue in both medicinal services related and network obtained neonatal diseases. [21]

The antimicrobial obstruction example of gram-positive life forms has obviously shown that Ampicillin being opposition in 90 % of cases, would never be prescribed as a first-line observational anti-infection. Aminoglycosides rather would be a superior decision with an opposition rate of 0-12 %. Gram-positive life forms showed better affectability to vancomycin and linezolid (100%) and can be utilized specifically when an authoritative living being is distinguished. Our investigation result certified the finding of the past examinations like by Marwah et al, who announced 100% affectability to vancomycin and linezolid in *S. aureus* strains from a tertiary consideration focus in Northern India. [15]

For gram-negative life form, colistin was found to have the least opposition (0%) trailed via carbapenems (20%) and ofloxacin (27%) among all fluoroquinolones. Unpredictable utilization of these save medication must be stayed away from. Third era cephalosporin like cefotaxime has likewise been inadequate with reported obstruction in 55 % of cases. Thus piperacillin-tazobactam or aminoglycoside which indicated opposition in and around 40 % of cases, can be utilized experimentally as beginning anti-infection agents. The perception was very like a couple of reports distributed from North India. [10,11,15] Anyway after blood culture report is accessible the objective ought to be to move to monotherapy with the tightest range delicate anti-infection. India being the world's biggest customer of anti-infection agents for human wellbeing in 2010 at 12.9 x 10⁹ units (10.7 units per individual), silly abuse of anti-toxins is dependably a probability which has driven the issue of anti-toxin opposition. [22]

In India by and by the debilitated infant care is experiencing the period of fast extension with the presentation of various wiped out infant care units, however quick blood culture office is still past the range of the greater part of the units. Without legitimate identification of life forms and documentation of defenselessness by fast blood culture technique at neonatal consideration units, the abuse of anti-microbials and even the hold medications like carbapenems and colistin is making the upsurge of deadlier MDR pathogens. Thus blood culture office ought to be benefited to the every neonatal unit particularly at the fringe units to check undue dependence on immovable parameter like C-responsive protein to heighten and proceed with anti-toxins at the circumstance while really they are not justified.

We have not secluded the way of life positive cases into ahead of schedule or late-beginning sepsis, in light of the fact that the previous information has just appeared there are relatively few contrasts in the detaches, particularly in the Indian situation. [3,7,18] Disease control arrangement to adequately shorten the spread of these safe living beings. Early bacterial discovery by quick and computerized blood culture strategies at NICU can accelerate the determination and encourage focused on treatment to diminish the weight of antimicrobial obstruction.

Irreconcilable situation: No irreconcilable situation found.

Subsidizing: This exploration did not get a particular give from financing organizations in people in general, business or not - for - benefit divisions.

MDR: multi medicate obstruction, CONS: coagulase negative staphylococcus, ESBL: broadened range b-

lactamase,

MRSA: methicillin opposition staphylococcus aureus

5. Conclusion

We finish up by saying that gram negative pathogens having a place with Enterobacteriaceae were increasingly common and progressively deadly with more MDR living beings contrasted with others in neonatal sepsis and MDR were related with more neonatal passings than helpless ones. At long last, it is to be noticed that regardless of ongoing advances in human services, horribleness and mortality because of neonatal sepsis and expanding pattern in MDR living beings remains a noteworthy reason for worry in neonates. There is a requirement for exacting adherence to hand cleanliness rehearses, occasional reconnaissance of pathogens, and a need to implement antibiotic stewardship program in neonatal consideration units under clear

6. References

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