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Original Article

Risk Factors for Carbapenem-Resistant Organisms Pneumonia in the Pediatric and Neonatal Intensive Care Units: A Study at Dr.Kariadi Hospital

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Abstract

Background : Inappropriate antibiotic use has led to bacterial resistance, including carbapenem-resistant organisms (CROs), which cause severe infections in neonatal intensive care unit (NICU) and pediatric intensive care unit (PICU) patients. CRO infections are associated with high morbidity and mortality rates, with limited treatment options. Risk factors such as prolonged hospitalization, broad-spectrum antibiotic use, invasive procedures, and prior infections contribute to these cases. This study is the first in Indonesia to specifically examine CRO pneumonia risk factors in NICU and PICU children.
Objectives : This study aimed to analyze the risk factors for pneumonia caused by carbapenem-resistant organisms (CROs) in children in the pediatric and neonatal intensive care unit.
Methods : This case-control study was conducted in neonatal intensive care unit (NICU) and Pediatric Intensive Care Unit (PICU) of Dr. Kariadi Hospital, Semarang, using medical records of patients admitted between November 2022 and October 2024. This study analyzed the relationship between various risk factors, including hospitalization duration, antibiotic use, mechanical ventilation, catheterization, prior surgery, and bacterial infection history, with CRO pneumonia in NICU and PICU patients.
Results : This case-control study in NICU and PICU on 87 pediatric pneumonia patients found that 55.2% had CRO pneumonia. Multivariate analysis revealed that carbapenem use for >7 days ($p = 0.049$), mechanical ventilation ($p = 0.044$), and urinary catheterization ($p = 0.020$) were independent risk factors for CRO pneumonia.
Conclusion : CRO infections in NICU and PICU patients are highly prevalent, with prolonged carbapenem use, mechanical ventilation, and urinary catheterization as independent risk factors for CRO pneumonia.

Keywords : Antimicrobial resistance, Carbapenem-Resistant Organisms, Intensive Care Unit, pediatrics, pneumonia.

INTRODUCTION

Pneumonia is an inflammatory condition of the lung parenchyma, distal to the terminal bronchioles and causes consolidation of lung tissue and disruption of local gas exchange caused by microorganisms (bacteria, viruses, fungi, protozoa).[1] Excessive and inappropriate antibiotic use has driven an increase in pathogen resistance,[2] particularly multidrug-resistant organisms (MDROs) especially in children with pneumonia infection.[3] In recent years, infections caused by MDRO have shown a significant rise.[4] Based on expert consensus, the CDC, and ECDC, MDRO is categorized into three main types: Multi-Drug Resistance (MDR), eXtensive Drug Resistance (XDR), and Pan Drug Resistance (PDR). One of the most concerning MDRO groups is carbapenem-resistant organisms (CRO), which include carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA).[5] CRO infections is a major cause of health care-associated infections (HAIs) with a high level of resistance, making treatment difficult and significantly contributing to mortality.[6]

The WHO has designated CRO as a critical priority pathogen for the development of new antibiotics due to its increasing resistance.[7,8] Resistance of CRO occurs through various mechanisms, such as carbapenemase enzyme production and structural modifications of the bacterial cell membrane.[9] Infections caused by CRO in children primarily occur in healthcare facilities, particularly in neonatal intensive care units (NICU) and pediatric intensive care units (PICU).[10] Surveillance studies on central line-associated bloodstream infections (CLABSI) in children have reported a high prevalence of CRO, with varying resistance percentages in *Klebsiella spp., Enterobacter spp.*, and *Pseudomonas aeruginosa*.[10] Children admitted to the PICU are more vulnerable to these infections due to frequent broad-spectrum antibiotic therapy, using the invasive medical devices such as mechanical ventilation and catheters, and underlying comorbid conditions.[9,11]

