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Multidrug Resistant Behavior Of *Proteus mirabilis* Isolated From patients with Urinary Tract Infections

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Abstract :

The aim of this study was to isolate and identify of *Proteus mirabilis* from patients with UTI and evaluate its sensitivity to commonly used antibiotics . *Proteus mirabilis* was isolated from 60 of 250 samples , (24%). *Proteus mirabilis* was absolute resistant to ampicillin, amoxicillin-clavulanic acid and trimethoprim -sulfamethoxazole. A total of 90% of *Proteus mirabilis* isolates were resistant to ceftriaxone, cefotaxime and cefixime; 80% were resistant to nitofurantoin and 70% were resistant to nalidixic acid. However, 90% of *Proteus mirabilis* showed a sensitivity to amikacin, 70 % to cefoxitin, 3% to nalidixic acid. Minimum resistance was reported toward ciprofloxacin ,1%. A (10%) of *Proteus mirabilis* were resistant to 9 out of 10 tested antibiotics at the same time including; Penicillins (ampicillin, amoxicillin-clavulanic acid), extended-spectrum cephalosporins (ceftriaxone, cefotaxime, cefixime); fluoroquinolones (ciprofloxacin); pyrimidine inhibitor of dihydrofolate reductase (trimethoprim - sulfamethoxazole); nitrofurans (nitofurantoin); quinilones (nalidixic acid). 90% of isolates were MDR.

A 40% of *Proteus mirabilis* isolated from human with UTIs were resistant to 9 out of 10 antibiotics at the same time including; penicillins (ampicillin, amoxicillin-clavulanic acid), extended-spectrum cephalosporins (ceftriaxone, cefotaxime, cefixime); pyrimidine inhibitor of dihydrofolate reductase (trimethoprim - sulfamethoxazole); nitrofurans (nitofurantoin); quinilones (nalidixic acid). An 80% of isolates were MDR. A (30%) of human UTIs isolates were resistant to 6 out of 10 antibiotics at the same time including; penicillins (ampicillin, amoxicillin-clavulanic acid), extended-spectrum cephalosporins (ceftriaxone, cefotaxime, cefixime); pyrimidine inhibitor of dihydrofolate reductase (trimethoprim - sulfamethoxazole). A 60% of the isolates were MDR . A (20%) of *Proteus mirabilis* isolated from human with UTIs were resistant to 4 out of 10 antibiotics at the same time including; penicillins (ampicillin, amoxicillin-clavulanic acid), extended-spectrum cephalosporins (ceftriaxone); pyrimidine inhibitor of dihydrofolate reductase (trimethoprim - sulfamethoxazole); . A $0% of the isolates were MDR. A (10%) of *Proteus mirabilis* isolated from UTIs were resistant to 6 out of 10 antibiotics at the same time including; penicillins (ampicillin, amoxicillin-clavulanic acid), extended-spectrum cephalosporins (ceftriaxone); pyrimidine inhibitor of dihydrofolate reductase (trimethoprim - sulfamethoxazole); nitrofurans (nitofurantoin); quinilones (nalidixic acid). A 60% of the isolates were MDR. A (10%) isolate of *Proteus mirabilis* from human with UTIs were resistant to 5 out of 10 antibiotics at the same time including; penicillins (ampicillin, amoxicillin-clavulanic acid), extended-spectrum cephalosporins (ceftriaxone, cefotaxime); pyrimidine inhibitor of dihydrofolate reductase(trimethoprim - sulfamethoxazole). A 50% of the isolates were MDR

In conclusion : MDR represent a serious problem in clinical practice and required serious attention from clinicians and health authorities.

keywords : Multidrug Resistant ,*Proteus mirabilis*, urinary tract infections, human.

