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Are We Effectively Treating Urinary Tract Infections or Contributing to Increased Antibiotic Resistance? A Review of 3 Case Vignettes from Rural Kenya

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Abstract

Urinary tract infections (UTIs) are common, with up to 150 million global cases annually. UTIs manifest as pyelonephritis, cystitis, urethritis, and asymptomatic bacteriuria. The most common causative organisms in Kenya are E. coli, Klebsiella spp., and S. aureus. Distinguishing UTIs from urinary tract contaminations and colonizations, which do not require drug treatment, is crucial. Inappropriate empirical use of antibiotics to treat UTIs, including penicillins, cephalosporins, quinolones, and sulfamethoxazole-trimethoprim, has led to increasing cases of documented antimicrobial resistance (AMR) to these drugs in Kenya, especially the emergence of extended-spectrum β-lactamase (ESBL)-producing isolates, which also develop cross-resistance to other antibiotic classes. This creates serious multidrug-resistant (MDR) bacterial phenotypes that are very difficult to treat, may require last-resort antibiotics, and are associated with severe morbidity and mortality, with far-reaching socio-economic costs. In this study, we share the stories of 3 patients with MDR E. coli and Klebsiella spp. who were treated at a rural hospital in Kenya and look at how they were given antibiotics for UTIs in the year before they were diagnosed with MDR bacteria. We propose that such indiscriminate use of antibiotics possibly contributed to the isolation of the MDR organisms, which unfortunately could have led to the death of 2 of the patients. We underscore the need for institutional Antimicrobial Stewardship Programs (ASPs) as the answer to AMR.

Keywords: *Antimicrobial resistance, urinary tract infections, ESBL, antimicrobial stewardship program, Kenya*

1. INTRODUCTION

Antimicrobial resistance (AMR) occurs when bacteria, fungi, viruses, protozoa, and parasites no longer respond to antimicrobial medications. This leads to infections that are difficult or even impossible to treat being spread in the communities with increasing morbidity and mortality (1). AMR is a major global public health threat that is estimated to have directly caused 1.27 million global deaths in 2019 and contributed to 4.5 million deaths (2) and could result in US$ 1 trillion in additional healthcare costs by 2050 and US$ 1 to 3.4 trillion in gross domestic product (GDP) losses per year by 2030 (3). Any bacteria can develop AMR but still remain susceptible to many other antimicrobials, thus allowing for successful treatment. The most important group of bacteria associated with the majority of AMR is identified by the acronym "ESKAPE," which refers to *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species.*

This acronym has been modified to "ESCAPE," where the "C" refers to *Clostridium difficile* and the "E" refers to *Enterobacteriaceae,* that covers all gram-negative enteric bacteria, including *Escherichia coli, Klebsiella pneumoniae, Proteus spp.*, and *Enterobacter spp.* (4). *E. coli*

and *K. pneumoniae* are some of the most frequent pathogens causing both community-acquired and nosocomial urinary tract infections (UTIs). Other bacterial causes of UTIs include *Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus, Streptococcus,* and *Enterococcus* species (5).

UTIs occur when bacteria infect any part of the urinary system and include pyelonephritis, cystitis, urethritis, and asymptomatic bacteriuria (6). A diagnosis of UTI is made on the basis of compatible clinical symptomatology (e.g., frequency, urgency, dysuria, frank pyuria, or suprapubic pain) and bacteriuria detected on urine microscopy, culture, and sensitivity studies. Several clinical guidelines on definitions of uncomplicated versus complicated UTIs and diagnosis and management exist among various infectious disease societies. The South African Antibiotic Stewardship Program (SAASP) guidelines define an uncomplicated UTI as "either a lower urinary tract infection or upper urinary tract infection (pyelonephritis) in non-pregnant women with structurally and neurologically normal genitourinary tracts." (7). Any UTI outside this definition is regarded as "complicated." UTIs are some of the most common infections, with up to 150 million annual cases globally (8), especially among the aged, the pregnant, those with indwelling catheters, women, hospitalized patients, and those with immunosuppression from any cause, especially diabetes (9). In a Kenyan study, the overall prevalence of UTIs was 27.6% with *Escherichia coli, Staphylococcus aureus,* and *Klebsiella pneumoniae* being the most prevalent bacterial pathogens at 38.5%, 21%, and 19.3%, respectively (10). In Kenya, UTIs have usually been treated in clinics and hospitals with common antibiotics like β-lactam antibiotics (penicillins and cephalosporins), fluoroquinolones (especially ciprofloxacin and levofloxacin), sulfamethoxazole-trimethoprim (known as 'Septrin' and 'Bactrim'), aminoglycosides, and nitrofurantoin.

