

ESBL—Multi-Drug-Resistant UTI Creating Outpatient Treatment Challenge

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ABSTRACT

Urinary tract infections (UTIs) are more common in female patients than males in all age groups. Some of the underlying risk factors increase the chances of UTI in male patients as well. Known risk factors like previous antibiotic use, catheterization history, nursing home residence, and previous hospitalizations are associated with drug-resistant UTIs, especially extended-spectrum beta-lactamase (ESBL). The presence of ESBL narrows down the treatment options. This case represents the patient with *Klebsiella pneumoniae* ESBL multidrug resistance (MDR) UTI, which was complicated by the history of previous *pseudomonas* UTI. The bacteria were sensitive only to injectable antibiotics, leaving no oral antibiotic options for treatment. This posed a significant challenge in managing the patient's condition. UTI is the most commonly known cause of delirium and confusion in old age patients, so prompt treatment of UTI in these patients is paramount. This case highlights the need for further research to establish optimal antibiotic choices, particularly in the outpatient setting, for timely and adequate treatment of ESBL MDR UTI cases.

Keywords: Extended-spectrum Beta-lactamase, fosfomycin, multi-drug resistant, Urinary tract infection.

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1. INTRODUCTION

The spread of ESBL-producing *Enterobacteriaceae* (ESBL-PE) has dramatically increased worldwide. This ongoing issue is one of the most critical public health threats. On one hand, this growing problem is the rapid spread and dissemination of resistance mechanisms. On the other hand, the injudicious overuse of antimicrobial agents and inadequate infection control measures have raised the dilemma of the devil and the deep blue sea. ESBL-producing *Klebsiella pneumoniae* and *Escherichia coli* prevalence rates are significantly higher among patients in intensive care units (ICUs) [1].

Patients infected with ESBL-positive organisms have limited treatment options, especially oral antibiotics, and they often need parenteral antibiotic therapy. Empirical antibiotics should be administered promptly at the presentation of a suspected UTI after urine analysis and sending the urine for culture and sensitivity. Unfortunately, many commonly used empirical antibiotic regimens are ineffective against ESBL-positive bacteria, leading to delays in appropriate treatment until susceptibility data becomes available [2].

Catheter-associated urinary tract infections (CAUTIs) are a significant healthcare concern, particularly in patients requiring long-term urinary catheterization. These infections are among the most prevalent nosocomial infections [3].

This case report underscores the importance of ESBL MDR UTI diagnosis and management, especially with oral antibiotics after discharge from the hospital.

2. CASE REPORT

A 76-year-old male with a significant medical history including stage III chronic kidney disease (CKD), diastolic heart failure, liver cirrhosis, hypertension, pulmonary embolism, type 2 diabetes, and benign prostatic hyperplasia (BPH) with a chronic indwelling Foley catheter presented to the emergency department with a significant bilateral lower limb swelling extending up to his thighs and penile edema. The patient did not have urinary symptoms and did not have a fever.

Due to the presence of extensive edema, the patient was hospitalized and started on intravenous ceftriaxone therapy after getting routine labs, including urine analysis and



TABLE I: URINE CULTURE SENSITIVITY RESULTS FOR *Klebsiella pneumoniae*

<i>Klebsiella pneumoniae</i>				
Drug	MIC interpretation	MIC dilution	EI	ED
Ampicillin	R	>=32	–	–
Ampicillin/sulbactam	R	>=32	–	–
Cefazolin	R	>=64	–	–
Ceftriaxone	R	>=64	–	–
Cefuroxime	R	>=64	–	–
Cefuroxime/Axetil	R	>=64	–	–
Fosfomycin	–	–	R	>=256
Gentamicin	S	<=1	–	–
Levofloxacin	R	>=8	–	–
Meropenem	S	<=0.25	–	–
Nitrofurantoin	R	128	–	–
Piperacillin/Tazobactam	R	>=128	–	–
Trimethoprim/Sulfamethoxazole	R	>=320	–	–

Note: **Abbreviations:** MIC: Minimum Inhibitory Concentration, EI: Extended Interpretation, ED: Extended Dilution.

urine culture. The urine culture identified *Klebsiella pneumoniae* as producing extended-spectrum beta-lactamases (ESBL), which exhibited susceptibility only to gentamicin and meropenem.

Based on these results, intravenous meropenem was commenced, and the Foley catheter was replaced. The patient's creatinine clearance was 1.21, and GFR was 62. The patient received a slow intravenous push of Meropenem 500 mg every 8 hours. Please refer to Table I for urine culture and sensitivity results for *Klebsiella pneumoniae*.

Despite clinical improvement and readiness for discharge following a 3-day course of intravenous meropenem, there was still uncertainty regarding the appropriate outpatient antibiotic therapy. A consultation with an infectious disease specialist recommended adding Fosfomycin sensitivity testing to an earlier urine sample and prescribed fosfomycin. The patient was administered a single 3-gram dose of fosfomycin. However, later susceptibility testing revealed resistance to this antibiotic as well.

Given the patient's resistance to oral antibiotics, a second infectious disease consultation was sought. Following the specialist's recommendation, the patient was discharged home with instructions for close follow-up by their primary care physician and urologist without oral antibiotic therapy. During the follow-up appointment with the primary care physician, the patient tested negative for urine analysis, and the urine culture did not grow any bacteria.

The patient had been under regular urological care, with the most recent visit occurring four days before the current hospitalization, during which his Foley catheter was replaced. A review of his medical history revealed a previous hospitalization two months ago for a urinary tract infection (UTI). Laboratory tests, including serum creatinine, were normal at that time. Urinalysis confirmed UTI, leading to the initiation of intravenous ceftriaxone therapy. Urine culture identified *Pseudomonas* and *Enterococcus* species, both susceptible to multiple antibiotics, including cephalosporins. Please refer to Table II for urine culture and sensitivity results for *Pseudomonas aeruginosa*.