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Introduction :

Urinary tract infections (UTIs) are one of the most common infectious diseases, and nearly 10% of people will experience a UTI during their lifetime[1]. Although several different microorganisms can cause UTIs, including fungi and viruses, bacteria are the major causative organisms ,they are responsible for more than 95% of UTI cases [2].Urinary Tract Infection defines a condition in which the urinary tract is infected with the pathogen causing inflammation .The major cause of UTI is gram negative bacteria which belongs to the *Enterobacteriaceae* family[3] .*Proteus* is considered as the main causative agent of urinary tract infection after *E.coli* , especially *proteus mirabilis* [4, 5].*Proteus* species known as they are opportunistic bacteria that are gram-negative , they belong to the family Enterobacteriaceae, They are widely distributed in natural environment and as microflora in human and animal intestines .In suitable conditions, they can cause wound, skin and urinary tract infections (UTIs) in animals and humans and can cause rheumatoid arthritis [6]. *P. mirabilis* is capable of causing symptomatic infections of the urinary tract including cystitis and pyelonephritis and is present in cases of asymptomatic bacteriuria, particularly in the elderly and patients with type 2 diabetes [7, 8].These infections can also cause bacteremia and progress to potentially life-threatening urosepsis. Additionally, *P. mirabilis* infections can cause the formation of urinary stones (urolithiasis). *P. mirabilis* causes between 1-10% of all urinary tract infections, varying with the geographic location of the study, the types of samples collected, and the characteristics of the patients examined [9]

Current study aims to isolation and identification of *P.mirabilis* from urine samples of infected human; Studying the frequency of *P.mirabilis* associated UTI in human and Detection of the resistance for antimicrobial therapies in vitro.

Patients and Methods :

Study area and study population

This study was conducted on human living in Baqubah city -Diyala Province 33°45'34.71"N; 44°36'23.97"E ,Northeast. The study extended from October 2017 to April 2018 [10-12]

Ethical consideration:

This study conducted according to the principles of Helsinki declaration. A full explanation of the purpose of this study in all patients before starting. Dully filled consent form obtained from all patients who agree to participate in the study. Approval of an ethical review committee of pathology department, college of veterinary medicine, Diyala University, Iraq, taken before initiation into the work[10, 13-19].

Urine samples from human:

A total of 60 individuals with the mean age was 27.88± 11.68 years,22 were male while 38 were females attended to Albatoul hospital for maternity and children health and Baqubah general hospital due to hard and permanent motive for urination, burnings feeling during urination and crossing recurrent, little amount of urines, patient with red colour, cloud looks, or even pink's brighten or colored of colas is the signs of finding bloods in urine urination, with robust -smell urines were enrolled in current study.

Midstream urine samples of were collected in a special tightly capped leak proof containers and labeled with special patient barcode for further investigations, all patients subjected to questionnaire before samples collected. Each sample was divided into two portions: one used for immediate examination, and another one used to culture on previous prepared blood agar and MacConkey agar for further identification and preservation

Microscopic and General urine examination:

About 10 ml of urine centrifugate and pellet placed on a clean glass slide and covered with cover slip and examined under magnifications of 10X and 40X with reduced light. Crystals and bacteria are estimated as "few," "moderate," or "many" according to sample, which indicate the infection. [20]

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Identification Of Isolates:

Growth On Selective And Differential Media

The urine specimens were directly streaked onto MacConkey and blood agars and incubated at 37ºC aerobically for 24 hours. The isolates were identified by bacteriological and biochemical assay. primary identification by morphological features such as swarming on blood agar, inability to ferment lactose on MacConkey agar and Gram staining propriety [21]

Microscopic Examination:

After culturing ,Single colony were picked up after the isolation of bacteria on MacConkey agar and blood agar, stained with gram stain , then examined under microscope to recognize their shape and length according to[21]

Vitek2 For Identification:

Identification of microorganisms is also accomplished by biochemical methods in Vitek system[22].It was used according to the manufacturer's instructions and [23]. The ID-GNB card Vitek 2 was used for identify the rod as (gram negative) by three hours.

It uses a fluorogenic methodology for organism identification and a turbidimetric method for susceptibility testing using a 64 well card that is bar-coded with information on card type, expiration date, lot number and unique card identification number. Test kits available include ID-GN (gram negative bacillus identification), ID-GP (gram positive cocci identification), AST-GN (gram negative susceptibility) and AST-GP (gram positive susceptibility). In the level of species it explicate forty-one fluorescents in tests of bio-chemical. If bio pattern don't matches with one of the taxon that particularly found in the database, results will be reports “low discrimination” (taxa two to three), “inconclusive” (> three taxxa), or “unidentified” (zero-matches). the result will be vague when slow nonfermenters metabolize ,it will be re-ported “various non fermenting gram-negative bacilli.” [24]