These drugs are readily available in rural and urban chemists and pharmacies in Kenya and are obtainable with and without prescriptions (11). AMR to several of these drugs has been reported in Kenya. In a cross-sectional study done in 8 different healthcare centers in Kenya, the percentages of AMR to commonly used antibiotics for UTI treatment were trimethoprim (64%), sulfamethoxazole (57%), nalidixic acid (57%), ciprofloxacin (27%), amoxicillin-clavulanic acid (5%), nitrofurantoin (9%), and cefixime (9%) (12).

The main AMR mechanism for *E. coli* and *K. pneumoniae* is the production of extended-spectrum β-lactamases (ESBLs) (13) that hydrolyze the β-lactam ring of the given antibiotics and make them resistant to broad-spectrum penicillins and cephalosporins (14). The ESBL producers can also develop co-resistance to other classes of antibiotics, such as fluoroquinolones, cotrimoxazole, or aminoglycosides, due to the coexistence of genes that encode ESBL with similar genes for resistance to other antimicrobial agents, thereby creating a multidrug-resistant (MDR) phenotype that is very difficult to treat and may require last-resort antibiotics to be deployed (15, 16, 17).

Some factors linked to ESBL-producing *E. coli* and *K. pneumoniae* include prior hospitalizations, previous use of penicillins and cephalosporins, longer hospital stays, having diabetes, repeated UTIs, being female, and using urinary catheters. Some of the factors associated with ESBL-producing *E. coli* and *K. pneumoniae* include prior hospitalizations, prior exposures to penicillins and cephalosporins, longer hospital stays, diabetes mellitus (DM), recurrent UTIs, the female sex, and urinary catheterization (18). A study at the largest referral hospital in Kenya on antibiotic susceptibility to common organisms causing UTIs found *E. coli* (30%), *K. pneumoniae* (18%), *Enterococcus* (18%), and *Enterobacter* (9%) to be most prevalent, with ESBL isolates found to be resistant to the antibiotics used, i.e., Co-amoxiclav (37%), Levofloxacin (37%), Cefoperazone (37%), Ampicillin (39%), Doxycycline (41%), Gentamicin (30%), and Nalidixic Acid (38%) (19). In another 18-year survey of resistant genotypes from isolates (including urine samples) among *E. coli* strains in Kenya, the ESBL phenotype was detected in 27% of the isolates (20). We present 3 case vignettes from a rural Kenyan hospital and demonstrate how a possible indiscriminate empirical use of antibiotics to treat UTIs could have driven the emergence of AMR in the form of MDR *E. coli* and *K. pneumoniae* in each of them, with subsequent deaths in two of them. We therefore underscore the need for institutional Antimicrobial Stewardship Programs (ASPs) to combat the progress of AMR. ASPs consist of systematic and coordinated interventions that promote the optimal use of antimicrobial agents (including their choice, route of administration,

dosing, and duration of treatment) for all patients to optimize clinical outcomes, minimize complications of antimicrobial use, improve susceptibility rates to targeted antimicrobials, reduce the risk of developing AMR and health care-associated infections (HAIs), and optimize resource utilization (21, 22). Table 1 below shows the principles of rational antibiotic prescribing according to the South African Antibiotic Stewardship Program (SAASP) (7).

