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RESEARCH

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# *Klebsiella* infections in a pediatric intensive care unit: incidence, antimicrobial susceptibility, and resistance genes

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## Abstract

**Background:** Infections with multidrug-resistant *K. pneumoniae* is associated with high morbidity and mortality especially among critically ill patients. This was the main principle to conduct a detailed study about this organism, its resistance pattern, and type of its resistance genes

**Subjects and methods:** A cross-sectional study was carried out in a pediatric intensive care unit on patients with age range from 1 month to 12 years over a period of 1 year with positive *K. pneumoniae* using standard microbiological culture and antibiogram sensitivity testing. All collected samples were processed using multiplex PCR technique to identify the most relevant resistant genes.

**Results:** Forty-four patients had 54 positive cultures for *K. pneumoniae*, out of which 17 patients (38.6%) passed away. The most prevalent-resistant gene was New Delhi metallo-beta lactamase (NDM) gene (65.4%) followed by cefotaximase (CTX-M) gene (57.7%). Extensively drug-resistant *K. pneumoniae* was detected in (15.9%) of the results and was proved to be independent risk factor increasing mortality odds 139 folds.

**Conclusion:** The evolution of resistance of *Klebsiella pneumoniae* was proved to be associated with a high mortality rate. Continuous widespread surveillance of *Klebsiella* pathogen focusing on identification of resistance genes and antibiotic resistance pattern is highly recommended.

**Keywords:** Klebsiella pneumoniae, Resistant genes, Extensive drug-resistant

## Background

*Klebsiella pneumoniae* (*K. pneumoniae*) is the causative agent of a range of infections including but not limited to pneumonia, sepsis, bacteremia, and urinary tract infections (UTI) whether community or health care acquired infections [1]. Worryingly, there is a significantly higher risk of *K. pneumoniae* being multidrug-resistant (MDR) in nosocomial infections than in community-acquired infections because of the misuse of antibiotics, and thus, most patients carry flora which are resistant to antibiotics [2, 3]. Infections with multidrug-resistant *K. pneumoniae* are widespread in developed and developing countries with bad prognosis, high mortality rate, and very high-associated economic costs [4]. Only few drugs such as tigecycline and polymyxins may be effective against carbapenem-resistant *K. pneumoniae* infections. Although new sensitive antimicrobial agents for treatment of carbapenem-resistant *K. pneumoniae* (CR-KP) infections such as ceftazidime-avibactam have emerged in recent years, they are still ineffective against New-Delhi metallo-beta-lactamase (NDM)-producing CR-KP [5]. Moreover, a wide range of antimicrobial resistance genes further restricts the available options to effectively treat infections [6].

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The evolution of *K. pneumoniae* into resistant strain that was responsible for increased morbidity and mortality especially among critically ill patients was the main principle to conduct a detailed study about this organism, its resistance pattern, and type of its resistance genes.

## Methods

### Study design

A cross-sectional study was carried out on critically ill patients with age range from 1 month to 12 years admitted to a university-affiliated Pediatric Intensive Care Unit (PICU) over a period of 1 year (first of January to the end of December 2021).

### Data collection

All patients were subjected to detailed history taking and thorough clinical examination including pediatric index of mortality (PIM-2) and Pediatric Logistic Organ Dysfunction (PELOD) scores [7, 8]. Meticulous follow-up of patients during their PICU length of stay (LOS) for identification of any type of infection, routine laboratory, and radiological diagnosis of the infection and recording the fate of these patients whether survived or deceased.

### Laboratory identification of K. pneumoniae

Different bacteriological cultures were obtained upon specific infection case definition: urine, stool, blood (venous), nasopharyngeal swab, cerebero-spinal fluid (CSF) culture, and non-bronchoscopic broncho-alveolar lavage (NB-BAL) for mechanically ventilated cases.