Antimicrobial resistance increases morbidity, mortality, hospitalization duration, and healthcare costs. Therefore, prudent antibiotic therapy and the identification of risk factors for MDRO infections, particularly CRO, are crucial.[12] Although several studies have assessed the risk factors for CRO infections in pediatric patients, most research has focused on a single type of microorganism and general pediatric populations.[13,14] Further studies are needed to comprehensively understand the risk factors for CRO infections in intensive care unit patients. This study is the first study in Indonesia focusing specifically on CRO-related pneumonia in critically ill pediatric patients in both NICU and PICU settings. Unlike previous studies addressing general CRO infections,[15–20] our study highlights a high prevalence of CRO pneumonia-specific risk factors in NICU and PICU populations, highlighting modifiable hospital practices associated with CRO emergence.

METHODS

This case-control study was conducted in the Neonatal Intensive Care Unit (NICU) and Pediatric Intensive Care Unit (PICU) of Dr. Kariadi Hospital, Semarang, using medical records of patients admitted between November 2022 and October 2024. Children aged 1 month to 18 years with pneumonia caused by CRO or non-CRO pathogens based on culture results were included. Cases had a positive CRO culture as their first recorded infection, while controls had a positive non-CRO culture as their last recorded infection without prior CRO diagnosis. Exclusion criteria included incomplete medical records, infections caused by *Stenotrophomonas maltophilia*, or neonates under one month admitted to the NICU. A sample size of 87 patients (48 patients with CRO and 39 patients with non-CRO) was calculated using a significance level of 0.05, power of 95%, and expected odds ratio of 3.095. Consecutive sampling was applied.

Patient data included demographics (age, gender, socioeconomic status, nutritional status), clinical history, comorbidities, and prior bacterial colonization. Hospitalization details such as length of stay, invasive procedures, and antibiotic use were recorded. Information on mechanical ventilation, central venous catheterization (CVC), urinary catheterization, and surgical history was also collected.

Data analysis was performed using SPSS version 29.0.2.0 for Mac OS. Categorical variables were presented as frequencies/percentages. Chi-square and Fisher's Exact tests were used for bivariate analysis, with $p < 0.05$ considered significant. Variables with $p < 0.25$ were included in multivariate logistic regression (Backward Stepwise LR method) to determine independent risk factors, presented as odds ratios (OR) and 95% confidence intervals (CI).

This study was approved by the Ethics Committee of the Faculty of Medicine, Diponegoro University – Dr. Kariadi General Hospital (Approval No. 16426/EC/KEPK-RSDK/2025). All patient data were anonymized, confidential, and used solely for research. The study followed ethical guidelines, with all costs covered by the investigators.

RESULTS

A total of 87 pediatric patients between November 2022 to October 2024 diagnosed with pneumonia and positive bacterial cultures for Gram-negative pathogens were identified in the Neonatal Intensive Care Unit (NICU)

TABLE 1
General Characteristics of Variables

Variables	Frequency	%
Pneumonia		
CRO	48	55.2
Non-CRO	39	44.8
Gender		
Male	50	57.5
Female	37	42.5
Socioeconomic status		
High	3	3.4
Medium	42	48.3
Low	42	48.3
Age		
>10 years	17	19.5
5–10 years	6	6.9
1 month – 5 years	64	73.6
Chronic disease		
Yes	11	12.6
No	76	87.4
Malnutrition		
Yes	45	51.7
No	42	48.3
Previous bacterial colonization		
Yes	25	28.7
No	62	71.3
Length of Stay		
> 7 days	48	55.2
≤ 7 days	39	44.8
Duration of non-carbapenem antibiotic use		
> 14 days	18	20.7
≤ 14 days	69	79.3
Duration of carbapenem antibiotic use		
> 7 days	25	28.7
≤ 7 days	62	71.3
Use of mechanical ventilator		
Yes	53	60.9
No	34	39.1

