Research article

Antimicrobial Resistant Trend of *E. coli* and ESKAPE Pathogens from Urine Cultures in Central Alabama

Tracy Camara[1*], Li Qian[2], Angelique Korbecki[2], Ngoc Le[2], Ann Chambers[2]

[1] Baptist Health, Montgomery, AL, USA
[2]Medical & Clinical Laboratory Sciences, Auburn University at Montgomery, AL, USA

The purpose of this research is to identify the antimicrobial resistant pattern to provide scientific evidence for improving antimicrobial therapy for *Escherichia coli* and ESKAPE organisms in urine samples recovered from Central Alabama in 2020. A total of 3498 organisms were identified by matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) and the sensitivities were performed on MicroScan WalkAway 96 by using the Clinical Laboratory Science Institute (CLSI) microdilution method. The identified organisms were from clean-catch midstream, foley catheter, and straight catheterized urine. For the 69.4% of *E. coli* isolates, ampicillin/sulbactam had the lowest sensitivity at 54%. Among the 920 ESKAPE pathogens, *Enterococcus faecium* was most resistant to ampicillin with sensitivity at 8%. *Staphylococcus aureus* was most resistant to penicillin with sensitivity at 7%; *Klebsiella pneumoniae* was most resistant to nitrofurantoin at 35%; *Acinetobacter baumannii* lacked samples for statistical analysis; *Pseudomonas aeruginosa* was most resistant to levofloxacin with sensitivity at 68%; *Enterobacter species* was most resistant to ertapenem at 83%. Overall, the resistant patterns of *E. coli* and the ESKAPE organisms isolated in the hospital system were comparable to those reported globally and nationally; however, because these organisms are becoming resistant faster than new antibiotics are being introduced to the market, diligence must take place to conserve and appropriately use current antibiotics in patient treatments.

Keywords: Antimicrobial resistance, urine cultures, E. coli, ESKAPE pathogens

---

Accepted: January 31, 2024
*Corresponding author: Tracy Camara, E-mail TLCamara@baptistfirst.org

Introduction

Urinary tract infections (UTIs) have been identified as the fifth most common type of healthcare-associated infection with an estimated 62,700 urinary infections occurring in acute care settings and an estimated 150 million UTIs occurring annually worldwide.[1,2,3] Majority of urinary infections that occur is predominantly caused by uropathogenic *Escherichia coli* (UPEC), which contributes to 80% of all UTIs, with 83.9% sensitive to extended-spectrum cephalosporins, 65.2% sensitive to fluoroquinolones, and 98.9% sensitive to carbapenems.[4,5]

Urinary tract infections are classified as either complicated or uncomplicated. Complicated UTIs occur due to urinary obstructions, urinary retention, kidney calculi, renal failure, renal transplants, pregnancy, or indwelling devices. [2,6,7] In addition, complicated UTIs have a higher risk of treatment failure and may require longer courses of antibiotic treatment.[8] Uncomplicated UTIs most frequently occur in healthy individuals as a result of cystitis, sexual activity, diabetes, and obesity.[2, 9,10] Complicated and uncomplicated UTIs are most often caused by *Candida species, Enterococcus faecalis, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus saprophyticus,* and *Streptococcus agalactiae*, also known as group B *Streptococcus* (GBS).[2,7,11-15] The most commonly isolated organism for both complicated and uncomplicated UTIs is UPEC.[2]

The treatment of complicated and uncomplicated UTIs can have undesirable effects. The use of antibiotics can alter gastrointestinal and vaginal normal flora, which can lead to drug resistant organisms.[2, 16] The replacement of normal flora with antimicrobial resistant microorganism can cause colonization resulting in treatment failures.[2] Most patients with uncomplicated UTIs, are treated with broad-spectrum antibiotics and recover without any issues. However, individuals with complicated UTIs become more difficult to treat due to increased antibiotic resistance.[8] In fact, there is a 25% risk that a bacteriuria will become a complicated UTI.[8] In the United States, it has been reported that over 626,000 hospital admissions occur annually due to complicated UTIs.[8]

Enterococcus species, Klebsiella pneumoniae, Staphylococcus aureus, and *Pseudomonas aeruginosa* are commonly found in both complicated and uncomplicated UTIs and are part of an emerging group of antimicrobial resistant organisms called the ESKAPE pathogens. The ESKAPE pathogens were defined, in 2008 by the Infectious Disease Society of America, as a group of pathogenic organisms that causes hospital infections which escapes antimicrobial therapies.[17,18,19] The ESKAPE organisms are *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*. Included in this group are the vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamase (ESBL), and carbapenem-resistant enterobacteriaceae (CRE).[19, 20]

In majority of clinical settings, patients are initially treated empirically for UTIs without knowing the identification or susceptibility of the causative organism; therefore, understanding the resistance patterns of the ESKAPE and UPEC organisms is beneficial especially in cases of complicated UTIs. Accordingly, this study was performed to determine the percent recovery and resistance patterns for the ESKAPE and UPEC organisms from three hospitals in Central Alabama. Findings from this study will provide scientific evidence to physicians and antibiotic stewardship programs to improve initial experiential treatment for uropathogens.

