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Ossama Alrehaili
Emergency Medicine, King Fahd Medical City, Saudi Arabia
Oussama AlThobyane
Emergency Medicine, King Fahd Medical City, Saudi Arabia
Adel Korairi
Emergency Medicine, King Fahd Medical City, Saudi Arabia
Rizq Badawi
Emergency Medicine, King Salman bin Abdulaziz Medical City, Saudi Arabia

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Email: Alrehaili.osama@gmail.com

Failure Rate of Oral Nitrofurantoin in Treating UTIs caused by ESBL-Producing *Escherichia coli* and *Klebsiella pneumoniae*: A Retrospective Cohort Study

Ossama Alrehaili, Oussama AlThobyane, Adel Korairi, Rizq Badawi

***Abstract*— *Background*: Urinary tract infections (UTIs) caused by extended-spectrum beta-lactamase (ESBL)-producing organisms limit oral treatment options. Nitrofurantoin is frequently used, but regional data on its activity against ESBL-producing *Escherichia coli* (ESBL-EC) and *Klebsiella pneumoniae* (ESBL-KP) are lacking in Saudi Arabia. This study aimed to determine the 90-day failure rate of oral nitrofurantoin in treating ESBL-UTIs and explore secondary outcomes.**

***Methods*: This was a retrospective cohort study conducted at a tertiary hospital in Riyadh, Saudi Arabia. The target population was adult ED patients, discharged on oral nitrofurantoin for UTIs caused by ESBL-EC or ESBL-KP, between February 2021 and June 2024. We aimed to identify the failure rate of oral nitrofurantoin in this population. Treatment failure was defined as any ESBL-positive urine culture within 90 days of treatment initiation.**

***Results:* Among 13,421 UTI cases, 347 (2.6%) were ESBL-positive; 41 received oral nitrofurantoin, and 18 met the final inclusion criteria. The 90-day recurrence rate was 22.2% (4/18), with 77.8% having no early recurrence. Three patients had recurrence between 90–180 days. Half of all nitrofurantoin-treated patients were later hospitalised, with severe cases requiring ICU.**

***Conclusion*: Nitrofurantoin showed a 22% failure rate in treating ESBL-UTIs, yet remained effective in most cases, especially those involving ESBL-EC. Given its accessibility, nitrofurantoin remains a viable option but requires close follow-up. Larger studies are needed to refine its role in ESBL-UTI management.**

***Index terms*— Bacterial; Drug Resistance; *Escherichia coli*; Extended-Spectrum Beta-Lactamases; *Klebsiella pneumoniae*; Nitrofurantoin; Retrospective Studies; Urinary Tract Infections.**

I. INTRODUCTION

Urinary tract infections (UTIs) have a very high prevalence, being the second-most common infectious disease and affecting more than 150 million people worldwide annually [1]. UTIs continue to place a significant burden on the healthcare system in the Kingdom of Saudi Arabia (KSA), accounting for approximately 10% of all infections and representing the second-most common reason for emergency department visits [2]. An issue of growing concern is the rising prevalence of UTIs caused by extended-spectrum beta-lactamase-producing *Escherichia coli* (ESBL-EC) and *Klebsiella pneumoniae* (ESBL-KP) [3].

Extended-spectrum beta-lactamases (ESBLs) are enzymes that confer resistance to most beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam [4]. A seven year surveillance in China found that 27% of *Klebsiella* urinary isolates were ESBL-positive and showed high multidrug resistance [5]. Globally, ESBL-producing *Enterobacteriaceae* are responsible for nearly 40% of community-acquired UTIs in some regions, representing a major challenge to oral therapy selection [6].

Risk factors for infections caused by ESBL-producing uropathogens include recurrent UTIs, vesicoureteral reflux, prior antibiotic exposure, younger age, and infection with *Klebsiella* species [7]. While there are many available options for treating UTIs, including both intravenous and oral agents, limited options exist for those caused by ESBL-producing organisms, due to their high resistance. In a Saudi cohort (n=137 UTIs), resistance

Ossama Alrehaili (Alrehaili.osama@gmail.com); Oussama AlThobyane (Oussamaalthobyane@gmail.com); Adel Korairi (Dr.Korairi@gmail.com) are with the Emergency Medicine, King Fahd Medical City, Saudi Arabia; Rizq Badawi is with the Emergency Medicine, King Salman bin Abdulaziz Medical City, Saudi Arabia.

