Original Article

Outcome of MDR Klebsiella Sepsis among Neonates Admitted in NICU at a Tertiary Care Centre of Western India — A Retrospective Study

Sayan Kumar Das[1], Nisha Prajapati[2]

Background : A significant problem in the field of global health care is the rise in clinical cases of Multi Drug Resistant (MDR) bacteria. One of the most hazardous superbugs in India as well as in the world is Klebsiella Pneumoniae (KP). The aim of study was to determine the clinical traits and different risk factors of sepsis caused by KP with emphasis on the antibiotic sensitivity pattern in SNCU at a Tertiary Care Centre of Western India.

Materials and Methods : A Retrospective study was done at NICU, Department of Paediatrics, GMERS Medical College, Gandhinagar, Gujarat from 1st January, 2021 to 30th June, 2023 (2.5 years). Study done on with specified inclusion group and analysed on various parameters.

Results : The study comprised of 6576 newborns in total. Out of which 2476 (37.65%) were total sepsis cases. Out of 2476 sepsis cases, 78 (3.15%) comes out to be MDR KP. MDR KP cases shows overlapping Clinical symptoms. The most frequent perinatal risk factor, which occurred in 69.23% of cases, was prolonged labor (>24 hours). In the study it reveals, 92% of the patients, the C-reactive protein (CRP) level was positive followed by Low platelet counts (90.7%). Expiry rates were 1.33%. Colistin (61.53%), Polymyxin B (55.12%), Cefoperazone/Avibactam (51.28%) were among the most sensitive antibiotics to MDR KP strains.

Conclusions : In the Study, it reveals that Maternal Prolonged Labor, Repeated Vaginal Examinations and Sclerema, Oedema, Bleeding etc. developing as early as DOL 4 in the cases are an early suspicion of MDR Klebsiella Sepsis. Severe Thrombocytopenia (Platelet <50,000) along with Increased CRP (>200) and severe low S. Albumin (<2g/dl) on consequent blood investigations is a clue for diagnosis when Culture reports are still awaited. Neonatal care should include regular antimicrobial stewardship Program for appropriate antibiotic therapy in order to limit resistant cases.

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Key words **: Klebsiella Pneumoniae, Multi Drug Resistance, Antibiotic Susceptibility, Antibiotic Stewardship.**

Sepsis is one of the main causes of Neonatal Mortality and Morbidity[1]. A significant problem in the field of global health care is the rise in clinical cases of Multi-Drug Resistant (MDR) bacteria[2].

One of the most hazardous superbugs in India as well as in the world is Klebsiella Pneumoniae (KP). India is targeting NMR≤12 by 2030 as per SDG. At present, we are far away from achieving that and rising trends of Sepsis more specifically MDR cases is one of the major obstacles (Fig 1).

State of Gujarat is one of the most developing states at present in India. If we look into the NMR of Gujarat, it also shows a lack of research in areas of MDR cases to cut short NMR and achieve the SDG targets (Fig 2).

There were substantial rates of MDR (resistance to any three of five antibiotic classes) in Klebsiella pneumoniae, according to clinical and microbiological data from three sizable tertiary care NICUs on 1005 culture-positive cases reported by the Delhi Neonatal Infection Study (DeNIS)[3].

Editor's Comment :

- MDR klebsiella is one of the most notorious organisms causing Neonatal deaths in NICUs of all over the country.
- Early intervention with timely judicial administration of antibiotics can help to combat the problem which will help us to reduce NMR and get the Target MDG.

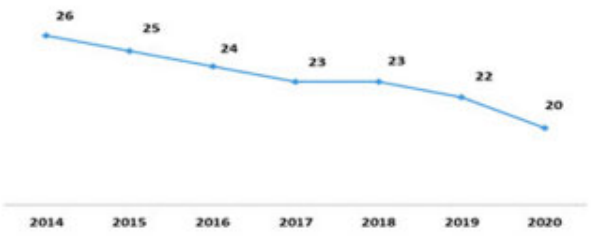

Fig 1 — India's NMR Trends (Source- Niti Aayog's Report, 2022).

The mortality burden of antibiotic resistance in India is still largely unstudied, despite the fast rise in MDR Cases and the general recognition of the problem[4].

