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Phenotyping Of Extended-Spectrum B-Lactamases, Ampc B-Lactamases, And Carbapenemases Among Carbapenem Resistant In Proteus Mirabilis Isolated From Clinical Samples

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Abstract
Background and aims: *Proteus mirabilis is an enterobacterial species that naturally colonizes the gastrointestinal lumen and is present in many environmental features, such as water, soil, and feces-contaminated material. It is an opportunistic pathogen responsible for serious infections of the human urinary tract, respiratory tract, wounds, otitis media, and blood. It poses a potential threat to patients via the production of β-lactamases, which decrease the efficacy of antimicrobial treatment and impair the management of its pathogenicity. This study was established to determine the prevalence of extended-spectrum β-lactamases (ESBLs), AmpC, and carbapenemases of P. mirabilis isolated from various clinical specimens.*
Materials and methods: *In this study clinical samples were collected from (urine, wound and ear swab), and among these isolates, Proteus mirabilis was identified by phenotype and genotype*
Results: *The study included the collection of 250 samples from different clinical sources, including urine 101 (40.4%), wounds 109 (43.6%) and ear swabs 40 (16%) from patients attending Al-Kut Hospitals and private clinics, The prevalence of P. mirabilis was 10.4% among all collected samples. Female infection rate was 30.7% and male infection rate was 69.2%. The age group ≥ 50 years was most commonly infected with P. mirabilis. Whole Proteus mirabilis isolates were examined for their resistance against 17 antibiotics belonging to different classes, the highest rates of resistance were against class Tetracyclines antibiotic (doxycyclin) with (100%) and maximal sensitivity has been to ciprofloxacin and levofloxacin at 80.7%; as well as for norfloxacin, meropenem, and doprapemen at 92.3%. In phenotypic analysis extended spectrum B-lactamases production, it was discovered that 58.3% of clinical isolates were P. mirabilis, while AmpC ß-lactamase detect 19.2% and carbapenemase for P. mirabilis 11%.*
Conclution: *There is an urgent need to monitor hospitalized patients and improve healthcare in order to reduce the incidence of infection and outbreaks of infection with antibiotic-resistant Proteus.*
Keywords*: Proteus mirabilis, Extended-spectrum β-lactamase, AmpC, Carbapenemase*

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I. Introduction

Proteus mirabilis belongs to family *Enterobacteriacea* and can cause different clinical diseases including urinary tract infection, wound infection, meningitis in infant, rheumatoid, endocarditis, septicemia, and cystic fibrosis because it produces many virulence factors include (adhesion, toxins, flagella, enzymes production like urease, biofilm and highly resistance phenotype to antibiotics) [3]. *Proteus mirabilis* is one of the most common causative agents of urinary tract infections (UTIs), particularly in catheterized patients [4]. Proteus mirabilis is an opportunistic pathogen, causing a variety of community-acquired and nosocomial illnesses. Proteus mirabilis biofilm production is a significant resistance mechanism because it enhances resistance gene transfer, renders bacterial colonies antibiotic-resistant, increases antibiotic metabolism [5]. Additionally, the rise of *Proteus mirabilis* infections that form biofilms and are multi-drug resistant is a significant worldwide public health concern that calls for non-antibiotic therapy [6] Proteus mirabilis is poses a potential threat to patients via the production of β-lactamases, which decrease the efficacy of antimicrobial treatment and impair the management of its pathogenicity β-lactam resistance, mediated by the synthesis of β-lactamases, is being more and more frequently reported among P. mirabilis. Extended-spectrum β-lactamases (ESBLs), AmpC, and carbapenemases are the most common β-lactamase enzymes [7]. Carbapenems are the remaining treatment option against serious ESBL- and AmpC-related infections [8]. Unfortunately, treatment

failure is observed due to the rapid propagation of carbapenem-resistant isolates co-expression of AmpC, ESBL, or carbapenemase enzymes are the most common mechanisms of carbapenem resistance in *Enterobacteriaceae* [9]. The extensive resistance of Gram-negative bacteria is associated with the transfer of resistance genes via transferable genetic elements such as plasmids, which can readily pass through mutant clones and spread rapidly between countries. Most of this spread is therefore undetected as the normal human flora acquires those resistance genes and becomes a silent source of endogenous infections[10].In view of the increasing prevalence of Proteus resistance to various antimicrobials, especially β-lactam antibiotics, the objective of this study is to detect mechanisms of resistance to β-lactams (i.e., ESBLs, AmpC, and carbapenemases) among *P. mirabilis* isolates collected from healthcare facilities using phenotypic and molecular testing, to support the potential therapeutic options for treating these complicated clinical infections. Then, we determined the genetic diversity of different β-lactamase producing P. mirabilis isolates.