TABLE 1. *Continued.*

Variables	Frequency	%
Use of central venous catheter		
Yes	50	57.5
No	37	42.5
Use of urinary catheter		
Yes	38	43.7
No	49	56.3
Use of immunosuppressant		
Yes	5	5.7
No	82	94.3
History of surgery		
Yes	20	23.0
No	67	77.0

and Pediatric Intensive Care Unit (PICU) of Dr. Kariadi General Hospital, Semarang. Among these, 48 patients (55.2%) were infected with Carbapenem-Resistant Organisms (CROs), while 39 patients (44.8%) were infected with non-CRO bacteria (Table 1). These findings indicate that the prevalence of pneumonia caused by CRO is higher than that of non-CRO infections in the NICU and PICU, highlighting the significant burden of carbapenem resistance among critically ill pediatric patients.

The majority of patients were between the ages of one month and five years (73.6%), with a male-to-female ratio of 1.35:1. Malnutrition was present in 51.7% of patients, while 12.6% had underlying chronic illnesses. A substantial proportion of CRO-infected patients had a history of prior bacterial colonization (28.7%) and prolonged hospitalization, with 55.2% of patients having a length of stay exceeding seven days (Table 1). Invasive procedures were notably more frequent among patients with CRO pneumonia, with 60.9% requiring mechanical ventilation, 57.5% undergoing central venous catheter (CVC) insertion, and 43.7% having urinary catheterization (Table 1).

Antimicrobial Resistance Patterns of CRO Isolates in the NICU and PICU

Analysis of resistance patterns showed that CRO isolates from pediatric patients in the NICU and PICU exhibited high resistance rates across multiple antibiotic classes. Most isolates demonstrated significant resistance to third-generation cephalosporins, aminoglycosides, and fluoroquinolones. Colistin remained the only antibiotic with a low resistance rate, making it the last-line therapeutic option for severe infections caused by CRO. Additionally, it was found that patients with a history of carbapenem antibiotic use for more than seven days had a significantly higher likelihood of developing CRO infections compared to those with shorter or no prior carbapenem exposure ($p < 0.001$, OR = 13.924, 95% CI: 3.778–51.290) (Table 2).

Bivariate analysis identified several risk factors significantly associated with the development of CRO pneumonia. Prior bacterial colonization ($p = 0.007$, OR = 4.875, 95% CI: 1.616–14.595), prolonged hospitalization exceeding seven days ($p <0.001$, OR = 11.020, 95% CI: 4.050–29.983), carbapenem antibiotic use for more than seven days ($p <0.001$, OR = 10.154, 95% CI: 2.747–37.538), mechanical ventilation ($p <0.001$, OR = 13.179, 95% CI: 4.606–37.702), central venous catheterization ($p <0.001$, OR = 11.030, 95% CI: 4.034–30.160), and urinary catheterization ($p <0.001$, OR = 11.000, 95% CI: 3.823–31.648) were all found to be significantly associated with CRO pneumonia (Table 2). Variables with a p-value <0.25 in the bivariate analysis were included in a multivariate logistic regression model, which determined that prolonged carbapenem antibiotic use, mechanical ventilation, and urinary catheterization were independent risk factors for CRO pneumonia. Patients who received carbapenem antibiotics for more than seven days had a 4.4-fold higher risk of developing CRO pneumonia ($p = 0.049$), those who required mechanical ventilation had a 3.8-fold increased risk ($p = 0.044$), and patients with urinary catheterization had a 4.5-fold higher risk ($p = 0.020$) (Table 3).

