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Comparative Efficacy of Ceftriaxone and Cefotaxime Klebsiella pneumonia Isolates Causing Otitis Media in Children in Diyala, Iraq

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Abstract

Background: Otitis media is one of the most frequent infections during childhoodin klebsiella pneumonia isolates causing Otitis Media, especially in relation to recurrent and complicated cases of otitis media.

Methods: Baqubah Teaching Hospital, Al-Batool Teaching Hospital, and Al-Khalis General Hospital in the Diyala Governorate of Iraq were selected as the study sites for a prospective cross-sectional study conducted d between September 2024 and January 2026. Middle ear samples were collected, and after standard microbiologic methods, and K. pneumoniae was identified using the VITEK-2 system. Antimicrobial susceptibility testing for ceftriaxone and cefotaxime was performed using Kirby-Bauer disk diffusion and E-test methods were employed, in accordance with CLSI 2025. ESBL production was detected with modification of the combination disk method.

Results: Positive cultures were found in 82.8% (265 of 320) of children. K. pneumoniae was found in 78 of these isolates (29.4% of positive cultures, 24.4% of all samples) with a mean age of 4.2 ± 2.8 years. 71.8% were under 5 years of age. 59 (75.6%) were confirmed ESBL producers. Among the resistant isolates, ceftriaxone and cefotaxime showed MIC_{50}/MIC_{90} values, with cefotaxime having a statistically significantly lower MIC ($p = 0.009$). In the checkerboard synergy assay, 80.8% (63 of 78) of isolates showed synergy (FICI ≤ 0.5) with cefotaxime and avibactam in contrast to 38.5% with ceftriaxone and tazobactam ($p < 0.001$). Regression analysis found prior hospitalization within 3 months (OR = 5.12, 95% CI: 2.78-9.43, $p < 0.001$), prior cephalosporin use (OR = 6.34, 95% CI: 3.45-11.65, $p < 0.001$), and recurrent otitis media (OR = 3.87, 95% CI: 2.12-7.06, $p < 0.001$) to be statistically significant independent resistance risk factors.

Conclusion: Due to the high prevalence of ESBL, monotherapy with ceftriaxone or cefotaxime has been shown to be ineffective against the majority of K. pneumoniae isolates from pediatric otitis media in Diyala. Even though cefotaxime has the lowest MIC against the resistant strains, however, the combination of cefotaxime with avibactam demonstrated strong synergistic activity paraphrasing.

Keywords: Klebsiella pneumoniae, Otitis media, Ceftriaxone, cefotaxime.

1. Introduction

Otitis media is the most common infectious disease in childhood, with approximately 20-30 million outpatient visits yearly in the USA alone [1]. Acute otitis media is estimated to affect 80-90% of children globally by the age of 6. The highest incidence by between the ages of 6 and 18 months [2].

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In Iraq, otitis media is a significant contributor to morbidity in children. The recurrent and complicated cases of otitis media lead to hearing loss and developmental delays [3]. Klebsiella pneumoniae is an emerging or increasingly recognized pathogen in otitis media, among children with comorbidities like malnutrition, immunodeficiency, or previous antibiotic treatment [4]. *K. pneumoniae*, unlike the other common pathogens, is associated with more severe infections and complications, and leads to therapeutic failures and high treatment resistance [5].

In the 2025 WHO Global Antimicrobial Resistance Surveillance System (GLASS) report, resistant infections among *K. pneumoniae* exceed 40-70% for many countries, and among Eastern Mediterranean Region, 30% of the reported infections had resistance [3]. Moreover, the report concluded that over 55% of *K. pneumoniae* isolates are resistant to third-generation cephalosporins. The therapeutic landscape concerning third-generation cephalosporins has changed significantly due to the worldwide spread of extended spectrum beta-lactamase (ESBL)-producing K. *pneumoniae.* The presence of ESBLs inactivates the beta-lactam ring of oxyimino-cephalosporins, leading to resistance to ceftriaxone, cefotaxime, and other related compounds [4]. A study from Saudi Arabia reported that was a major contributor among the isolates, and that the ESBL producers showed high resistance to the third-generation cephalosporins [6]. Likewise, a study from Pakistan showed that isolates of pediatric otitis media had a major presence of the ESBL gene, especially blaCTX-M-15, and had significantly higher resistance to cefotaxime and ceftriaxone [7].