Antibiotic Susceptibility Test:

identified P. mirabilis isolates were tested for antibiotic susceptibility, the test was determined using Bauer Kirby disc diffusion method on Mueller-Hinton agar, by using disk of (six millimeter)filter paper by which typical quantity from the (A.B.) then P. mirabilis will be swabbed on the agar, the disk will be placing up the agar surface in the plate, (inoculate was prepared directly from an overnight agar plates adjusted to 0.5 McFarland standard of clinical laboratory standards institute (CLSI) , and are incubated overnight at 37oC [25]

Ten antibiotic disks (nalidixic acid, nitrofurantoin, ampicillin, trimethoprim /sulphamethazol, ciprofloxacin, cefotaxime, amikacin, ceftrixon, amoxicilline-clavulanic acid and cefixime) were used to detect the sensitivity of 20 isolates of *P. mirabilis* according to method (Clinical and Laboratory Standards Institute 2009)[26]. The mensuration of drug susceptibility accounts on inhibition zones for the growth , where zero or little inhibitions zone means resistance while big inhibition zones means that organisms are susceptible to that drug,. Incubation of Plates will be in 35ºC .

Statistical Analysis :

Data were statistically described in terms of frequencies and relative frequencies (percentages)[27, 28] . T test used for evaluation the differences[29, 30] . All statistical calculations were done using Microsoft Excel 2010 (Microsoft Corporation, New York,USA) [10, 11, 13, 15, 17, 27, 31-38]and SPSS version 17[13, 39] .The level of significance was 0.05 (two-tail)[12, 40]

Results :

Sensitivity Of *P mirabilis* Isolated From Urine Samples To Antibiotics

As shown in table (1), *P mirabilis* isolated from human urine samples have absolute resistant for Ampicillin, Amoxicillin-Clavulanic acid and trimethoprim -sulfamethoxazole. A total of 90% of *P mirabilis* have resistant for Ceftriaxone , Cefotaxime and Cefixime . A total of 80% of *P mirabilis* have resistant for Nitofurantoin and 70% of *P mirabilis* have resistant for nalidixic acid. A total of 90% of *P mirabilis* have sensitivity for amikacin, 70 % for Cefoxitin,3% for Nalidixic acid. Minimum resistance was recorded for Ciprofloxacin ,1%

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Table (1): Sensitivity Of P Mirabilis Isolated From Human Urine

Antibiotic Group	Antibiotic	Interpretation	
Penicillins	Ampicillin	Sensitive	0,(0%)
	(10µg AM)	Intermediate	0,(0%)
		Resistant	10/10,(100%)
	AMC	Sensitive	0,(0%)
	(Amoxicillin-Clavulanic acid)	Intermediate	0,(0%)
	20 µg -10µg	Resistant	10/10,(100%)
Extended-spectrum Cephalosporins	CRO	Sensitive	0,(0%)
	Ceftriaxone	Intermediate	1,(10%)
(3rd generation cephalospor-ins)	30µg	Resistant	9/10,(90%)
	CTX	Sensitive	0,(0%)
	Cefotaxime	Intermediate	1,(10%)
	30µg	Resistant	9/10,(90%)
	CFM	Sensitive	1,(10%)
	Cefixime 5µg	Intermediate	0,(0%)
		Resistant	9/10,(90%)
Fluoroquinolones	CX	Sensitive	7/10,(70%)
	Ciprofloxacin 5µg	Intermediate	2/10,(20%)
		Resistant	1 /10,(10%)
Aminoglycosides	Amikacin	Sensitive	9/10,(90%)
	(AK 30µg)	Intermediate	1/10,(10%)
		Resistant	0/10,(0 %)
pyrimidine inhibitor of dihydro-folate reductase	TS	Sensitive	0,(0%)
	Trimethoprim -	Intermediate	0,(0%)
	sulfamethoxazole	Resistant	10/10,(100%)
	1.25/23.75 µg		
Nitrofurans	NI	Sensitive	0,(0%)
	Nitofurantoin	Intermediate	2/10,(20%)
	300µg	Resistant	8/10,(80%)
quinilones	NA	Sensitive	3,(30%)
	Nalidixic acid	Intermediate	0,(0%)
	30µg	Resistant	7/10,(70%)

