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Characterization of antimicrobial resistance among *Proteus mirabilis* isolates from catheter-associated urinary tract infections and non-catheter-associated urinary tract infections in Egypt

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Abstract

Background Recent worldwide reports of increased numbers of multidrug-resistant (MDR) *Proteus mirabilis* (*P. mirabilis*) isolates, particularly those producing extended-spectrum β-lactamases (ESBLs), are alarming. *P. mirabilis* is a common causative agent of complicated urinary tract infections (UTIs), particularly in patients with long-term urinary catheterization. This study aimed to assess the prevalence, antibiotic resistance patterns, and determinants of *P. mirabilis* among catheter-associated UTIs (CAUTI) and non-catheter-associated UTIs (non-CAUTI).

Methods One hundred and three *Proteus* strains isolated from 613 UTI patients in Minia, Egypt, were examined for antibiotic resistance patterns, ESBL production, and sulphonamide resistance phenotypically. Class 1 and 2 integrons, ESBL, and *sul* resistance genes were detected by Polymerase chain reaction (PCR), followed by molecular typing of ESBL-producing isolates from catheterized UTI patients using ERIC-PCR.

Results *Proteus* isolates were detected in 20% of the UTIs, with a higher rate among inpatients (27.3%) compared to outpatients (10.6%). *Proteus* was more significantly isolated from catheterized UTI patients (28.2%, 55/195) than from non-catheterized patients (14.9%, 48/321). Of the 103 *Proteus* isolates, 99 (96.1%) were identified as *P. mirabilis*. High resistance was observed against trimethoprim/sulfamethoxazole (SXT) (80.6%), amoxicillin-clavulanic (AMC) (57.3%), ceftazidime (55.3%), and imipenem (46.6%) antibiotics. Significantly higher resistance rates were observed among *Proteus* isolates from inpatients and catheterized patients. Of the 103 *Proteus* strains, 81 (78.6%) were MDR, with 70.9% of the isolates from catheterized patients. About 74.6% of the isolates from inpatients were MDR. *Sul* genes were detected in 77 isolates (74.7%). The frequency of ESBL-producing *Proteus* isolates was 37.9% which was significantly higher in catheterized patients with increasing dissemination of bla_{TEM} genes and $bla_{CTX\text{-}M}$ genes. *Int1 and Int2* genes were detected in 92.2% and 68.9% of isolates, respectively. ERIC-PCR revealed moderate similarity (65%) between ESBL-producing *Proteus* isolates from catheterized patients.

Conclusion The high frequency of MDR *P. mirabilis* strains isolated from UTIs in Egypt, particularly among catheterized patients, is a major concern, especially with disseminating class 1 and 2 integrons among isolates. The study also highlights the decreased susceptibility to sulphonamides, 3rd generation cephalosporins, and imipenem,

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commonly used to treat UTIs. Increased dissemination of ESBL-producing *Proteus* isolates among CAUTIs complicates their treatments. This important pathogen deserves more attention in the future for a better understanding of resistance mechanisms and the dissemination potential of resistant strains.

Keywords *Proteus mirabilis*, Catheter-associated, Urinary tract infection, Multidrug resistance, Beta-lactamases, Integrons

Background

Proteus species are gram-negative members of the *Morganellaceae* family, which forms, together with *Enterobacteriaceae,* the order *Enterobacteriale* [1]. *Proteus mirabilis* (*P. mirabilis*) and *Proteus vulgaris* (*P. vulgaris*) were the most frequent opportunistic pathogenic species of *Proteus* in humans. They widely exist in the environment and the gut microbiota of humans and animals [2]. Urinary tract infection (UTI) is a common health problem in communities and hospitals. Every year, almost 150 million individuals throughout the globe suffer from UTIs, making it a serious public health issue [3]. *P. mirabilis* is responsible for 90% of diverse *Proteus* infections, especially UTIs. *P. mirabilis* is a common causative agent of complicated UTIs, particularly in patients with long-term urinary catheterization [4].

Catheter-associated urinary tract infection (CAUTI) is the most common healthcare-associated infection that can cause secondary bloodstream infections, which makes it a severe healthcare burden. *P. mirabilis* produces a urease enzyme that causes hydrolysis of urea, leading to an increase in the urinary pH, thus generating calcium crystals and magnesium ammonium phosphate precipitates. Together, this leads to the formation of crystalline biofilms on catheters [5]**.** According to guidelines published by the Centre for Disease Control and Prevention (CDC); CAUTI is diagnosed if the patient has an indwelling urinary catheter for more than 2 days in the hospital setting and one sign or symptom including fever, suprapubic tenderness, costovertebral angle tenderness in addition to urine culture with more than 10^5 CFU/mL of one bacterial species [6].

Antibiotic-resistant bacteria are an escalating global health threat. Potent antibiotics are now less effective due to bacterial evolution and gene exchange [7]. *Proteus* isolates that were once largely susceptible to standard antibiotics are now increasingly resistant to UTI treatments. Recent global studies confirm this increasing resistance trend [8–10]. ESBL-producing bacteria are a growing health concern. Recently, the $bla_{\text{CTX-M}}$ genotype has emerged, replacing bla_{TEM} and bla_{SHV} in Enterobacteriaceae isolates [11].