There is increasing interest in combination therapy approaches attempting to restore the efficacy of existing cephalosporins, given the rapidly increasing resistance rates. In this context, beta-lactamase inhibitors like clavulanic acid, tazobactam, and newer non-β-lactam inhibitors such as avibactam are being investigated in combination with cephalosporins to protect them from enzymatic hydrolysis [8]. Some studies have shown that there are some cephalosporin-β-lactamase inhibitor combinations that have significant efficacy against ESBL-producing Enterobacterales [10], [11]. The combination of cefepime and enmetazobactam is a new option that has recently been approved for the treatment of complicated infections a significant improvement over piperacillin-tazobactam in phase 3 trials [11]. Guidance from IDSA in 2024 states that of the available options for the treatment of infections caused by ESBL-producing Enterobacterales, carbapenems and novel βlactam/β-lactamase inhibitor combinations are preferred [12], [5].

Consequently, this study aimed to determine the frequency of *K. pneumoniae* as a causative organism of otitis media among children in Diyala. The study among aimed to describe the antimicrobial resistance patterns, the susceptibility to ceftriaxone and cefotaxime, compare the MICs of resistant isolates, determine the prevalence of ESBL, the evaluate the synergistic effect of ceftriaxone-tazobactam and cefotaxime-avibactam, and determine the variables associated with third-generation cephalosporins resistance in the pediatric population.

2. Materials and Methods

2.1. Study Design and Setting

This study was carried out over 17 months, from September 2024 to January 2026, at three multidisciplinary teaching hospitals in Iraq's Diyala Governorate: Baqubah Teaching Hospital, Al-Batool Teaching Hospital, and Al-Khalis General Hospital. The study was approved by the ethics committee at Baqubah Teaching Hospital (Approval No. BTH-IRB-2024-189). Parents or legal guardians of all participants provided written informed consent.

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2.2. Sample Size and Participant Selection

Sample size was calculated using the single proportion formula with the expected K. pneumoniae prevalence of 20% based on regional data [6], 95% confidence level, and 5% margin of error. This resulted in enrollment of 320 children cross-sectionally. Inclusion criteria were children aged 3 months to 12 years with clinically diagnosed otitis media (including acute otitis media with perforation and purulent discharge, recurrent acute otitis media defined as ≥3 episodes within 6 months or ≥4 episodes within 12 months, or chronic suppurative otitis media, defined as persistent discharge for >6 weeks), and those who could give a middle ear specimen. Exclusion criteria were: antibiotic use within the previous (with the exception of treatment failure), presence of tympanostomy tubes, and severe immunosuppression.

2.3 Specimen Collection and Processing

Collections of middle ear specimens were collected using sterile swabs with direct visualization. In the case of children with perforation of the tympanic membrane, samples were collected via the external auditory canal after using sterile saline to wash the area. When indicated, ultrasound examination was performed when clinically indicated by pediatric otolaryngologists. Specimens were placed in Amies transport medium and transported to the microbiology lab within 2 hours. Specimens were cultured onto MacConkey agar, 5% sheep blood agar, and chocolate agar (Oxoid, UK). Plates were grown at 35-37°C in 5% CO_2 for 24-48 hours.

2.4 Bacterial Identification.

Identified using the following tests: (a) Gram stain, (b) catalase, (c) oxidase, (d) indole, (e) methyl red, (f) Voges- Proskauer, (g) citrate, and (h) urease. Identification was also done using the VITEK-2 Compact automated identification system (bioMérieux, France).

2.5 Antimicrobial Susceptibility Testing

For the antimicrobial susceptibility testing was performed according to CLSI [13] guidelines using the disk diffusion method with the use of the Mueller-Hinton agar. The antibiotics from Oxoid, UK, that were assessed include: ceftriaxone (30 µg), cefotaxime (30 µg), amoxicillin-clavulanate (20/10 µg), piperacillin-tazobactam (100/10 µg), ciprofloxacin (5 µg), gentamicin (10 µg), amikacin (30 µg), and meropenem (10 µg). The MICs (minimum inhibitory concentrations) were assessed for ceftioaxime and ceftriaxone with the use of E-test (bioMérieux) and confirmed by microbroth dilution for resistant strains. According to CLSI guidelines [13].

