Rate of Multidrug-resistance to Antimicrobial Drugs in Patients in Pediatric Neurointensive Care

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Abstract

Background: Multidrug-resistant (MDR) organisms in the critical care unit are a worldwide concern. The vulnerability to MDR infection in pediatric patients admitted in neurocritical care are due to altered mental status, immature immune system, higher risk of aspiration, and more frequent use of invasive devices. We aimed to measure the burden of MDR infection in pediatric neurosurgical intensive care unit (NSICU) patients.

Methods: All pediatric patients between 1 and 18 years for intracranial and spine surgeries admitted for more than 48 hours in NSICU were enrolled in the study. If patients showed a clinical picture of pneumonia, bloodstream infection (BSI), or urinary tract infection (UTI) after receiving mechanical ventilation or an indwelling device for at least 48 hours, samples of tracheal aspirates, urine, blood, and cerebrospinal fluid (CSF) were sent for microbiological culture. We noted the type of organism, MDR infection rate, and associated risk factors. Pearson Chi-squared test and Fisher's test were used for statistical analysis; $p < 0.05$ was considered statistically significant.

Results: A total of 274 pediatric patients were studied. In 1 year, there was a total of 1,790 patient days. The inclusive MDR infection rate was 17.3/1,000 patient days. Also, *Klebsiella pneumoniae* (38.7%) was the commonest MDR pathogen. The commonest source of infection was BSI (32.3%). The risk factors associated with MDR infections were the length of stay in NSICU, mechanical ventilation of more than 5 days, emergency surgery, respiratory and cardiac comorbidities, and poor nutrition status ($p < 0.05$).

Conclusion: The MDR infection rate in our study was 17.3/1,000 patient days in pediatric patients. Also, *K. pneumoniae* was found to be the commonest MDR pathogen. Bloodstream was the commonest source of infection.

Keywords: Antimicrobial drugs, Multidrug-resistance, Neurointensive care, Pediatric.

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Highlights

- Multidrug-resistant organisms in patients in pediatric neurointensive care are of paramount importance.
- *Klebsiella pneumoniae* is the commonest isolated pathogen across all MDR infections.
- The commonest source of infection is the bloodstream.

Introduction

The global rise in the use of antibiotics has led to the development of resistant bacteria and increasing costs in health care.[1,2] The epidemiology of MDR bacteria varies across institutions and countries. Despite scientific advances in managing nosocomial infections and improvement in practices to reduce the burden of such infections, the major cause of mortality and morbidity in intensive care units (ICUs) remains MDR. Multidrug-resistant infections are common in pediatric patients due to relatively underdeveloped immune systems.[3] They are highly prone to MDR organisms following increased use of invasive lines or devices during hospitalization.[4] Other contributing factors in a special subgroup of pediatric neurosurgical patients include immunosuppression, altered mental status, and risk of aspiration. The prevalence of nosocomial infections in pediatric ICU patients ranges 5–23.6%.[5–7] Also, pediatric patients have often been prescribed antibiotics with a low threshold in comparison to adult patients.[8] Majority of children receive antimicrobials when they are undergoing surgery, have a central venous catheter, require prolonged mechanical ventilation, or remain hospitalized for more than 14 days.[9] Although infections caused by MDR organisms have manifestations, clinically similar to infections caused by susceptible pathogens, these infections are often extremely limited.[10] For evaluating the quality of health care in hospitals, surveillance of health-associated infections is recommended as part of an effective infection control program.[11] The knowledge about the burden of MDR organisms in pediatric neurointensive care patients is of paramount importance as it will help in implementing an appropriate antimicrobial stewardship program with an appropriate selection of antibiotics, adequate dose, and duration. This will reduce the injudicious use of antibiotics leading to the high prevalence of MDR, reduce the cost of health care, length of hospital stay, morbidity, and mortality and improve patient outcomes. Multiple studies have reported varying incidences of MDR in pediatric ICU or adult patients in NSICUs. However, there is a paucity of information on the burden of MDR in the pediatric neurosurgical subgroup of patients. Therefore,