Gram-negative bacteria have been linked to an increase in sepsis cases recently, particularly in

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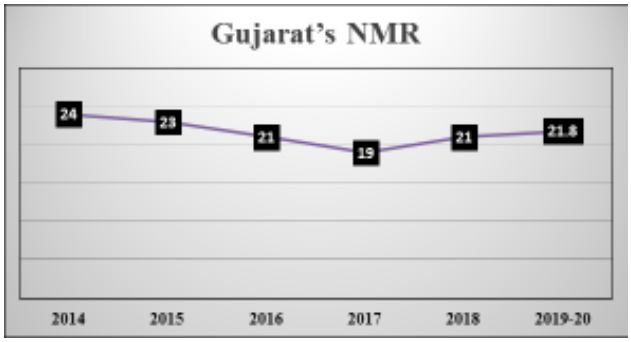

Fig 2 — Gujarat's NMR Trends (Source- Niti Aayog's Report, 2022)

developing countries. Unintentional use of broad-spectrum antibiotics is a contributing factor to the growth of multi-drug resistant Gram-negative bacteria, according to studies[5-7]. Klebsiella species are vitally crucial in this regard[8-12]. This bacteria causes sepsis in 4-9% of cases in affluent countries, whereas it affects 16-28% of cases in less developed nations[13].

According to a paper from 2016, 12.7% of isolates MDR KP causes various virulent diseases in Germany[14]. It is unclear what part MDR virulent K pneumoniae strains play in infections in newborns.

Materials and Methods

Aims :

To monitor the Outcome of MDR Klebsiella Sepsis among Neonates admitted to NICU.

Objectives :

Primary Objective —

- To study the clinical patterns of MDR KP sepsis.
- The antibiotic sensitivity of MDR *Klebsiella pneumoniae.*

Secondary Objectives —

- To identify various risk factors of MDR Klebsiella Sepsis

Study Centre : Department of Paediatrics, GMERS Medical College, Gandhinagar.

Study Duration: 1st January, 2021 to 30th June, 2023 (2.5 years).

Study Design : Retrospective Cross-sectional Study.

Sample Size : All the Cases that met our inclusion criteria in the defined period is taken into consideration.

Inclusion Criteria :

- NICU admissions showing positive blood cultures of MDR KP only.

Exclusion criteria :

- Neonates with positive blood culture for any other organism and drug-Sensitive KP.

Criteria for defining MDR, XDR and PDR in *Enterobacteriaceae*[15].

MDR : Resistant to ≥1 drug in >3 antimicrobial categories.

XDR : Resistant to ≥1 drug in all but ≤2 categories.

PDR : Resistant to all antimicrobial drugs listed.

Data Collection and analysis :

The Hospital Record Section (HRS), which produces daily reports, was used to collect data. Laboratory parameters have been assessed from the case records and the Pathology, Biochemistry and Microbiology departments of our college.

Collected data was entered into MS Excel and analyzed by descriptive statistics. All numeric values were expressed in exact numbers and percentages. All results thus generated are duly complied with and analyzed accordingly.

Results

The study comprised 6576 infants who were hospitalized in the NICU of the GMERS Medical College in Gandhinagar, India. Out of which 2476 (37.65%) were total sepsis cases (both blood culture and septic screen positive). Total Culture Positive 1121 (31.34%). MDR KP 78 and Other Culture Positive (Including Sensitive KP) 1043. 78 (2.18%) of the 3576 neonates were MDR KP. 48 expired, Mortality rate 61.53%. Out of 2476 sepsis cases, There were 1251 (34.98%) preterm low birth weight infants, 286 (7.99%) preterm very low birth weight infants, 23 (0.64%) preterm extremely low birth weight infants, and 2016 (56.37%) term infants (Figs 3&4).

Out of 78 MDR KP cases, Male – 43 (55.06%), Female – 55 (44.94%) and Inborn – 33(42.30%), Outborn – 45(57.30%). So, Occurrence is more in Males and Outborns (Figs 5&6).

Most newborns begin to exhibit symptoms on day four of life, predominantly Late Onset Sepsis (LOS). Out of 78 MDR KP cases, Early Onset Sepsis (EOS) (within 72 hours of Birth) was 11 (14.10%) and LOS-was 67(85.89%). Table 1 display the date the

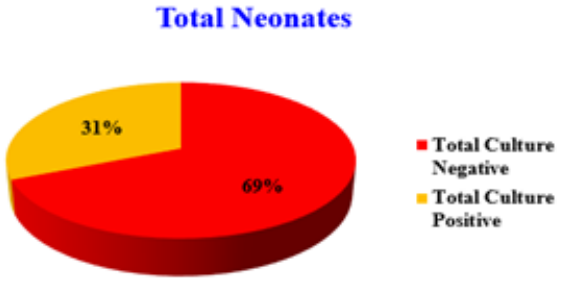

Fig 3 — Culture Positives and Negatives

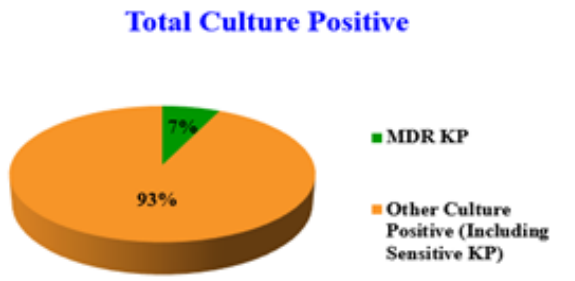

Fig 4 — MDR KP and Other Sentitive KP

symptoms first appeared.