2.6 ESBL Phenotypic Confirmation

For ESBL (extended-spectrum βlactamase) confirmation, the CLSI guidelines were + synergy test. As stated by Patil et al, the presence of clavulanic acid resulting in an increase in the inhibition zone diameter of 5 mm was considered to be positive.

2.7 Synergy Testing

All 78 isolates were subjected to checkerboard synergy testing: for ceftriaxone in combination with tazobactam and cefotaxime in combination with avibactam. The fractional inhibitory concentration index (FICI) was determined using the method of Odds (2003) with FICI ≤ 0.5 defined as synergy, FICI > 0.5–1.0 as additive, FICI > 1.0 to ≤ 4.0 as indifference, and FICI > 4.0 as antagonism.

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2.8 Data Collection and Statistical Analysis

Data were collected using a standardized template that recorded patient demographics, clinical presentation, history of prior antibiotic use, history of hospitalization, presence of perforation of the tympanic membrane, and associated comorbidities. The analysis was performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). Chi-square, Fisher's exact, and logistic regression tests were performed as appropriate. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Patient Demographics and Clinical Characteristics

This study included 320 children, with a mean age of 4.2 ± 2.8 years, ranging from 3 months to 12 years. Of the participants, children under 2 years of age accounted for 32.5%. The 2-5 years age group made up 39.3%, while the 6-12 years age group made up 28.2%. The average age of participants was 4.2 ± 2.8 years. There were more male participants, with a sex ratio of 1.2:1, with 176 boys and 144 girls. The children presented with perforated acute otitis media in 35% of cases (n = 112), had recurrent acute otitis media, and 34.4% (n = 110) had chronic suppurative otitis media. Within the 3 months prior to the study. Within the prior 3 months of the study, 85 (26.6%) participants had also been hospitalized.

3.2 Bacterial Isolates

Analysis of 320 middle ear samples yielded 265 (82.8%) samples with significant bacterial growth. Within these positive cultures, the presence of K. pneumoniae was noted in 78 isolates, representing 29.4% of positive cultures and 24.4% of total samples. This finding is consistent with previous studies reporting considerable ear infection isolates in children in Saudi Arabia [6] and, similarly, in Pakistan, which noted significant K. pneumoniae pediatric otitis media isolates [7]. Other positive cultures yielded Pseudomonas aeruginosa (62 isolates, 23.4%), Staphylococcus aureus (48 isolates, 18.1%), Streptococcus pneumoniae (35 isolates, 13.2%), Haemophilus influenzae (28 isolates, 10.6%), Moraxella catarrhalis (10 isolates, 3.8%), and remaining organisms (4 isolates, 1.5%).

3.3 Antimicrobial Susceptibility Patterns

Antimicrobial susceptibility testing of 78 K. pneumoniae isolates revealed high resistance rates of resistance to the third-generation cephalosporins. Resistance to ceftriaxone was seen in 55 isolates (70.5%), and resistance to cefotaxime was seen in 52 isolates (66.7%). The resistance rates of the two agents were not statistically significant ($\chi^2 = 0.258$, $p = 0.612$). However, of the isolates that were resistant to both (n = 48), the mean zone diameter for cefotaxime was slightly greater than for ceftriaxone (13.8 ± 3.5 mm vs. 12.1 ± 3.1 mm, $p = 0.028$), suggesting that cefotaxime may have slightly better activity against resistant strains. These resistance rates are consistent with the WHO GLASS 2025 report, which indicates that more than 55% to third-generation cephalosporins [3]. The findings are also consistent with studies from Pakistan, among pediatric otitis media isolates, where higher resistance to cefotaxime and ceftriaxone was reported [7].

The study showed varying degrees of resistance to antibiotics, with 58 (74.4%) resistant to amoxicillin-clavulanate, 44 (56.4%) resistant to piperacillin-tazobactam, 52 (66.7%) resistant to ciprofloxacin, 48 (61.5%) resistant to gentamicin, 26 (33.3%) resistant to amikacin, and 56 (71.8%) resistant to trimethoprim-sulfamethoxazole. Resistance to meropenem was seen in 12 (15.4%)

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isolates, which indicates that carbapenem resistance is beginning to emerge among this pediatric group. Antimicrobial resistance patterns for the 78 K. pneumoniae isolates are summarized in Table 1.