Materials and Methods

This study was performed by retrospective analysis of inpatient urine culture data from three teaching hospitals within a hospital system in Central Alabama between January-December 2020. This hospital system has an estimated 207 admissions per month or seven admissions per day. Urine cultures were

collected from clean-catch, midstream, foley and straight catheter, pediatric, and other sources, such as suprapubic collection. The antimicrobial susceptibility results were reported based on the CLSI minimum inhibitory concentration (MIC) breakpoints.

The twenty-three antimicrobials included in this study were from the classes' aminoglycosides (gentamicin, tobramycin), other beta-lactams (ampicillin/sulbactam, ampicillin, amoxicillin/clavulanate, oxacillin, penicillin, piperacillin/tazobactam), carbapenems (ertapenem, meropenem), cephalosporins (cefepime, ceftriaxone, ceftazidime, cefazolin, cefuroxime), fluoroquinolones (ciprofloxacin, levofloxacin), and others (trimethoprim/sulfamethoxazole, tetracycline, nitrofurantoin, linezolid, vancomycin, and daptomycin). Quality control was performed weekly using the organisms *P. aeruginosa* ATCC 27853, *E. coli* ATCC 35218 and 25922, *K. pneumoniae* ATCC 700603, *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213 and BAA-977, MRSA ATCC 43300, and VRE ATCC 51299. The CLSI (M100) performance standards for antimicrobial susceptibility testing served as interpretive criteria for each antimicrobial and organism evaluated. Chi-square test or Fisher's exact *t-test* was used to determine the significant difference in antimicrobial sensitivity on IBM SPSS for Windows (version 28 software package).[21] The level of significant difference was defined at $p \leq 0.05$.

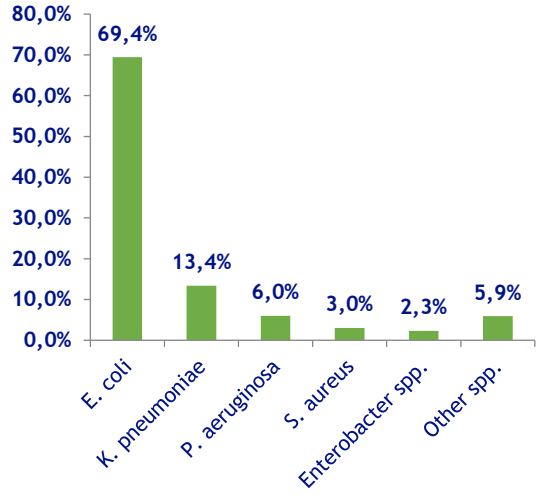

Figure 1. Frequency Distribution of Pathogens Isolated from Urine Cultures

Results

A total of 3498 organisms (Figure 1), from urine cultures performed between January and December 2020 from a Central Alabama hospital system, were identified by MALDI-TOF MS. Antimicrobial sensitivities were performed by MicroScan WalkAway 96 based on the CLSI microdilution method. Among the 3498 identified organisms (Figure 2), 83.2% were isolated from clean-catch midstream urine specimens, 10.5% from foley catheter urine, 5.5% from straight catheterized urine, and 0.8% from pediatric urine and other sources.

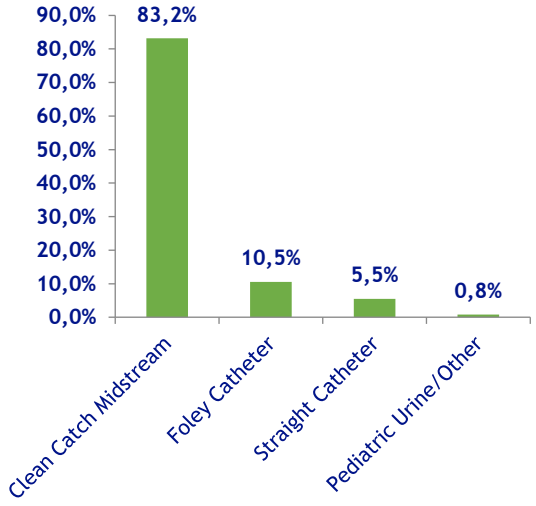

Figure 2. Frequency Distribution of Types of Urine Specimens

The results (Figure 1) demonstrated that *E. coli* contributed to 69.4% of all the infections, followed by *K. pneumoniae* (13.4%), *P. aeruginosa* (6.0%), *S. aureus* (3.0%), *Enterobacter species* (2.3%), and other species (*Acinetobacter species, Enterococcus species, Klebsiella species, and Pluralibacter gergoviae*, 5.9%). Among the 920 ESKAPE organisms identified (Figure 3), *K. pneumoniae* was the most common organism isolated at 50.9%, followed by *P. aeruginosa* (22.7%), *S. aureus* (11.3%), *Enterobacter species* (8.6%), *E. faecium* (5.7%), and *A. baumannii* (0.8%). For the 2428 *E. coli* isolates, cefepime, ertapenem, meropenem, ceftazidime, ceftriaxone, and piperacillin/tazobactam had the highest sensitivities at 99-100%, followed by nitrofurantoin (98.0%) and were most resistant to

