A COMPARATIVE STUDY OF ANTIMICROBIAL SENSITIVITY IN PATIENTS WITH ACUTE PYELONEPHRITIS AND EMPHYSEMATOUS PYELONEPHRITIS

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ABSTRACT

Introduction: Urinary tract infections (UTIs) are common in people, with acute pyelonephritis affecting the renal pelvis and parenchyma, primarily due to bacterial pathogens. Individuals with conditions like obesity, diabetes, or immunosuppression are at a higher risk of complications. Emphysematous pyelonephritis (EPN) is a severe infection associated with gas formation in the kidneys, predominantly caused by *E. coli* and *K. pneumoniae*.

Objective: To determine the pathogens responsible for emphysematous pyelonephritis and compare it with acute pyelonephritis and their antimicrobial sensitivity patterns in these patients.

Methodology: A twelve-month prospective comparative observational study from July 2023 to June 2024, was conducted on 145 patients diagnosed with either acute pyelonephritis or EPN at the Institute of Kidney Disease, Peshawar. The patients over 18 years of age with a clinical diagnosis of acute or emphysematous pyelonephritis and a positive urine culture were included. Exclusion criteria included recent antibiotic use (within 14 days), pregnancy, chronic kidney disease, congenital urogenital anomalies, immunocompromised states, and incomplete patient data. Urine samples were cultured to identify causative microbes and assess their antibiotic sensitivity. The results were analyzed using SPSS 23.

Results: Among 145 patients, 72.4% had acute pyelonephritis and 27.6% had EPN. E. coli was the predominant pathogen in both conditions (64.8% in APN vs 60.0% in EPN, p=0.632). In acute pyelonephritis, highest sensitivity was observed for colistin (96.5%), amikacin (93.1%), and imipenem (93.1%). However, in EPN cases, sensitivity to these antibiotics was significantly lower (p=<0.01): colistin (76.3%), amikacin (76.3%), and imipenem (57.9%).

Conclusion: The study highlights a concerning rise in antimicrobial resistance, particularly in EPN cases. Colistin, aminoglycosides, and carbapenems remain effective, but potentially contributing to the resistance of these drugs. Adherence to WHO guidelines for antimicrobial prescription is essential to combat multidrug resistance.

Keywords: Acute Pyelonephritis, Emphysematous Pyelonephritis, Antibiotic Resistance, Antimicrobial, Sensitivity, Urinary Tract Infections (UTIs)

INTRODUCTION

Urinary tract infections (UTIs) are one of the most prevalent nosocomial, or community-acquired infections in men. UTIs also encompass many clinical entities ranging from non-symptomatic bacteriuria to overwhelming renal infection with accompanying sepsis.(1)

Females are more liable to have urinary tract infections than men due to anatomical reasons like short urethra and proximity to anal orifice.(2) As UTI is a comprehensive term that includes infections of the entire urinary tract—from the urethra and bladder to the ureters and kidneys—this study focuses specifically on pyelonephritis, which refers to infection of the kidneys. Among the various sorts of UTIs, pyelonephritis is the most severe and possibly fatal, especially when accompanied by complications or comorbidities. The term acute pyelonephritis (APN), refers to infection of the renal pelvis and parenchyma, typically caused by ascending infections from the urinary bladder, and less commonly by hematogenous spread. Patients having underlying conditions like obesity, diabetes mellitus, obstruction, or immunosuppression are vulnerable to complications like renal abscess and emphysematous pyelonephritis.(3)