Table 1. *The principles of rational antibiotic prescription (7).*

1.	Is there an infection for which an antibiotic is indicated in the first place?
2.	Perform cultures before administering antibiotics in hospitalized patients or outpatients with recurrent infections.
3.	Choose an appropriate empiric antibiotic based on the most likely pathogen and the likelihood of antibiotic resistance, rule out any potential contraindication of the drug chosen (e.g., due to allergy or toxicity), consider adequate tissue penetration to the target site, and aim for a single drug with the desired spectrum of activity.
4.	Ensure the correct dose and route of administration (the oral/enteral route is preferred for mild to moderate infections, while the intravenous route is preserved for severe infections of CSF, endocarditis, etc.).
5.	Start the appropriate antibiotic rapidly in severe infections, with the first dose given within one hour of the diagnosis.
6.	Practice early and effective source control, e.g., debridement of devitalized tissues, incision and drainage of abscess, chest tube for empyema thoracis, etc.
7.	Evaluate the appropriateness of antibiotics every day and know when to de-escalate to oral forms, oral routes, or when to stop altogether.

2. CASE 1

A 67-year-old nun from Nakuru Town, Nakuru County, Kenya, with poorly controlled metabolic syndrome complicated by stage 2 chronic kidney disease and peripheral neuropathy. Her most current medications are metformin, glimepiride, dapagliflozin, atorvastatin, telmisartan, hydrochlorothiazide, and atenolol. Treated several times for UTIs with ciprofloxacin, levofloxacin, nitrofurantoin, co-amoxiclav, sulfamethoxazole-trimethoprim (Bactrim), clindamycin, and cefuroxime on the basis of urinalysis reports showing "white blood cells" since June 2019.

In the year preceding her MDR *E. coli* diagnosis, she was treated with antibiotics, as shown in Table 2 below, derived from her clinic records.

Table 2. *A record of antibiotic treatment for Case 1 prior to her MDR E. coli diagnosis.*

Date	Urinalysis			Symptomatology (Genito-urinary)	Antibiotic and duration
	Leucocytes (n/hpf)	Nitrites	Urine culture & sensitivity		
05/03/2024	5-10	Nil	No	Nil	Levofloxacin x5/7
09/01/2024	5-10	Nil	No	Dysuria	Nitrofurantoin x5/7
14/11/2023	5-10	Nil	No	Nil	Ciprofloxacin x5/7
06/10/2023	Many	Nil	No	Nil	Co-amoxiclav x5/7
08/09/2023	10-15	+1	No	Dysuria	Ciprofloxacin x5/7
08/07/2023	Many	Nil	No	Nil	Ciprofloxacin x5/7
14/06/2023	Many	+3	No	Right flank pains	IV Ceftriaxone x2/7 then Ciprofloxacin x5/7
11/05/2023	5-10	Nil	No	Nil	Ciprofloxacin x5/7
06/04/2023	Many	Nil	No	Nil	Bactrim x5/7
09/03/2023	15-20	Nil	No	Nil	Clindamycin x5/7

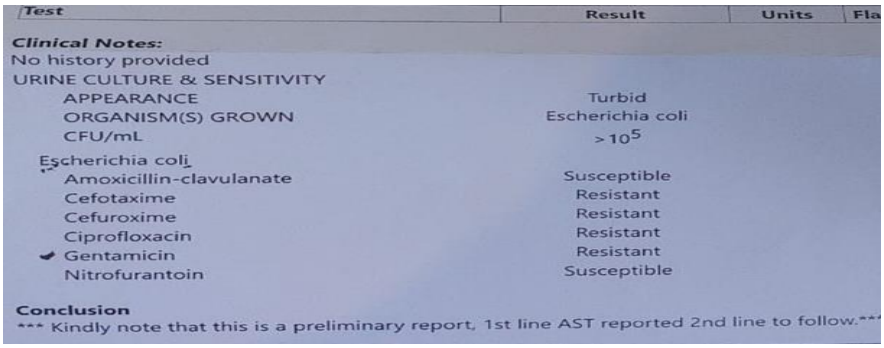


Figure 1. *Urine culture showing MDR E. coli diagnosis.*

3. CASE 2

An 81-year-old man, a widower and father of 8, a farmer from Ol-Rongai, Nakuru County, Kenya, with poorly controlled metabolic syndrome complicated by chronic kidney disease stage 3B baseline, peripheral neuropathy, and left ventricular hypertrophy.