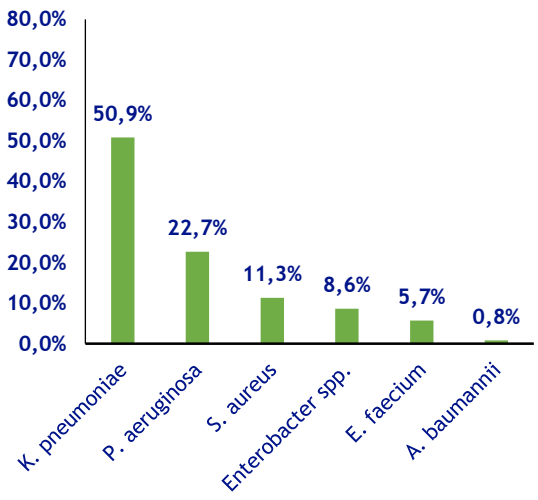

Figure 3. Frequency Distribution of the ESKAPE Organisms Isolated from Urine Cultures

ampicillin/sulbactam (54.0%). For the ESKAPE pathogens, *E. faecium* was most sensitive to daptomycin (100%) and most resistant to ampicillin (8.0%). *S. aureus* was most sensitive to vancomycin, ceftriaxone, and cefazolin (100%) and most resistant to penicillin (7.0%); *K. pneumoniae* was most sensitive to cephalosporins, aminoglycosides, and quinolones (97-100%) and most resistant to nitrofurantoin (35.0%); *A. baumannii* was sensitive to the antibiotics tested, but there were not enough samples for statistical analysis with sensitivities ranging from 86% to100%; *P. aeruginosa*

Table 1. Antibiotic Spectrum (%) of *E. coli* and ESKAPE Pathogens from Urine Cultures in Central Alabama.

Antibiotic agent	E. coli		K. pneumoniae		P. aeruginosa		S. aureus		E. faecium		Enterobacter spp.		A. baumannii	
	S	R	S	R	S	R	S	R	S	R	S	R	S	R
Aminoglycosides														
Gentamicin	92	8	99	1	72	28	--	--	--	--	97	3	100	0
Tobramycin	95	5	99	1	96	4	--	--	--	--	--	--	100	0
Other ß-lactams														
Ampicillin/Sulbactam	54	46	86	14	--	--	--	--	--	--	--	--	100	0
Ampicillin	--	--	--	--	--	--	--	--	8	92	--	--	--	--
Amoxicillin/Clavulanate	87	13	96	4	--	--	--	--	--	--	--	--	--	--
Oxacillin	--	--	--	--	--	--	53	47	--	--	--	--	--	--
Penicillin	--	--	--	--	--	--	7	93	--	--	--	--	--	--
Piperacillin/Tazobactam	99	1	97	3	93	7	--	--	--	--	--	--	--	--
Carbapenems														
Ertapenem	100	0	97	3	--	--	--	--	--	--	83	17	--	--
Meropenem	100	0	98	2	90	10	--	--	--	--	100	0	100	0
Cephalosporins														
Cefepime	100	0	100	0	90	10	--	--	--	--	92	8	86	14
Ceftriaxone	99	1	100	0	--	--	100	0	--	--	--	--	--	--
Ceftazidime	99	1	100	0	82	18	--	--	--	--	--	--	100	0
Cefazolin	92	8	97	3	--	--	100	0	--	--	--	--	--	--
Cefuroxime	97	3	97	3	--	--	--	--	--	--	--	--	--	--
Fluoroquinolones														
Ciprofloxacin	82	18	98	2	70	30	--	--	--	--	92	8	100	0
Levofloxacin	83	17	98	2	68	32	--	--	--	--	92	8	100	0
Others														
Trimethoprim/ Sulfamethoxazole	73	27	92	8	--	--	98	2	--	--	--	--	--	--
Tetracycline	80	20	85	15	--	--	--	--	--	--	--	--	--	--
Nitrofurantoin	98	2	35	65	--	--	--	--	30	70	--	--	--	--
Linezolid	--	--	--	--	--	--	--	--	97	3	--	--	--	--
Vancomycin	--	--	--	--	--	--	100	0	30	70	--	--	--	--
Daptomycin	--	--	--	--	--	--	--	--	100	0	--	--	--	--

S= sensitive; R=resistant

Table 2. Percent Sensitivity Comparison for ESKAPE Organisms Isolated from Urine Cultures