The perinatal risk factors that caused the sepsis are listed in Table 2, which demonstrates that a relatively large percentage of the infants had these risk factors. The most frequent risk factor (>24 hours of labor) was observed in 69.23% of cases, whereas the least frequent risk factor Foul-smelling liquor / Maternal fever within 2 weeks (>38^{0}C) was observed in 2.56% of cases. In many instances, many factors were present at the same time.

Table 3 displays the overlapping symptoms and indications of newborns with blood cultures that are positive for KP. The most frequent manifestation was refusal to eat (89.73%), followed by vomiting (78.20%) and shock (70.51%), whereas apnea (8.97%) and convulsion (12.82%) were the least frequent.

KP exhibited resistance to meropenem, vancomycin, amikacin, and amoxicillin-clavulanate in this investigation. Colistin, Polymyxin B, Cefoperazone/Avibactam, were highly sensitive and Linezolid and Aztreonam exhibited moderate sensitivity (Table 4). Out of a total of 78 MDR KP cases, 33 (42.30%) neonates died and 45 (57.69%) made a full recovery. The overall mortality rate among 2476 sepsis patients was 1.33% owing to MDR KP. The beginning of feeding was used to measure clinical progress. On average, feeding began on the fourth day of starting therapy. The causative agent was responsive to intravenous antibiotics, which were given for 14 days.

In our study, it reveals in 92% of the patients, the C-reactive protein (CRP) level was abnormally high (>200mg/l) followed by Severe Thrombocytopenia (Platelet <50,000/mm^3) (90.7 %) and Severe Low

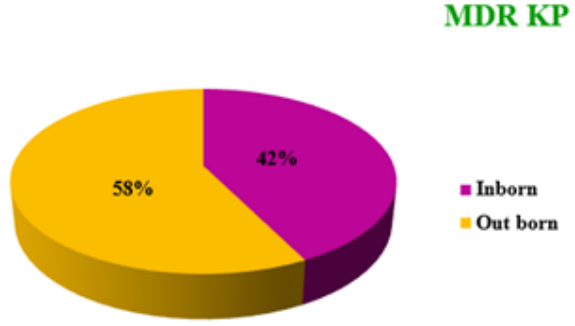

Fig 5 — Inborn & Outborn Proportions

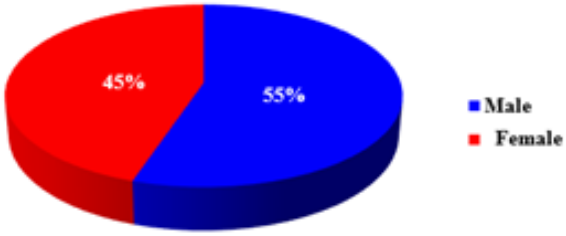

Fig 6 — Male and Female Proportions in MDR KP

Table 1 — *Onset of Symptoms (n=78)*

Onset of Symptoms	Number	Percentage
Within 48 hours	2	2.56
49-72 hours	9	11.53
Day 4	48	61.53
Day 5-7	10	12.82
Beyond 1st Week	9	11.53

Table 2 — *Perinatal risk factors for MDR Klebsiella Sepsis (n=78)*

Risk factors	Number	Percentage
Prolonged labour (more than 24 hours)	54	69.23
Unclean or >3 sterile vaginal examinations	13	16.66
PROM (more than 18 hours)	4	5.12
Birth asphyxia	3	3.84
Foul-smelling liquor	2	2.56
Maternal fever within 2 weeks (>38^{0}C)	2	2.56

Table 3 — *Overlapping Clinical Features of MDR Klebsiella cases (n=78)*

Symptom/Sign	Number	Percentage
Feeding Problems (Vomiting, FTT etc)	70	89.73
Shock (CRT>3 Sec)	55	70.51
Sclerema	46	58.97
Generalised Oedema	40	51.28
Bleeding	38	48.72
Fever	36	46.15
Mottling	36	46.15
Hypothermia	28	35.89
Abdominal distension	18	23.07
Lethargy	12	15.38
Convulsion	10	12.82
Apnoea	7	8.97

Table 4 — *Lab Parameters in MDR Klebsiella Cases*

Lab Parameters	Percentage
CRP (>200mg/l)	92.00
Severe Thrombocytopenia (<50,000/mm^3)	90.71
Severe Low Serum Albumin (<2g/dl)	82.76
Increased WBC (>15,000/mm^3)	42.91
Increased Hct (>40%)	26.94
Mean Platelet Volume (>9.5)	21.08

Serum Albumin (<2g/dl) (82.7%) Depicted in Table 4.