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to nitrofurantoin and fosfomycin was approximately 20% and 23%, respectively; both drugs outperforming TMP–SMX (resistance ~43%) [8].

In a 2018 Indian study of 464 ESBL-UTIs-positive urine samples, fosfomycin appeared to be a promising oral treatment option, showing 93% and 57% sensitivity against ESBL-EC and ESBL-KP, respectively [9,10]. Moreover, fosfomycin maintained ≥94 susceptibility in a study conducted in Pakistan [11]. Nitrofurantoin may also serve as an alternative for treating uncomplicated UTIs caused by ESBL-EC [9]. Globally, meta-analyses have reported clinical cure rates between 79–92% for nitrofurantoin in uncomplicated lower UTIs [12]. Another study reported clinical cure rates of 69% in patients with ESBL-EC cystitis [13].

Further evidence, from a study in Taiwan evaluating the susceptibility of seven antimicrobial agents, found that nitrofurantoin had a susceptibility rate of approximately 80% against ESBL-EC isolates, but only 13.6% against ESBL-KP isolates [14]. In a recent Korean study analysing 117 ESBL-positive urine isolates, nitrofurantoin susceptibility was high in *E. coli* (96.3%) but low in *K. pneumoniae* (33%) [15].

Despite extensive research, a history of ESBL infection remains one of the strongest predictors for hospitalization, regardless of the patient's clinical status. This is primarily due to the high resistance of these organisms and the potential for catastrophic complications if not treated properly.

UTIs comprise approximately 10% of all emergency department visits in Saudi Arabia, presenting a significant regional burden [2]. The lack of regional studies on ESBL-UTIs leaves room for further research. Additionally, there are currently no national guidelines for the oral treatment of ESBL infections.

In this study, we focus on the oral agent nitrofurantoin, which is commonly used in the treatment of UTIs caused by ESBL. Nitrofurantoin is a cost-effective and widely available option. Leading IDSA and ESCMID guidelines recommend nitrofurantoin as a first-line therapy for uncomplicated cystitis in women [16], and recent reviews support its use in uncomplicated ESBL-UTIs in both sexes [9]. We hypothesize that it would be associated with a low to moderate failure rate and could serve as effective oral therapy for a substantial proportion of ESBL-UTIs, potentially reducing the need for hospitalization and intravenous antibiotics.

Preserving effective oral agents such as nitrofurantoin is critical to reduce reliance on carbapenems and slow antimicrobial resistance, especially in community-onset UTIs [17]. This study aims to help guide appropriate antibiotic use and reduce the risk of recurrence and complications commonly associated with ESBL-producing organisms.

II. METHODS

Study Design and Setting:

We conducted a single-arm retrospective cohort study at a tertiary hospital in Riyadh, Saudi Arabia. The study period was from February 1, 2021 to June 1, 2024, corresponding to the time-frame for which electronic medical records were available prior to the review start date. All data were obtained from the hospital's electronic health record system. The study was reviewed and approved by the Institutional Review Board (IRB No. 24-576).

A single-arm retrospective cohort design was selected on the basis of the study's primary goal—to evaluate the failure rate of oral nitrofurantoin in treating ESBL-UTIs. This approach was necessitated by the limited number of eligible monotherapy patients, which precluded a meaningful comparative analysis. Moreover, the objective outcome (90-day recurrence) and retrospective nature supported the choice of a single-arm approach.

Participants:

We included adults aged 18 years or older who presented to a tertiary hospital ED and were diagnosed with a UTI caused by an ESBL-producing organism, confirmed by urine culture, and who were discharged on oral nitrofurantoin therapy. ESBL-producing bacteria were identified based on the patients' microbiology report. Patients were excluded if they were younger than 18 years, were confirmed to be pregnant, or were admitted outside the specified study period. We also excluded those with incomplete or missing data, those with incomplete clinical outcomes data, and those with more than three non-consecutive episodes of ESBL-positive urine cultures, in order to avoid cases of chronic colonization or relapsing UTIs beyond the scope of a single treatment course. Patients with a documented allergy or clinical contraindication to any of the selected medications were also excluded, as were those who received multiple antibiotics on discharge (e.g., nitrofurantoin alongside a full course of another antibiotic).