Sulfonamides are a group of chemotherapeutic agents that act as competitive inhibitors of the *folP* gene encoding dihydropteroate synthase enzyme (DHPS). The plasmid- and integron-borne *sul1-3* genes cause widespread sulfonamide resistance through coding for mutant DHPS enzymes that do not bind to sulfonamides [12]. Trimethoprim/sulfamethoxazole (SXT) is used commonly in developing countries as an empiric treatment of UTI as it is very cost-affordable. ESBLs have been associated with resistance to other antibiotic classes, such as trimethoprim/sulfamethoxazole [13].

Integrons are natural recombination and expression systems that can acquire genes in the form of gene cassettes. In the past two decades, the incidence of integrons in enteric bacteria has increased dramatically with the evolution of multiple gene cassettes, novel gene arrangements, and complex chromosomal integrons [14]. Class 1 and 2 integrons have been associated with antibiotic resistance in *Enterobacteriaceae* such as beta-lactam resistance and sulphonamide resistance, class 2 integrons have been reported with lower prevalence in gram-negative bacteria than class 1 integrons [15].

Despite the increased reports of resistance among *Proteus* strains in the last decade, few studies have addressed this issue in Egypt. In this study, we aimed to determine antimicrobial resistance patterns among *Proteus* isolates obtained from CAUTI and non-CAUTI patients admitted to Minia University Hospitals, Egypt. Then molecular screening of resistant isolates for ESBL, and sulfonamide genes (*sul* genes) was also carried out. All isolates were screened for class 1 and 2 integrons (*int*I1, *int*I2 genes).

Methods

Study design

This cross-sectional study included 613 urine samples collected from 336 inpatients and 277 outpatients presenting with UTI symptoms from different departments in Minia University Hospitals. The study was conducted in the Microbiology and Immunology Department, Faculty of Medicine, Minia University, between April 2022 and June 2023. The recruited patients met the following inclusion criteria: adults ≥ 18 years, had no history of receiving antibiotics 48 h before sample collection, patients had one or more of the UTI symptoms (fever, frequent urination, dysuria, incomplete bladder emptying, suprapubic or flank pain). Samples collected from inpatients were obtained 48 h after admission (UTI symptoms appeared 48 h after admission). Demographic

data and relevant clinical history data were also collected, including history of catheterization and no history of administration of antimicrobial agents. Informed consent was obtained from all study participants. The Research Ethics Committee of the Faculty of Medicine of Minia University had approved the study protocol with Approval No.276:2/2022.

Bacterial isolation and identification

Midstream clean-catch urine samples were collected under complete aseptic precautions in sterile screw-capped containers. From catheterized patients, urine was aspirated from the catheter tube after cleaning it with alcohol and puncturing it using a sterile syringe and needle. All samples were transported within 2 h to the microbiology laboratory for immediate examination. Urine samples with pus cells >10/HPF were streaked on chromogenic media (CHROMagar™ Orientation, Paris, France) by calibrated loop technique [16] Positive cultures with more than 10^5 CFU/mL colonies were initially identified based on characteristic growth on nutrient agar and MacConkey's agar media (Oxoid, UK). *Proteus mirabilis* isolates *were* identified phenotypically based on the following tests*:* Oxidase negative, Catalase positive, Indole negative, Methyl red positive, Voger Proskauer negative, Citrate positive, H_2S production, sugar fermentation of glucose and positive motility test [17]. A total of 103 non-repetitive *proteus* isolates were recovered from all urine samples. Identified isolates were stored by mixing incubated Trypticase soy broth (Oxoid, UK) with sterilized glycerol 20% at −20 °C for further molecular testing.

Antibiotic susceptibility testing

The antimicrobial susceptibility testing was performed using the Kirby-Bauer disc diffusion technique using Muller-Hinton agar (Oxoid, U.K) according to Clinical Laboratory Standard Institute (CLSI) guidelines, 2023 [18]. The following 11 commercially available discs were used: Amoxicillin/clavulanic acid (AMC) 20/10µg, Ceftriaxone (CRO) 30µg, Ceftazidime (CAZ) 30µg, Imipenem (IPM) 10µg, Amikacin (AK) 30µg, Trimethoprim-Sulfamethoxazole (SXT) 25µg, Cefotaxime (CTX) 30µg, Ciprofloxacin (CIP) 5µg, Cefoxitin (FOX) 30µg, Aztreonam (ATM) 30µg (Oxoid, UK), and Gentamicin (CN) 10µg (Thermo Scientific™, UK). *Escherichia coli* (ATCC 25922) was used as a quality control strain. Isolates that showed resistance to three or more classes of antimicrobial agents have been classified as multidrug-resistant (MDR) [19]. Multiple antibiotic resistance index (MARI) was calculated by the ratio between the sum of antibiotics against which the *proteus* strain displayed resistance and the total number of antibiotics to which the isolate was tested [20].

The minimum inhibitory concentration (MIC) of trimethoprim-sulfamethoxazole (SXT) was evaluated by the broth microdilution method using Muller-Hinton broth (Oxoid, U.K). Ten dilutions of SXT (EIPICO Pharmaceutical Company, Egypt) were tested by the two-fold dilution method in 96 well microtiter plates using a concentration range from 0.25/4.7 µg/ml to 128/2432 µg/ml. According to the CLSI guidelines, MIC ≤2/38 µg/mL was considered sensitive and MIC ≥4/76 µg/mL was considered resistant to SXT [18].