II. Materials and Methods

A total 250 specimens (urine, wound and otitis media) were collected from patients with different ages admitted to Al-Zahraa teaching hospital, Al-Karama teaching hospital, Al-Kut hospital and from private clinics in Waist province from both sex male and female during a period from 15th of December 2022 to 15th of march 2023. Each patient's has been recorded name, age, gender, underlying clinical condition and the date the sample was collected. *Proteus mirabilis* was provisionally identified based on characteristic growth on blood agar, non-lactose-fermenting colonies on MacConkey's agar media, and various biochemical reactions [11,12], and were confirmed using the automated Vitek 2 system. The purified isolates were preserved at -80°C in glycerol (25% v/v). A routine antimicrobial susceptibility test was performed by the Kirby–Bauer disk diffusion method against all P. mirabilis isolates on Mueller Hinton agar and the results were interpreted in accordance with the Clinical and Laboratory Standards Institute criteria [13]. The antibiotics used were piperacillin amoxicillin/clavulanic acid, aztreonam, imipenem, doprapemen, meropenem, doxycyclin cefoxitin, ceftazidime, cefotaxime, ciprofloxacin, gentamicin and amikacin.

A double-disk synergy test (DDST) was performed to examine the release of ESBL enzymes by used Ceftazidime (30 µg) and cefotaxime (30 µg) disks were applied on the MHA plates away from the centered amoxicillin–clavulanic acid (20/10 µg) diskplates were incubated at 37°C for 24 h. Cefoxitin-cloxacillin DDST (CC-DDS) was conducted A disk of cefoxitin (30 µg) only were placed on MHA plate, Any increase in the size of the inhibitory zone by ≥ 4 mm for cefoxitin indicate AmpC production [14]. Detection of carbapenemase enzyme A modified Hodge test to confirm the release of carbapenemases from P. mirabilis isolates in accordance with CLSI guidelines [15]. Phenotypically confirmed ESBL-, AmpC, and carbapenemase positive Proteus isolates were subjected to PCR using specific primers for ESBL genes (blaTEM, blaSHV, blaCTX-2, blaCTX-M), AmpC-encoding genes (blaAmpC, blaACT, blaACC, blaFOX), and carbapenemase genes (blaKPC, blaIMP, blaNDM, blaVIM and blaSIM) [16]. Statistical analysis was carried out using the One-Way ANOVA in the Microsoft Office Excel (*version 2016*) at the significant differences of $P<0.05$ [17].

III. Results

The current study was conducted on a total of 250 clinical specimens, including (urine, wound and ear swab), urine 101 (40.4%), wounds 109 (43.6%) and ear swabs 40 (16%) which were collected from patients with different ages admitted in hospital Table (1). Out of 250 samples proportion of bacterial growth was isolated: 200 (80%) positive culture, whereas no growth specimens are 50 (20%). The prevalence of P. mirabilis was 26 (10.4%) among all collected samples, Isolates were identified by traditional phenotypic and biochemical tests as well as molecular methods, where the confirmation rate was 100%. Female infection rate was 8(30.7%, male infection rate was 18 (69.2%). The age group ≥ 50 years was most commonly infected with P. mirabilis. The results showed that wounds infected 18 (69%) with *P. mirabilis* were more common from urine and ear sample. Diabetic 13 (50%) wounds were more affected by P. mirabilis than surgical wounds 5 (19.2%).