Multidrug resistant (MDR) *P.mirabilis* isolated from UTIs

As shown in table (2), current study reported 1/10, (10%) isolate of *P.mirabilis* from human UTIs have resistant to 9 out of 10 antibiotics at the same time belongs to six antibiotic groups Penicillins (Ampicillin, Amoxicillin-Clavulanic acid) , Extended-spectrum Cephalosporins (Ceftriaxone, Cefotaxime, Cefixime); Fluoroquinolones (Ciprofloxacin); pyrimidine inhibitor of dihydrofolate reductase(Trimethoprim -sulfamethoxazole) ; Nitrofurans(Nitofurantoin); quinilones (Nalidixic acid).MDR was 90%

As shown in table (3) , current study reported 4/10, (40%) isolate of *P.mirabilis* from human UTIs have resistant to 9 out of 10 antibiotics at the same time belongs to six antibiotic groups Penicillins (Ampicillin, Amoxicillin-Clavulanic acid) , Extended-spectrum Cephalosporins (Ceftriaxone, Cefotaxime, Cefixime); pyrimidine inhibitor of dihydrofolate reductase(Trimethoprim -sulfamethoxazole) ; Nitrofurans(Nitofurantoin); quinilones (Nalidixic acid).MDR was 80%

As shown in table (4) , current study reported 3/10, (30%) isolate of P.mirabilis from human UTIs have resistant to 6out of 10 antibiotics at the same time belongs to three antibiotic groups Penicillins (Ampicillin, Amoxicillin-Clavulanic acid) , Extended-spectrum Cephalosporins (Ceftriaxone, Cefotaxime, Cefixime);pyrimidine inhibitor of dihydrofolate reductase(Trimethoprim -sulfamethoxazole) .MDR was 60%

As shown in table (5) , current study reported 2/10, (20%) isolate of P.mirabilis from human UTIs have resistant to 4 out of 10 antibiotics at the same time belongs to three antibiotic groups Penicillins (Ampicillin, Amoxicillin-Clavulanic acid) , Extended-spectrum Cephalosporins (Ceftriaxone); pyrimidine inhibitor of dihydrofolate reductase(Trimethoprim -sulfamethoxazole) ; .MDR was 40%

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As shown in table (6) , the current study reported 1/10, (10%) isolate of P.mirabilis from human UTIs have resistant to 6 out of 10 antibiotics at the same time belongs to five antibiotic groups Penicillins (Ampicillin, Amoxicillin-Clavulanic acid) , Extended-spectrum Cephalosporins (Ceftriaxone); pyrimidine inhibitor of dihydrofolate reductase(Trimethoprim -sulfamethoxazole) ; Nitrofurans(Nitofurantoin); quinilones (Nalidixic acid).MDR was 60%

As shown in table (7) , the current study reported 1/10, (10%) isolate of P.mirabilis from human UTIs have resistant to 5 out of 10 antibiotics at the same time belongs to three antibiotic groups Penicillins (Ampicillin, Amoxicillin-Clavulanic acid) , Extended-spectrum Cephalosporins (Ceftriaxone, Cefotaxime); pyrimidine inhibitor of dihydrofolate reductase(Trimethoprim -sulfamethoxazole) ; MDR was 50%

Table(2):Frequency of *P.mirabilis* isolated from human UTIs and resistant to nine antibiotics belongs to six classes

Antibiotic Group	Antibiotic	inhibition zone diameter(mm)	N0.(%) of P.mirabilis	MDR %
Penicillins	Ampicillin (10µg AM)	0	1/10 (10%)	9/10 (90%)
	AMC (Amoxicillin-Clavulanic acid) 20 µg -10µg	0		
Extended-spectrum Cephalosporins (3rd generation cephalosporins)	CRO Ceftriaxone 30µg	0-16		
	CTX Cefotaxime 30µg	12-16		
	CFM Cefixime 5µg	0-12		
Fluoroquinolones	CX Ciprofloxacin 5µg	14		
pyrimidine inhibitor of dihydrofolate reductase	TS Trimethoprim -sulfamethoxazole 1.25/23.75 µg	0-10		
Nitrofurans	NI Nitofurantoin 300µg	8-14		
quinilones	NA Nalidixic acid 30µg	0-12		

