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Multidrug resistance in Paediatric infections - problem and possible solution

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BACKGROUND

The unique landscape of epidemiology with **a dense population, significant infectious diseases burden**, and **diverse healthcare practices** in India make it challenging to address the threat of antimicrobial resistance (AMR). The significant contributors being the **overuse and misuse of antibiotics and poor infection control practices**.[1]

Children are known to receive antibiotics more often than any other class of drug, as they are susceptible to common childhood and vaccine preventable infections. Of particular interest are those admitted to the intensive care units with life threatening infections which could either be community or hospital acquired gram negative or gram-positive bacterial infections.[2]

Within the **Enterobacterales *spp***. published data from the Indian Council of Medical Research Annual report in 2021 suggest the increase in Carbapenem resistance by 20% for Klebsiella pneumoniae (65%) and that for E.coli is to the tune of 60%.

OBJECTIVES

To analyze the following parameters in neonates and children admitted to the intensive care with a positive blood culture:

1. Clinical data
2. Microbiological diagnoses
3. To estimate the incidence of Carbapenemase gene detection and synergy testing in invasive infections caused by Carbapenem resistant Enterobacterales- Gene-expert ™ (CEPHEID)
4. Antibiotic susceptibility patterns
5. Clinical Outcomes

MATERIALS AND METHODS - RETROSPECTIVE ANALYSIS

- Records of all children admitted to the neonatal and pediatric intensive care in whom blood cultures were positive over a period of 1 year were analyzed.
- All blood cultures with Carbapenem Resistant Enterobacterales were tested for Carbapenemase gene using the Carba- R ™ platform(Gene X pert- Cepheid Diagnostics)
- Synergy testing for Ceftazidime- Avibactam PLUS Aztreonam was carried out on all NDM or NDM+ OXA-48 positive isolates using the double gradient diffusion method, along with an E test MIC for Colistin.

RESULTS - OVERALL, CLINICAL MICROBIOLOGICAL, MOLECULAR DATA

PARAMETER	NUMBER
Total number of records with positive blood culture children that were analyzed	n– 98
Positive isolates- NICU	n– 40
Children admitted to the PICU	n– 58
Commonest Enterobacterales spp isolated in the NICU (n-40)	Klebsiella pneumoniae n- 34, (85%)
Commonest Enterobacterales spp isolated in the PICU (n-58)	Klebsiella pneumoniae n- 47, (81%)
Commonest Carbapenemase gene detected in the NICU (n-34)	NDM (New Delhi Metallo-beta-lactamase) n- 17 (50%)
Commonest Carbapenemase gene detected in the PICU (n-47)	NDM (New Delhi Metallo-beta-lactamase) n- 25 (53%)
Isolates that demonstrated synergy to Ceftazidime-Avibactam - Aztreonam in NICU (n-34)	n– 28 (82.3%)
Isolates that demonstrated synergy to Ceftazidime- Avibactam-Aztreonam in PICU (n-47)	n– 44 (93%)
Isolates that showed Colistin susceptibility in NICU (n-34)	n– 28(82.3%)
Isolates that showed Colistin susceptibility in PICU (n-47)	26(55.31%)

RESULTS - NEWBORN COHORT- NEW-BORN INTENSIVE CARE

Parameter	Value
Total number of positive isolates	N-40
Out-born (transferred from else-where) In-born	N-34 (90%) N-6 (10%)
o Gestation • Extreme preterm : (< 28 weeks) • Preterm neonates: (28-36 weeks) • Late Preterm: (34- 37 weeks) • Term neonates: (>37 weeks)	 2 (5%) 19 (47.5%) 14 (35%) 3 (7.5%)
o Risk factors and complications • Respiratory distress requiring non-invasive ventilation • Deranged coagulation • Mechanical ventilation • Surgery for an anatomic anomaly or a pathology • Surfactant • Necrotizing Enterocolitis	24 (60%) 17(42.5%) 16 (40%) 14(35%) 11 (27.5%) 5 (12.5%)
o Outcomes • Survived • Succumbed • Extreme prematurity with Co morbidities • NEC • Laryngomalacia with Glossoptosis with subglottic stenosis - • Systemic sepsis following Necrotizing fasciitis – • Co infection (Polymicrobial bacteremia with Candidiasis) –	 32 (80%) 8 (20%) 4 4 1 1 3