	Central Alabama	NHSH*	Karlowsky, Hoban, et. al.
Enterococcus faecium			
Vancomycin	30.0%	14.9%	---
Staphylococcus aureus			
Oxacillin	53.0%	---	---
Oxacillin/Methicillin/Cefoxitin	---	48.0%	---
Klebsiella pneumoniae			
Cefepime, Ceftriaxone, Ceftazidime	100%	---	48.9%
Cefepime, Cefotaxime, Ceftriaxone, Ceftazidime	---	77.5%	---
Levofloxacin	98.0%	---	57.3%
Ertapenem	97.0%	---	---
Meropenem	98.0%		
Imipenem, Meropenem, Doripenem	---	90.5%	---
Ertapenem, Imipenem	---	---	78.5%
Acinetobacter baumannii			
Cefepime, Ceftriaxone, Ceftazidime	99.3%	---	13.9%
Levofloxacin	100%	---	11.6%
Meropenem	100%	---	---
Imipenem, Meropenem, Doripenem	--	36.0%	---
Imipenem	---	---	18.6%
Pseudomonas aeruginosa			
Gentamicin	72.0%	---	---
Tobramycin	96.0%	---	---
Amikacin, Gentamicin, Tobramycin	---	78.9%	
Amikacin	---	---	75.2%
Levofloxacin	68.0%	---	55.2%
Ciprofloxacin, Levofloxacin	--	67.4%	---
Meropenem	90.0%	---	---
Imipenem	---	---	60.0%
Imipenem, Meropenem, Doripenem	---	76.1%	---
Enterobacter species			
Cefepime	92.0%	---	---
Cefepime, Cefotaxime, Ceftriaxone, Ceftazidime	---	59.5%	---
Cefepime, Ceftriaxone, Ceftazidime	---	---	61.0%
Ertapenem	83.0%	---	79.4%
Meropenem	100%	---	---
Imipenem, Meropenem, Doripenem	---	93.5%	---
Imipenem	---	---	86.1%
Levofloxacin	92.0%	---	76.4%
Escherichia coli			
Cefepime, Ceftriaxone, Ceftazidime	99.0%	---	---
Cefepime, Cefotaxime, Ceftriaxone, Ceftazidime	---	83.9%	---
Ciprofloxacin	82.0%	---	---
Levofloxacin	83.0%	---	---
Ciprofloxacin, Levofloxacin, Moxifloxacin	---	65.2%	---
Ertapenem, Meropenem	100%	---	---
Imipenem, Meropenem, Doripenem	---	98.9%	---

**NHSN comparison susceptibility data from year 2014.*

was most sensitive to tobramycin (96.0%) and most resistant to levofloxacin (68.0%); *Enterobacter species* had the highest sensitivity to meropenem (100%), and the lowest sensitivity to ertapenem (83.0%). The antibiotic spectrum for *E. coli* and the ESKAPE organisms is summarized in Table 1.

Discussion

Findings of this study were compared with published literature from the National Healthcare Safety Network (NHSN) at the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and others; and no previous studies were found on antimicrobial resistance of *E. coli* or ESKAPE pathogens in Central Alabama. There may be limitations in this study as the NHSN reported pathogens from catheter associated urinary tract infections (CAUTI) whereas this study evaluated *E. coli* and ESKAPE organisms from all urine culture isolates. However, a comparison can be made between isolates recovered in Central Alabama and those on a national and global level as shown in Table 2.

During 2011-2014, *Enterococcus faecium* accounted for 3.7% of all pathogens reported to the NHSN, with 2.7% occurring in CAUTIs.[5] In addition, 14.9% were reported as sensitive to

vancomycin.[5] In comparison, this study demonstrated that *E. faecium* was isolated 1.5% from all urine specimens with 30.0% of them sensitive to vancomycin demonstrating a lower isolation and resistance rate.

Enterococci can have a high-level of acquired vancomycin resistance due to the alteration of the peptidoglycan cell wall precursors by amino acid substitution that causes D-alanyl-D-alanine dipeptide to become D-alanyl-D-lactate depsipeptide.[22] The *vanA* gene encodes for this amino acid substitution which causes reduced ability of vancomycin to bind to the bacterial cell wall.[22] *E. faecium* strains with this type of vancomycin high level resistance are classified as class A resistance. This type of resistance can be shared with other gram positive organisms through conjugation.[22] On the other hand, strains of *E. faecium* that have high to low levels of vancomycin resistance are classified as class B resistance. This level of resistance is caused by the *van*B gene and can be shared through conjugation with other *Enterococcus* strains.[22] Other non-faecium enterococci strains, such as *Enterococcus gallinarium, Enterococcus casseliflavus*, and *Enterococcus flavescens* have low levels of vancomycin resistance and are designated as class C resistance.[22] This type of resistance is caused by the genes *van*C_1, *van*C_2, and *van*C_3. *E. faecium* also has resistance to beta-lactam drugs, such as ampicillin, due to the alteration of the target enzyme penicillin-binding protein 5 (PBP5), which is the main resistance determinant for this organism.[23] In addition, resistance to quinupristin-dalfopristin occurs in *E. faecium* by enzymatic inhibition, efflux, and target modification.[22]

NHSN reported *Staphylococcus aureus* accounted for 11.8% of all urine cultures reported with 1.6% occurring in CAUTIs.[5] Of the *S. aureus* isolated from CAUTIs, 48.0% were sensitive to oxacillin, methicillin, and cefoxitin.[5] In this study, 3.0% of the *S. aureus* was isolated from all urine cultures with 7.0% sensitive to penicillin and 53.0% sensitive to oxacillin, which is lower than the total number of isolates reported to the NHSN, but comparable to the susceptibility rate for beta-lactams. There were no vancomycin intermediate *Staphylococcus aureus* (VISA), or vancomycin resistant *Staphylococcus aureus* (VRSA) isolates identified in this study or in the NHSN study.