All collected samples were processed according to standard microbiological procedures for each type of specimen. Specimens were inoculated using the following media: the blood, chocolate, MacConkey's agar, and the plates were incubated at 37°C. Blood culture were performed using automated blood culture system (BACT/ALERT 3D system; BioMérieux). The blood culture bottles were incubated in the BACT/ALERT 3D system as recommended by the manufacturer for seven consecutive days. All isolated organisms were identified according to colonial morphology (hemolytic or non-hemolytic colonies on blood agar, lactose or non-lactose colonies on MacConkey's agar), Gram staining reaction, and biochemical reactions (triple sugar iron, urease, citrate, motility, ornithine decarboxylation, indole tests) according to the standard microbiological methods [9].

Antibiotic susceptibility tests were performed for bacterial isolates using Bauer-Kirby disc diffusion method according to the latest Clinical and Laboratory Standard Institute (CLSI) recommendations [10].

NB-BAL, CSF, and earliest positive blood culture samples were subjected to an immediate multiplex PCR assessment using an automated closed system (Film-Array, Bio-Fire, USA, Serial Number 2FA06414) [11] to detect the possible bacteria and viruses, and the corresponding resistance genes were identified within 60–70 min from admission and management plans were designed accordingly.

### Statistical analysis

The SPSS-IBM software statistical package was used for the computer statistical analysis of data [12]. Data was presented as a range, mean, median, standard deviation, and standard error. Descriptive statistics in the form of frequencies and percent were used to describe the categorical data variables while scale data were expressed by mean and standard deviation for normally distributed variables and median with range for skewed variables. The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test. If it revealed normal data distribution, parametric tests were applied. If the data were abnormally distributed (skewed), non-parametric tests were used. The univariate and multivariate logistic model were used to estimate the probability of a binary response based on one or more predictor (or independent) variables. An alpha level was set to 5% with a significance level of 95%, and a beta error accepted up to 20% with a power of study of 80%.

## Results

Out of 246 patients admitted to PICU during the study period (first of January to the end of December 2021), 44 patients had 54 positive cultures for *K. pneumoniae*, out of which 27 patients (61.4%) survived their infection and 17 patients (38.6%) passed away as shown in Fig. 1.

Patients with worse PIM2 and PELOD scores were more subjected to longer length of stay (LOS) in PICU, and those suffering from extensively drug-resistant (XDR) strains of *K. pneumoniae* were more associated with fatal outcome (Table 1). The most prevalent resistant gene was New Delhi metallo-beta lactamase (NDM) gene (65.4%) followed by cefotaximase (CTX-M) gene (57.7%) as shown in Table 2. Table 3 shows that NDM and CTX-M-resistant genes showed high although not significant resistance to carbapenems (29.3% and 33.4%, respectively) and to colistin (23.5% and 26.7%, respectively). In univariate analysis of mortality risk factors, PIM2, PELOD scores, LOS, and XDR were associated with significant risk of mortality. After adjusting all confounders, only PELOD score and XDR were considered significant risks for mortality with odds ratio of 2.4 and 139.5, respectively (Table 4).

Kaplan-Meier cumulative of survival curve (Fig. 2) showed a significant difference between patients with XDR and non-XDR *K. pneumoniae*-infected patients ($p = 0.016$).