He also had a history of prostate adenocarcinoma, status post prostatectomy, and chemo-radiotherapy. He had an indwelling catheter for 6 months preoperatively. His most recent medications were furosemide, losartan, nifedipine, hydralazine, atenolol, atorvastatin, and insulin. Since March 2023, he received several treatments for "recurrent UTI" and "recurrent orchitis with hydrocele," including ciprofloxacin, levofloxacin, sulfamethoxazole-trimethoprim (Bactrim), ceftriaxone, clindamycin, and co-amoxiclav. In the year preceding his MDR *Klebsiella spp.* diagnosis, he was treated with antibiotics as shown in Table 3 below, derived from his clinic records. He died of septic shock and multiple organ failure.

Table 3. *A record of antibiotic treatment for Case 2 prior to his MDR Klebsiella spp. diagnosis.*

Date	Urinalysis			Symptomatology (Genito-urinary)	Antibiotic and duration
	Leucocytes (n/hpf)	Nitrites	Urine culture & sensitivity		
05/08/2024	Many	Nil	No	Dysuria, Right orchitis	Ciprofloxacin x1/52
December 2023 to July 2024 (Records from other facilities)	Pyelonephritis, Urosepsis, Severe cystitis		No x3	Admitted x3	IV Ceftriaxone then oral Ciprofloxacin x5/7, IV Cefuroxime then Ciprofloxacin x5/7, IV Meropenem then oral Nitrofurantoin x5/7
	Bilateral orchitis		No	Admitted x2	IV Levofloxacin x1/52, IV Meropenem then oral Levofloxacin x5/7
	Suppurative orchitis (right)		Yes	Admitted, Incision and drainage done	IV Meropenem then oral co-amoxiclav x5/7
01/11/2023	5-10	Nil	No	Foley catheter in situ	Ciprofloxacin x1/52
18/10/2023	Many	Nil	No	Foley catheter in situ	Ciprofloxacin x1/52
26/06/2023	Many	+1	No	Foley catheter in situ	Nitrofurantoin x5/7
20/06/2023	Many	Nil	No	Foley catheter in situ	Levofloxacin x1/52