ESBL phenotypic confirmation test

Isolates resistant to 3rd generation cephalosporins (ceftazidime zone ≤22 mm and cefotaxime zone ≤27 mm) were suggested as ESBL producers. The double disc synergy test (DDST) was used to confirm the phenotypic ESBL production according to CLSI guidelines 2023 [18]. Amoxicillin clavulanic acid disk was placed aseptically in the center of the plate containing Mueller–Hinton agar inoculated with standardized inoculum (corresponding to 0.5 McFarland). Then, two test disks of 3rd generation cephalosporins (ceftazidime 30µg and cefotaxime 30µg) were placed at a 15 mm distance from the center of the AMC disk. After overnight incubation at 37 °C, an enhanced zone of inhibition toward AMC (formation of a characteristic keyhole-shaped zone of inhibition between the disks) was considered a synergy between clavulanic acid and any one of the tested antibiotics. This was a phenotypic indication of ESBL production.

DNA extraction

The genomic DNA of all *Proteus* isolates was extracted using the modified boiling method [21]. Three to five colonies from each isolate were inoculated into tryptone soya broth. Then, 1.5 ml of overnight culture was centrifuged for 5 min at 12,000 rpm at 4 °C. The supernatant was removed carefully, and the pellet was mixed with 200 µl of sterile distilled water. After boiling the suspended pellet for 10 min in a water bath, it was immediately placed in ice for 20 min and then centrifuged at 12,000 rpm for 5 min at 4 °C. The supernatant containing extracted DNA was transferred into a new tube and stored at −20 °C for subsequent PCR amplification.

Detection of sulfonamide resistance genes

Screening of SXT-resistant isolates of *Proteus* was performed by PCR amplification of *sul1* and *sul2* genes using specific primers to produce PCR products of 347bp and 506bp, respectively; strains positive for *sul1* and *sul2* genes were used as positive controls [22]; (Table 1s in Supplementary File).

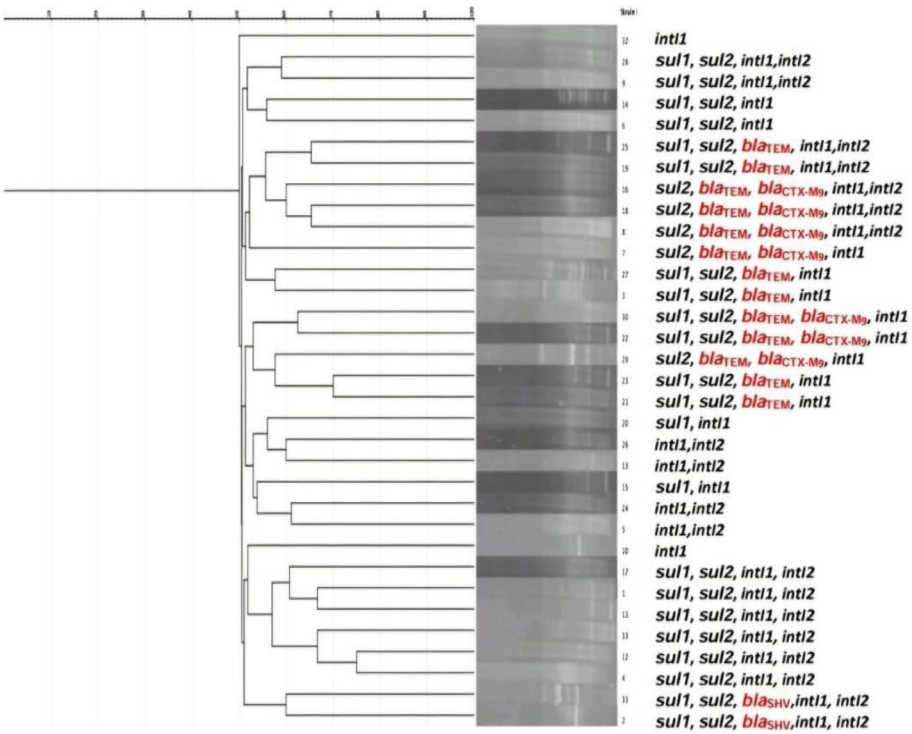


Fig. 1 Dendrogram analysis of DNA fingerprinting by ERIC-PCR of ESBL-producing *P. mirabilis* isolates from catheterized patients showing similarity of 65%

Detection of ESBL genes

All phenotypic ESBL-producing *Proteus* isolates were screened for the presence of the ESBL genes: bla_{TEM}, bla_{SHV}, and $bla_{\text{CTX-M 1, 2, 8, 9, 25}}$ genes. Single PCR reactions were used for the amplification of bla_{TEM} and bla_{SHV} genes and a multiplex PCR was used to examine the presence of $bla_{\text{CTX-M 1, 2, 8, 9,25}}$ genes; positive controls were used [23, 24]

Detection of Class 1 and 2 integron

All isolates were tested for the presence of the conserved regions of class 1 and class 2 integrases [25]. Primer sequences and annealing temperature used for the amplification of *intI*1 and *intI*2 genes were shown in Table 1 s in the Supplementary File).

Molecular typing by enterobacterial repetitive intergenic consensus-PCR (ERIC-PCR)

ESBL-producing *P. mirabilis* isolates from catheterized patients were fingerprinted by ERIC-PCR for the level of genetic similarity using the primer sequences shown in Table 1 s in the Supplementary File. PCR conditions used were as follows: an initial denaturation step at 92 ∘C for 4 min, followed by 40 denaturation cycles of 1 min at 94 ∘C, annealing at 48 ∘C for 1 min, an extension at 72 ∘C for 5 min, and a final extension at 72 ∘C for 5 min [26]. The banding patterns of PCR products were analyzed on a 1.5% agarose gel containing ethidium bromide dye, and the gel was visualized under a UV transilluminator. ERIC-PCR was performed on triplicates to confirm the reproducibility of the amplified band patterns obtained. A similarity dendrogram was constructed by band profile analysis using GelJ software by the unweighted pair group mean method, tolerance value of 1, and Dice's similarity coefficient.