Data Collection:

We developed a data extraction sheet for the purpose of data collection. From the hospital's electronic records, we collected: patient demographics (age, sex, comorbidities), details of the index UTI episode (date of visit, laboratory results), urine culture and sensitivity results (organism identified, ESBL confirmation, antibiotic susceptibilities), details of antimicrobial treatment (confirmation that nitrofurantoin was prescribed, dose and duration, and whether it was dispensed, as well as any other antimicrobials), and outcome data. Outcome data included any return visits to the ED or hospital admissions within 90 days of the index encounter, repeat urine culture results within 90 days (to identify recurrent infections), and any documented treatment failures or changes. Hospital admission records were reviewed for those who required inpatient care after initial discharge, including length of stay and whether ICU care was needed, to assess the severity of the infection. All data were handled in a confidential manner and stored in a password-protected electronic database accessible only to the research team.

Definitions:

The primary outcome was treatment failure, defined as a repeat positive culture with the same organism as the index infection within 90 days. This corresponded to a "recurrent ESBL-UTI" within 3 months, which could represent either relapse or re-infection with an ESBL strain. We considered this a clinically relevant failure threshold, consistent with previous studies. Patients without a repeat culture or symptoms within 90 days were assumed to have successful outcomes. A secondary outcome was recurrence within 180 days (6 months), used to assess later relapses. We also examined hospitalization rates, with hospitalization defined as any inpatient admission related to the UTI within 90 days of the ED discharge, as well as length of stay.

Statistical Analysis:

Data analysis was primarily descriptive. Continuous variables (e.g., patient age) were reported as mean and standard deviation, as appropriate to the distribution. Categorical variables (e.g., failure rate, admission rate) were summarized as frequencies and percentages. Given the small sample size, no complex inferential statistics were performed; however, basic comparisons were noted.

III. RESULTS

Baseline Patient Characteristics:

Over the study period, a total of 13,421 patients were diagnosed with a UTI in the ED under investigation. Among these, 347 cases (2.59%) were confirmed to be caused by ESBL-producing organisms (either *E. coli* or *K. pneumoniae*). Of the ESBL-UTI cases, 41 patients (11.8%) received oral nitrofurantoin as part of their treatment regimen; these 41 patients form the initial cohort for analysis. The majority of this cohort were female (approximately 61% female vs 39% male) and adults of varied ages (range 30–92 years; mean age 66). Comorbid conditions were common, including diabetes mellitus (DM) (68%), hypertension (70%), and a history of prior UTIs. In terms of organism distribution, 30 patients (73.2%) had ESBL-producing *E.coli* infections and 11 patients (26.8%) had ESBL-producing *K. pneumoniae* infections.

Before assessing outcomes, we applied the exclusion criteria to isolate those patients who received nitrofurantoin monotherapy. Twenty-four of the 41 patients were excluded from the primary efficacy analysis due to one or more exclusion factors:

14 patients had received a full course of IV meropenem in addition to nitrofurantoin (combination therapy); 2 patients were prescribed nitrofurantoin only as prophylaxis (not for active infection); 1 patient was found to be pregnant; 2 had incorrect or incomplete data entries; 3 patients never actually took the nitrofurantoin (medication not dispensed); and 2 patients had three non-consecutive ESBL-positive cultures (indicating a complex recurrent pattern beyond our study scope). Exclusions are shown in Figure 1.

After these exclusions, 18 patients remained in the final study group who were treated for an ESBL-UTI with nitrofurantoin alone. This final analytical sample of 18 patients represents 43.9% of the original 41. Their baseline characteristics were similar to the pre-exclusion cohort: 72% were female; the mean age was approximately 64 years (SD ±18); and the infection organism was ESBL-EC in 14 cases (78%) and ESBL-KP in 4 cases (22%). The distribution of organisms in the final cohort is shown in Figure 2, with ESBL-EC comprising the majority. Comorbid conditions were similar, with hypertension (73%) and DM (68%) predominating. No patients in the final cohort were immunocompromised or had indwelling catheters at discharge, aside from one patient with a neurogenic bladder managed with clean intermittent catheterization.