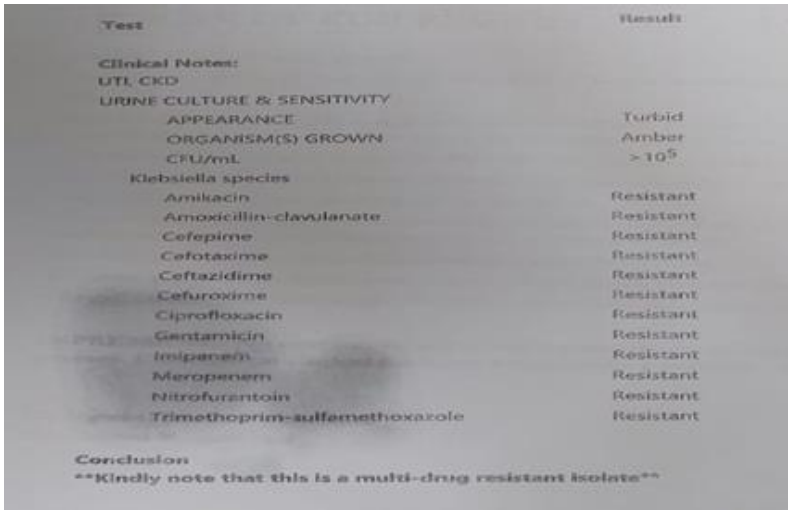


Figure 2. *Urine culture showing MDR Klebsiella spp. diagnosis.*

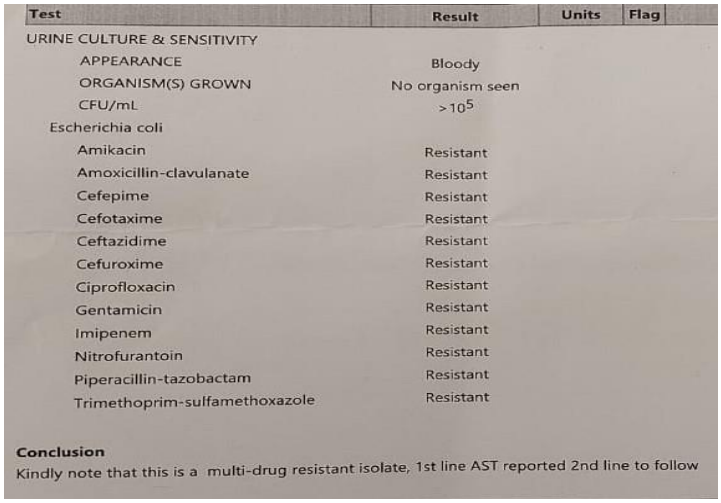
4. CASE 3

A 48-year-old woman, a married mother of 6 from Eldama Ravine, Baringo County, Kenya, with no underlying cardiovascular risk factors, was on follow-up at the local health center, being treated several times for “recurrent persistent UTI” over a 13-month period. Old records from the local clinics showed that she had been treated with amoxicillin, co-amoxiclav, ciprofloxacin, nitrofurantoin, and sulfamethoxazole-trimethoprim (Bactrim) between 2022 and 2023, prior to her diagnosis with MDR *E. coli*. Her main symptom was right flank pain and hematuria during all the hospital visits. In July 2023, an abdominal ultrasound done showed a tumor on the left kidney, and a subsequent CT

scan confirmed a right renal mass with metastases to the lungs, lumbosacral vertebrae, and liver. Histology confirmed renal cell carcinoma. She came to us in August 2024 with severe urosepsis and gross hematuria with multiple organ failure, from which she died. In the year preceding her MDR *E. coli* diagnosis, she was treated with antibiotics, as shown in Table 4 below, derived from her clinic records.

Table 4. *A record of antibiotic treatment for Case 3 prior to her MDR E. coli diagnosis.*

Date	Urinalysis			Symptomatology (Genito-urinary)	Antibiotic and duration
	Leucocytes (n/hpf)	Nitrites	Urine culture & sensitivity		
February 2022- June 2023 (old records from the local health center)	5-10 on 4 visits 10-20 on 3 visits Many on 6 visits	Nil on 12 visits +1 on 1 visit	No	Right flank pain, lower abdominal pain, gross hematuria.	Ciprofloxacin x5/7 on 6 visits Bactrim x5/7 on 2 visits Co-amoxiclav x5/7 on 1 visit Cefuroxime x5/7 on 1 visit Nitrofurantoin x1/52 on 2 visits Amoxicillin x5/7 on 1 visit
11/07/2023	Many	Nil	No	Right flank pain, lower abdominal pain, gross hematuria, progressive weight loss, anorexia CT scan showed right renal mass with metastases	IV Levofloxacin then oral Ciprofloxacin x5/7
August 2023 to July 2024				Missing records	
16/08/2024	Many	+2	No	Right flank pain, gross hematuria, progressive weight loss, anorexia	IV Levofloxacin then referred to a tertiary center