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Emphysematous pyelonephritis (EPN) is a gas-producing necrotizing infection of the renal parenchyma and peri-renal region mainly caused by diabetes mellitus.(4), however, other risks are described before. Members of the Enterobacteriaceae family are commonly implicated in cases of urinary tract infections. Amongst them, E. coli is a well-recognized bacteria with an incidence of presence up to 71%, and it is resistant to commonly used antimicrobials.(5) Other Gram-negative organisms, such as P. aeruginosa, and Gram-positive organisms, such as Enterococcus spp., are usually involved in hospital-acquired urinary tract infections.(6) The major pathogens causing emphysematous pyelonephritis are Escherichia coli and Klebsiella pneumonia, preceding pathogens are Proteus, Enterococcus, Pseudomonas and Clostridium.(7) Recent investigations in Peshawar, Pakistan, show a significant frequency of multidrug-resistant uropathogens in UTIs. The most common isolates, Klebsiella pneumoniae and E. coli, were highly resistant to cefuroxime. Carbapenems (imipenem, meropenem) and fosfomycin were the most effective treatments. One study found 82.2% multidrug resistance, with E. coli being the most prevalent infection. Nitrofurantoin demonstrated the highest oral efficacy, while ciprofloxacin and cephalosporins had limited sensitivity. These findings emphasise the critical necessity for region-specific antibiotic recommendations (8, 9). Empirical antibiotics are frequently used as the first-line treatment for UTIs before culture results are available. However, in most cases, prophylactic antimicrobial therapy needs to be commenced before culture and sensitivity reports are available. Antimicrobials are highly valued drugs that target microorganisms, predominantly bacteria, by either inhibiting their growth or reducing their activity and, hence, controlling the infections. Uncomplicated UTIs are mostly treated with oral antimicrobial drugs, yet, complicated UTIs like EPN pose a serious threat in the said patients with comorbidities and can result in a significant financial burden to both the patient and hospital.(10) In most cases, UTIs are treated with empirical antibiotics chosen based on clinical judgement and regional resistance patterns. This rising health challenge is rooted in the inappropriate use of antimicrobials in human health and inadequate resources to control the spread of infections.(11) Several drawbacks lies with the threat of antimicrobial resistances, including higher costs of treatment, increased stay of hospitalization, and decreased quality of patient care. In developing countries, cost of the medications is a big concern for healthcare professionals and patients. During the past few years, there has been widespread inappropriate use of antimicrobial drugs as studies indicate that around 50% of the prescribed antimicrobials are inappropriately selected.(12) In turn, this misuse confers microbial resistance to the normally applied antimicrobials, requiring the development and use of novel and pricier antibiotics to fight this emerging crisis.(13) This study aimed to investigate the antimicrobial resistance pattern in patients with emphysematous pyelonephritis, compared this with acute pyelonephritis, and recommend empiric antimicrobial therapy based on data.

OBJECTIVE

To compare the causative organisms and their antimicrobial sensitivity patterns between patients with acute pyelonephritis and emphysematous pyelonephritis

METHODOLOGY

It was a single-centered prospective comparative observational study conducted on 145 patients for twelve months from July 2023 to June 2024 in the Urology Department at the Institute of Kidney Disease, Peshawar, using a non-probability convenience sampling technique. Ethical approval was obtained from the ethical review board of our institute, ensuring adherence to ethical standards by the declaration of Helsinki. Sample size was calculated using the formula for comparing two proportions, considering expected antimicrobial resistance rates of 30% in acute pyelonephritis versus 60% in EPN, with 80% power and 5% significance level, yielding a minimum required sample of 145 patients. The patients of age greater than 18 years, clinically diagnosed with acute pyelonephritis or emphysematous pyelonephritis and those having a positive urine culture and sensitivity were included in study. Those with antibiotic usage within 14 days as interfere with the cultures, pregnancy, chronic kidney diseases as an immunocompromised state, presence of known congenital urogenital structural abnormalities, and cases with insufficient data of the patient who are diagnosed with pyelonephritis were excluded from the study. The patients were diagnosed with acute pyelonephritis and emphysematous pyelonephritis using clinical evaluation i.e. history and examination. At the time of presentation, investigations i.e. blood count, renal function tests, HbA1c, urine analysis, abdominal radiography, abdominopelvic