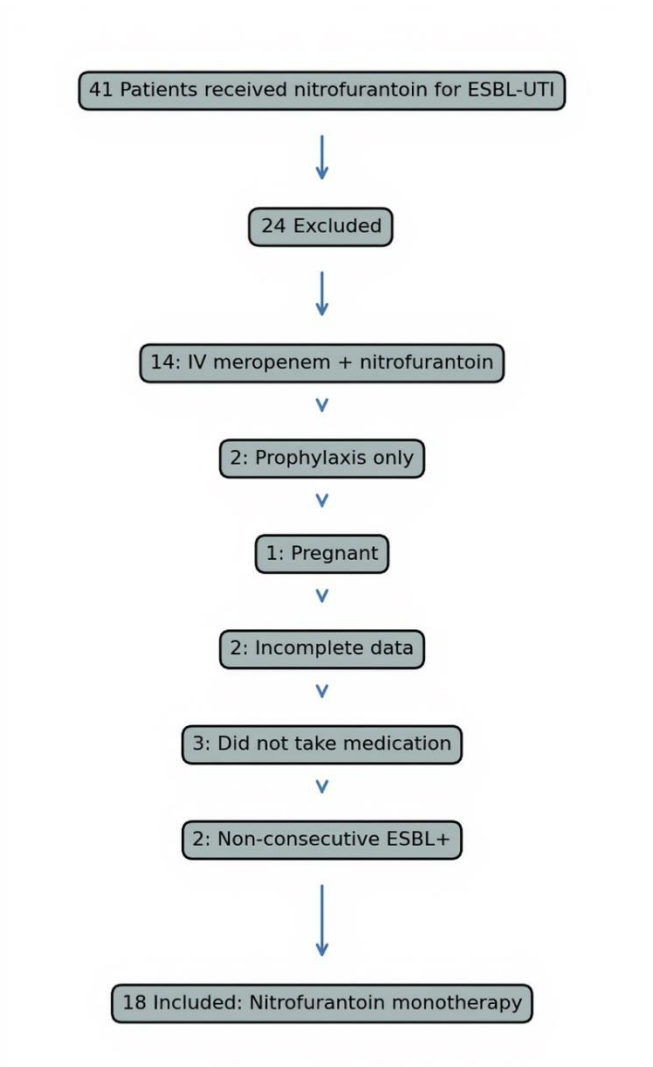

Figure 1. Patient selection process showing exclusion criteria and final cohort included in the nitrofurantoin monotherapy analysis

Primary Outcome – Nitrofurantoin Failure Rate:

Of the 18 patients treated with nitrofurantoin monotherapy, 4 experienced treatment failure by the 90-day follow-up, yielding a failure rate of 22.2%. These 4 patients had a repeat positive urine culture of the same ESBL-producing organism within 90 days of the index UTI, along with recurrent UTI symptoms requiring additional intervention. Conversely, 14 patients (77.8%) had no evidence of recurrence within 90 days, meeting our criteria for clinical success.

Notably, of the 4 failures, 3 were originally ESBL-EC infections and 1 was ESBL-KP. The difference in failure rates between *E. coli* (21% failure) and *K. Pneumoniae* (25% failure) infections was not substantial in this small sample. Of note, 3 of the 4 treatment failures occurred in patients with diabetes.

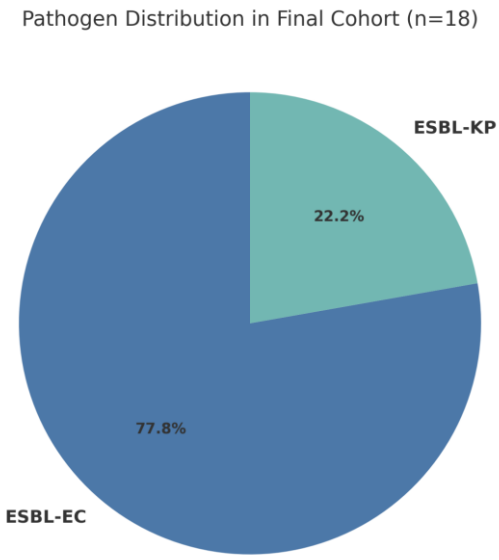

Figure 2. Pathogen distribution in final cohort

Beyond 90 days, we observed additional recurrences in a small number of cases. By 180 days after the initial treatment, 3 patients (16.7%) who had not failed within the first 90 days had developed another ESBL-UTI (i.e., between 3 and 6 months post-treatment). These were considered late recurrences rather than primary failures. All three late recurrences were *E. coli* infections in female patients. If we extend the definition of "failure" to include recurrences up to 180 days, the overall failure rate would be 38.9% (7 of 18 patients). However, for the primary endpoint of 90-day outcomes, those late cases are counted as initial successes. Detailed outcomes including both early and late failures are illustrated in Figure 3.