Table (1): Bacteria distribution according to samples

Sample	**Total No.**	***P. miirabilis* isolates**	**No growth**	**Sex**	
				M	**F**
Urine	101 (40.4%)	8 (7.9%)	14 (13.8%)	2	6
Wound	109 (43.6%)	18 (16.5%)	21 (19.2%)	16	1
Ear	40 (16%)	0	15 (37.5 %)	0	0
Total	**250**	**26 (10.4%)**	**50 (20%)**	**18**	**8**

Whole *Proteus mirabilis* isolates were examined for their resistance against 17 antibiotics belonging to different classes, the highest rates of resistance were against class Tetracyclines antibiotic (doxycyclin) at 100%,

followed by class Cephalosporin antibiotic (ceftazidim, ceftiaxon and cefatoxim) at 65.3%, and then class Penicillin antibiotic (amoxilin clavulanic acid, and piperacillin) at 53.8%, and then class aminoglycoside antibiotic (gentamicin) at 50%, and then lowest resistance with carbapenem (impenem) at 26.9%, aminoglycoside (amikacin) at 23% and (azthromycin, aztrenam, Cefoxitin) at 19.2%, and maximal sensitivity has been to ciprofloxacin and levofloxacin at 80.7% as well as norfloxacin, meropenem and doprapemen at 2.3% (Figure 1)

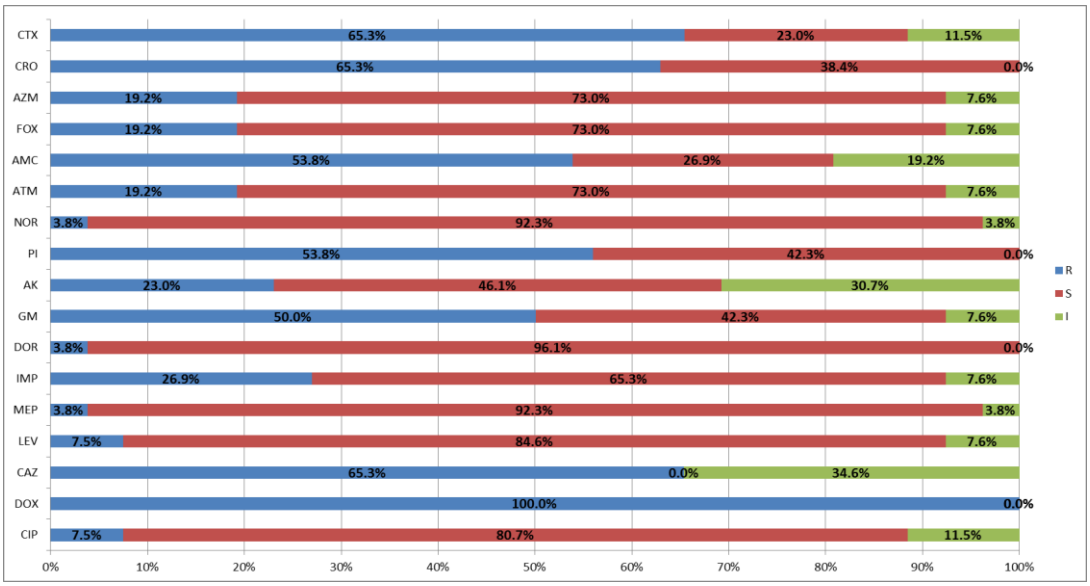

Figure (1): Frequency of antibiotics resistance profiles of Proteus mirabilis

In a phenotypic analysis extended spectrum B-lactamases production, it was discovered that 17(65.3%) of the clinical isolates of *P. mirabilis* were ESBLs produced by confirmatory testing whereas 10 (58.8%) were ESBL producers by screening testing. AmpC ß-lactamase was detected by phenotypic and genotypic procedures, phenotypically AmpC producers for P. mirabilis 5 (19.2%). Phenotypically survey of carbapenemase for *P. mirabilis* was 3 (11%) isolates.