TABLE 2
Bivariate Analysis of General Characteristics and Pneumonia

Variables	Pneumonia				*p*	OR	95% CI
	CRO		Non CRO				
	n	%	n	%			
Gender					0.690¥	1.308	0.556 – 3.076
Male	29	60.4	21	53.8			
Female	19	39.6	18	46.2			
Socioeconomic Status					0.282‡	1.231	0.103 – 14.696
High	2	4.2	1	2.6		0.559	0.235 – 1.334
Medium	20	41.7	22	56.4			
Low	26	54.2	16	41			
Age					0.956‡	0.737	0.252 – 2.152
> 10 years	8	16.7	9	23.1		4.143	0.458 – 37.491
5 – 10 years	5	10.4	1	2.6			
1 month – 5 years	35	72.9	29	74.4			
Chronic disease					0.394£	1.494	0.404 – 5.529
Yes	7	14.6	4	10.3			
No	41	85.4	35	89.7			
Malnutrition					1.000¥	1.033	0.443 – 2.405
Yes	25	52.1	20	51.3			
No	23	47.9	19	48.7			
Previous bacterial colonization					0.007¥*	4.857	1.616 – 14.595
Yes	20	41.7	5	12.8			
No	28	58.3	34	87.2			
Length of Stay					<0.001¥*	11.020	4.050 – 29.983
> 7 days	38	79.2	10	25.6			
≤ 7 days	10	20.8	29	74.4			
Duration of non-carbapenem antibiotic use					0.172¥	2.526	0.812 – 7.852
> 14 days	13	27.1	5	12.8			
≤ 14 days	35	72.9	34	87.2			
Duration of carbapenem antibiotic use					<0.001¥*	10.154	2.747 – 37.538
> 7 days	22	45.8	3	7.7			
≤ 7 days	26	54.2	36	92.3			
Use of mechanical ventilator					<0.001¥*	13.179	4.606 – 37.702
Yes	41	85.4	12	30.8			
No	7	14.6	27	69.2			
Use of central venous catheter					<0.001¥*	11.030	4.034 – 30.160
Yes	39	81.3	11	28.2			
No	9	18.8	28	71.8			

TABLE 2. *Continued.*

Variables	Pneumonia				*p*	OR	95% CI
	CRO		Non CRO				
	n	%	n	%			
Use of urinary catheter					<0.001¥*	11.000	3.823 – 31.648
Yes	32	66.7	6	15.4			
No	16	33.3	33	84.6			
Use of immunosuppressant					0.599£	1.233	0.196 – 7.776
Yes	3	6.3	2	5.1			
No	45	93.8	37	94.9			
History of surgery							
Yes	13	27.1	7	17.9	0.453¥	1.698	0.602 – 4.787
No	35	72.9	32	82.1			

Notation:
* Significant ($p < 0.05$);
¥ Continuity Correction;
‡ Mann–Whitney (alternative χ2);
£ Fisher's Exact

TABLE 3
Multivariate Analysis of Independent Risk Factors for CRO Pneumonia

Variables	B	*p*	OR	95% CI
Previous bacterial colonization	0.198	0.816	0.643	0.137 – 3.030
Duration of treatment	-0.766	0.361	1.574	0.343 – 7.214
Duration of carbapenem antibiotic use	-1.485	0.049*	4.413	1.004 – 19.404
Use of mechanical ventilator	-1.332	0.044*	3.788	1.038 – 13.827
Use of central venous catheter	-0.271	0.766	0.635	0.259 – 9.141
Use of urinary catheter	-1.514	0.020*	4.544	1.268 – 16.285

Notation : * Significant ($p < 0.05$)

DISCUSSION

Pneumonia caused by carbapenem-resistant organisms (CROs) represents a significant proportion of infections in neonatal and pediatric intensive care units. In the present study, 48 of 87 patients (55.2%) with pneumonia were infected with CRO pathogens, whereas 39 patients (44.8%) had non-CRO bacterial infections at Dr. Kariadi General Hospital between November 2022 and October 2024. These findings are consistent with previous observations reported by Nawawi, which demonstrated that resistant pathogens predominated among intensive care unit infections. In that study, 36 cases of hospital-acquired bacterial infections were identified in the PICU among 264 admitted patients, of which 35 cases were caused by multidrug-resistant (MDR) bacteria. Although the previous study did not specifically differentiate between CRO and non-CRO pathogens, the high burden of MDR organisms in PICU-acquired infections supports the present finding that resistant bacteria, including CROs, tend to predominate over susceptible organisms in pediatric pneumonia requiring intensive care management.[21]