Secondary Outcomes – Hospital Admission and Clinical Course:

Our secondary outcomes examined the broader cohort of patients who received nitrofurantoin (including those later excluded due to combination therapy). The goal was to assess hospital admission rates and severity of illness.

Of a total of 32 patients with active ESBL-, 16 (50%) ultimately required hospital admission related to the UTI or its complications. Hospital admission rates are stratified by treatment group in Figure 4.

Notably, in the monotherapy group of 18, 4 patients (the same 22% who failed) required hospitalization. In the combination-therapy subgroup (those who had initially received IV antibiotics such as meropenem), a number of patients had already

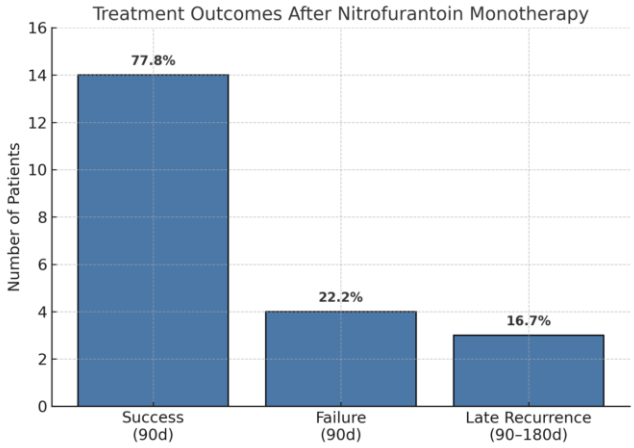

Figure 3. Treatment outcomes after Nitrofurantoin therapy

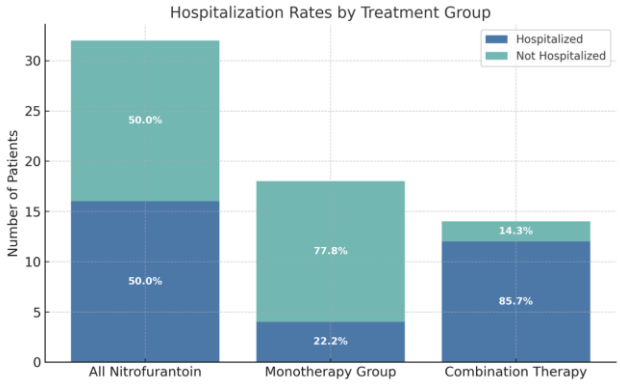

Figure 4. Hospitalization rate by treatment group

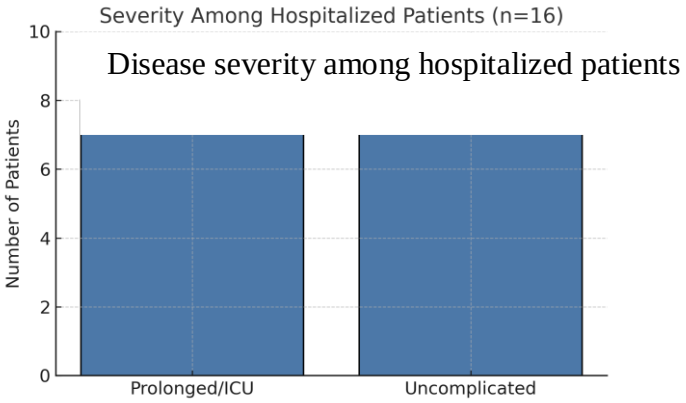

Figure 5. Disease severity among hospitalized patients

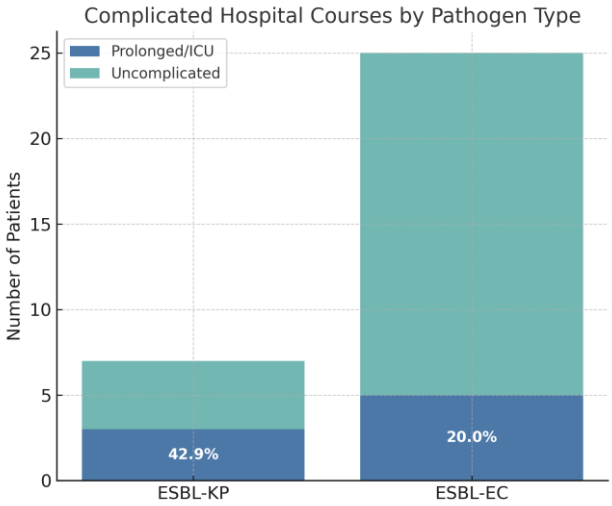

Figure 6. Pathogen types in hospitalized patients.

been admitted or had prolonged initial stays; among those, 3 patients experienced treatment failure, developing a recurrent infection despite the aggressive initial treatment. Overall, of the 16 admitted patients in the entire nitrofurantoin-treated cohort, 8 (50%) had prolonged hospital stays beyond 7 days or needed ICU-level care due to severe UTI manifestations (e.g., urosepsis). The proportion of admitted patients requiring prolonged or ICU-level care is summarized in Figure 5.