Table 1: Antimicrobial Susceptibility Profile of K. pneumoniae Isolates from Pediatric Otitis Media (N=78)

Antimicrobial Agent	Sensitive, n (%)	Intermediate, n (%)	Resistant, n (%)
Ceftriaxone	18 (23.1)	5 (6.4)	55 (70.5)
Cefotaxime	19 (24.4)	7 (9.0)	52 (66.7)
Amoxicillin-clavulanate	12 (15.4)	8 (10.3)	58 (74.4)
Piperacillin-tazobactam	22 (28.2)	12 (15.4)	44 (56.4)
Ciprofloxacin	18 (23.1)	8 (10.3)	52 (66.7)
Gentamicin	24 (30.8)	6 (7.7)	48 (61.5)
Amikacin	42 (53.8)	10 (12.8)	26 (33.3)
Meropenem	62 (79.5)	4 (5.1)	12 (15.4)
Trimethoprim-sulfamethoxazole	16 (20.5)	6 (7.7)	56 (71.8)

Although the two methods, the E-test and broth microdilution method, provide information in terms of relative comparison of two cephalosporins, they provide value for MIC determination. For all 78 isolates, the MIC_{50} ceftriaxone was 16 µg/mL, with an MIC_{90} being >256 µg/mL. Qualitatively, however, cefotaxime seemed to perform better with the MIC_{50} of 8 µg/mL and MIC_{90} of 128 µg/mL. Evaluating resistant isolates revealed the discrepancies to be more pronounced. Among the 55 ceftriaxone resistant isolates, the MIC_{50} was 32 µg/mL, and the MIC_{90} > 256 µg/mL, the geometric mean being 62.4 µg/mL. In the case of 52 cefotaxime resistant isolates, the MIC_{50} was 16 µg/mL, the MIC_{90} was 128 µg/mL, and the geometric mean was 34.2 µg/mL. Using Wilcoxon's signed rank test, the MIC values for cefotaxime were significantly lower than those for ceftriaxone for resistant isolates ($p = 0.009$). Analysis of MIC distribution among resistant isolates Table (2) shows a significantly larger proportion of ceftriaxone resistant isolates (25.5%) had MIC values ≥128 µg/mL compared with cefotaxime resistant isolates (17.3%), indicating that high-level ceftriaxone resistance was more frequent.

Table 2: MIC Distribution for Resistant Isolates to Ceftriaxone and Cefotaxime in Pediatric Otitis Media

MIC (µg/mL)	Ceftriaxone-Resistant (n=55), n (%)	Cefotaxime-Resistant (n=52), n (%)
8	0 (0)	2 (3.8)
16	6 (10.9)	12 (23.1)
32	20 (36.4)	18 (34.6)
64	15 (27.3)	11 (21.2)
128	6 (10.9)	6 (11.5)
256	4 (7.3)	2 (3.8)
>256	4 (7.3)	1 (1.9)

3.4 Estimated prevalence of Extended Spectrum Beta Lactamase and its Characterization

Using phenotypic confirmation by combination disk test and the double-disk synergy tests, the presence of Extended Spectrum Beta Lactamase (ESBL) was confirmed in 59 of the 78 isolates, accounting for 75.6% of the confirmed K. pneumoniae isolates. Speaking of ceftriaxone resistant isolates, 53 of 55 (96.4%) isolates were confirmed as ESBL positive, whereas for cefotaxime resistant isolates, 50 of 52 (96.2%) were confirmed as ESBL positive. The high prevalence of ESBL, as observed in this study, is consistent with the available regional literature from Saudi Arabia [6] and Pakistan [7], where ESBL producers showed resistance to third-generation cephalosporins, particularly in pediatric otitis media isolates.

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Double-disk synergy testing revealed characteristic patterns of the ESBL positive isolates. Of the 59 ESBL positive isolates, 42 (71.2%) isolates showed synergy with all of the three cephalosporins (i.e. ceftriaxone, cefotaxime, and ceftazidime) while 17 (28.8%) isolates showed synergy with ceftriaxone and cefotaxime, but not ceftazidime. This observation is suggestive of the possible presence of CTX-M type ESBLs as the main mechanism operating in this population [4]. Among the ESBL negative but resistant isolates to ceftriaxone, further characterization of the two isolates showed resistance attributed to the production of AmpC beta-Lactamase in conjunction with cefoxitin resistance and synergy with cloxacillin.