Statistical analysis

All collected and laboratory data were analysed using statistical analysis by IBM SPSS software (version 19.0). A chi-square test was used for the comparison between groups, and the results were considered significant if the P value was < 0.05.

Results

Identification of clinical isolates

Based on the results of urine culture on Chrome agar medium, out of 613 urine samples, 516 (84.2%) of them showed bacteriuria (CFU $> 10^5$) while 97 (15.8%) urine samples showed no bacterial growth. Out of 516 UTI patients, *Proteus* species were isolated from 103 samples (20%), while uropathogens other than *Proteus* were isolated from 413 samples (80%) (Fig. 1s Supplementary

Table 1 Patient characteristics, clinical data, percentage of antibiotic resistance patterns, and molecular genes among *Proteus* isolates from catheterized and non-catheterized patients

		Total N = 103	Catheterized group (*N* = 55)	Non-catheterized group(*N*= 48)	*P*-value
Patients'characteristics					
Age	Mean ± SD	46.1 ± 15.6	47.07 ± 15.7	45 ± 15.9	0.511
	Range	18–84	19–84	18–71	
Gender	Male	40 (38.8%)	22 (40%)	18 (37.5%)	0.864
	Female	63 (61.2)%	33 (60%)	30 (62.5%)	
Type of patient	Outpatient	24 (23.3%)	0 (0%)	24 (50%)	**0.000***
	Inpatient	79 (76.7%	55 (100%)	24 (50%)	
Department	Gynaecology and obstetrics	33 (32%)	11 (20%)	22 (45.8%)	**0.000***
	ICU	22 (21.4%)	22 (40%)	0 (0%)	
	Surgery	14 (13.6%)	10 (18.2%)	4 (8.3%)	
	Internal medicine	10 (9.7%)	4 (7.3%)	6 (12.5%)	
	Urology	24 (23.3%)	8 (14.5%)	16 (33.3%)	
Dysuria	Yes	60 (58.3%)	14 (25.5%)	46 (95.8%)	**0.000***
	No	43 (41.7%)	41 (74.5%)	2 (4.2%)	
Fever	Yes	72 (69.9%)	40 (72.7%)	32 (66.7%)	0.504
	No	31 (30.1%)	15 (27.3%)	16 (33.3%)	
Antimicrobial resistance					
Amoxicillin-clavulanic		59 (57.3%)	35 (63.6%)	24 (50%)	0.215
Cefoxitin		24 (23.3%)	14 (25.5%)	10 (20.8%)	0.855
Ceftriaxone		31 (30.1%)	21 (38.2%)	10 (20.8%)	**0.015***
Cefotaxime		35 (34%)	27 (49.1%)	8 (16.7%)	**0.001***
Ceftazidime		57 (55.3%)	37 (67.3%)	20 (41.7%)	**0.004***
Azetronam		32 (31.1%)	22 (40%)	10 (20.8%)	0.065
Imipenem		48 (46.6%)	28 (50.9%)	20 (41.7%)	0.460
Ciprofloxacin		21 (20.4%)	11 (20%)	10 (20.8%)	0.926
SXT		83 (80.6%)	41 (74.5%)	42 (87.5%)	0.169
Amikacin		14 (13.6%)	6 (10.9%)	8 (16.7%)	0.2
Gentamicin		8 (7.8%)	4 (7.3%)	4 (8.3%)	0.841
SXT-MIC		73 (70.9%)	39 (70.9%)	34 (70.8%)	0.993
ESBL phenotypic detection					
Double disc synergy test		39 (37.9%)	33 (60%)	6 (12.5%)	**0.000***
Molecular Detection of resistance genes and integrons					
sul1		62 (60.2%)	34 (61.8%)	28 (58.3%)	0.719
***sul* 2**		67 (65%)	37 (67.3%)	30 (62.5%)	0.612
bla_{TEM}		11 (10.7%)	11(20%)	0 (0%)	**0.001***
bla_{SHV}		2 (1.9%)	2 (3.6%)	0 (0%)	0.182
bla_{CTXM9}		6 (5.8%)	6 (10.9%)	0 (0%)	**0.018***
***intI*1**		95 (92.2%)	53 (96.4%)	42 (87.5%)	0.094
***intI*2**		71 (68.9%)	37 (67.3%)	34 (70.8%)	0.697

* (significant *P* value)

File). Of the 103 *Proteus* isolates, ninety-nine were identified as *P. mirabilis* (96.1%).

Demographic characteristics of the study subjects

The prevalence of *Proteus* was higher in catheterized UTI patients (28.2%; 55/195) than in non-catheterized patients (14.9%; 48/321); which was highly significant (P value of < 0.001). The prevalence of *Proteus* among UTI patients was higher in inpatients representing hospital-acquired UTIs (27.3%; 79/289) than in outpatients representing community-acquired UTIs (10.6%; 24/227) which showed high significance (P value of < 0.001). *Proteus*

Table 2 Genotypic profile in 15 ESBL gene-producing *P. mirabilis* isolates

Number of isolates (15)	ESBL genes			*sul* genes		Integron genes	
	bla_{TEM}	bla_{SHV}	$bla_{CTX\text{-}M\text{-}9}$	*Sul1*	*Sul2*	*intI1*	*intI2*
2	+	ND	ND	+	+	+	ND
2	+	ND	ND	+	+	+	+
3	+	ND	ND	ND	+	+	+
2	+	ND	+	ND	+	+	ND
2	+	ND	+	+	+	+	ND
2	ND	+	ND	+	+	+	+
2	ND	ND	+	+	+	+	ND

(+ gene detected; ND gene not detected)

strains were isolated from patients with a mean age of 46.1 ± 15.6 years; 85 (82.5%) of them were adult patients (18–59 years) and 18 (17.5%) aged above 60 years. *Proteus* strains were more predominant among female patients (63/103, 61.2%) than males (40/103, 38.8%). Ten *Proteus* strains (9.7%) were isolated from pregnant women with UTI (Table 2s Supplementary File).