A meta-analysis conducted in Indonesia by Widyawati also reported that Gram-negative bacteria were the predominant pathogens causing pneumonia. *Klebsiella pneumoniae* had the highest combined prevalence of 0.21 (95% CI: 0.16–0.27), followed by

Acinetobacter baumannii with a combined prevalence of 0.20 (95% CI: 0.13–0.26) and *Pseudomonas aeruginosa* at 0.12 (95% CI: 0.09–0.15). These pathogens are strongly associated with nosocomial pneumonia, particularly in intensive care units.[22] The most common CRO pathogens include *A. baumannii, Escherichia coli*, and *K. pneumoniae*, frequently associated with Ventilator-Associated Pneumonia (VAP) and Hospital-Acquired Pneumonia (HAP). Resistance mechanisms in *A. baumannii* include β-lactamase production, efflux pumps, porin mutations, and plasmid-mediated gene transfer, while carbapenem resistance in Gram-negative bacteria generally involves β-lactamase hydrolysis, reduced PBP affinity, and altered outer membrane proteins. [23,24]

In this study, gender was not significantly associated with CRO pneumonia. Male patients constituted a slightly higher proportion in the CRO group compared to the non-CRO group, but this difference was not statistically significant (p = 0.690, OR 1.308, 95% CI 0.556–3.076). In this study, 73.6% of patients were aged 1 month–5 years, with a male-to-female ratio of 1.35:1, aligning with previous research from Hegazy (2022) that reporting higher Carbapenem-resistant Gram-negative Bacteria (CR-GNB) infection rates in males (61.4%).[13] This finding is consistent with the study from Cai (2024), where gender is not considered an independent risk factor for Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) infection, and susceptibility is more strongly influenced by healthcare exposure and invasive procedures rather than biological sex.[25] This aligns with prior study where biological sex rarely affects colonization by multidrug-resistant organisms unless hormonal, behavioral, or exposure differences are prominent.[26]

Socioeconomic status (high, medium, low) was also not significantly associated with the occurrence of CRO pneumonia (p = 0.282).[25] Although not significantly associated, low socioeconomic status was predominant among children with CRO pneumonia (54.2%). These findings are consistent with a study by Karki *et al*., which reported that socioeconomic status was not significantly associated with pneumonia. However, these results differ from many other studies that have identified low socioeconomic status and low maternal education as risk factors for pneumonia in children. Therefore, although the results of this study did not demonstrate a significant association, socioeconomic factors are still widely recognized in the literature as important determinants of childhood pneumonia.[27]

Age distribution (>10 years, 5–10 years, and 1 month–5 years) was not significantly association with CRO pneumonia in this study (p = 0.956). These findings are consistent with the Cohort study by Espetia–Acero *et al.*, which reported no statistically significant association between CRO colonization and patient sex (p = 0.70) and similarly found that age was not a determining factor for CRO colonization in that cohort. [26] Similar results were reported by Dalfi *et al*., who found no significant association between age and pneumonia (p = 0.855).[28] Although not statistically significant, most CRO pneumonia cases occurred in children aged 1 month–5 years (72.9%). This finding is in line with a study conducted by Fadl *et al.* in Alexandria, Egypt, which reported that children under 12 months of age were independently associated with pneumonia. This may be explained by the immature immune system of infants and young children, making them more susceptible to infections such as pneumonia.[28,29] However, in the present hospital-based population, other clinical factors such as the use of invasive devices may have a greater influence on the risk of CRO infection than age alone.[26,30]