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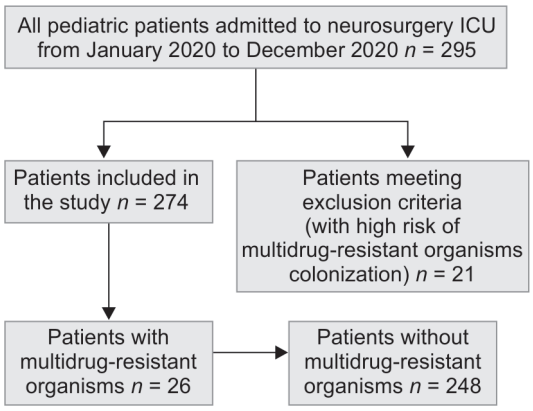
Flowchart 1: STROBE study flowchart



we aimed to determine the rate and type of MDR organisms in pediatric NSICU patients. We also aimed to study the risk factors causing MDR.

Methods

This article adheres to the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines (Flowchart 1). Postoperative pediatric patients were enrolled in this prospective observational cohort study between 1 and 18 years of age admitted in NSICU from 1 January 2020 to 31 December 2020, following the approval of the Institute Ethics Committee (Registration No. INV03464, Reference No. IECPG-439/27.06.2019), [Clinical Trials Registry (CTRI) No. CTRI/2019/10/021721]. The parents of the patient gave written informed consent for the recruitment in the study. We included all pediatric patients posted for all elective and emergency intracranial and spine surgeries admitted for more than 48 hours in NSICU. Patients with no consent, age of more than 18 years admitted for less than 48 hours in NSICU with a high risk of MDR organism colonization,[12–15] having antibiotic exposure history (within last 3 months), presence of any underlying diseases, previous surgery (within last 1 month), exposure to other MDR organisms colonized patients, transferred from other facilities with a known high prevalence of MDR organism carriage, history of recent hospitalization were excluded from the study. The non-susceptibility to at least one agent in three or more antimicrobial categories has been described as MDR.[2]

Data Collection

The data for risk-related factors (age, gender, and previous hospitalization), any comorbidity, past history of exposure to antimicrobials, contact with health care within 6 months, diagnosis on admission, immunosuppression, infection upon admission, NSICU length of stay, use of invasive lines or devices [tracheal intubation and mechanical ventilation, central venous catheterization (CVC), urinary catheterization], date of onset, and antibiotic therapy were collected. The condition at discharge was also noted.

As per clinical and laboratory criteria set by the Centers for Disease Control and Prevention (CDC), the type of specific hospital-acquired infection (HAI) was diagnosed.[16] After being on mechanical ventilation or having an indwelling device for at least 48 hours, device-associated HAI [ventilator-associated pneumonia (VAP), BSI, and catheter-related urinary tract infection (CR-UTI)] was diagnosed if the patient developed a clinical picture of pneumonia, BSI, and UTI (as per CDC criteria). The microbiological culture samples including tracheal aspirates, urine, and CSF were sent, once the infection was suspected according to clinical criteria set by CDC.[17] For each type of specimen, standard microbiological procedures for sample collection were followed. Using blood, chocolate, MacConkey's agar, and plates incubated at 37°C, specimens were inoculated. The blood culture bottles with screw caps were used for blood culture. For our population subgroup, 1 mL in 10 mL of BHI broth in MaCartney's bottles was used. We used the automated blood culture system, BacT/ALERT at our institute. The Kirby–Bauer disk diffusion method as per Clinical Laboratory Standard Institute (CLSI) guidelines was used to identify the antimicrobial susceptibility.[18]

Infection Rates Calculation

During the study period, the total number of patients admitted, the total number of patients with each device, the total number of device days, the total number of patient days, and the number of patients with each device-associated infection were calculated.

Device utilization (DU) ratio = Number of device days/Number of patient days

- *Patient Days:* A count of the number of patients in a patient care location during a defined time period (the total number of days that patients are in the location during the selected time period).
- *Device Utilization Ratio:* A measure of the use of invasive devices. It constitutes an extrinsic risk factor for healthcare-associated infection.

  Device-associated infection rate = Number of device-associated infections for specific site/Number of device days × 1,000
- *Device-associated Hospital-acquired Infections (DA-HAI):* The infections acquired by a patient who was admitted for a reason other than that infection during hospital stay [as defined by the CDC's National Healthcare Safety Network (NHSN) 2008].