Severe cases were more frequently observed in patients with ESBL-KP: 3 out of 7 patients (42%) with active ESBL-KP infection required a complicated stay, defined as ICU-level care or hospitalization exceeding 7 days. In comparison, 5 out of 25 patients (20%) with ESBL-EC infection required a complicated stay. Despite the small sample size, ESBL-KP were more frequently observed to result in a complicated clinical course. The distribution of severe outcomes by organism is depicted in Figure 6.

None of the patients who remained infection-free on nitrofurantoin required any subsequent admission for ESBL-UTIs. The difference in admission rate, between those with treatment failure and those with successful treatment, was obvious, underlining the clinical significance of treatment failure.

Microbiological Findings:

In the four cases of treatment failure, repeat cultures showed that the organism remained the same ESBL producer. Furthermore, there was no evidence of developing nitrofurantoin resistance; the follow-up cultures of all four patients tested nitrofurantoin susceptible, suggesting that the failures were not due to acquired resistance but perhaps due to inadequate source control or suboptimal medication effect. Likewise, in the patients with late recurrences, all cultures tested positive for the initial causative organism (suggesting relapse).

These results indicate that while oral nitrofurantoin monotherapy can successfully treat a majority of ESBL-UTIs, there remains a noteworthy failure rate of 1 in 5 patients who will experience failure within the first 90 days, and 2 in 5 within 180 days. Clinical vigilance is essential, therefore, to identify early signs of recurrence. Patients who fail nitrofurantoin often require further intervention, whereas those who respond can avoid hospitalization.

IV. DISCUSSION

This was a retrospective study of ESBL-producing UTI cases at a large tertiary hospital in Riyadh, which found that oral nitrofurantoin monotherapy had a clinical failure rate of approximately 22% within 90 days, with late recurrences adding a further 16% failure within a 180-day period. Conversely, about 78% of patients achieved successful treatment at 3 months, and 62% at 6 months, suggesting that nitrofurantoin can be an effective oral treatment option in a substantial proportion of cases. Nonetheless, 1 in 5 failures within 90 days is still a marked number. These findings provide valuable evidence from Saudi Arabia, where data on oral treatment outcomes for ESBL-UTIs have been insufficient, with no such previous studies conducted in the region. The observed failure rate aligns with some prior international studies: for example, Tasbakan et al. [13] reported a 31% failure rate for nitrofurantoin in ESBL *E. coli* UTIs, similar to our result of 22% by 90 days and 38% by 180 days. It is encouraging that over 75% of our patients did not experience early recurrence; this suggests that nitrofurantoin remains a useful oral agent against ESBL-producers in the context of uncomplicated lower UTIs, and particularly for *E. coli*, which comprised the majority of our cases. In line with these results, a multicenter ESBL-*Enterobacterales* UTI cohort reported a 77.3% clinical cure rate with nitrofurantoin—nearly identical to our rate of 78% [18].

Our findings showed no major difference in failure rate between ESBL-KP and ESBL-EC cases, (25% and 21%, respectively). On the other hand, 42% of patients with ESBL-KP had a complicated hospital course (defined as an admission exceeding 7 days or ICU-level care), as opposed to only 20% of those with ESBL-EC. This is in line with the findings of a multicenter surveillance, which confirmed >90% susceptibility to nitrofurantoin in ESBL *E. coli* versus <57% in ESBL *Klebsiella pneumoniae* [12].

These findings have significant clinical implications with regard to patient selection for outpatient management versus inpatient therapy, as well as highlighting the need for close follow-up and monitoring.