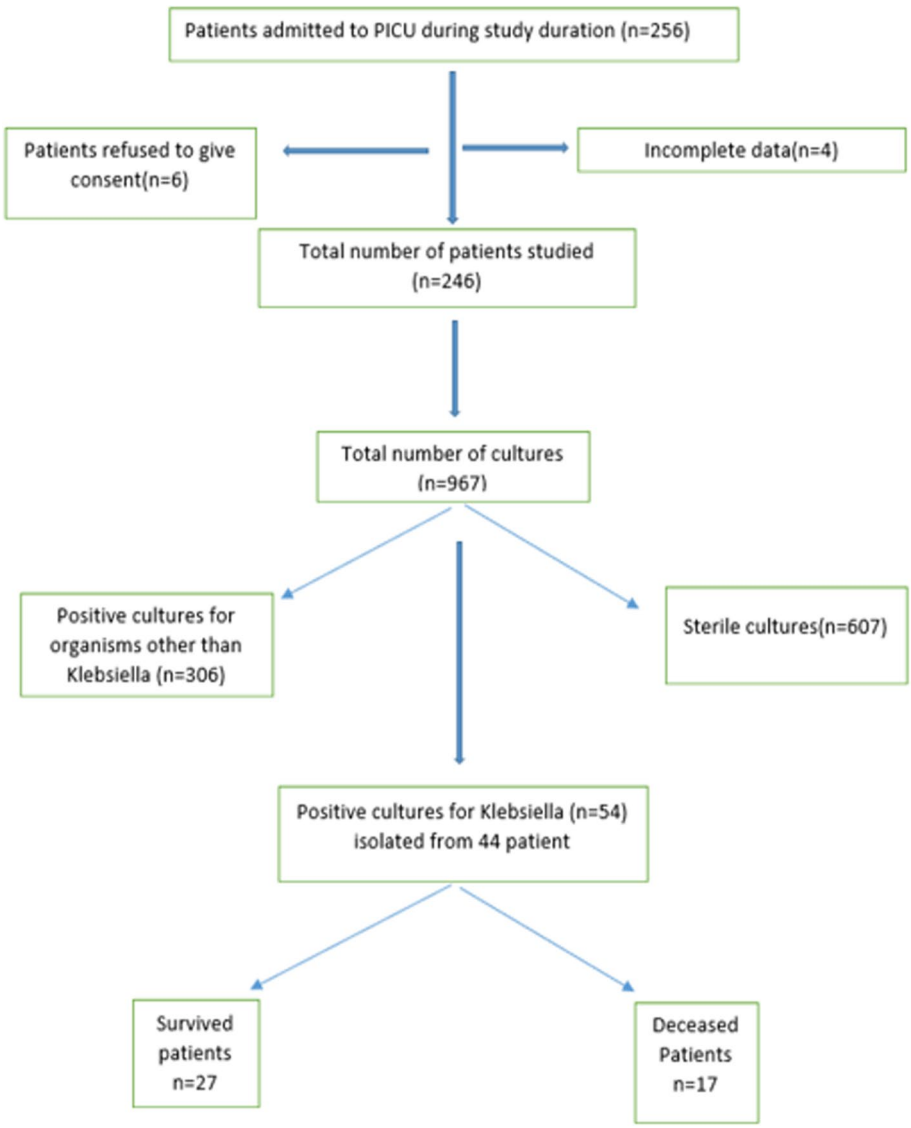


**Fig. 1** RECORD strategy of the recruitment of the studied population

## Discussion

During this 1-year study duration, *K. pneumoniae* infections was retrieved in 15% of the positive culture results (54/360) in this PICU. In the current study, 84.1% of *K pneumoniae* were considered multidrug-resistant (MDR) which are resistant to at least one agent in three or more antimicrobial groups and 15.9% were considered XDR that means these isolates were resistant to at least one agent in all but two or fewer antimicrobial categories [13]. This high prevalence of antimicrobial resistance detected in this study could be attributed to the overuse of antibiotic and the permission to buy different forms of antibiotics even the injectable ones and the last resort antimicrobial therapy as over the counter.

During the last decade, a growing number of *K. pneumoniae*, *pseudomonas*, and *E. coli* have developed resistance against third generation cephalosporins due to extended spectrum beta lactamases (ESBL). Moreover, the emergence of carbapenem-resistant organisms are particularly dangerous as only few treatment options remain for patients and the outcomes are generally poor [14]. Carbapenemase production had become the predominant mechanism of resistance in carbapenem-resistant *K. pneumoniae*, followed by high production of ESBL and Amp C Beta lactamases, coupled with reduced membrane permeability [15].