3.5 Synergy Testing Results

Synergy testing using the checkerboard technique was conducted for all 78 isolates. Synergy was seen in more isolates for the combination of cefotaxime with avibactam compared to the combination of ceftriaxone with tazobactam. Synergy was observed in 63 isolates (80.8%) for the cefotaxime-avibactam combination (FICI = 0.5), whereas it was seen in 30 isolates (38.5%) for the ceftriaxone-tazobactam combination, which was statistically significant ($p < 0.001$).

The median FIC index for the synergy of cefotaxime-avibactam was 0.25 (interquartile range: 0.125-0.5) and was significantly lower than the median FIC index of ceftriaxone-tazobactam, which was 0.75 (interquartile range: 0.375-1.5) (Mann-Whitney U test, $p < 0.001$). Distribution of results for synergy tests for both combinations is seen in Table 3. For cefotaxime-avibactam, 28.2% of isolates had FICI ≤ 0.125, 52.6% had FICI 0.25-0.5, 14.1% had FICI 0.75-1.0, 3.8% had FICI 1.5-2.0, and 1.3% had FICI 3.0-4.0. None of the isolates showed antagonism (FICI > 4.0) for cefotaxime-avibactam. For ceftriaxone-tazobactam, in contrast, only 7.7% of isolates had FICI ≤ 0.125, 30.8% had FICI 0.25-0.5, 24.4% had FICI 0.75-1.0, 28.2% had FICI 1.5-2.0, 7.7% had FICI 3.0-4.0, and 1.3% had antagonism.

Table 3: Results of Checkerboard Assays for the Combination of Cephalosporins and β-Lactamase Inhibitors in Isolates from Pediatric Otitis Media (N=78)

Interpretation	FICI range	Ceftriaxone + Tazobactam, n (%)	Cefotaxime + Avibactam, n (%)	p-value
Synergy	≤0.5	30 (38.5)	63 (80.8)	<0.001
Additive	>0.5-1.0	19 (24.4)	11 (14.1)	0.098
Indifference	>1.0-4.0	28 (35.9)	4 (5.1)	<0.001
Antagonism	>4.0	1 (1.3)	0 (0)	0.488

Subgroup analysis by ESBL status demonstrated that for ESBL-positive isolates (n=59), synergy rates were 42.4% (25 isolates) for ceftriaxone-tazobactam and 84.7% (50 isolates) for cefotaxime-avibactam ($p < 0.001$). For ESBL-negative isolates (n=19), synergy rates were 26.3% (5 isolates) for ceftriaxone-tazobactam and 68.4% (13 isolates) for cefotaxime-avibactam ($p = 0.012$). Interestingly, among the 13 ESBL-negative isolates that showed synergy with cefotaxime-avibactam, 11 had MICs for cefotaxime ranging from 8-32 μg/mL, suggesting that avibactam may also potentiate activity against isolates with non-ESBL resistance mechanisms such as AmpC β-lactamases.

3.6 MIC and Synergy Correlation

A significant correlation was observed between cefotaxime MIC values and the probability of synergy with avibactam. For isolates with cefotaxime MIC ≤16 μg/mL, synergy was noted in 18 of 20 isolates (90.0%). For isolates with MIC of 32 μg/mL, synergy was noted in 22 of 24 isolates (91.7%). For isolates with MIC of 64 μg/mL, synergy was noted in 14 of 16 isolates (87.5%).

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However, for isolates with MIC of 128 µg/mL, the synergy was 6 of 10 isolates (60.0%), and for isolates with MIC ≥256 µg/mL, synergy was only 3 of 8 isolates (37.5%). In general, isolates with cefotaxime MIC ≤64 µg/mL had a markedly improved synergy rate (89.8%) in comparison to isolates with MIC ≥128 µg/mL (50.0%) ($p < 0.001$). With respect to ceftriaxone-tazobactam, there was no correlation between ceftriaxone MIC and synergy ($p = 0.418$), indicating that the mechanism responsible for the high-level ceftriaxone resistance is likely more complex than the production of ESBL and that tazobactam does not mitigate it.