ultrasound, and abdominopelvic computerized tomography (CT-scan)) were conducted. Acute pyelonephritis (APN) was defined as temperature ≥38.0°C with at least one of the following: urgency, frequency, dysuria, supra-pubic tenderness, or flank pain, together with a positive dipstick test result for leukocyte esterase or nitrate, or >5 to 9 WBCs observed on a high-power microscopy field. (14) Emphysematous pyelonephritis (EPN) was defined as a necrotizing infection of the renal parenchyma and its surrounding areas, which produces gas. (15), confirmed on a CT scan based on radiological findings by Huang and Tseng. (16) After the diagnosis, the aseptic mid-stream urine samples of the patients were taken and sent for culture and sensitivity to the pathology department. The body mass index was calculated by the standard formula of weight/height2 (kg/m2). The patients previously diagnosed with diabetes mellitus using anti-diabetic medications or having HbA1c > 6.2% were considered as diabetes mellitus. The patients having acute deranged renal functions secondary to obstructions such as stones were added to the category of obstructive uropathy. A bacterial concentration of 105 colony forming units (CFU)/ml was considered significant after inoculating 0.2 µl of urine on Cysteine Lactose Electrolyte Deficient agar, using the semi-quantitative strip method of MAST, Bacteruritest. The culture media was incubated at 37°C for 24 to 48 hours. Microorganisms were identified by Gram staining, biochemical tests, and serology. The Enterobacteriaceae and related organisms were identified with the help of the Analytical Profile Index API20E (Biomerieux, France), following the instructions provided by the manufacturer. (17) The antibacterial susceptibility of these isolates was tested by the Kirby-Bauer disk diffusion method according to the CLSI protocol using commercially available standard antibiotic discs. As per the CLSI, the zones of inhibition were measured and recorded. In the guidelines, Susceptible "S" and Resistant "R" are standard nomenclature. (18) The isolates were then characterized as multidrug-sensitive (Multi-S), monodrug-resistant (MoDR), multidrug-resistant (MDR), and extensively drug-resistant (XDR) based on antibiotic sensitivity patterns according to the standard definitions. Susceptible to all antibiotic classes are the Multi-S, resistant to a single antibiotic class is the MoDR, MDR are resistant to at least one agent in three or more antimicrobial categories, and XDR are non-susceptible to at least one agent in all but two or fewer antimicrobial categories. (19) Data was analyzed using SPSS version 23. Categorical variables were presented as frequencies and percentages, while continuous variables were presented as means ± standard deviation. Chi-square test was used for comparing categorical variables between groups, and independent t-test was used for continuous variables. Fisher's exact test was applied when expected cell counts were <5. Statistical significance was set at p-value <0.05.

RESULTS

Among 145 patients, 64.1% (n=93) were males and 35.9% (n=52) were females, with a mean age of 43.3 ± 14.5 years ranging from 18 to 75 years. Of these patients, 72.4% (n=105) were diagnosed with acute pyelonephritis, while the remaining 27.6% (n=40) were cases of emphysematous pyelonephritis. In 86.2% (n=125) of the cultures showed bacterial growth. The average body mass index (BMI) observed was 28.6 ± 6.1 kg/m2. Table 1 shows the demographics and risk factors contributing to pyelonephritis. Among the patients, 35.9% (n=52) had history of diagnosed diabetes mellitus and 20.0% (n=29) had obstructive uropathy. Diabetes mellitus was significantly more prevalent in EPN patients (82.5% vs 18.1%, p<0.001).

Table 1: Demographics of acute pyelonephritis and emphysematous pyelonephritis

Factors		Acute pyelonephritis n=105	Emphysematous pyelonephritis n=40	p-value
Age (mean, in years)		38.7	55.3	**0.01**
Gender (%)	Male	74 (70.5)	19 (47.5)	**0.01**
	Female	31 (29.5)	21 (52.5)	
BMI (mean, kg/m2)		27.3	32.0	0.05
Diabetes mellitus (%)		19 (18.1)	33 (82.5)	**<0.001**
Obstructive uropathy (%)		16 (15.2)	13 (32.5)	**0.03**
Continuous variables: independent T-test, Categorical variables: Chi-square test is used, p-value				

<0.05 is significant

In 125 cultures showing isolated bacterial growths, 87 of the patients had acute pyelonephritis and 38 of the patients were of emphysematous pyelonephritis. Figure 1 displays the frequency of bacterial growths in the medium with different types of bacteria, *Escherichia coli* (63.4%), *Klebsiella pneumonia* (10.3%), *Pseudomonas aeruginosa* (4.1%), *Proteus mirabilis* (3.4%), *Streptococcus spp.* (2.1%), *Enterobacter spp.* (1.4%), *Citrobacter spp.* (0.7%). and *Staphylococcus aureus* (0.7%). Further, table 2 summarizes the frequency of bacterial growths observed in patients with acute pyelonephritis and emphysematous pyelonephritis. E. coli remained the predominant pathogen in both groups, though K. pneumoniae **(p=0.04)** and P. aeruginosa **(p=0.01)** were significantly more common in EPN cases.