It has been documented that urinary catheterization is the most important risk factor for MRSA in complicated UTIs.[4,24,25] The cause of MRSA is due to the *mec*A gene, which encodes for penicillin binding protein 2A (PBP2A).[22] The PBP2A protein has a low affinity for beta-lactam antibiotics, which causes resistance to methicillin, nafcillin, oxacillin, and cephalosporins.[22] *S. aureus* not only has resistance due to the alteration of the target enzyme PBP2A protein, but also due to penicillinase production otherwise known as beta-lactamase. Since vancomycin is the drug of choice in the treatment of MRSA, vancomycin intermediate and vancomycin resistant strains have been observed. The first VRSA was isolated in 2002.[22] VRSA occurs due to the sharing of *van*A genes from VRE through a plasmid-mediated transfer.[22] VISA occurs as a result of bacterial cell wall thickening, which binds the drug and prevents it from reaching its designated target.[22]

Klebsiella pneumoniae has been isolated an average of 7.0% from both complicated and uncomplicated UTIs.[2] *K. pneumoniae* has demonstrated antibiotic resistance to the extended spectrum cephalosporins, fluoroquinolones, and aminoglycosides.[5, 26] In this study, *K. pneumoniae* was isolated 13.4% from all urines with 100% sensitive to the extended spectrum cephalosporins, 98.0% sensitive to levofloxacin, and 97.5% sensitive to carbapenems. In comparison, the NHSN's study grouped *K. pneumoniae* and *Klebsiella oxytoca* together with 10.1% isolated and 77.5% sensitive to the extended spectrum cephalosporins, and 90.5% sensitive to carbapenems.[5] Another study by Karlowsky, Hoban, and et. al, reported 48.9% of *K. pneumoniae* sensitive to the extended spectrum cephalosporins, 57.3% were sensitive to levofloxacin, and 78.5% sensitive to carbapenems.[26] *K. pneumoniae* isolated from

urine cultures in Central Alabama were more sensitive when compared to those reported in the NHSN and the Karlowsky, Hoban, et. al. study and had a higher isolation rate when compared to the NHSN.

Klebsiella pneumoniae resistance to beta-lactam drugs occurs due to enzyme inhibition of penicillinases, ESBL, and carbapenemases (i.e., New Delhi metallo-beta-lactamase (NDM-1)), as well as through decreased outer membrane permeability.[22] The NDM-1 enzyme is encoded by bla_{NDM-1}, which contributes to the increased presence of carbapenem-resistant *Klebsiella pneumoniae* (KPC) infections.[27] The decrease in outer membrane permeability is due to the reduction of porins, which are used by antibiotics to enter the bacterial cell. The reduction in porins causes beta-lactam resistance. The resistance to fluoroquinolones occurs due to the alteration of target enzymes, efflux, and target site protection.[22] DNA gyrase (bacterial topoisomerase II) is a target enzyme that plays a role in the cell division of gram negative organisms. This enzyme is encoded by *gyr*A and when mutated, resistance to fluoroquinolones occurs.[22] Another gene, *qnr,* is a plasmid-mediated fluoroquinolone resistance gene that produces binding proteins to the DNA gyrase antibiotic target site; therefore, protecting this enzyme from binding to fluoroquinolones,[22] allows *K. pneumoniae* to be resistant to the inhibitory effects of this drug class. Aminoglycoside resistance occurs due to enzymatic inhibition and alteration of ribosomal targets. Enzymatic inhibition is caused by aminoglycoside-modifying enzymes that confer resistance through *N*-acetylation, *O*-nucleotidylation, and *O*-phosphorylation of the drug as it transported across the bacterial cytoplasmic membrane.[22] The alteration of the ribosomal target occurs due to the methylation of the 16s rRNA, which is where aminoglycosides bind to stop protein synthesis.[22] The genes *armA, rmtA, rmtB, rmtC, rmtD, rmtE*, and *npmA*[22, 28] all contribute to this methylation.

Acinetobacter baumannii is commonly found in intensive care units and is intrinsically resistant to antibiotics due to outer membrane protection, efflux pump system, and reduction of porins.[29] In this study, *A. baumannii* was reported <1%; therefore, the validity of this study's analysis will be skewed. Of the seven *A. baumannii* isolates recovered, 99.3% were sensitive to the extended spectrum cephalosporins, 100% sensitive to levofloxacin, and 100% sensitive to carbapenems. In comparison, the NHSN reported a total of 276 isolates from CAUTIs with 36.0% sensitive to the carbapenems.[5] In the Karlowsky, Hoban, et. al. study, 43 isolates of *A. baumannii* reported 13.9% sensitive to extended spectrum cephalosporins, 11.6% sensitive to levofloxacin, and 18.6% sensitive to carbapenems.[26] This study indicated higher sensitivities than those of the NHSN and Karlowsky, Hoban, et. al, studies, which can be contributed to the low number of *A. baumannii* isolates recovered in this study. However, the CDC susceptibilities reported in 2017, 25.0% of *Acinetobacter* isolates were sensitive to any extended-spectrum beta-lactam and 11.0% were sensitive to any fluoroquinolone, which is comparable to the NHSN and the Karlowsky, Hoban, et. al studies.[30]