The prevalent carbapenemases in *K. pneumoniae* are *K. carbapenemase* (KPC), the metallo-beta–lactamases

**Table 1** Comparison between the studied groups according to demographic data

| Demographic data | Total ($n$ =44) | Outcome | | $p$ |
|---|---|---|---|---|
| | | Discharged ($n$ = 27) | Deceased ($n$ =17) | |
| **Sex *n* (%)** | | | | |
| Male | 23 (52.3%) | 13 (48.1%) | 10 (58.8%) | 0.490 |
| Female | 21 (47.7%) | 14 (51.9%) | 7 (41.2%) | |
| **Age (months) *n* (%)** | | | | |
| <12 | 33 (75.0%) | 21 (77.8%) | 12 (70.6%) | $^{MC}p$=0.648 |
| 12–60 | 8 (18.2%) | 5 (18.5%) | 3 (17.6%) | |
| >60 | 3 (6.8%) | 1 (3.7%) | 2 (11.8%) | |
| **PIM2** | | | | |
| Min.–Max. | 2.0–100.0 | 2.0–72.50 | 9.0–100.0 | **0.037*** |
| Mean ± SD. | 39.4 ± 26.6 | 32.0 ± 22.0 | 51.1 ± 29.6 | |
| Median (IQR) | 34.0 (20–56.87) | 25.6 (18.25–55.7) | 49.0 (32–71.50) | |
| **LOS (weeks)** | | | | |
| Min.–Max. | 0.14–12.0 | 1.14–12.0 | 0.14–4.0 | **<0.001*** |
| Mean ± SD. | 2.60 ± 2.33 | 3.42 ± 2.49 | 1.31 ± 1.27 | |
| Median (IQR) | 2.0 (1.07–4.0) | 3.0 (2.0–4.0) | 0.71 (0.43–2.0) | |
| **PELOD** | | | | |
| Min.–Max. | 6.0–30.0 | 6.0–21.0 | 16.0–30.0 | **<0.001*** |
| Mean ± SD. | 17.16 ± 5.87 | 13.93 ± 4.28 | 22.29 ± 4.15 | |
| Median (IQR) | 17 (14.0–21.5) | 14.0 (11–16.5) | 22 (18.0–24.0) | |
| **Resistance** | | | | |
| MDR | 37 (84.1%) | 26 (96.3%) | 11 (64.7%) | **0.009*** |
| XDR | 7 (15.9%) | 1 (3.7%) | 6 (35.3%) | |
| PDR | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |

*PIM2* pediatric index of mortality 2, *LOS* length of stay, *PELOD* pediatric logistic organ dysfunction, *MDR* multidrug-resistant, *XDR* extensive drug-resistant, *PDR* pan-drug-resistant

* $p$ value significant

**Table 2** Comparison between the studied groups according to the presence of antibiotic-resistant genes in PCR positive cases

| Resistant genes | Total ($n$ =26) | | Outcome | | | | $\chi^2$ | $^{FE}p$ |
|---|---|---|---|---|---|---|---|---|
| | | | Discharged ($n$ = 19) | | Died ($n$ =7) | | | |
| | No. | % | No. | % | No. | % | | |
| **CTX-M** | 15 | 57.7 | 10 | 52.6 | 5 | 71.4 | 0.740 | 0.658 |
| **IMP** | 1 | 3.8 | 1 | 5.3 | 0 | 0.0 | 0.383 | 1.000 |
| **KPC** | 1 | 3.8 | 1 | 5.3 | 0 | 0.0 | 0.383 | 1.000 |
| **NDM** | 17 | 65.4 | 13 | 68.4 | 4 | 57.1 | 0.287 | 0.661 |
| **OXA-48-like** | 3 | 11.5 | 2 | 10.5 | 1 | 14.3 | 0.071 | 1.000 |
| **VIM** | 1 | 3.8 | 1 | 5.3 | 0 | 0.0 | 0.383 | 1.000 |