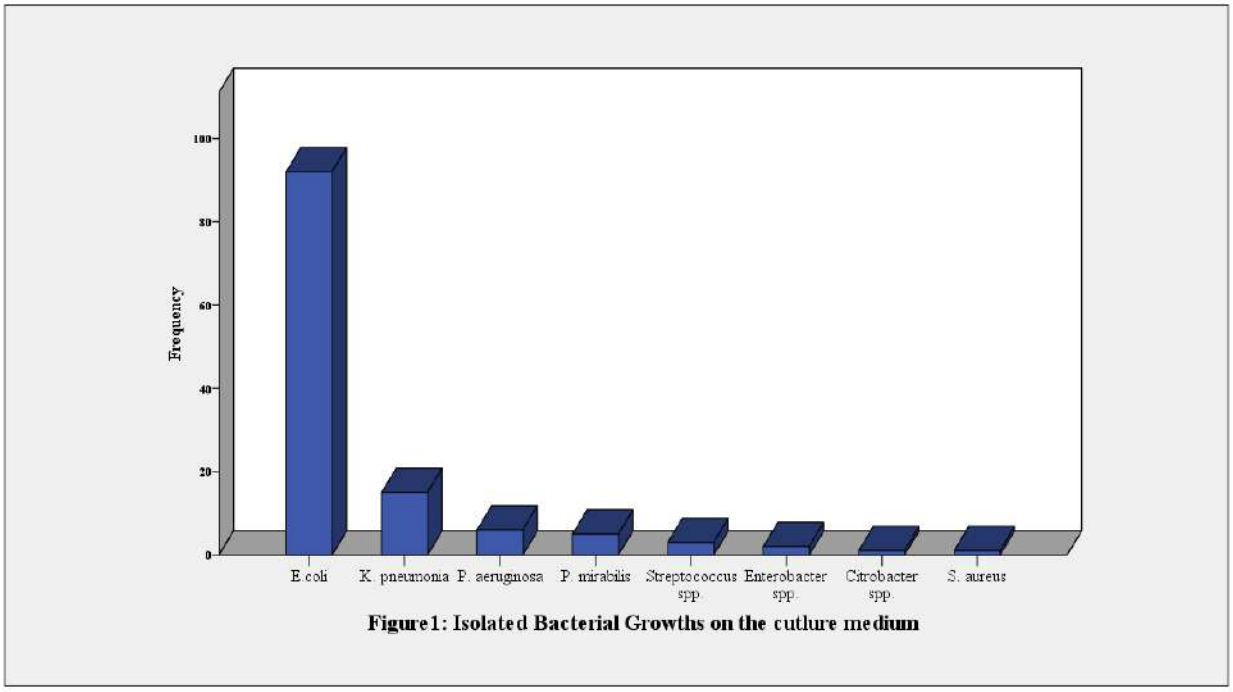

Figure 1: Isolated Bacterial Growths on the culture medium

Table 2: Isolated bacterial growth in patients of acute pyelonephritis and emphysematous pyelonephritis

Bacteria	Acute pyelonephritis n=105 (%)	Emphysematous pyelonephritis n=40 (%)
Escherichia coli	68 (64.8)	24 (60.0)
Klebsiella pneumonia	7 (6.7)	8 (20.0)
Pseudomonas aeruginosa	1 (1.0)	5 (12.5)
Proteus mirabilis	4 (3.8)	1 (2.5)
Streptococcus spp.	3 (2.8)	0
Enterobacter spp.	2 (1.9)	0
Citrobacter spp.	1 (1.0)	0
Staphylococcus aureus	1 (1.0)	0

In patients with bacterial growth, the antimicrobial drugs that showed the highest sensitivity to pathogens were colistin (90.4%), amikacin (88.0%), piperacillin/tazobactam (82.4%), imipenem (82.4%), gentamicin (82.4%), meropenem (80.0%), Fosfomycin (75.2%), nitrofurantoin (63.2%), trimethoprim/sulfamethoxazole (60.0%), Cefoperazone/sulbactam (53.6%), levofloxacin (53.6%), ciprofloxacin (52.0%), ceftriaxone (51.2%), amoxicillin/clavulanic acid (47.2%) and ampicillin (44.0%). Table 3, summarizes the sensitivities of antimicrobial drugs in both groups, acute pyelonephritis and emphysematous pyelonephritis.

Table 3: Sensitivities of antimicrobial drugs in both groups, acute pyelonephritis and emphysematous pyelonephritis