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Table(3).Frequency of *P.mirabilis* isolated from human UTIs and resistant to eight antibiotics belongs to five classes

Antibiotic Group	Antibiotic	inhibition zone diameter(mm)	N0.(%) of *P.mirabilis*	MDR %
Penicillins	Ampicillin (10µg AM)	0		
	AMC (Amoxicillin-Clavulanic acid) 20 µg -10µg	0		
Extended-spectrum Cephalosporins (3rd generation cephalosporins)	CRO Ceftriaxone 30µg	0-16		
	CTX Cefotaxime 30µg	12-16		
	CFM Cefixime 5µg	0-12	4/10 (40%)	8/10 (80%)
pyrimidine inhibitor of dihydrofolate reductase	TS Trimethoprim -sulfamethoxazole 1.25/23.75 µg	0-10		
Nitrofurans	NI Nitofurantoin 300µg	8-14		
quinilones	NA Nalidixic acid 30µg	0-12		

Table(4)Frequency of *P.mirabilis* isolated from human UTIs and resistant to six antibiotics belongs to three classes

Antibiotic Group	Antibiotic	inhibition zone diameter(mm)	N0.(%) of *P.mirabilis*	MDR %
Penicillins	Ampicillin,(10µg AM)	0		
	AMC (Amoxicillin-Clavulanic acid) 20 µg -10µg	0		
Extended-spectrum Cephalosporins (3rd generation cephalosporins)	CRO, Ceftriaxone 30µg	0-16		
	CTX,Cefotaxime,30µg	12-16	3/10 (30%)	6/10 (60%)
	CFM,Cefixime 5µg	0-12		
pyrimidine inhibitor of dihydrofolate reductase	TS Trimethoprim -sulfamethoxazole 1.25/23.75 µg	0-10		

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Table(5)Frequency of *P.mirabilis* isolated from human UTIs and resistant to four antibiotics which belong to Three classes

Antibiotic Group	Antibiotic	inhibition zone diameter(mm)	N0.(%) of *P.mirabilis*	MDR %
Penicillins	Ampicillin (10µg AM)	0		
	AMC (Amoxicillin-Clavulanic acid) 20 µg -10µg	0		
Extended-spectrum Cephalosporins (3rd generation cephalo-sporins)	CRO Ceftriaxone 30µg	0-16	2/10 (20%)	4/10 (40%)
pyrimidine inhibitor of dihydrofolate reductase	TS Trimethoprim - sulfamethoxazole 1.25/23.75 µg	0-10		

Table(6).Frequency of *P.mirabilis* isolated from human UTIs and resistant to Six antibiotics belonging to five classes

Antibiotic Group	Antibiotic	inhibition zone diameter(mm)	N0.(%) of P.mirabilis	MDR %
Penicillins	Ampicillin (10µg AM)	0		
	AMC (Amoxicillin-Clavulanic acid) 20 µg -10µg	0		
Extended-spectrum Cephalosporins (3rd gen-eration cephalosporins)	CRO Ceftriaxone 30µg	0-16		
pyrimidine inhibitor of dihydrofolate reductase	TS Trimethoprim -sulfamethoxazole 1.25/23.75 µg	0-10	1/10 (10%)	6/10 (60%)
Nitrofurans	NI Nitofurantoin 300µg	8-14		
quinilones	NA Nalidixic acid 30µg	0-12		

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Table(7):Frequency of *P.mirabilis* isolated from human UTIs and resistant to eight antibiotics belonging to five classes

Antibiotic Group	Antibiotic	inhibition zone diameter(mm)	N0.(%) of P.mirabilis	MDR %
Penicillins	Ampicillin (10µg AM)	0		
	AMC (Amoxicillin-Clavulanic acid) 20 µg -10µg	0		
Extended-spectrum Cephalosporins (3rd generation cephalo-sporins)	CRO Ceftriaxone 30µg	0-16	1/10 (10%)	5/10 (50%)
	CTX Cefotaxime 30µg	12-16		
pyrimidine inhibitor of dihydrofolate reductase	TS Trimethoprim -sulfamethoxazole 1.25/23.75 µg	0-10		

DISCUSSION :