3. DISCUSSION

ESBL MDR UTI is increasing, especially in patients with known risk factors. A study conducted in New Zealand found that ESBL-producing *enterobacteria* were isolated from more than 100 infected patients. *Escherichia coli* was the most identified organism in more than 80 percent of cases, with urine being the primary source of infection in almost all the patients studied. The study revealed that several factors were significantly associated with infection, including residence in a care home, recent hospital admission, recent antibiotic use, advanced age, and a urinary catheter [4].

In another study, the most frequently identified risk factor was prior antibiotic use, with the time frame for defining previous antibiotic usage varying widely from a few days to one year. Other risk factors that showed the most substantial evidence included urinary catheterization, previous hospitalizations, and residence in a nursing home [5].

Our patient had several risk factors for an ESBL UTI, including a long-standing urinary catheter, advanced age (>75 years), and recent hospital admission with antibiotic use. Within two months of hospitalization for a *pseudomonas* UTI, the patient developed an ESBL UTI with multi-drug resistance. The risk factors discussed in the above two studies were also present in our patient.

A European study indicates that Fosfomycin trometamol could be a potential option due to its broad-spectrum activity against Gram-positive and Gram-negative bacteria. Microbiological data supports this potential, showing high susceptibility rates, particularly against *Klebsiella pneumoniae* and, more notably, *Escherichia coli* [6].

Multidrug resistance was found to be more common in males compared to females, in patients over 65 years old compared to those between 18 and 65, and inpatients compared to outpatients. Among the antibiotics tested, nitrofurantoin and ciprofloxacin showed the lowest resistance rates, while ampicillin had the highest. Our patient exhibited resistance to all antibiotics except for gentamicin and meropenem [7].

As treatment options for MDR uropathogens are limited, the study of epidemiological risk factors is advised

TABLE II: URINE CULTURE SENSITIVITY RESULTS FOR *Pseudomonas aeruginosa*

Drug	<i>Pseudomonas aeruginosa</i>	
	MIC interpretation	MIC dilution
Cefepime	S	<=1
Gentamicin	S	<=1
Levofloxacin	S	0.05
Piperacillin/Tazobactam	S	8
Tobramycin	S	<=1

Note: **Abbreviations:** **MIC Interpretation:** Minimum Inhibitory Concentration, **MIC Dilution:** Minimum Inhibitory Concentration Dilution.

to find the best possible treatment option. In another study, fosfomycin and nitrofurantoin's activity remained high for most MDR *Escherichia coli* UTIs. Trimethoprim-sulfamethoxazole retained clinical efficacy, but resistance rates were increasing internationally. Beta-lactam agents had the highest rates of resistance and lowest rates of clinical success. Fluoroquinolones have high resistance rates among MDR uropathogens and are strongly discouraged as first-line agents for UTIs [8], [9].

In our patient, the infectious disease specialist initially prescribed oral Fosfomycin, anticipating that the *Klebsiella* infection would be susceptible, given that the patient had never previously used Fosfomycin. However, it was later determined that the infection was resistant to Fosfomycin, which complicated the treatment plan.

Based on a study that recommended once-daily intravenous or intramuscular ertapenem for outpatient treatment of patients with MDR UTI, our patient may have used this option, too [10]. However, he was doing much better during a follow-up visit with a primary care physician without recurrence of symptoms, and he continued to follow up with a urologist.

Therapeutic options are limited due to the rise of multidrug-resistant organisms. Most β -lactams are ineffective against ESBL-producing *Enterobacteriaceae*. Until new antibiotics are developed, revisiting older, lesser-known antibiotics like pivmecillinam, fosfomycin, and nitrofurantoin may offer a valuable alternative [11].

Further studies are needed for these oral agents to determine the optimal dosing and effectiveness of combination therapy in reducing the risk of treatment failure [12].

Because of limited treatment options and cross-resistance between oral antibiotics from different classes, these patients often need intravenous therapy, which not only raises healthcare costs but also diminishes the overall efficiency of healthcare delivery [13].

Delirium is found as a main symptom of underlying urinary tract infection (UTI) in old age care facilities, making UTI the most common cause of delirium in this population. In a study done on old patients with UTIs, exacerbation of some of the neuropsychiatric symptoms, such as delirium confusion, was observed. Our patient is a more than 75-year-old man, and prompt, adequate treatment of his MDR UTI is warranted to avoid these neuropsychiatric symptoms [14].

In another study done on very old women with UTI and delirium, UTI was found to be a common cause of delirium. It was advised in that study that there should be more focus on detecting, preventing, and treating UTIs to

avoid unnecessary suffering among old-age patients with complicated neuropsychiatric symptoms [15].

Control of infection and treatment are challenged by the emergence of resistance mechanisms. Limiting the spread of resistance and use of available antibiotic agents is paramount. Several new antimicrobials are getting approved, and some are in the pipeline to fight the battle of resistance. The appropriate use of these new options is required until the true benefits of these agents are to be recognized in the clinical care setting [16].

4. CONCLUSION

ESBL-MDR UTI cases are increasing daily. Finding the appropriate treatment option for these patients is the biggest challenge. There are no clear guidelines for outpatient antibiotic therapy of ESBL MDR UTI patients. Further research is needed to establish optimal antibiotic choices. This case report underscores the importance of studying risk factors and prompt treatment of ESBL MDR UTI to prevent related complications in old-age patients.

PATIENT CONSENT

Verbal informed consent was obtained from the patient to publish this case report.

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We would like to thank you, the patient, for providing informed verbal consent to publish this case report.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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