Interpretation of Culture Result

Central line-associated bloodstream infection (CLABSI) was established if a pathogen was isolated from a single blood culture or an original contaminant pathogen was isolated from two blood cultures or if same pathogen was detected from a peripheral and a central blood culture.[19]

Urinary tract infection was established when the count exceeded 10^5 colony-forming units (CFUs)/mL (with no more than two microorganisms) detected.[19]

Respiratory samples were diagnostic of pneumonia when the count of more than 10^4 CFU/mL [for broncho–alveolar lavage (BAL) and 10^6 CFU/mL (for sputum)] was detected.[19]

Statistical Analysis

For statistical analyses, Statistical Package for the Social Sciences (SPSS) software, version 10 was used. Mean ± standard deviation is used to present continuous variables and the number (percentages) for categorical variables. The Pearson Chi-squared test and Fisher's exact test was used to find out correlation of risk factors with laboratory findings; $p < 0.05$ was considered statistically significant.

Results

Over a period of 1 year, 295 patients who underwent both elective and emergency neurosurgical procedures for supratentorial tumors, infratentorial space occupying lesions, spine malformations,

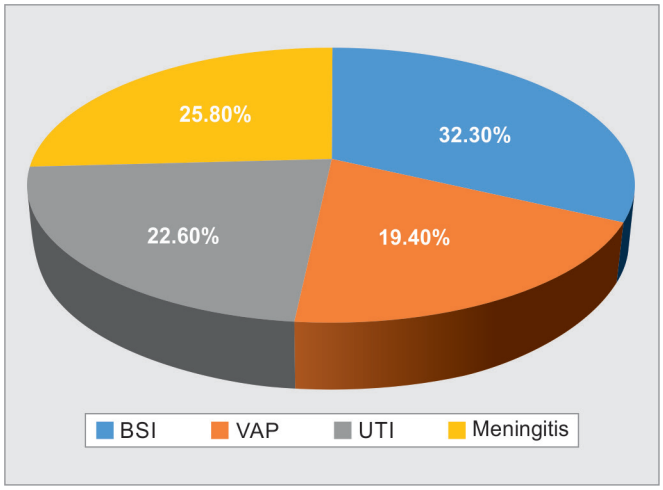


Fig. 1: Site-specific MDR infection. BSI, bloodstream infection; VAP, ventilator-associated pneumonia; UTI, urinary tract infection

Table 1: Device utilisation ratio and device associated MDR infection rate

Parameters	*Device utilization ratio*	*Device-associated MDR infection rate (per 1,000 device days)*
Central line	0.24	4.7
Ventilator	0.18	15.5
Urinary catheters	0.21	19.0
External ventricular drain (EVD)/shunts	0.14	12.1

craniosynostosis, epilepsy, and hydrocephalous were admitted to NSICU out of which 274 pediatric patients were studied (Flowchart 1) during 1,790 patient days. Out of these, 170 were males and 104 were females. Out of 274 pediatric patients, 26 patients with age of 8.8 ± 4.5 years were infected with MDR organisms, of which 16 were male and 10 were female. Three patients had multiple episodes with a total of 31 episodes of MDR organisms overall. The MDR infection rate in this study was 17.3/1000 patient days. Laboratory confirmed BSI was commonest (32.3%), followed by meningitis (25.8%), UTI (22.6%) and VAP (19.4%) (Fig. 1). Overall MDR, BSI, VAP, UTI, and meningitis rate was found to be 5.6, 3.3, 3.9, and 4.4 per 1,000 patient days, respectively. The DU ratio of central line was highest (0.24), followed by urinary catheters (0.21) and ventilator (0.18) (Table 1). All UTIs were found to be catheter associated. In 2 out of 10 episodes of MDR, BSI were associated with central lines. A total of 31 episodes of infection were MDR seen over a period of 1 year and related to the site-specific infections (Fig. 1). Multidrug-resistant *K. pneumoniae* was the commonest isolated pathogen (38.7%) across all MDR infection episodes followed by MDR *Pseudomonas aeruginosa* (22.5%) and MDR Escherichia coli (12.9%) (Table 2). In our study, central line-associated MDR infection rate was 4.7/1,000 catheter days, ventilator associated MDR infection rate was 15.5/1,000 ventilator days and urinary catheter associated MDR infection rate was 19.0/1,000 catheter days (Table 1). The duration of NSICU stay (more than 3 days), mechanical ventilation more than 5 days, respiratory and cardiac comorbidities, emergency surgery, and poor nutritional status were associated with MDR infections. However, age, gender, immunosuppression, and poor economic status were not associated with MDR (Table 3). Mortality in patients with MDR infection was (n = 14; 54%) whereas in patients with non-MDR infection mortality was (n = 13; 5%).