Antimicrobial drugs	Acute pyelonephritis n=87 (%)	Emphysematous pyelonephritis n=38 (%)	p-value
Colistin	84 (96.5)	29 (76.3)	**<0.001**
Imipenem	81 (93.1)	22 (57.9)	**0.008**
Amikacin	81 (93.1)	29 (76.3)	**<0.001**
Meropenem	80 (91.9)	20 (52.6)	**<0.001**
Piperacillin/tazobactam	79 (90.8)	24 (63.2)	**<0.001**
Gentamicin	79 (90.8)	24 (63.2)	**<0.001**
Fosfomycin	79 (90.8)	15 (39.5)	**<0.001**
Nitrofurantoin	69 (79.3)	10 (26.3)	**<0.001**
Trimethoprim/sulfamethoxazole	66 (75.9)	9 (23.7)	**<0.001**
Levofloxacin	63 (72.4)	4 (10.5)	**<0.001**
Cefoperazone/sulbactam	61 (70.1)	6 (15.8)	**<0.001**
Ciprofloxacin	59 (67.8)	6 (15.8)	**<0.001**
Ceftriaxone	58 (66.7)	6 (15.8)	**<0.001**
Amoxicillin/clavulanic acid	55 (63.2)	4 (10.5)	**<0.001**
Ampicillin	50 (57.5)	5 (13.2)	**<0.001**
Chi-square test is used, p-value <0.05 is significant			

Table 4: The resistance pattern in both groups, acute pyelonephritis and emphysematous pyelonephritis

Resistance Pattern	Total n=125 (%)	Acute Pyelonephritis n=87 (%)	Emphysematous Pyelonephritis n=38 (%)	p-value
Multidrug-sensitive (Multi-S)	35 (28.0)	31 (35.6)	4 (10.5)	**0.003**
Monodrug-resistant (MoDR)	31 (24.8)	26 (29.9)	5 (13.2)	0.05
Multidrug-resistant (MDR)	39 (31.2)	23 (26.4)	16 (42.1)	0.08
Extensively drug-resistant (XDR)	20 (16.0)	7 (8.0)	13 (34.2)	**<0.001**
Chi-square test is used, p-value <0.05 is significant				

EPN cases showed significantly higher rates of extensively drug-resistant organisms (34.2% vs 8.0%, **p<0.001)** and lower rates of multidrug-sensitive organisms (10.5% vs 35.6%, **p=0.003).**

DISCUSSION

Community-acquired bacterial UTI is one of the common clinical conditions for which patients seek medical care. For the effective treatment of bacterial UTIs, it is important to isolate the causative microbe and then select an appropriate antibiotic for treatment. About 50% of sexually active females experience UTI once in their lifetime and are prone to develop these due to short urethra, in close vicinity to the anal orifice, or high bacterial load in the urothelial mucosa (20), either due to other factors like pregnancy or urinary tract obstruction(21). As in our study is a male dominant region, still 35% of females' encountered pyelonephritis. Emphysematous pyelonephritis is also common in females for the reasons mentioned as supported by studies. (22) (23) Interestingly, our study found a female predominance in EPN patients (52.5% vs 47.5% males), which supports prior observations that anatomical features that predispose women to UTIs also contribute to severe consequences such as EPN. And has been observed in this study. Diabetes mellitus is the one of the predominant factor of emphysematous pyelonephritis, and up to 95% of the patients have this condition. (22) (24) However, in the study, about 80% of the patients with emphysematous pyelonephritis had diabetes mellitus, and even those having acute pyelonephritis along with diabetes mellitus are susceptible to developing emphysematous pyelonephritis. (3) Developing emphysematous pyelonephritis is a risk when there is obstructive uropathy along with other factors like diabetes mellitus or advancing age. In context to obstruction, the study found that 49% of patients developed emphysematous pyelonephritis, while our study showed a rate of 32.5%, occurs because of the increased pelvic pressures impair the

renal circulation thus leading to a cascade of thrombosis, necrosis, and infarction. (22)

E. coli remained the most common pathogen in both situations, consistent with global literature(6,8,24) and from Pakistan (25,26). However, our investigation found significant changes in pathogen distribution across APN and EPN. K. pneumoniae and P. aeruginosa were much more common in EPN patients, which has important therapeutic implications given their intrinsic resistance patterns. In contrast to previous research, our findings show a far greater incidence of K. pneumoniae in EPN (21.1% vs. 8.0% in APN), which well exceeds the 19.6% reported by in the Taiwanese cohort of EPN patients (14,25). This disparity may reflect geographical differences in pathogen distribution and emerging resistance patterns. Similarly, the significantly higher P. aeruginosa occurrence in our EPN patients (13.2% vs. 1.1% in APN) is a disturbing divergence from previous findings, in which P. aeruginosa was very uncommon in EPN cases.