Proteus strains were isolated from patients from different departments (32% from the Gynaecology and Obstetrics Departments, 23.3% from the Urology Department, 21.4% from the ICU, 13.6% from the Surgery Department, and 9.7% from the Internal Medicine Department; Table 1.

Antimicrobial susceptibility of Proteus isolates

Antimicrobial susceptibility testing of the 103 *Proteus* isolates was done for 11 antibiotics belonging to eight different antimicrobial categories using the disk diffusion method. The highest antimicrobial resistance was observed against the SXT (80.6%), then AMC (57.3%), ceftazidime (55.3%), and imipenem (46.6%) antibiotics. The high susceptibility was to gentamycin, amikacin, and cefoxitin (Fig. 2s Supplementary File). *Proteus* isolates from catheterized patients showed higher resistance to most tested antibiotics than *Proteus* isolates from non-catheterized patients; with significant differences for cefotaxime, ceftazidime, and ceftriaxone (P values were 0.001, 0.004, and 0.015, respectively); Table 1. Also, *Proteus* strains isolated from inpatients were more resistant to third-generation cephalosporins, cefoxitin, imipenem, aztreonam, amikacin, and gentamicin than those isolated from outpatients. Among 83 SXT-resistant *Proteus* isolates by the disc diffusion method, only 73 isolates (70.9%) were found to be resistant to SXT by the broth microdilution method. There was no significant difference in resistance to SXT among isolates from catheterized and non-catheterized patients; Table 1.

A high frequency of MDR was observed among all the studied isolates. Out of 103 *Proteus* strains, 81 (78.6%) were MDR. It was found that 39 MDR isolates were isolated from catheterized patients, representing 70.9% of all catheterized patients. Also, 74.6% (59/79) of *Proteus* isolates from inpatients were MDR. The 81 MDR *Proteus* isolates showed 28 antibiotic resistance profiles to 3–11 antibiotics, with MARI ranging from 0.27 to 1. Eight isolates were resistant to all tested antibiotics. MDR *Proteus* isolates were classified according to the number of resistant antimicrobial categories into five groups (Fig. 3s Supplementary File).

ESBL phenotypic confirmation test

A double disc synergy test was done on 43 *Proteus* strains, suspected to be ESBL producers by the disc diffusion method. Out of the suspected ESBL producer isolates, 39 stains were confirmed as a phenotypic indication of ESBL production by DDST. From the total studied 103 *Proteus* strains, there were 39 ESBL producers (37.9%) and 64 non-ESBL producers (62.1%). Thirty-three ESBL-producing *Proteus* isolates (84.6%) were from catheterized patients, and only six ESBL-producing *Proteus* isolates (15.4%) were from non-catheterized patients with a significant difference (P value 0.0001*); Table 1. All 39 ESBL-producing *Proteus* isolates were MDR. The majority of ESBL-producing *Proteus* isolates were isolated from the ICU (15 isolates), Gynaecology and Obstetrics Departments (12 isolates), and Urology Department (8 isolates). There were significant differences between the ESBL-producers and ESBL non-producers isolates in terms of the antibiotic resistance rates of imipenem, aztreonam, cefoxitin, and gentamycin antibiotics (P value: 0.007, < 0.001, 0.025, and 0.024, respectively); Table 3s Supplementary File.

Detection of sulphonamide resistance genes

All 103 *Proteus* isolates (73 isolates phenotypically SXT resistant + 30 isolates as control samples) were molecularly tested for the presence of the following sulphonamide-resistant genes: *sul1* and *sul2* genes. *Sul* genes were detected in 77 isolates (74.7%); with no significant differences between catheterized and non-catheterized patients; Table 1. All isolates were identified as *P. mirabilis*. Six strains harboured the *sul1* gene only, and thirteen strains harboured the *sul2* gene only. There were 58 strains harboured both *sul1* and *sul2* genes. All 73 phenotypically SXT-resistant isolates carried *sul* genes. However, four isolates had the *sul II* gene but didn't show SXT resistance by the broth microdilution method.

Detection of ESBL genes

All 39 ESBL-producing *Proteus* isolates (*P. mirabilis*) were molecularly tested for ESBL genes bla_{TEM}, bla_{SHV}, $bla_{\text{CTX-M-1, 2, 8, 9, and 25}}$ genes. Out of 39 isolates, 15 (38.5%) carried ESBL genes. Eleven isolates had the bla_{TEM} gene (28.2% of ESBL producers), and only two isolates had the bla_{SHV} gene (5.1%). $Bla_{\text{CTX-M-9}}$ was the only detected CTX-M gene in six isolates (15.4%, two isolates harbored $bla_{\text{CTX-M-9}}$ alone and 4 carried it with bla_{TEM}), but $bla_{\text{CTX-M 1, 2, 8, and 25}}$ were not detected in any isolate. All the isolates carrying ESBL genes were from catheterized patients and were all *P. mirabilis* type (Table 1). The antibiotic resistance profile of ESBL gene-producing isolates showed differences in resistance among isolates with one or two ESBL genes. There were differences in the inhibition zones in isolates with 2 ESBL genes than those with one ESBL gene. Table 4 s in the supplementary file.