$\chi^2$ chi-square test, *FE* Fisher's exact, *CTX-M* cefotaximase, *IMP* imipenemases, *OXA* oxacillinase, *KPC Klebsiella pneumonaie carbapenemases*, *NDM* New-delhi M, *VIM* Veronem integron M

especially the one first detected in New-Delhi (NDM), veronem integeron M (VIM), imipenemases (IMP), and the oxacillinase type mainly (OXA-48). These carbapenemases encoding genes are usually carried on MDR transmissible plasmid that confer resistance to multiple antibiotics [16].

Recently, Colistin has been considered the last resort antibiotic for multidrug-resistant *K. pneumoniae* and its use has led to the appearance of colistin-resistant strains. This evolution of *Klebsiella* resistant to antibiotics has been observed repeatedly everywhere [17–19]. The present study PCR results revealed that the predominant

**Table 3** The relation between the presence of antibiotic resistance genes by PCR and the results of disc diffusion antimicrobial susceptibility test for carbapenems and colistin by standard microbiological tests

| Resistant genes | Carbapenems resistance | | | | Colistin resistance | | | |
|---|---|---|---|---|---|---|---|---|
| | S ($n = 17$) | | R ($n = 9$) | | S ($n = 20$) | | R ($n = 6$) | |
| | No. | % | No. | % | No. | % | No. | % |
| **CTX-M ($n = 15$)** | 10 | 66.7 | 5 | 33.3 | 11 | 73.3 | 4 | 26.7 |
| **$\chi^2$($p$)** | 0.026 ($^{FE}p$=1.000) | | | | 1.262 ($^{FE}p$=0.356) | | | |
| **IMP ($n = 1$)** | 1 | 100.0 | 0 | 0.0 | 1 | 100.0 | 0 | 0.0 |
| **$\chi^2$ ($p$)** | 0.551 ($^{FE}p$=1.000) | | | | 0.248 ($^{FE}p$=1.000) | | | |
| **KPC ($n = 1$)** | 1 | 100.0 | 0 | 0.0 | 1 | 100.0 | 0 | 0.0 |
| **$\chi^2$ ($p$)** | 0.551 ($^{FE}p$=1.000) | | | | 0.248 ($^{FE}p$=1.000) | | | |
| **NDM ($n = 17$)** | 12 | 70.6 | 5 | 29.4 | 13 | 76.5 | 4 | 23.5 |
| **$\chi^2$ ($p$)** | 0.588 ($^{FE}p$=0.667) | | | | 0.584 ($^{FE}p$=0.628) | | | |
| **OXA-48-like ($n = 3$)** | 1 | 33.3 | 2 | 66.7 | 2 | 66.7 | 1 | 33.3 |
| **$\chi^2$ ($p$)** | 1.539 ($^{FE}p$=0.268) | | | | 0.434 ($^{FE}p$=0.488) | | | |
| **VIM ($n = 1$)** | 1 | 100.0 | 0 | 0.0 | 0 | 0.0 | 1 | 100.0 |
| **$\chi^2$ ($p$)** | 0.551 ($^{FE}p$=1.000) | | | | 4.368 ($^{FE}p$=0.192) | | | |

$\chi^2$ chi-square test, *FE* Fisher's exact, *S* susceptible, *R* resistant, *CTX-M* cefotaximase, *IMP* imipenemases, *KPC Klebsiella pneumonaie* carbapenemases, *NDM*, New-Delhi, M, *OXA* oxacillinase, *VIM* veronem integron M