The increased prevalence of K. pneumoniae in EPN (21.1% vs. 8.0%) is especially noteworthy because this bacterium is associated with more severe infections and higher rates of antibiotic resistance. Similarly, the much higher P. aeruginosa incidence in EPN (13.2% vs 1.1%) provides a considerable therapeutic challenge, as this organism is intrinsically resistant to many routinely used antimicrobials. Still in patients with emphysematous pyelonephritis, E.coli was predominant as in other studies. (16) (25)

As emphysematous pyelonephritis is a complicated UTI, and needs an aggressive approach in management, whereas the pathogens displaying a resistive nature in this study, raising an alarming situation to coupe-up. Our resistance patterns differ dramatically from previously reported sensitivities. While a previous Peshawar study found remarkably high sensitivity rates to colistin, imipenem, meropenem, gentamicin, and amikacin (26), our current findings show a concerning decline in these rates, indicating a rapid evolution of antimicrobial resistance in our region.

Overall, colistin was the most sensitive drug, followed by amikacin, then imipenem, piperacillin/tazobactam & gentamicin, and the least sensitive were penicillin, cephalosporin, and fluoroquinolones. However, in patients with emphysematous pyelonephritis, the results were quite different, with the most sensitive being colistin and amikacin, followed by piperacillin/tazobactam and gentamicin, then imipenem and meropenem. Yet, penicillin, cephalosporin, and fluoroquinolones had the same resistive behavior. A study in Peshawar showed a higher sensitivity pattern than this study with 99.9% sensitivity to colistin, 99.6% imipenem, 99.5% meropenem, 97.4% gentamicin, and 96.7% amikacin,(26) Which is considerably decreased in this study. This is pointing towards a situation where strings of antimicrobials will no longer hold the infectious pathogens.

When compared to international statistics, our study's fluoroquinolone resistance patterns are particularly noteworthy. While Lu et al. reported 24% fluoroquinolone resistance in E. coli and 22% in K. pneumoniae isolates from EPN patients (14), our study shows even higher resistance rates to this antibiotic class, reflecting the global trend of increasing fluoroquinolone resistance documented by WHO, which reports that one in every five E. coli UTI cases now has reduced susceptibility to standard antibiotics, including fluoroquinolones (27). This development is especially troubling because fluoroquinolones were formerly regarded first-line oral therapy for severe UTIs.

The resistance pattern analysis reveals concerning trends, especially in EPN situations. Most impressively, our analysis discovered that 34.2% of EPN isolates were extensively drug-resistant (XDR), compared to only 8.0% in APN cases, representing a more than 4-fold increase. This is a substantially greater XDR prevalence than previously reported in the literature for EPN, where thorough resistance categorization is limited. This conclusion is especially concerning when compared to global AMR surveillance statistics, which identify antimicrobial resistance as a primary cause of death worldwide, with the largest burden in resource-limited settings (28). The much higher incidence of extensively drug-resistant pathogens in EPN (34.2% vs 8.0%) poses a severe treatment challenge and poor prognosis. This finding implies that EPN cases may necessitate both antibiotic medication and vigorous care strategies.

Furthermore, a major decrease in multidrug-sensitive organisms in EPN patients (10.5%) compared to APN patients (35.6%) - a 70% decrease - marks a paradigm change in the microbiology of this illness. This is in stark contrast to previous research, which found that multidrug-sensitive isolates were more

common in EPN cases, implying that current empirical treatment methods may need to be significantly revised.The decreased incidence of multidrug-sensitive organisms in EPN (10.5% vs 35.6%) suggests that empirical antibiotic therapy for suspected EPN should include broad-spectrum, high-potency drugs rather than traditional UTI therapies.

LIMITATIONS

The limitations of this study were that it was a single-centered study and the number of patients with emphysematous pyelonephritis was small. The patient's history could not verify the prior use of antibiotics. This could be attributed to the study being conducted within a tertiary care hospital, which could have amplified the antimicrobial resistance as compared to the primary healthcare setting.

CONCLUSION

This study found a larger resistance load in emphysematous pyelonephritis (EPN) than in acute pyelonephritis (APN). Extensively drug-resistant (XDR) organisms were over four times more abundant in EPN (34.2% vs 8.0%). Additionally, resistant bacteria such as Klebsiella pneumoniae (21.1%) and P. aeruginosa (13.2%) were more common in EPN cases. The study identified an extensive drug resistance pattern among patients with urinary tract infections, particularly emphysematous pyelonephritis. The results revealed that colistin, aminoglycosides, and carbapenems are still effective against the resilient uropathogens. On the other hand, misuse of these drugs may be contributing to extensive drug resistance. Healthcare practitioners should recognize EPN as a separate clinical entity requiring vigorous antimicrobial therapy and avoid using fluoroquinolones and standard beta-lactam antibiotics in suspected instances.

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