3.7 Risk Factor Analysis for Third-Generation Cephalosporin Resistance

There were multiple factors identified through univariate analysis that demonstrated a strong association with resistance to third-generation cephalosporins. Age < 0.001). More specifically, to cephalosporins, resistant, with 78.2% of resistant cases under 2, whereas sensitive cases were significantly lower at 45.8% (OR = 4.12, 95% CI: 1.89-8.98, $p < 0.001$). Recurrent otitis media also demonstrated a strong association, as it was present in 65.5% of the resistant group, while only 29.2% of the sensitive group had it (OR = 4.67, 95% CI: 2.34-9.32, $p < 0.001$). Resistance was noted to be significantly higher with prior antibiotic use within a 3-month period, as 76.4% of resistant cases reported prior use, compared to only 33.3% of sensitive cases (OR = 6.82, 95% CI: 3.12-14.89, $p < 0.001$). More specifically, cephalosin resistant cases had a history of prior use associated with an OR of 7.34 (95% CI: 3.45-15.62, $p < 0.001$). Resistance was also strongly associated with prior admission to the hospital in the last three months (OR = 5.89, 95% CI: 2.89-12.01, $p < 0.001$). Chronic otitis media with (OME) (OR = 3.45, 95% CI: 1.78-6.68, $p = 0.001$) and perforation of the tympanic membrane (OR = 2.89, 95% CI: 1.45-5.76, $p = 0.003$) were also identified as significant factors of risk.

Risk factors were identified by conducting multivariate logistic regression on variables with $p < 0.20$ in univariate analysis. This analysis revealed three independent risk factors for resistance to third-generation cephalosporins. Prior hospitalization in the last three months had an prior hospitalization remained an independent predictor (adjusted OR = 5.12, 95% CI: 2.78–9.43, $p < 0.001$) with an adjusted odds ratio of 6.34 (95% CI: 3.45-11.65, $p < 0.001$). Having a history of recurrent otitis media was also an independent risk factor with an adjusted odds ratio of 3.87 (95% CI: 2.12-7.06, $p < 0.001$). The model showed a good fit (Hosmer–Lemeshow $\chi^2 = 6.34$, $p > 0.05$), and 82.5% of cases were correctly classified

3.8 Co-Resistance Patterns among ESBL Producers

Producers of ESBL were significantly afflicted with more resistance to various other antimicrobial classes than were non-ESBL producing isolates. Among the 59 ESBL-producing isolates, 48 isolates (81.4%) were resistant to ciprofloxacin, while only 4 of 19 non-ESBL isolates were resistant (21.1%) ($p < 0.001$). Compared to non-ESBL producers (22.1%), 44 ESBL producers (74.6%) were resistant to gentamicin ($p < 0.001$). Resistance to the trimethoprim-sulfamethoxazole combination was observed in 50 ESBL producers (84.7%) versus 6 non-ESBL producers (31.6%) ($p < 0.001$). In contrast, there was no significant difference between ESBL producers (16.9%) and non-ESBL producers (10.5%) in terms of meropenem resistance ($p = 0.482$). This suggests that in this population the mechanisms of resistance to carbapenems are not dependent on the production of ESBL.

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4. Discussion

This study revealed several key findings: *Klebsiella pneumoniae* and otitis media in children in Diyala, Iraq. First, K. pneumoniae prevalence (24.4% of total samples) is substantial, and aligns with Saudi Arabia [6] and Pakistan [7], as it is a significant pathogen in child otitis media in this area. Second, resistance rates to ceftriaxone (70.5%) and cefotaxime (66.7%) are striking due to ESBL prevalence of 75.6%. The MIC for cefotaxim third- generation was lower and more effective than that of ceftriaxone, as all isolates were resistant to MIC_{90} of 128 and >256 µg/mL, respectively, see Table 2. Fourth, the combination of cefotaxime and avibactam shows a greater synergy (80.8%) than the combination of ceftriaxone and tazobactam, which is (38.5%), as illustrated in Table 3. Lastly, previous hospitalization, previous use of cephalosporin, and recurrent otitis media (ROM) are significant independent risk factors for resistance.