The presence of chronic disease did not significantly increase the risk of CRO pneumonia (p = 0.394, OR 1.494, 95% CI 0.404–5.529). Patients with high comorbid conditions may increased the risk although it was not statistically significant. This finding is consistent with a meta-analysis by Oktafia *et al*. and a study by Wexler *et al*., which reported that comorbidities were not significantly associated with complicated pneumonia.[31,32] However, other studies have suggested that comorbid diseases may worsen pneumonia outcomes by weakening the immune system and increasing susceptibility to severe illness.[25,33] Despite the lack of statistical significance, comorbidity remains a biologically plausible risk factor because chronic conditions can impair host defenses, increase hospitalization, and require the use of broad-spectrum antibiotics and invasive device.[30] This discrepancy may be explained by the fact that comorbid conditions in the present study were analyzed as a broad category, whereas previous studies often evaluated specific chronic diseases that may have stronger associations with CRO infections.[31,32]

Antibiotic therapy was a major contributor, with 86.4% of CRO pneumonia patients receiving broad-spectrum antibiotics, and 55.9% previously exposed to carbapenems. Prior carbapenem use (≥7 days) increased the risk of CRO infection 13.9-fold (p < 0.001, OR = 13.924, 95% CI: 3.778–51.290), while hospitalization for >7 days raised the risk 9.95-fold (p < 0.001, OR = 9.951, 95% CI: 3.738–26.507). Other significant risk factors included mechanical ventilation (OR = 13.179, p < 0.001), central venous catheterization (OR = 11.148, p < 0.001), and urinary catheterization (OR = 9.778, p < 0.001). Lin and Lan's (2014) study also mentioned that previous antibiotic use was an independent risk factor for resistance. Repeated or inappropriate antibiotic use applies selective pressure that triggers enzymatic and non-enzymatic resistance pathways. *A. baumannii* adapts and develops multidrug-resistant or even extensively drug-resistant phenotypes. This means patients previously treated with broad-spectrum or multiple antibiotics are far more likely

to acquire Carbapenem-resistant *Acinetobacter baumannii* (CRAB).[33]

According to the Infectious Disease Society of America (IDSA), major risk factors for Multi-Drug Resistant (MDR) pathogens, including CRO in VAP, include prior intravenous antibiotic use within 90 days, septic shock at the time of VAP, Acute Respiratory Distress Syndrome (ARDS), hospitalization ≥5 days before VAP, and renal replacement therapy.[23] Independent risk factors for CRAB infection in critically ill children include prior carbapenem exposure, invasive procedures, severe pneumonia, and low hemoglobin levels. Invasive procedures, particularly gastric intubation, can disrupt skin integrity, leading to bacterial translocation from the intestines to systemic circulation. Prolonged antibiotic use, especially carbapenems, increases the likelihood of genetic mutations in *A. baumannii*, driving resistance.[3]

Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) infections pose significant challenges in children due to limited treatment options and poor prognosis. Risk factors for CRKP bloodstream infections (BSI) include age, comorbidities, prior hospitalizations, intravascular catheterization, immunosuppressive therapy, and prior antibiotic use.[7,24] Misuse and overuse of antibiotics contribute to antimicrobial resistance by promoting CRKP proliferation, with carbapenem use identified as the highest risk factor.[14] Infants and young children are vulnerable to Carbapenem-Resistant *Enterobacteriaceae* (CRE) infections, including bloodstream infections (BSI), pneumonia, and urinary tract infections (UTI).[8] ICU patients face higher transmission risks due to airborne and contact-based spread, invasive procedures, and prolonged broad-spectrum antibiotic therapy, leading to carbapenem resistance.[34]

Malnutrition showed no significant association with CRO pneumonia (p = 1.000, OR 1.033, 95% CI 0.443–2.405). Malnutrition was observed in 51.7% of patients, and 12.6% had underlying chronic conditions. This contrasts with prior evidence suggesting impaired immunity and barrier dysfunction in malnourished patients. However, cohort study from Cai (2024) reports that malnutrition alone did not independently predict CRO infection.[25] Nutritional status did not affect the probability of CRO colonization. Even though malnutrition can weaken the immune system.[26] Immunosuppressant use was not significantly associated with CRO pneumonia (p = 0.599). Previous studies focusing on CRO bloodstream infections reported that immunocompromised patients did not differ substantially from immunocompetent patients in terms of pathogen distribution, infection source, disease severity, or proportion of appropriate antimicrobial therapy.[35] Although immunosuppression is widely recognized as a risk factor for severe infection, no independent association was found.[25] Immunocompromised and critically ill patients are particularly susceptible to colonization due to compromised immune responses and disrupted physical barriers.[30]