Detection of class 1 and 2 integrons

All 103 *Proteus* isolates were screened for *intI1* and *intI2* genes to detect class 1 and 2 integrons, respectively. Ninety-five isolates (92.2%) were positive for the *intI1* gene which was more frequently detected in catheterized patients (53/55; 96.4%) than in non-catheterized patients (42/48; 87.5%). The *intI2* gene was less frequently detected in *Proteus* isolates (71/103; 68.9%) with a slightly lower prevalence in catheterized (37/55; 67.3%) than in non-catheterized patients (34/48; 70.8%); Table 1. Sixty-seven *Proteus* isolates harboured both *intI1* and *intI2* genes, 28 isolates harboured the *intI1* gene only, and 4 isolates harboured the *intI2* gene only. Different seven gene profiles of ESBL, *sul,* and integron gene distribution were observed among positive ESBL gene *P. mirabilis* isolates. Four isolates carried 2 ESBL genes (bla_{TEM} and $bla_{\text{CTX-M-9}}$). All ESBL isolates harboured *sul1* and *intI1* genes. (Table 2).

DNA fingerprinting analysis by ERIC-PCR

The fingerprints obtained from a PCR assay with ERIC primers of the ESBL-producing *P. mirabilis* isolates from catheterized patients (33 isolates) showed a DNA banding profile consisting of amplified bands from 100 to 3000 bp in size. The isolates had different gene profiles, and all isolates carried the intI1 gene. Table 5 s in supplementary file A dendrogram was constructed according to the data of these isolates. The isolates showed a moderate degree of similarity. The overall similarity among the 33 isolates was 65%. The isolates with the same genotypic pattern showed some similarity in ERIC patterns. (Fig. 1).

Discussion

In recent years, *Proteus* bacteria have acquired considerable importance as causative pathogens associated with complicated UTIs. This study indicated that the rate of *Proteus* isolates was 20% among the UTI agents, with a significantly higher prevalence among CAUTIs (28.2%) than non-CAUTIs (14.9%). In the same locality; a previous study by Kotb et al.; 2019 [27], detected a lower prevalence of *Proteus* among UTI patients (4.5%) which is alarming for the dissemination of *Proteus species* within a few years, especially in hospital settings among CAUTIs which give rise to a serious health problem. In recent studies in Egypt, a similar frequency of *Proteus* among urine samples was reported [9, 28] as well as in Iraq [29]. On the other hand, Mohsin and Al-rubaii from Iraq isolated *P. mirabilis* from 29.4% of urine samples [30], which is slightly higher than our results while a lower prevalence (9.2%) was reported in Iran [8]. This different incidence of *Proteus* sp. could be attributed to different geographic regions, hygiene measures, age groups of patients, and whether the studies were hospital or community-based.

In the current study, the incidence of UTIs by *Proteus* was higher among females than males, as 63 *Proteus* isolates (61.2%) were isolated from females while 40 *Proteus* isolates (38.8%) were isolated from males. These data agree with the findings obtained by most previous studies in Egypt, Iran, and Brazil [31–33]. UTIs are more common in women than in men due to the shorter length of the female urethra which reduces the distance the organism has to travel to reach the bladder. Additionally, contamination of the urinary tract with fecal flora is more frequent.

In our study, *Proteus* isolates were more prevalent among inpatients (79 isolates, 76.7%), representing hospital-acquired UTIs, compared to outpatients (24 isolates, 23.3%), representing community-acquired UTIs. This emphasizes the important role of these bacteria as a cause of hospital-acquired infections. The prevalence of *Proteus* was significantly higher in catheterized UTI patients (28.2%) than in non-catheterized patients

(14.9%). Our findings agreed with previous studies in Egypt, which reported that *Proteus* was mostly isolated from catheterized patients [31, 34]; on the other hand, a lower prevalence of proteus in CAUTI was reported in Iran (35%) [32] *Proteus* infection rates are rising in catheterized patients because of biofilm formation and the presence of several virulence factors that promote adhesion, such as flagella and IgA protease. There has been considerable investigation regarding catheter coatings designed to prevent microbial colonization and biofilm formation, termed "antifouling" [5]. Catheter coatings, catheter materials, and vaccination are novel preventive strategies for CAUTI. There has been considerable effort to develop catheters either coated or impregnated with various antibiotics e.g. nitrofurazone catheters which are available commercially. Modifying the material used for the production of catheters, such as latex, polyvinyl chloride (PVC), siliconized latex and hydrogel-coated latex [5].

Different degrees of resistance to the investigated antimicrobial drugs were detected in the antimicrobial sensitivity patterns of isolated *Proteus* species. The highest rates of resistance were against the SXT (70.9%) which matches with previous studies in Egypt (81.7%) and Iran (75%) [28, 35]. However, higher rates were reported between 90 and 100% [32, 34], as well as lower rates in Brazil (21.9%) [33] and Egypt (61%) [9]. High resistance to SXT is due to the overuse of trimethoprim/sulfamethoxazole as an empiric treatment for UTI in our country.