A. baumannii has become more resistant to antibiotic classes over the years due to beta-lactamases, enzyme inhibition by AmpC cephalosporinases, plasmid-acquired beta-lactamases of the TEM, SHV, Cefotaxime (CTX-M), PER, BEV families, metallo-beta-lactamases of the IMP (bla_{IMP}), VIM (bla_{VIM}), SIM families, and Oxacillin (OXA)-type serine carbapenemases (bla_{OXA}).[22, 26, 27] Aminoglycoside resistance and quinolones and tigecycline resistance also occurs due to enzymatic inhibition by aminoglycoside modifying enzymes and efflux pumps, respectively.[22]

Pseudomonas aeruginosa is known for its opportunistic infections in cystic fibrosis, cancer, and burn patients.[29] In this study, 6.0% of the Central Alabama urine isolates recovered *P. aeruginosa* with 72.0% sensitive to gentamicin, 96.0% sensitive to tobramycin, 68.0% sensitive to levofloxacin, and 90.0% sensitive to meropenem. In the NHSN study, *P.*

aeruginosa contributed to 10.3% of CAUTIs, with 78.9% sensitive to aminoglycosides, 67.4% sensitive to fluoroquinolones, and 76.1% sensitive to carbapenems.[5] In the Karlowsky, Hoban, et. al. study, 55.2% of *P. aeruginosa* isolates were sensitive to levofloxacin and 60.0% were sensitive to imipenem.[26] The aminoglycosides, gentamicin and tobramycin, had a combined sensitivity of 84.0% and is comparable to the NHSN study; however, the aminoglycoside sensitivities in the NHSN study were not separated out to determine if the susceptibility rate for the aminoglycosides was due to the disparity between gentamicin and tobramycin as seen in Central Alabama. In addition, Karlowsky, Hoban, and et. al. study only used amikacin reporting for aminoglycoside with a 75.2% sensitivity.[26] However, all three studies with aminoglycoside susceptibility are comparable. In contrast, when comparing the carbapenems, this study demonstrated a much higher sensitivity than what was reported in the other studies. Despite the higher sensitivity of *P. aeruginosa* in Central Alabama, concern over carbapenem-resistant strains must remain a top priority because 2.0% - 3.0% of carbapenem-resistant *P. aeruginosa* strains carry a mobile gene that is easily shared between bacteria resulting in increased resistance of this species.[30] In addition, *P. aeruginosa* resistance can also occur for other drugs. The beta-lactam drugs become resistant due to enzymatic inhibition by AmpC cephalosporinases, ESBL, and metallo-beta-lactamases; in addition, beta-lactam resistance occurs due to active efflux pump (MexAB) and reduced permeability of the outer membrane due to the loss of the OprD channel.[22] The MexAB pump is one of the largest multi-drug resistant pumps in *P. aeruginosa* and contributes to fluoroquinolone, tetracycline, and trimethoprim resistance.[22,31] The aminoglycosides have resistance to *P. aeruginosa* due to enzymatic inhibition caused by aminoglycoside modifying enzymes, efflux, and ribosomal methlyation.[22]

Enterobacter species are common isolates of UTIs and demonstrates resistance to antibiotics due to ESBLs and carbapenemases caused by VIM, OXA, metallo-beta-lactamases, and KPC (encoded by bla_{KPC}).[27] In this study, *Enterobacter species* was recovered at a rate of 2.3% with 92.0% sensitive to cefepime, 92.0% sensitive to levofloxacin, 83.0% sensitive to ertapenem, and 100% sensitive to meropenem. In the NHSN study, *Enterobacter species* contributed to 3.7% of CAUTIs with 59.5% sensitive to extended spectrum cephalosporins and 93.5% sensitive to carbapenems.[5] The Karlowsky, Hoban, et. al. study, reported 61.0% sensitive to cephalosporins, 79.4% sensitive to ertapenem, 86.1% sensitive to imipenem, and 76.4% sensitive to levofloxacin. This study only reported cefepime for the extended- spectrum cephalosporins, while the NHSN and Karlowsky, Hoban, et. al, studies reported cefepime, ceftazidime, and ceftriaxone for the extended spectrum cephalosporins, which can contribute to a discrepancy between the sensitivity of this study and published literature.

Escherichia coli is the most isolated organism from urine cultures.[5] In this study, *E. coli* was recovered at 69.4% with 99.0% sensitive to the extended spectrum cephalosporins, 82.5% sensitive to the fluoroquinolones, and 100% sensitive to the carbapenems. In the NHSN study, *E. coli* contributed to 23.9% of all CAUTIs with 83.9% sensitive to extended spectrum cephalosporins, 65.2% sensitive to fluoroquinolones, and 98.9% sensitive to the carbapenems. Central Alabama recovered a higher percentage of *E. coli*, which contributed to this study by encompassing all urine culture isolates instead of only CAUTIs as reported to the NHSN. In addition, the susceptibility of *E. coli* in Central Alabama appeared to be more sensitive to the fluoroquinolones than isolates reported to NHSN. This is understandable as CAUTIs are considered complicated infections and can result in longer treatment plans and treatment failures.[8] In the Global Antimicrobial Resistance and Use Surveillance System (GLASS) through the WHO, 8.4% to 92.9% of *E. coli* isolates are resistant to ciprofloxacin, which is

commonly used to treat UTIs.[32] In this study we observed that bacteria are more resistant to fluoroquinolones than to other antibiotic classes.