A history of surgery was not significantly associated with CRO pneumonia (p = 0.453, OR 1.698, 95% CI 0.602–4.787). Undergoing surgery did not elevate the risk of CRO colonization. This suggests that the operating room environment adhered to strict sterility and did not contribute significantly to CRO exposure.[26] Surgery can disrupt physical barriers, alters gut microbiota, and exposes patients to perioperative antibiotics and invasive devices. These factors combine to create an environment highly conducive to CR-GNB acquisition.[30] Prolonged hospitalization (>7 days) was found in 55.2% of patients, while 28.7% had a history of prior bacterial colonization, consistent with studies linking prior CRE colonization to CRE infections.[10] A hospital stay longer than 7 days was strongly associated with CRO pneumonia (p < 0.001, OR 11.020, 95% CI 4.050–29.983). Patients with prior MDR colonization have a mortality risk exceeding 15%, and ICU stays are strongly associated with CRKP infections due to prolonged hospitalization and invasive procedures.[5,34] The longer a child remains in the hospital, the greater the exposure to contaminated environments, healthcare workers, and invasive procedures. Long of stays also increase the likelihood of receiving broad-spectrum antibiotics.[26,30]

Patients admitted to ICU infected with MDR/CRAB were higher than those in non-ICU. ICU is the center of the birth of antibiotic-resistant Gram-negative bacteria due to high antibiotic usage. *Acinetobacter baumannii* is commonly found on ventilator surfaces causing VAP. *A. baumannii*, which survives well on surfaces, frequently causes VAP and bloodstream infections in ICUs. The lack of statistical significance likely reflects the sample size, not true absence of association. Mechanistically, ICU exposure increases colonization and resistance evolution through repeated antibiotic exposure and nosocomial transmission.[33,36] Previous bacterial colonization was significantly associated with CRO pneumonia in bivariate analysis (p = 0.007, OR 4.857, 95% CI 1.616–14.595). Colonized patients act as reservoirs, and endogenous translocation is a major mechanism for secondary infection. However, in multivariate analysis, this variable lost statistical significance, suggesting that its effect may be mediated by other factors such as invasive devices and antibiotic exposure.[25] Colonization by CR-GNB itself predisposes to future CR-GNB infection.[30] Colonization is often asymptomatic but can precede infection and contribute to hospital outbreaks. Colonized patients serve as reservoirs for MDR pathogens and facilitate transmission to other patients.[37]

Patients requiring mechanical ventilation (60.9%), central venous catheters (57.5%), and urinary catheters (43.7%) had significantly higher CRO infection risks, as these procedures increase bacterial colonization and immune suppression.[14] The use of CVC was significantly associated with CRO pneumonia in bivariate analysis (p < 0.001, OR 11.030, 95% CI 4.034–30.160). CVC use might have emerged as a contributing factor.[26] Central Venous Catheters breach the skin barrier and provide direct access for microorganisms into the bloodstream or surrounding tissues. Frequent handling of the catheter and repeated access increase opportunities for contamination by resistant organisms.[30] Central Venous Catheter use is a classic invasive procedure that allows bloodstream entry of bacteria, supports biofilm formation, and increases exposure to healthcare flora.[37]