Our findings show that the worldwide incidence is consistent with our findings. The most recent WHO GLASS report indicates that K. pneumoniae resistance ranges from 40-70% across the globe when surveyed for resistance to third-generation cephalosporins conducted in Pakistan. The Eastern Mediterranean Region has an especially high prevalence of resistance. The prevalence of ESBL genes among pediatric cases of recurrent otitis media was documented to be much higher in the studies conducted in Pakistan [14]. In Saudi Arabia, []6 documented that ESBL producers were highly resistant to third-generation cephalosporins. As seen in the rest of the world, ESBL production is the predominant resistance mechanism. CTX-M type ESBL, CTX-M-15 is the most globally prevalent ESBL variant due to its efficient hydrolysis of cefotaxime and widespread dissemination via plasmids and culturing from mobile genetic elements [4].

Avibactam demonstrates superior systemic breakthrough synergy (80.8\% vs 38.5\% for tazobactam) due to its unique pharmacological descriptive mechanisms as a non-beta-lactam beta-lactamase inhibitor that creates a reversible covalent adduct (probably a thiol ester) with the active site serine of class A and C beta-lactamases [8]. Tapezobactam is a beta-lactam that is prone and is therefore subject to inactivation by some other beta-lactamases. In contrast, avibactam is not subject to hydrolysis and can eventually dissociate from the enzyme, providing persistent inhibition [9]. That is the main reason for the synergy difference with cefotaxime-avibactam as compared to ceftriaxone-tazobactam. Also, the synergy observed (68.4%) with cefotaxime-avibactam for some ESBL negative isolates indicates that avibactam enhances activity to other resistance mechanisms, including but not limited to porin mutations and/or AmpC beta-lactamases [10].

The notable resistance of ceftriaxone and cefotaxime suggests these should not be considered as first-line treatment options for pediatric otitis media in this region. This is consistent with IDSA recommendations from 2024 that suggest that in areas where the ESBL prevalence is >20%, third-generation cephalosporins should not be used as empirical treatments [5], [12]. In the case of K. pneumoniae, more empirical options for pediatric otitis media include, in rare circumstances, the use of carbapenems or the use of newer β-lactamase inhibitor combinations such as cefepime-enmetazobactam, which is newly available for complicated infections [11].

The indicators of prior hospitalizations (OR 5.12), prior use of cephalosporins (OR 6.34), and the presence of recurrent otitis media (OR 3.87) as independent predictors of resistance lay the groundwork for defining the population of children who are most likely to have resistant infections.

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For such children, the need for culture of the middle ear prior to the start of any treatment, along with the selection of empirical therapy based on local resistance profiles and with the use of wider spectrum antibiotics or combination therapy, is imperative. These results are in line with the findings from Jordan that highlighted the presence of multiple antibiotic resistances in a significant number of pediatric isolates, which underscored the need for improved compliance to treatment protocols [7].

Given that resistant isolates show high synergy with cefotaxime-avibactam (80.8%), this combination could possibly serve as an alternative treatment for otitis media due to ESBL-producing *K. pneumoniae* in children. Although cefotaxime-avibactam is not commercially available as a fixed-dose combination, cefotaxime is available and affordable, while avibactam can be accessed along with ceftazidime as a combination. The sample size (320 children, 78 K. pneumoniae isolates) is large and offers sufficient power for the primary analyses. Standardized prospective design of the study minimizes the recall bias. The multiple methods used for susceptibility testing and synergy testing are more than adequate.

5. Conclusion

The study reveals that Klebsiella pneumoniae strains isolated from children suffering from Otitis Media in Diyala, Iraq, show high levels of resistance to Ceftriaxone and Cefotaxime. This resistance is due to 75.6% of strains producing Extended Spectrum Beta-Lactamases. Both of these antibiotics showed similar rates of resistance; however, Cefotaxime had much lower Minimum Inhibitory Concentration (MIC) values against the resistant strains, with an MIC_{90} value of 128 µg/mL compared to an MIC_{90} of >256 µg/mL for Ceftriaxone. The combination of Cefotaxime and Avibactam showed synergistic effects in 80.8% of cases, which is much greater than the 38.5% synergy seen in the combination of Ceftriaxone with Tazobactam. The factors identified as increasing resistance included prior hospitalization, prior use of cephalosporins, and recurrent otitis media. Of these, prior use of cephalosporins was associated with the greatest risk of resistance (OR 6.34). Empirical treatment with monotherapy of third-generation cephalosporins is not recommended for Otitis Media in children in this population, and alternative treatment regimens involving combination therapy and susceptibility testing should be utilized. The combination of Cefotaxime and Avibactam has the potential to be an effective treatment for children with Otitis Media and infections due to ESBL producing strains of Klebsiella pneumoniae, however further studies are required to determine the safety of this combination therapy in children.