Conclusion

Escherichia coli was the most isolated organism from urine cultures submitted to a hospital system in Central Alabama and did not demonstrate an increased pattern of resistance when compared to other studies. Overall, we can say the resistant patterns of the ESKAPE organisms isolated in the hospital system were comparable to those reported globally and nationally. However, despite Central Alabama having slightly higher sensitivity rates for the ESKAPE organisms when compared to the NHSN and the Karlowsky, Hoban, and et. al studies, these organisms should still be treated with concern because they are becoming resistant faster than new antibiotics introduced to the market. Therefore, due diligence must take place to conserve and appropriately use current antibiotics by implementing antibiotic stewardship programs in hospitals and providing physicians with education on proper antibiotic use in ambulatory settings. By maintaining focus on these organisms and developing ways to reduce resistance, the rate of resistance can be diminished to prevent increased mortality or morbidity.

Acknowledgements

The authors would like to thank Dr. Melanie Hyte, Pharm D. for her assistance in obtaining the antibiotic susceptibility data.

References

1. Urinary Tract Infection (Catheter-Associated Urinary Tract Infection [CAUTI] and Non-Catheter-Associated Urinary Tract Infection [UTI]) Events. National Healthcare Safety Network. Center for Disease Control, January 2023. Available from: Urinary Tract Infection (cdc.gov)
2. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015 May;13(5):269-84. doi: 10.1038/nrmicro3432. Epub 2015 Apr 8. PMID: 25853778; PMCID: PMC4457377.
3. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. J Infect Dis. 2001 Mar 1;183 Suppl 1: S1-4. doi: 10.1086/318850. PMID: 11171002.
4. Klein RD, Hultgren SJ. Urinary tract infections: microbial pathogenesis, host-pathogen interactions and new treatment strategies. Nat Rev Microbiol. 2020 Apr;18(4):211-226. doi: 10.1038/s41579-020-0324-0. Epub 2020 Feb 18. PMID: 32071440; PMCID: PMC7942789.
5. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, Edwards JR, Sievert DM. Antimicrobial-Resistant Pathogens Associated with Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol. 2016 Nov;37(11):1288-1301. doi: 10.1017/ice.2016.174. Epub 2016 Aug 30. PMID: 27573805; PMCID: PMC6857725.
6. Lichtenberger P, Hooton TM. Complicated urinary tract infections. Curr Infect Dis Rep. 2008 Nov;10(6):499-504. doi: 10.1007/s11908-008-0081-0. PMID: 18945392.
7. Levison ME, Kaye D. Treatment of complicated urinary tract infections with an emphasis on drug-resistant gram-negative uropathogens. Curr Infect Dis Rep. 2013 Apr;15(2):109-15. doi: 10.1007/s11908-013-0315-7. PMID: 23378123.
8. Sabih A, Leslie SW. Complicated Urinary Tract Infections. [Updated 2023 Jan 18]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK436013/
9. Nielubowicz GR, Mobley HL. Host-pathogen interactions in urinary tract infection. Nat Rev Urol. 2010 Aug;7(8):430-41.