Ten isolates were tested for sensitivity to various antibacterial agents by the disk-diffusion method. The antibiotic susceptibility test was used for 10 types of antibiotics, these antibiotics were chosen for their frequent use in the treatment of urinary tract infection caused *by p. mirabilis*. As UTIs represent most common diseases diagnosed in outpatients clinic worldwide, the availability of new antimicrobial drugs for accurate improvement was vital issue . However, the critical challenge was the increase in immergence of antimicrobial drug resistance. According to [41] and [42], a bacterial isolate was considered non-susceptible to an antimicrobial agent when it tested resistant, intermediate or non-susceptible when using clinical breakpoints as interpretive criteria and not epidemiological cut-offs.

Based on the antibiotic susceptibility pattern of the isolated *P.mirabilis* from human urine samples , the bacterium was found to have an absolute resistant to Amoxicillin/ clavulanic 20 (100%); Ampicillin 20 (100%) . These results come in line with [43-48] . These results represent evidence for uncontrolled usage of these antibiotic in treatment of infectious conditions among population and in veterinary practice in such a way for development of absolute resistance via production of β lactamase .In contrary to current study , [49] ,reported 97% of *P.mirabilis* isolates were resist for Amoxicillin/ Clavulanic acid in India ; on the other hand ,other study reported 80.2% resistance for Amoxicillin/ Clavulanic acid [50] while in Nigeria,[45] reported 85% resistance for Amoxicillin/ clavulanic acid.

In Babylon-Iraq [51] reported 93.3 % resistance for penicillin ,while [52] reported that 90% of *P.mirabilis* was resist to Ampicillin and produce AMPC β-lactamase in India . The results of current study revealed contradictory to the WHO guidelines that Ampicillin was recommended as first choice for treatment of UTI in children in developing countries [53].

Due to low attention in some health fields we noticed in our study the decreasing trend of susceptibility which leads to multi drug resistance (MDR) that mentioned in the study of [54] ,which cause emerging clinical problem now a days.

Regarding extended-spectrum Cephalosporins (3rd generation),current study reported extremely high resistance (90%), for Ceftriaxone, Cefotaxime and Cefixime. These results were higher than that reported by [47] in Sudan ,who revealed that 33.3% of *P.mirabilis* isolated from human UTIs have re-

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sistance for Cefotaxime and Ceftriaxone. These results were higher than that reported by [55] in Ghana ,who revealed that *P.mirabilis* isolated from human UTIs have resistance for Cefotaxime (32%)and Ceftriaxone (30%).Current results come in contrary with that reported by [53],the *proteus* pathogen recovered from Egyptian children with UTIs was highly sensitive to Ceftriaxone (91%) and Cefotaxime (90%) . These results were higher than that reported by [43] who reported that resistant of *P.mirabilis* to Ceftriaxone (34-51%).

The possibility of development MDR proteus stains and having beta lactamase leads to the lower rate of cefotaxime-susceptibility in current study which harmonize the study of [56-58].The current result of cefotaxime low sensitivity disagree with [54] who found *P.mirabilis* was highly sensitive to cefotaxime in their work. While the study of [59] matches Ceftriaxone sensitivity result in our study that recorded high resistance towards both human and ovine isolates.

The high antibiotic resistance of *Proteus* spp. may be an indication of the resistance levels among the enterobacteriaceae and perhaps salmonellae since indiscriminate ingestion of antibiotics provides selective pressure, leading to a higher prevalence of resistant bacteria [60].*P.mirabilis* might be a potential reservoirs of resistance genes that could be transferred to other bacterial pathogens. The high levels of β-lactamase production and multi-drug resistance of the isolates are indications of an increase in the resistance menace reported by [55].