Data Availability Statement

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request. Raw MIC data, synergy testing results, and patient demographic information have been archived at the University of Diyala College Of Medicine.

Conflict of Interest Statement: The authors declare no conflicts of interest.

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Reference

[1] Foxman B , Salzman E , Gesierich C, Gardner S , Ammerman M , EisenbergM , Wigginton K. 2025. Wastewater surveillance of antibiotic-resistant bacteria for public health action: potential and challenges. American Journal of Epidemiology, 194, 1192–1199.

[2] Flores-Mireles AL, Hultgren SJ. 2025. Urinary tract infections in women: pathogenesis, host responses, and emerging therapeutic approaches. Nature Reviews Microbiology, 23(4), 210–225. DOI: 10.1038/s41579-024-01123-2.

[3] -World Health Organization. 2025. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report: 2025 Summary. Geneva: WHO Press

[4] Bush K, Bradford PA. 2024. Epidemiology, mechanisms, and clinical impact of β-lactamase-producing pathogens. Clinical Microbiology Reviews, 37(1), e00111-23. DOI: 10.1128/cmr.00111-23 1.

[5] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D. 2024. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant Gram-negative infections. Clinical Infectious Diseases, 79(2), e1–e42. DOI: 10.1093/cid/ciae287, 1.

[6] Al-Hamad AM, Al-Abdulkarim IM, Al-Otaibi FE, et al. 2025. Epidemiology and antimicrobial resistance of uropathogens in a tertiary care center in Riyadh, Saudi Arabia: a one-year retrospective analysis. Pathogens, 14(12), 1023. DOI: 10.3390/pathogens14121023.

[7] Ashraf Z, Abbas S, Khan A, et al. 2025. Antimicrobial resistance and virulence profiling of Klebsiella pneumoniae isolated from urinary tract infections in community and hospital settings in Pakistan. Pakistan Journal of Pharmaceutical Sciences, 38(2), 395-405. PMID: 40501238. 1.

[8] Shields RK, Clancy CJ. 2024. The role of novel beta-lactamase inhibitor combinations in the era of carbapenem resistance. Current Opinion in Infectious Diseases, 37(6), 546–554. DOI: 10.1097/QCO.0000000000001067. 1.

[9] Kaye KS, Pogue JM. 2025. Treatment of extended-spectrum beta-lactamase-producing Enterobacterales infections: a clinical update. Journal of Antimicrobial Chemotherapy, 80(Supplement_1), i3–i12. DOI: 10.1093/jac/dkae412.

[10] Rodriguez-Baño J, Paterson DL. 2025. A decade of ESBLs: lessons learned and future challenges. JAC-Antimicrobial Resistance, 7(1), dlaf001. DOI: 10.1093/jacamr/dlaf001.

[11] Bhowmick T, Canton R, Pea F, Quevedo J, Santerre Henriksen A, Timsit JF, Kaye KS. 2025. Cefepime-enmetazobactam: first approved cefepime-β-lactamase inhibitor combination for multi-drug resistant Enterobacterales. Future Microbiology, 20(4), 277-286. DOI: 10.1080/17460913.2025.2450223.

[12] Ratliff A, Oliphant C. 2025. Chapter 72: Patient assessment, antimicrobial selection, and stewardship. In: AccessAPN. McGraw-Hill Medical. Updated July 2025.

[13] Clinical and Laboratory Standards Institute. 2025. Performance Standards for Antimicrobial Susceptibility Testing. 35th ed. CLSI supplements M100. Wayne, PA: CLSI.

[14] Al Momani W, Al-Batayneh K, Al-Sheyab N, et al. 2025. Extended spectrum β-lactamase (ESβL)-producing E. coli causing urinary tract infection among pregnant women and pediatric patients in public hospitals in northern Jordan. PLOS One, 20(4), e0302456. DOI: 10.1371/journal.pone.0302456.