Discussion

The important findings of our study are as follows:

- Overall rate of MDR infection in pediatric patients admitted to NSICU is 17.3/1,000 patient days.
- Multidrug-resistant *K. pneumoniae* is the commonest pathogen (38.7%) isolated across all MDR infection episodes, followed by MDR *P. aeruginosa* (22.5%) and MDR *E. coli* (12.9%).
- The associated risk factors for MDR infection include the following: The NSICU length of stay, the mechanical ventilation duration of more than 5 days, cardiac and respiratory comorbidities, emergency surgery, and poor nutritional status. ($p < 0.05$).

The incidence of nosocomial infections varies with the type of hospital or ICU, patient population, and the precise definition and surveillance techniques used to identify nosocomial infection.[20] The MDR organisms pose a threat to pediatric patients during ICU stay worldwide due to their relatively underdeveloped immune systems as compared to healthy adults. They are associated with high treatment costs and high mortality. Various factors such as long-term antimicrobial therapy, cross-transmission, duration of hospital stay, and invasive procedures are related to the risk of MDR bacterial infection.[21,22] Literature on MDR infection in the pediatric neurosurgical population is scarce, so we compared our findings with patients in the pediatric ICU or adults in NSICU.

In a study conducted by El-Nawawy et al., the incidence of pediatric ICU-acquired infection caused by MDR bacteria was noted to be 13.63 (n = 36/264 episodes); equivalent to 15.6 cases/1,000 patient days. Moreover, *K. pneumoniae* was the commonest Gram-negative bacteria acquired from PICU that was resistant to antibiotics (30.5%), followed by *Acinetobacter baumannii* (22.22%).[23]

Table 2: Pathogen distribution across the healthcare-associated infections

Organism	*MDR BSI (n = 10)*	*MDR VAP (n = 6)*	*MDR UTI (n = 7)*	*MDR meningitis (n = 8)*
A. baumanii	1	0	1	1
P. aeruginosa	2	1	2	2
K. pneumoniae	4	2	2	2
Coagulase-negative staphylococci	0	1	0	0
Enterococcus	0	0	0	0
E. coli	2	1	2	1
Candida albicans	0	0	0	0
Burkholderia cepacia	0	0	0	0
Candida glabrata	1	0	0	0
Proteus	0	1	0	1
Serratia marcescens	0	0	0	0
Enterobacter cloacae	0	0	0	1
Haemophilus influenzae	0	0	0	0
Total	10	6	7	8

Table 3: Association of risk factors with multidrug resistant infections

				CI for OR	
Factors	*n*	*p-value*	*OR*	*Upper*	*Lower*
Age below 2 years	22	0.402	1.871	0.43	8.08
Gender	M = 170, F = 104	0.681	1.232	0.45	3.33
Poor socioeconomic status	29	0.330	1.884	0.53	6.30
Poor nutrition status	28	0.0001	6.312	2.31	17.20
Mechanical ventilation above 5 days	27	0.002	1.276	0.42	3.85
Length of ICU stay above 3 days	75	0.0001	6.2	2.12	15.21
Comorbidities (cardiac/respiratory)	15	0.0001	12.2	3.11	47.93
Emergency invasive surgery	49	0.045	0.096	0.01	0.94

CI, confidence interval; OR, odds ratio

In our study, the rate of MDR infection was 17.3/1,000 patient days, which is slightly higher compared to the previous study. The higher rate may be due to the longer duration of stay in the ICU in neurosurgical patients. At the same time, indwellings are usually put early in the course of treatment and for a longer duration when compared to pediatric ICU patients. In a study by Rezk et al., authors evaluated 282 pediatric ICU patients of which only 9.2% were colonized with MDR Gram-negative bacteria; of them, nearly half were affected by Acinetobacter species (50%).[24] In another study by Rhim et al., in subarachnoid hemorrhage (SAH) patients, extended-spectrum β-lactamase producing bacteria were the commonest (*E. coli* and *K. pneumoniae*) followed by methicillin-resistant *Staphylococcus aureus*, MDR Gram-negative rods, and vancomycin-resistant enterococci.[25] In our study, out of 274 patients enrolled, 31 MDR episodes were identified. Multidrug-resistant *K. pneumoniae* was the commonest pathogen (38.7%) isolated across all MDR infection episodes followed by MDR *P. aeruginosa* (22.5%) and MDR *E. coli* (12.9%).