RESULTS - INFANT AND CHILD COHORT-PAEDIATRIC INTENSIVE CARE

Parameter	Number
Total number of positive isolates	58
Medical conditions • Lymphoreticular malignancies & Leukemias • Long term Structural Lung disease • Dengue shock syndrome with MODS / DIC • Structural renal disease with urosepsis requiring surgery • Biliary atresia / Wilson's with Liver transplantation • Cardiovascular structural disease - surgery • HSCT for Fanconi's anemia / Mucopolysaccharidoses • Surgery for Acute Intra- abdominal events • DiGeorge's syndrome with sepsis	 14 (24.1%) 9 (15.5%) 8 (13.7%) 5 (8.6%) 4(6.8%) 4 (6.8%) 3 (5.17%) 3 (5.17%) 1 (1.7%)
Outcomes • Survived • Succumbed 1. Respiratory failure secondary to Lung disease 2. Neutropenia with overwhelming sepsis 3. Transplant related surgical complications 4. HSCT related complications (GVHD) 5. Dengue shock syndrome 6. Neurosurgical complication 7. Di George's syndrome 8. Steroid dependent Nephrotic syndrome	 41 (70.6%) 17 (29.4%) 5 (29%) 4 (23%) 2 (11%) 2 (11%) 2 (11%) 1 (5.8%) 1 (5.8%) 1 (5.8%)

COMMON NICU AND PICU RESULTS- MICROBIOLOGY

Parameter	NICU	PICU
Positive blood cultures	(N-40)	(N-58)
Klebsiella pneumoniae	(N-34)	(N-47)
E.*coli*	(N-6)	(N-8)
Enterobacter spp	-	(N-3)

MOLECULAR DIAGNOSES/TYPE OF CARBAPENEMASE

PARAMETER	K. *pneumoniae* (N- 81,92%)		E.*coli* (N- 14, 7%)		Enterobacter spp (N-3, 3%)	
Location	NICU (N-34)	PICU (N-47)	NICU (N-6)	PICU (N-8)	NICU (N-3)	PICU
NDM producers	17 (50%)	25(53%)	3 (50%)	5(62%)	------- (100%)	3
NDM Plus OXA-48 producers	14(41%)	17(36%)	2 (33%)	1(12%)	------	--------
OXA-48 producers	3 (8.8%)	5(10%)	1 (26%)	2(24%)	------	---------

ANTIBIOTIC SUSCEPTIBILITY PATTERNS AND MORE…

PARAMETER	K. *pneumoniae* (N- 81, 92%)		E.*coli* (N- 14, 7%)		Enterobacter spp (N-3, 3%)	
Susceptibility patterns	NICU (n-34)	PICU (n-47)	NICU (n-6)	PICU (n-8)	NICU (n-3)	PICU
Ceftazidime- Avibactam	3 (8.8%)	5	1 (16%)	2(25%)	-------	-------
Colistin					-	3
Tigecycline	32 (94%)	26(55%)	6 (100%)	8(100%)	(100%)	0
	19 (55%)	17(36%)	3 (50%)	5(62%)	(0%)	3 (100%)
FICI results-						
Synergy	28 (82%)	44(93%)	4 (66%)	5(62%)		
Additive	3 (8.8%)	-------	1 (16%)	1 (12%)		
Antagonism	-------	1 (2%)				
Indifference	-------	2 (4%)	-------	-------		

CONCLUSIONS

- NDM producing Klebsiella spp remains the commonest identified blood stream infection in neonatal and pediatric patients in the intensive care.
- Carbapenemase gene detection with targeted synergy and directed therapy is recommended for favorable clinical outcomes of BSI's in the critically ill children.
- Infection control, antimicrobial stewardship protocols are the most important preventative and cost-effective interventions in prevention the further spread of AMR.

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WORKING ALGORITHM