Colistin (61.53%), Polymyxin B (55.12%) and Cefoperazone/Avibactam (51.28%) were among the most sensitive antibiotics to MDR KP strains shown in Table 5 with all the others sensitive antibiotics.

Table 5 — *Drug Sensitive to MDR Klebsiella pneumoniae*

Drugs	Number	Percentage
Colistin (*Intermediate Sensitive*)	48	61.53
Polymyxin B	43	55.12
Ceftazidime/Avibactam	40	51.28
Aztreonam	33	42.30
Meropenem	21	26.92
Piperacillin-tazobactam	5	6.41
Levofloxacin	3	3.84
Ampicillin	0	0
Gentamycin	0	0
Cefotaxime/Ceftriaxone	0	0
Ceftaroline	0	0
Netilmicin	0	0
Amoxicillin/ Amoxicillin-clavulanic acid	0	0
Amikacin	0	0

Discussions

In the Study, it reveals that Maternal Prolonged Labor, Repeated Vaginal Examinations and sclerema, Oedema, Mottling, Bleeding etc. developing as early as DOL 4 in the cases are an early suspicion of MDR Klebsiella Sepsis.

Severe Thrombocytopenia (Platelet <50,000) along with Increased CRP (>200) and severe low S Albumin (<2g/dl) on consequent blood investigations is a clue for diagnosis when Culture reports are still awaited. In contrast to our research, other investigations have found KP to be very resistant to Meropenem and Colistin[16,17].

We may infer from the results of our combined data that there are currently very few antibiotics that can effectively treat KP and the cost of these drugs are quite high in the open market. One study showed that the mean cost of treatment for MDRO Sepsis was INR 4,99,840 *versus* INR 180,592 for non-MDRO Sepsis[18].

We evaluated the different KP infection risk variables. We found that inborn newborns and neonates with birth weights under 2.5 kg were more vulnerable to KP infection. In general, birth weight and infection rate are inversely associated. This explains why newborns with birth weights under 2.5 kg were more likely to get KP infection. To reduce mortality from newborn Sepsis in low birth weight infants, prevention, early detection and early treatment are essential.

The capacity of this bacterium to live in the ICU environment and infect quickly, causing outbreaks, puts inborn newborns at higher risk for KP infection. Even though preterm newborns were shown to have a higher risk of KP infection. This may be brought on by the overall rise in the likelihood that viruses other than KP would infect preterm newborns. Prematurity was found to be one of the commonest risk factors for newborn Sepsis in research by Shitaye, *et al*[19], regardless of the pathogen.

In contrast to our research, other investigations have found KP to be susceptible to Meropenem. The KP pathogens were very resistant to Meropenem and highly susceptible to colistin/polymyxin B[20].

Limitation :

This study has three main flaws. First, some antibiotic disks periodically ran out of stock, which resulted in irregular antibiogram reporting. Second, the number of isolates per type of organism was insufficient for all bacteria, since CLSI advises at least 10 isolates/species of organism for a highly efficient antibiogram. Third, another restriction is the limitation of molecular typing in all MDR KP Cases to know the exact strain causing the Sepsis cases.

Conclusions

Before starting antibiotics, every effort should be taken to collect samples for culture and sensitivity testing. The most likely pathogens for the infection site should be known, as well as information on the patient's background (such as previous hospitalizations, exposure at work, travel and pet ownership) and area susceptibility. All patients taking antibiotics should be continuously checked for adverse drug responses and the disappearance of infectious signs and symptoms, such as a decline in fever and white blood cell count. Through antibiotic stewardship programs clinicians should strive toward optimizing antibiotic usage, appropriate drugs whenever needed and for correct duration.

Numerous findings from studies conducted across the world demonstrate that MDR bacteria are spreading around the world and posing serious threats to public health and healthcare[21]. We may infer from the results of our combined data that there are currently very few antibiotics that can effectively treat KP.

To create potential long-term solutions to combat resistance, more societal funding is required for basic and applied research as well as policy-related efforts. A few of the interventions on this list include using novel business models to encourage investment in antibiotic therapies, curving the spread of antibiotic resistance to lengthening the useful lives of antibiotics, discovering fresh methods to directly combat virulent

agents without fostering resistance and changing host-agent interactions to modify disease without directly combating microbes. In the past ten years, research on genomic mutations and the use of bacteriophages has shown promise since these more creative forms of stewardship may be utilized to create treatments that do not promote resistance.

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