IV. Discussion

In the present study, positive *P. mirabilis* isolates were 13% which isolated from various clinical samples; urine, wound, ear swab. The results showed that wounds infected 69% with *P. mirabilis* were more common from urine and ear sample. Diabetic 50% wounds were more affected by *P. mirabilis* than surgical wounds 19.2%. These percentage differences may be due to the difference in the geographical location of the source of the samples. The incidence of wound infection may be attributed to the high sensitivity of the exposed area of the wound to microbial invasion, whether the wound was spontaneous or resulting from a surgical operation. Just as the wounds become more susceptible to infections by not following the correct methods in terms of hygiene, and by not paying attention to sterilization rules by hospital staff, as well as other factors related to the personal hygiene of the patient himself and the medical staff [18]. Concerning urine samples, the percentage of Proteus mirabilis isolates that appeared in this study is 30.7% of the total 26 isolates of *Proteus mirabilis* and this result is close to the results of [19], as the Proteus mirabilis were isolated from urine samples with percentages 40% in the ear samples. In the present study, 100% of *Proteus mirabilis* isolates were high resistant to doxycycline, this observation was in accordance with results of other studies conducted by [20] who demonstrated that 90.6% of isolates were resistant to doxycycline, In addition it was in accordance with results of other studies conducted by [21] demonstrated that 95 % of isolates were resistant to doxycycline, but disagree with [22] recorded that the resistant to doxycycline antibiotic was 39.7%. Likewise, high resistance rate at 65.3% was reported against Cephalosporin antibiotic (ceftazidim, ceftiaxon and cefatoxim), the resistance rate was comparable with the study results with [23]. The majority of isolates, 70%, was exhibited resistance to Cephalosporins. Therefore, to decrease the chance of microorganisms attaining resistance to this drug should be carefully and wisely used. Also, resistance was shown against class Penicillin antibiotic (amoxilin clavulanic acid, piperacillin) with 53.8%, resistance another study recorded 64% [24] Gentamycin is an aminoglycoside antibiotic which is broad-spectrum and inhibitor for protein synthesis. In this study, P. mirabilis isolates show resistance to gentamycin (50%). This result agree with the researcher [25.] recorded 46.32%, In contrast another study recorded lower resistance 50% [26] while disagrees with [27] were the isolates show low resistance

(7.5%). The prevalence of ESBLs among Proteus mirabilis isolates in this investigation was 58.8%, which was comparable to the results of other studies conducted in Duhok City, Kurdistan Region, Iraq wa 57%) by [28], which is somewhat similar to the current findings [29] from Gorgan, Northeast Iran, where 58,3% of Proteus mirabilis produced ESBLs. The horizontal transfer of resistance genes between several species may be the cause of the findings in the current investigation. Antibiotic resistance may spread more easily thanks to plasmids that include the ESBL and for genes [30]. The choice of empirical and final antimicrobial therapy has been significantly impacted by ESBL-positive Proteus mirabilis. As a result, carbapenem use has grown in several hospitals in Al-Kut City, which has resulted in an increase in carbapenem resistance in these bacteria. The excessive and improper use of these drugs in the empirical treatment of wound infections and UTIs is responsible for the rise in the prevalence of ESBL-producing Proteus mirabilis, which is also spread by a variety of variables, including geography, population density, hygiene, and antibiotic use., clinical isolates were AmpC β-lactamases producers is 19.2%, similar results with another study [31], found 17.2 % of Proteus mirabilis isolates were resistant to this antibiotic. The present study was lower than previously recorded in Gorgan, Northeast Iran [32], found that 33.3% of *Proteus mirabilis* isolates were resistant to this antibiotic. AmpC enzyme production is one of the main mechanisms for drug resistance in *Enterobacteria*, conferring resistance to all β- lactams except fourth-generation cephalosporins and carbapenems [33] Infections caused by AmpC-positive bacteria are clinically and epidemiologically important and result in a higher degree of the patient mortality and morbidity [34]. By screening test found 30.7% of *Proteus mirabilis* clinical isolates, while 37.5% were carbapenemase producers by confirmatory test, which was comparable to results of other studies conducted in Baghdad City, 33.3% [35]. Carbapenemase enzymes confer resistance to broad-spectrum β-lactam antibiotic and it is a one of the important carbapenem resistant mechanisms in gram-negative bacteria. The differences in prevalence may be due to strains and time variations but overall indicate high incidence of MBLs among bacteria in our area [36].

Table (2): Phenotypic detection of ESBLs' production by Proteus mirabilis isolates from patients with UTIs, otitis media and wound infection

Characteristics	**Intermediate**	**Sensitive**	**Resistant**	**Total positive**
CTX	11,5%	23%	65,3%	65,3%
CAZ	34,6%	0	65,3%	65,3%
CRO	0	38,4%	65,3%	65,3%
ATM	7,6%	73%	19,2%	19,2%
Screening test	(17) 65,3 %			
Confirmatory test (DDST)	(10) 58,8 %			
ESBLs: extended spectrum ß-lactamase; CTX: cefotaxime; CAZ: ceftazidime; CRO: ceftriaxone; ATM: aztreonam; DDST: double disc synergy test; Positive: Resistance to CTX (≤ 27mm), CAZ (≤ 22mm), CRO (≤ 25mm) and AZT (≤ 27mm)				

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