In the current study, we recorded the resistance to third-generation cephalosporin antibiotics; ceftazidime (55.3%), cefotaxime (34%), and ceftriaxone (30.1%). Regarding ceftazidime resistance, the result was higher than in other studies [9, 28, 35]. Regarding cefotaxime resistance, the current study agreed with Shaaban et al. in Egypt (29.3%) [9]. For ceftriaxone resistance, similar results (27%) were reported [32], and very high resistance was reported (72.7%) in Bangladesh [36]. This difference in antibiotic resistance rates can be explained by the extent of use of each antibiotic and the variation of antibiotic usage policy in these countries. Resistance to 3rd generation cephalosporins was significantly higher in *Proteus* isolated from CAUTIs than non-CAUTIs as these agents are usually administrated in CAUTIs in hospital settings [37] which complicates treatments of hospital-acquired UTIs and is alarming for dissemination of ESBL-producing organisms.

The rate of resistance to carbapenem represented by imipenem was 46.6%. Once thought to be the most effective treatment for *Proteus* infections, the acquisition of genes encoding carbapenemases and β-lactamases is a leading cause of the increased resistance to carbapenems. Ciprofloxacin is a broad-spectrum synthetic antibiotic belonging to the fluoroquinolone class and is effective in the treatment of UTIs. Ciprofloxacin resistance was recorded in 20.4% of the isolates in this study. Gentamycin and amikacin are aminoglycoside antibiotics that inhibit protein synthesis. In our study, tested *Proteus* isolates showed very high susceptibility to gentamycin and amikacin, suggesting that these antibiotics can be used to treat *Proteus* infections.

A high frequency of MDR (78.6%, 81/103) was found among all the studied isolates. The high prevalence of MDR *Proteus* strains in the current study may be due to non-indicated, random, and excessive use of these antibiotics in UTI therapy. We found that 74.6% of *Proteus* isolates from inpatients were MDR. This draws attention to the fact that *Proteus* strains, particularly *P. mirabilis,* have become a threat to hospital-acquired infections. Furthermore, 39 (70.9%) of *Proteus* isolates from catheterized patients were MDR. Biofilm formation plays a crucial role in drug resistance; as urinary catheters in the initial stages are colonized by a single species, such as *Enterococcus faecalis*, *E. coli*, *S. epidermidis*, or *P. mirabilis*. Subsequently, mixed communities develop, containing organisms such as *Providencia stuartii*, *P. aeruginosa*, *Proteus mirabilis*, and *Klebsiella pneumonia* facilitating the horizontal transfer of resistance genes of antibiotics, as transmissible plasmids that carry multiple resistance genes to other drugs giving rise to multidrug-resistant strains [38]. Strict infection control measures must be established to reduce the burden of the onset of MDR, which is a matter of concern. The MARI value that was obtained varied from 0.27 to 1, indicating a considerable increase over the highest MARI value of 0.2 [9]. The high MARI values indicate the widespread usage of the tested antibiotics in our nation and point to a substantial risk of the spread of antibiotic resistance.

The prevalence of ESBL-producing *Proteus* spp. is increasing worldwide. Our study showed that 39 *Proteus* strains were phenotypically ESBL producers (37.9%) which agreed with other studies (39%) [39]. Higher rates were reported in Egypt (51.7%) and (46.6%) [9, 40] while lower rates were reported (28.3%) in Egypt [28], Korea 22.5% [41], and Iran (10%) [8]. The difference in the prevalence of ESBL-producing *Proteus* may be due to different sample sources, antibiotic overuse, and hospital cross-infection. Prevalence of ESBL-producing *Proteus* strains was significantly higher in CAUTI (60%) than non-CAUTIs (12.5%), which agreed with Sokhn et al. [42]. All ESBL-producing *Proteus* isolates were MDR and showed higher resistance rates than non-ESBL-producing isolates. The coexistence of resistance to multiple antibiotics demonstrates the tendency for MDR to emerge among *Proteus* strains and suggests a simultaneous and ongoing transfer of resistance traits among bacterial pathogens.

In the current study, we tested 39 phenotypic ESBL-producing *Proteus* isolates (*P. mirabilis*) molecularly for ESBL genes bla_{TEM}, bla_{SHV}, $bla_{\text{CTX-M 1, 2, 8, 9, and 25}}$. We found that 38.5% carried ESBL genes. From 15 isolates, 11 had the bla_{TEM} gene (28.2%). Then, $bla_{\text{CTX-M-9}}$ was the only CTX gene detected in six isolates (15.4%), but $bla_{\text{CTX-M 1, 2, 8, and 25}}$ were not detected in any isolate. Only two isolates had the bla_{SHV} gene (5.1%). A moderate correlation was found between the presence of bla_{TEM} and resistance to ceftriaxone and cefotaxime (r was 0.538 and 0.473, respectively). All the isolates carrying ESBL genes were of *P. mirabilis* type. Four isolates carried 2 ESBL genes (bla_{TEM} and $bla_{\text{CTX-M-9}}$). First, *Proteus* species have been recognized to possess the bla_{TEM} β-lactamase gene for a long time. Tonkić and his co-authors reported that *Proteus* isolates carried the bla_{TEM} gene and none of the isolates had $bla_{\text{CTX-M}}$ or bla_{SHV} genes [24]. The $bla_{\text{CTX-M}}$ gene appeared to emerge in combination with the bla_{TEM} gene at the beginning and then replace the others as the dominant gene spreading. In this study, the bla_{TEM} gene was the most prevalent ESBL gene. This agrees with recent results from Egypt [28, 40], Nigeria [43, 44], Iran [35], Korea [41], and China. [45]

Regarding the prevalence of $bla_{\text{CTX-M-1,2,8,9,25}}$ genes, only $bla_{\text{CTX-M-9}}$ was detected in our study, which agreed with other studies [33, 45]. The prevalence of $bla_{CTX\text{-}M}$ genes has been increasing in the last few years, as reported in some studies [9, 35, 44]. The bla_{SHV} gene was the least detected in this study (5.1%). This agrees with other studies [35, 44], while few studies have found a higher prevalence of the bla_{SHV} gene [9]. These differences in the distribution of ESBL genes may be due to different geographical distributions, sources of infections, and risk factors predisposing to the emergence of such genes and the spread of MDR strains.