Agarwal et al. reported that the most common (71.4%) infection is UTI which is followed by BSI and pneumonia.[26] In a study by Siwakoti et al. in ICU, MDR bacteria were most frequently isolated from the lower respiratory tract infection (72%) followed by BSI, UTI, and SSI.[27] In our study, laboratory confirmed BSI was the commonest (32.3%), followed by meningitis (25.8%), UTI (22.6%), and VAP (19.4%) (Fig. 1). This difference might be due to different patient populations, that is, general vs neurosurgical patients. A study by Agarwal et al. noted the highest device utilization ratio of urinary catheters (0.20) followed by ventilators (0.15), and central line (0.06).[26] We observed a device utilization ratio for the central line to be the highest (0.24), followed by urinary catheters (0.2) and ventilators (0.18). The central line utilization ratio was highest in our study probably due to our pediatric group where intravenous canulation is usually difficult. The urinary catheter and ventilator utilization ratio in our study is in accordance with the above study.

The risk factors associated with MDR organism carriage include age, increased usage of antibiotics,[28] previous exposure to hospitals, especially to the ICU,[29] and length of stay in the hospital.[30] In our study, we found that the associated risk factors for multidrug-resistant infections (MDRIs) include NSICU length of stay of more than 3 days, mechanical ventilation duration of more than 5 days, respiratory, and cardiac comorbidities, invasive emergency surgery and poor nutritional status ($p < 0.05$) but age, gender, immunosuppression, and poor socioeconomic status were not associated with MDR infections.

In a study by Wang and Xia[31] the pediatric length of ICU stay and the mechanical ventilation duration of more than 5 days were associated with MDR infections but age and gender were not associated with MDR organisms, which were similar to our findings.

Rezk et al. found a significant relationship between MDR organisms and underlying pulmonary disease.[24] In our study, cardiac disease was found as an additional risk factor along with respiratory disease for MDR infection. Age below 2 years along with more than 3 days of hospital stay was identified as a risk factor for the acquisition of MDR.[29] We did not find any association between age with MDR infection in our study. Although we did find NSICU stay of more than 3 days as a risk factor for MDR organisms acquisition. Allel et al. found a small but constant negative association between socioeconomic factors (income, education, and occupation) and overall antimicrobial resistance.[32] We also identified poor socioeconomic status as a risk factor for MDR organisms, probably because low income is associated with poor hygiene, crowded living, and poor nutrition status. Immunosuppression due to the use of systemic steroids was found to be a risk factor for MDR VAP in one study.[33] We did not find any association between immunosuppression and MDR infection. Tfifha et al. did not find an association between invasive procedures as a risk factor for MDR organisms during hospitalization in pediatric ICU.[29] On the contrary, in our study, invasive emergency surgery was identified as a risk factor for MDR infection.

Limitations

First, our study group included postoperative pediatric neurosurgical patients, in a tertiary care hospital and so the infection rates may not be representative of other population groups or patients in other healthcare settings. Second, our study was conducted during the COVID-19 pandemic with restricted admissions and limited healthcare staff caring for patients. Understandably, the rate of infection and outcomes may not be comparable to pre-COVID-19 healthcare settings. Third, we could not assess the nutritional status using anthropometric parameters owing to various patient-related factors. Fourth, since the identification of risk factors leading to MDR was not our primary objective, multivariate analysis was not done.

Conclusion

In our study, MDR rate is comparable to those reported in developing countries. Furthermore, *K. pneumoniae* is the commonest pathogen isolated across all MDR infection episodes. Bloodstream is the commonest source of infection followed by meningitis, UTI, and VAP. The NSICU length of stay, the mechanical ventilation duration of more than 5 days, invasive emergency surgery, cardiac and respiratory comorbidities, and poor nutritional status are found to be associated with MDR infections. We strongly propose that strict implementation of an infection control program is an absolute necessity.

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