**Table 4** Univariate and multivariate analysis for parameters affecting mortality

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | *P* | OR (95% C.I) | *p* | OR (95% C.I) |
| **Females** | 0.491 | 0.650 (0.191–2.215) | | |
| **Age (months)** | 0.296 | 1.011 (0.991–1.031) | | |
| **PIM2** | **0.026*** | 1.030*(1.003–1.058) | 0.952 | 1.002 (0.927–1.084) |
| **PELOD** | **0.001*** | 1.800*(1.261–2.568) | **0.032*** | 2.455* (1.079–5.586) |
| **Drug resistance (XDR)** | **0.020*** | 14.182*(1.523–132.1) | **0.041*** | 139.50* (1.238–15725.9) |
| **LOS (Weeks)** | **0.005*** | 0.375* (0.190–0.741) | 0.066 | 0.218 (0.043–1.105) |

*OR* odd's ratio, *C.I* confidence interval, *LOS* length of stay, *XDR* extensive drug-resistance, *PIM2* pediatric index of mortality 2, *PELOD* pediatric logistic organ dysfunction

* *p* value significant

resistant gene in the studied population was the NDM (65.4%) followed by CTX-M (57.7%) and OXA-48 was found in 11.5% of cases. The distribution of resistant genes varies geographically, but it was noted by many researchers the increasing prevalence of NDM. The emergence of bacteria carrying such genes represent a big challenge for physicians to treat. In a systematic review published 2017, Khan et al. [20] demonstrated the worldwide distribution of NDM variants across the globe where they stated that Asian continent serves as the major reservoir of NDM producers (58.15%) mostly in China and India. Europe showed around 16.8%. American continents and Africa carried around 10.8% each. The review also stated that Egypt demonstrated low prevalence of NDM producers. The current study showed different results proving that *klebsiella* have evolved in Egypt and has shown a predominance of NDM genes in 65.4% of the isolates. This serves as a good demonstration for the continued evolution of resistant markers as NDM among *Klebsiella pneumoniae* due to selection pressure, and this emphasizes the importance of continuous surveillance of such resistant genes.

Results of the current study shows that 23.5% of NDM *Klebsiella* producers were found resistant to colistin as well. This finding raises concern about the possible major health threat presented by *Klebsiella* if it acquires resistance to all last resort antibiotics leaving very limited if any option for its treatment, and this is another alarming finding about the evolution of *Klebsiella.* While not many new active antibiotics are developed against the organism, an additional antibiotic resistance against colistin was noticed in the current study.

Adjusting the different risk factors of mortality in *klebsiella*-infected patients to the PIM-2 score in a