Molecular analysis with PCR is used to amplify sulfonamide resistance genes (*sul1* and *sul2* genes). Our results showed a high prevalence of *sul* genes (*sul1*; 60.2% and *sul2*; 65%) All these isolates were identified as *P. mirabilis.* Danilo de Oliveira and his co-authors reported a high prevalence of *sul* genes among *P. mirabilis* in Brazil [33]. Local and global reports of high prevalence of *sul* genes in clinical isolates of *E. coli* were also documented [13]. This suggests that these genes are universally involved in the transmission and carriage of sulfonamide resistance among bacteria. The *sul* genes are widely distributed as they are linked to mobile genomic elements such as integrons, transposons, and insertion sequences. The *sul1* gene is a component of class I integrons, which play a major role in the expression and dispersal of "multidrug resistance phenotypes" as they often harbor multiple gene cassettes that confer resistance to multiple antibiotics [13]. Although all phenotypically SXT-resistant isolates carried *sul* genes, we detected four isolates carrying the *sul2* gene but didn't show SXT resistance by the broth microdilution method. This can be explained by the presence of silent antibiotic-resistance genes [46].

Class 1 and 2 integrons have been disseminated among gram-negative bacteria. Horizontal gene transfer by integrons could play vital roles in the spread of the resistance traits and the occurrence of MDR. This study reported a high prevalence of class 1 integrons (92.2%) and class 2 integrons (68.9%) similar prevalence for class 1 integrons was reported in Egypt among *proteus* isolates; 80% [47] while lower rates were reported by other studies [35, 48]. Dissemination of class 1 and 2 integrons is an alarming sign of the emergence of MDR strains. Emerging MDR bacteria are now a major cause of morbidity and mortality worldwide and are posing a treatment challenge. Effective measures for the establishment and implementation of active surveillance and infection control programs with coherent antibiotic policies in hospitals and clinics to stop and control the spread of MDR and ESBLs in hospitals and communities.

ESBL-producing *Proteus* isolates from CAUTIs were typable by ERIC-PCR. ESBL-producing isolates showed a moderate degree of genetic similarity. However, a high similarity was reported among *Proteus* strains in different previous studies. [9, 48]

Conclusions

Our study detected a high prevalence of *Proteus* mirabilis isolated from UTIs, particularly catheterized inpatients. This highlights the role of this organism as one of the major causes of CAUTIs. Multidrug resistance was reported in 78.6% of isolates. Gentamycin was the most effective antibiotic against *Proteus*, followed by amikacin, then cefoxitin. On the other hand, *Proteus* isolates showed high resistance to SXT (80.6%) with increasing dissemination of *sul* genes among *Proteus* isolates. The current study showed increased resistance to imipenem (46.6%), which forms a high risk as it is considered the most effective antibiotic against Enterobacterals. The frequency of ESBL-producing *Proteus* isolates was 37.9%. ESBL-producing isolates showed higher resistance against many antibiotics than non-ESBL isolates. This study reported the coexistence of bla_{TEM} genes with $bla_{\text{CTX-M}}$ genes in ESBL-producing *Proteus* isolates. We recommend further studies on *Proteus* due to insufficient available data in Egypt and continuous screening for antimicrobial susceptibility patterns of *Proteus* as one of the causes of UTI to establish updated antimicrobial policies for treatment. More antibiotic resistance genes should be examined among *Proteus* to better understand their role in increased multidrug-resistant strains and

limit their dissemination. Routine molecular surveillance of *Proteus* in CAUTI cases, implementation of hospital infection control measures, and re-evaluation of empiric therapy for UTIs considering MDR trends are needed.

Abbreviations

CAUTI	Catheter-associated urinary tract infections
CFU	Colony forming unit
CLSI	Clinical Laboratory Standard Institute guidelines
ERIC-PCR	Enterobacterial Repetitive Intergenic Consensus-PCR
ESBLs	Extended-spectrum beta-lactamases
MARI	Multiple antibiotic resistance index
MDR	Multiple drug-resistant
MIC	Minimum inhibitory concentrations
SUL	Sulphonamide
SXT	Trimethoprim-Sulfamethoxazole
UTI	Urinary tract infection
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
N.A.H. and S.S.A. designed the study. S.S.A. drafted the manuscript. M.L., S.S.A., and D.N.K. performed the experimental work. S.S.A., M.L., and D.N.K. collected and analyzed the data. All authors have revised and approved the final manuscript.

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Data availability
All data generated or analysed during this study are included in this article.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Research Ethics Committee, Minia University, Faculty of Medicine Institutional Review Board (MUFMIRB Approval No. 276:2/2022). MUFMIRB operates according to the guidelines of the Declaration of Helsinki and CIOMS (Council for International Organizations of Medical Sciences). Informed consents were obtained from all participants in the study for the use of the samples.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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