Test	Result	Units	Flag
URINE CULTURE & SENSITIVITY			
APPEARANCE	Bloody		
ORGANISM(S) GROWN	No organism seen		
CFU/mL	$>10^5$		
Escherichia coli			
Amikacin	Resistant		
Amoxicillin-clavulanate	Resistant		
Cefepime	Resistant		
Cefotaxime	Resistant		
Ceftazidime	Resistant		
Cefuroxime	Resistant		
Ciprofloxacin	Resistant		
Gentamicin	Resistant		
Imipenem	Resistant		
Nitrofurantoin	Resistant		
Piperacillin-tazobactam	Resistant		
Trimethoprim-sulfamethoxazole	Resistant		

Conclusion
Kindly note that this is a multi-drug resistant isolate, 1st line AST reported 2nd line to follow

Figure 3. *Urine culture showing MDR E. coli diagnosis.*

5. DISCUSSION

The main issue revealed in the 3 cases is the indiscriminate use of various empiric antibiotics (at various doses, routes of administration, and durations) for treating UTIs without guidance from urine cultures and drug sensitivity studies or considering published local patterns of antibiotic sensitivity and resistance (23). Besides, it is doubtful that the many episodes labeled "UTI" and treated with antibiotics on the basis of "white blood cells in the urine" were infections to begin with. It is possible that in several cases, they were either contaminations or colonization of the urinary tract rather than true infections. Colonization occurs when bacteria are present on a body surface and even become transmissible, but without causing an infection or disease (24). Contamination occurs when non-pathogenic bacteria and other microorganisms are present in the urine due to sampling errors and other external factors (25). While point-of-care urine dipstick tests and qualitative urinalysis are the

main methods used for diagnosing UTIs in most outpatient clinics in Kenya, these techniques face many problems that can impact the accuracy, quality, and usefulness of the results (26). A diagnosis of UTI requires compatible clinical symptoms plus bacteriuria or indirect evidence of infection, e.g., urine dipstick leukocyte esterase or nitrite positive, and urine microscopy showing > 1+ leukocytes (7). Urine culture with drug sensitivity testing is considered the "gold standard" for accurately diagnosing UTIs, identifying causative bacteria, and determining their drug sensitivity or resistance patterns. Urine culture is an expensive test that takes time. Therefore, we recommend it in cases such as complicated UTIs, outpatients with recurrent UTIs, and treatment failure, among others (27). Case 1 was treated multiple times for presumed asymptomatic bacteriuria (presence of leukocytes in urine without any corresponding genitourinary clinical symptoms). Most guidelines for infectious diseases do not suggest regular medication for asymptomatic bacteriuria unless there are specific situations, such as in pregnant women, before certain urological procedures, or possibly in the first few months after a kidney transplant (7, 28). In her case, she developed MDR *E. coli*, which was still sensitive to co-amoxiclav or nitrofurantoin. We decided to only treat her when she exhibited symptoms of a UTI. She has had further asymptomatic bacteriuria while on follow-up, which have not been treated with further antibiotics, and she has remained stable. Case 2 was treated repeatedly for UTI when he had an indwelling urinary catheter, raising doubts about possibilities of colonization, contamination, improper urine sampling methods, etc. Only a confirmed infection, while the indwelling catheter was in place, should have warranted antibiotic treatment (29). Case 3 was repeatedly treated for a presumed UTI although the symptomatology pointed to the eventually confirmed diagnosis of renal cell carcinoma, by which time she had developed MDR *E. coli.* She should have had a screening abdominopelvic ultrasound much earlier to reveal the renal tumor as the primary cause of her symptomatology, although this also increased her risk for a UTI, which then should have been properly diagnosed on urine culture. Unfortunately, both cases 2 and 3 succumbed to septic shock, with blood and urine cultures growing MDR *Klebsiella spp.* and *E. coli*, respectively. All these cases ultimately highlight the need for institutionalized antimicrobial stewardship programs (ASPs) to promote optimal antimicrobial use, improve patient outcomes, and reduce the risk of developing AMR and health care-associated infections (HAIs) (22). Accordingly, we have since adopted a modified version of the SAASP guidelines for our institutional ASP use.

6. Acknowledgment

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7. Ethical Consideration

Informed consent was obtained from each of the patients involved in this study.

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