doi: 10.1038/nrurol.2010.101. Epub 2010 Jul 20. PMID: 20647992.
10. Kline KA, Schwartz DJ, Lewis WG, Hultgren SJ, Lewis AL. Immune activation and suppression by group B streptococcus in a murine model of urinary tract infection. Infect Immun. 2011 Sep;79(9):3588-95. doi: 10.1128/IAI.00122-11. Epub 2011 Jun 20. PMID: 21690238; PMCID: PMC3165466.
11. Fisher JF, Kavanagh K, Sobel JD, Kauffman CA, Newman CA. Candida urinary tract infection: pathogenesis. Clin Infect Dis. 2011 May;52 Suppl 6: S437-51. doi: 10.1093/cid/cir110. PMID: 21498837.
12. Chen YH, Ko WC, Hsueh PR. Emerging resistance problems and future perspectives in pharmacotherapy for complicated urinary tract infections. Expert Opin Pharmacother. 2013 Apr;14(5):587-96. doi: 10.1517/14656566.2013.778827. PMID: 23480061.
13. Jacobsen SM, Stickler DJ, Mobley HL, Shirtliff ME. Complicated catheter-associated urinary tract infections due to Escherichia coli and Proteus mirabilis. Clin Microbiol Rev. 2008 Jan;21(1):26-59. doi: 10.1128/CMR.00019-07. PMID: 18202436; PMCID: PMC2223845.
14. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014 Mar;28(1):1-13. doi: 10.1016/j.idc.2013.09.003. Epub 2013 Dec 8. PMID: 24484571.
15. Hannan TJ, Totsika M, Mansfield KJ, Moore KH, Schembri MA, Hultgren SJ. Host-pathogen checkpoints and population bottlenecks in persistent and intracellular uropathogenic Escherichia coli bladder infection. FEMS Microbiol Rev. 2012 May;36(3):616-48. doi: 10.1111/j.1574-6976.2012.00339. x. PMID: 22404313; PMCID: PMC3675774.
16. Kostakioti M, Hultgren SJ, Hadjifrangiskou M. Molecular blueprint of uropathogenic Escherichia coli virulence provides clues toward the development of anti-virulence therapeutics. Virulence. 2012 Nov 15;3(7):592-4. doi: 10.4161/viru.22364. Epub 2012 Nov 15. PMID: 23154288; PMCID: PMC3545937.
17. Adler A, Friedman ND, Marchaim D. Multidrug-Resistant Gram-Negative Bacilli: Infection Control Implications. Infect Dis Clin North Am. 2016 Dec;30(4):967-997. doi: 10.1016/j.idc.2016.08.001. Epub 2016 Sep 19. PMID: 27660090.
18. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis. 2008 Apr 15;197(8):1079-81. doi: 10.1086/533452. PMID: 18419525.
19. Pogue JM, Kaye KS, Cohen DA, Marchaim D. Appropriate antimicrobial therapy in the era of multidrug-resistant human pathogens. Clin Microbiol Infect. 2015 Apr;21(4):302-12. doi: 10.1016/j.cmi.2014.12.025. Epub 2015 Jan 14. PMID: 25743999.
20. Bouch HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs, no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 2009 Jan 1;48(1):1-12, https://doi.org/10.1086/595011
21. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; 32nd edition. CLSI supplement M100. Clinical and Laboratory Standards Institute; January 2020.
22. Opal, SM, Pop-Vicas, A. 18-Molecular mechanisms of antibiotic resistance in bacteria.
Editor(s): John E. Bennett, Raphael Dolin, Martin J. Blaser, Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition). W.B. Saunders, 2015, Pages 235-251.e3, ISBN 9781455748013.
23. Montealegre MC, Roh JH, Rae M, Davlieva MG, Singh KV, Shamoo Y, Murray BE. Differential Penicillin-Binding Protein 5 (PBP5) Levels in the Enterococcus faecium Clades with Different Levels of Ampicillin Resistance. Antimicrob Agents Chemother. 2016 Dec 27;61(1):e02034-16. doi: 10.1128/AAC.02034-16. PMID: 27821450; PMCID: PMC5192164.

24. Al Mohajer M, Musher DM, Minard CG, Darouiche RO. Clinical significance of Staphylococcus aureus bacteriuria at a tertiary care hospital. Scand J Infect Dis. 2013 Sep;45(9):688-95. doi: 10.3109/00365548.2013.803291. Epub 2013 Jul 1. PMID: 23808717.
25. Routh JC, Alt AL, Ashley RA, Kramer SA, Boyce TG. Increasing prevalence and associated risk factors for methicillin resistant Staphylococcus aureus bacteriuria. J Urol. 2009 Apr;181(4):1694-8. doi: 10.1016/j.juro.2008.11.108. Epub 2009 Feb 23. PMID: 19233426.
26. Karlowsky JA, Hoban DJ, Hackel MA, Lob SH, Sahm DF. Resistance among gram-negative ESKAPE pathogens isolated from hospitalized patients with intra-abdominal and urinary tract infections in Latin American countries: SMART 2013-2015. Braz J Infect Dis 2017:21(3):343-348.
27. Santajit S, Indrawattana N. Mechanisms of Antimicrobial Resistance in ESKAPE Pathogens. Biomed Res Int. 2016; 2016:2475067. doi: 10.1155/2016/2475067. Epub 2016 May 5. PMID: 27274985; PMCID: PMC4871955.
28. Zhou Y, Yu H, Guo Q, Xu X, Ye X, Wu S, Guo Y, Wang M. Distribution of 16S rRNA methylases among different species of Gram-negative bacilli with high-level resistance to aminoglycosides. Eur J Clin Microbiol Infect Dis. 2010 Nov;29(11):1349-53. doi: 10.1007/s10096-010-1004-1. Epub 2010 Jul 8. PMID: 20614151.
29. Pendleton JN, Gorman SP, Gilmore BF. Clinical relevance of the ESKAPE pathogens. Expert Rev Anti Infect Ther. 2013 Mar;11(3):297-308. doi: 10.1586/eri.13.12. PMID: 23458769.
30. United States Department of Health and Human Services. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. 2019. Available from: 2019 Antibiotic Resistance Threats Report | CDC
31. Pan YP, Xu YH, Wang ZX, Fang YP, Shen JL. Overexpression of MexAB-OprM efflux pump in carbapenem-resistant Pseudomonas aeruginosa. Arch Microbiol. 2016 Aug;198(6):565-71. doi: 10.1007/s00203-016-1215-7. Epub 2016 Apr 8. PMID: 27060003.
32. World Health Organization. Antimicrobial Resistance. November 17, 2021. Available from: Antimicrobial resistance (who.int)