The duration of non-carbapenem antibiotic use (>14 days) was not significantly associated with CRO pneumonia (p = 0.172). This may reflect local antimicrobial-stewardship practices. The absence of correlation suggests that colonization might be more influenced by device-related exposures than antibiotic pressure in this setting.[26] Patients frequently receive broad-spectrum antibiotic therapy. Broad-spectrum antibiotic exposure promotes dysbiosis and selection of resistant bacteria. Longer durations of such antibiotics create selective pressure that favors bacterial survival and colonization.[30,37] Prolonged carbapenem use (>7 days) was a strong predictor of CRO infection, with a 4.4-fold increased risk (p = 0.049), while mechanical ventilation increased the risk 3.8-fold (p = 0.044), and urinary catheterization 4.5-fold (p = 0.020). Antibiotic exposure within the past 6–9 months increased the risk of CRAB infection, while longer ICU stays (>10 days) were associated with nosocomial infections, invasive procedures, and higher mortality rates.[13,38,39] Resistance patterns in PICU isolates showed high resistance to third-generation cephalosporins, aminoglycosides, and fluoroquinolones, supporting previous findings on CRKP and *Pseudomonas aeruginosa*.[11,34]

Exposure to carbapenem could lead to the decreased levels of OprD porin and upregulation of the multidrug efflux pump, with subsequent resistance to carbapenems. Carbapenem exposure directly drives resistance by reducing OprD porin channels, preventing antibiotics from entering the bacterium, increasing efflux pump activity, actively removing antibiotics, and creating selective pressure that favors resistant strains. Increased duration of treatment with carbapenems remained significantly associated with Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA) infection or colonization.[36] Carbapenems exert strong selective pressure against susceptible organisms, allowing carbapenem-resistant bacteria to thrive. Therefore, longer durations of carbapenem therapy significantly increase the likelihood of colonization.[30] Mechanical ventilation disrupts natural airway defenses and increases exposure to hospital pathogens, including CR-GNB. Ventilator circuits, suctioning, and frequent manipulation facilitate transmission. Thus, ventilator use correlates with higher colonization risk, especially in critically ill children.[30]

ICU setting significantly impacted the infection onset in colonized patients probably because of the use of invasive procedures such as mechanical ventilation and CVC. Ventilator dependence increases susceptibility of lower airways. Pharyngeal/nasal colonization is strongly associated with subsequent lower respiratory tract infections.[37] Ventilation bypasses natural airway defenses and provides a direct route for colonizing CRAB to enter lower respiratory tract.[40] Mechanical ventilation was highly associated with CRO pneumonia (p < 0.001, OR 13.179). In multivariate analysis, it remained an independent predictor (p = 0.044, OR 3.788). This is consistent with evidence identifying ventilator-associated pneumonia as a major clinical manifestation of CRKP infection, particularly in ICU settings, where invasive respiratory support compromises host defenses and facilitates pathogen entry.[25]

A key factor contributing to persistent bacterial infections is biofilm formation, which protects bacteria from antibiotics, particularly in ventilated patients and those with indwelling catheters.[19,41] Urinary catheters can indirectly cause pneumonia by increasing the risk of urinary tract infections (UTIs). Prolonged catheter use disrupts the natural defense mechanism of urinary flow, allowing bacteria like *Escherichia coli* and *Klebsiella pneumoniae* to ascend and cause infections. Recurrent UTIs may lead to antibiotic resistance, and in some cases, chronic bladder infections due to urine stasis. If the infection spreads into the bloodstream (bacteremia), it can reach the lungs and potentially cause pneumonia, especially in immunocompromised patients.[42,43] This study highlights the importance of antimicrobial stewardship, infection control measures, and cautious use of broad-spectrum antibiotics to reduce CRO pneumonia incidence in the PICU.

CONCLUSION

This study demonstrates that prolonged hospitalization, prior carbapenem exposure, and invasive procedures are major contributors to CRO pneumonia in critically ill pediatric patients. While our findings align with multiple studies, discrepancies in risk factor significance highlight the need for further multicenter research. Future investigations should focus on developing novel therapeutic approaches and strengthening infection control measures to combat carbapenem resistance in pediatric intensive care settings.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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