A failure rate of 22% at 90 days and 38% at 180 days represents a significant number of patients requiring an escalation of care. Our sample size is too small for definitive risk factor analysis; however, some observations can be made. All four early failures in our study had significant comorbidities, particularly DM and HTN—both of which conditions are known to predispose to complicated UTIs and treatment failure—as well as advanced age, with a mean age of 65.5 years. The severity of illness among admitted patients is also important to note, with half requiring a prolonged stay and/or ICU care. Notably, every patient who failed initial outpatient management eventually required admission. These finding highlights that when oral therapy fails, infections can progress significantly in severity.

Preventive strategies may be necessary for long-term management, especially in those with relapsing infections. Our findings emphasize the need for ongoing follow-up in ESBL-UTI patients treated with oral agents, as late recurrences may indicate unresolved infection or reinfection requiring adjusted management. Repeat urine culture and susceptibility testing helps guide the management of these patients. Moreover, a urology referral may be required to optimize management and address risk factors. Treatment options include different oral agents, longer treatment durations, and escalation to intravenous therapy [4].

Despite our small sample size, we demonstrated some evidence that treating selected ESBL-UTI patients with oral nitrofurantoin and close follow-up can avert the need for hospitalization in many cases. Avoiding unnecessary admission reduces resource consumption, hospital-acquired infections, and invasive interventions, as well as preserving the efficacy of IV antibiotic options. With a growing prevalence of ESBL-UTIs, an outpatient oral treatment pathway could be invaluable. Cost-effectiveness models indicate that nitrofurantoin reduces hospitalization rates while preserving broader-spectrum agents [19]. While we did not directly study fosfomycin, references indicate that it maintains good activity against both ESBL-EC and ESBL-KP [9,13]. Thus, further studies are needed

regarding the efficacy of both nitrofurantoin and fosfomycin.

This study has several limitations that must be acknowledged. First, the sample size is small, with only 18 patients in the final analysis. This limits our data analysis to a purely descriptive one, as well as limiting our ability to assess demographics and differences between organisms. We also relied on documentation from a single center, meaning that if a patient experienced a recurrence but presented to a different hospital, that outcome would have been missed (potentially underestimating failures); however, documentation was reviewed for evidence of visits to other hospitals, including alternative medication regimens or repeat cultures. Additionally, adherence to nitrofurantoin was not directly observed; three patients who did not collect their medication were excluded, but drug compliance was assumed in those who were included. Nonetheless, it is possible that some failures were partly due to non-adherence. Finally, since this was a single-center study in a tertiary hospital ED, the patient population and resistance patterns may differ from those in other settings.

The potential for confounding variables must also be noted: We did not account for all variables that could have influenced treatment outcomes. Patient-specific factors may include adherence, severity of infection, and prior antibiotic exposure. While we applied exclusion criteria to isolate monotherapy cases and reviewed for documented complications, we could not fully account for underlying differences between patients who succeeded versus those who failed therapy. In addition, treatment selection bias might exist, with providers potentially selecting patients deemed lower risk for nitrofurantoin therapy. These unmeasured or uncontrolled variables may confound the observed associations between nitrofurantoin use and clinical outcomes.

Clinical significance:

Oral nitrofurantoin monotherapy can successfully treat a majority of UTIs caused by ESBL-producing *E. coli* and *K. pneumoniae* in the outpatient setting, with a 22% failure rate observed in our study. This suggests that, in carefully selected patients (those with uncomplicated lower UTIs, susceptible isolates, and no contraindications), nitrofurantoin is a valid choice that can avert the use of carbapenems and potentially prevent hospitalization. However, a considerable minority of patients will fail this therapy, highlighting the need for close follow-up. Multisite data confirm that nitrofurantoin remains highly effective against ESBL-producing uropathogens and is a sound oral option [20].

V. CONCLUSION

In this single-center retrospective study, oral nitrofurantoin demonstrated a failure rate of 22% in treating ESBL-producing *E. coli* and *K. pneumoniae* UTIs. Approximately 1 in 5 patients experienced a recurrent infection within 90 days, while a further 16% saw recurrence within 180 days. The majority (78%) had no early recurrence, suggesting that nitrofurantoin can be an effective oral treatment option for many ESBL-UTIs, especially those caused by *E.coli*. Nonetheless, clinical vigilance is warranted, as a subset required hospitalization and some experienced late recurrences. These findings support the use of nitrofurantoin as a cost-effective, accessible oral therapy in select ESBL-UTIs, while highlighting the need for close follow-up and antibiotic stewardship to ensure timely escalation of care if treatment fails. Larger studies are needed to confirm these outcomes and to guide the development of local guidelines regarding oral therapy for ESBL-UTIs.

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