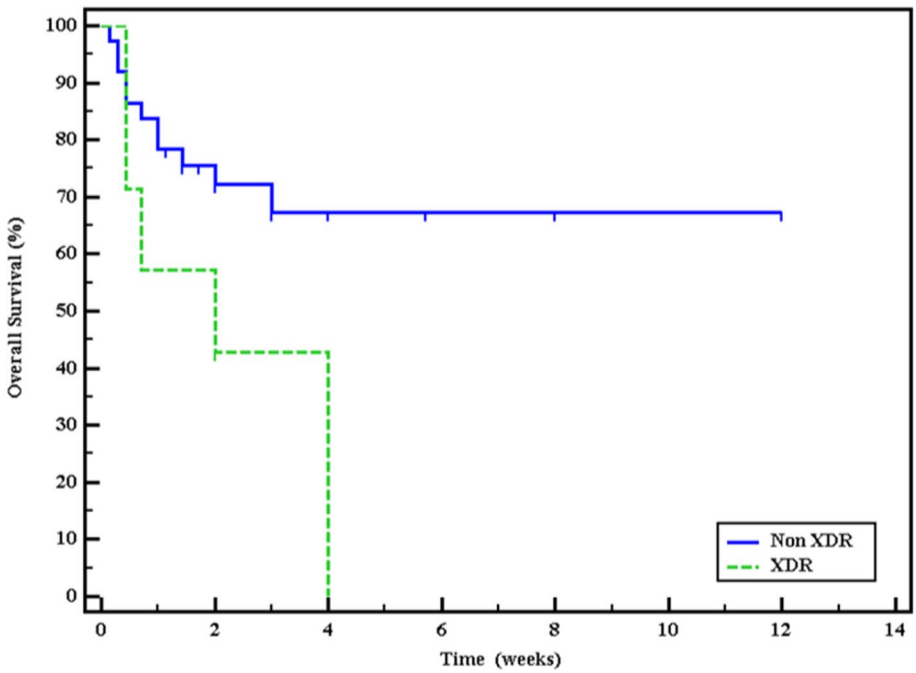


**Fig. 2** Kaplan-Meier survival curve for survival comparing extensive and non-extensive drug-resistant klebsiella-infected patients ($p = 0.016^{*}$)

multiple logistic regression model proved that PELOD score and antibiotic resistance especially XDR were independently related to mortality. The regression model shows that XDR *Klebsiella* infection increased the odds of mortality 139 times. Kaplan-Meier curve also proved that XDR *Klebsiella* infection was statistically related to shorter cumulative of survival. Comparable results were also reported by many authors. Pan et al. [21] stated that high APACHE II score, continuous renal-replacement therapy, and carbapenemase-producing *klebsiella* were independently related to mortality. Zhang et al. [22] specified that mechanical ventilation, septic shock, and isolation of carbapenem-resistant *K. pneumoniae* were independent risk factors for 28-day mortality, and they found that carbapenem resistance alone increased the odds of mortality 9 times compared to susceptible *Klebsiella*.

The current study is not without limitations. First, given the prospective study design, the sample size was relatively limited and number of *Klebsiella pneumoniae* isolates in the studied population was relatively small. Second, results of this study represent the experience of a tertiary care level university-affiliated PICU with a high-level certified performance. This does not reflect other centers' approach for treating *Klebsiella* infected patients, and thus, the results could not be generalized. A multicenter study would be highly recommended to enforce the results already discussed.

## Conclusion

Klebsiella isolates retrieved in this study showed high grade of resistance to antibiotics. PCR results showed that NDM was the most common resistance gene detected in *Klebsiella* isolates. About 23% of NDM containing Klebsiella showed resistance to colistin. This evolution of resistance of *klebsiella pneumoniae* was proved to be associated with a high mortality rate. Continuous widespread surveillance of *Klebsiella* pathogen focusing on identification of resistance genes and antibiotic resistance pattern is highly recommended.

### Abbreviations

*K. pneumoniae*: *Klebsiella pneumoniae*; UTI: Urinary tract infection; MDR: Multi-drug resistance; XDR: Extended-drug resistance; CR-KP: Carbapenem-resistant-*Klebsiella pneumoniae*; PICU: Pediatric intensive care unit; PIM 2: Pediatric index of mortality 2; PELOD: Pediatric logistic organ dysfunction; LOS: Length of stay; CSF: Cerebro-spinal fluid; NB-BAL: Non-bronchoscopic-bronchoalveolar lavage; PCR: Polymerase chain reaction; NDM: New-Delhi metallo-beta lactamase; CTX-M: Cefotaximase; VIM: Veronem integeron M; IMP: Imipenemases; OXA–48: Oxacillinase-48.

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### Authors' contributions

*AN* was responsible for the idea, data analysis, and revision of the manuscript. *MAM* was responsible for the microbiological aspect of the study. *AMB* was responsible for the protocol implementation and data collection. *MA* was responsible for the protocol, data analysis, and writing of the manuscript. The authors read and approved the final manuscript.

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**Availability of data and materials**
All raw data and materials are available upon request from the corresponding author via an email.

## Declarations

**Ethics approval and consent to participate**
This research was implemented after approval of the University Medical Ethical Committee. All methods were carried out in accordance with ethical standards of the 1964 Declaration of Helsinki and its later amendments. An informed consent was obtained from the parents or legal guardians of patients.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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## Publisher's Note