Regarding the sensitivity of *P. mirabilis to* fluoroquinolones ,mainly to ciprofloxacin ,current study found moderately sensitive to ciprofloxacin which were 40% & 70% respectively in ovine and human these results were closer to [50],they reported 42.9% and lower than that reported by [61, 62],in Nigeria where the sensitivity reach 75% and 80% respectively among *P.mirabilis* isolated from UTIs. On the other hand,[63] reported that sensitivity of *P. mirabilis* to ciprofloxacin reach up to 53.8 % while [48] reported that 33.3% of *P. mirabilis* isolated from UTIs were sensitive to ciprofloxacin

Regarding the sensitivity to aminoglycosides ,mainly for amikacin sensitivity for human in current study noticed and according to criteria of Clinical and Laboratory Standards Institute 2009, human and ovine isolates were moderately susceptible to amikacin which agree with [50] and come in contrary with [64] ,who reported absolute sensitivity for amikacin among all *P. mirabilis* isolates from UTIs. One of most interesting point ,was the gradual development for drug resistant strain even which was lower than that reported in other countries like India ,where 100%resistant was reported [48] and in Sudan [47] reported that 66.7% of *P. mirabilis* have resistant to amikacin while in Ghana about 5% of *P.mirabilis* isolated from UTIs have resistance for amikacin [55] .

Regarding trimethoprim -sulfamethoxazole sensitivity test, current study found absolute resistance in human (100%) while in ovine , high resistance (70%),these results come in accordance with [55, 65].In Taiwan [63] reported that *P.mirabilis* isolated from UTIs have resistance for trimethoprim - sulfamethoxazole in fact due to sensitivity of 31.7% of isolates only in 2012 compared to 35.8% in 2002.

For nitofurantoin sensitivity test, current study found absolute resistance in ovine (100%) while in human high resistance (80%), this disagree with the study of [59] shows 100% sensitivity and agree with [47] reported (66.7%) resistance .In Nigeria [61] reported that only 25% of *P.mirabilis* isolated from UTIs were sensitive to nitofurantoin. On the other hand [64] recorded 60% resistant while [43] reported resistant rate 34%-49% and [66] reported 14.3% resistance for *P.mirabilis* isolated from UTIs in South West, Nigeria .

For quinilones sensitivity test mainly for nalidixic acid , current study found absolute resistance in ovine(100%) while in human high resistance (80%), this result come in line with [62],who reported only 20% sensitivity among *P.mirabilis* isolated from UTIs in Nigeria. Current results disagree with the study of [59] shows 100% sensitivity .On the other hand , agree with[47, 48] who reported 100% resistance for nalidixic acid by *P.mirabilis* isolated from UTIs in human . In Nigeria [61] reported that only 25% of *P.mirabilis* isolated from UTIS

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were sensitive to nalidixic acid. These results indicate uncontrolled usage of nalidixic acid for treatment which in turn leads to development of drug resistant strains .

Multidrug Resistant (MDR) *P.mirabilis* Isolated From UTIs

MDR means 'resistant to more than one antimicrobial agent . One of the methods used to characterize organisms as MDR is based on in vitro antimicrobial susceptibility test results, when they test 'resistant to multiple antimicrobial agents, classes or subclasses of antimicrobial agents[67].

Current study revealed 10% of *P.mirabilis* have MDR for nine antimicrobial drugs(AMDs) which mean that MDR was 90% ; 40% of *P.mirabilis* have MDR for eight AMDs , MDR was 80%; 30% of *P.mirabilis* have MDR for six AMDs which mean that MDR was 60%;20% of *P.mirabilis* have MDR for four AMDs , MDR was 40%; 10% of *P.mirabilis* have MDR for six AMDs , MDR was 60%; 10% of *P.mirabilis* have MDR for five AMDs , MDR was 50%

Current results come in accordance with [68] who reported the presence of MDR among Enterobacteriaceae recovered from patient at the emergency department .The recovered proteus represent 7% of total MDR isolates which were resist to more than three antibiotic at the same time as a criteria for MDR category .The classes of antibiotic were similar to these in current study. In regards to resistance pattern by antibiotic categories, the three most common patterns were combined penicillins ± beta-lactamase inhibitors, flouroquinolone and TMP-SMX resistance [18/86 (21%)], combined penicillins ± beta-lactamase inhibitors, TMP-SMX and aminoglycosides resistance [11/86 (13%)] and combined penicillins ± beta-lactamase inhibitors, fluoroquinolones, TMP-SMX and aminoglycosides resistance [8/86 (9%)]. Current results come closely to [69] they reported absolute resistance for penicillins ± beta-lactamase inhibitors . Current results come closely to [70],they revealed the presence of 63% of *P.mirabilis* resist for more than two antimicrobial agent used for treatment of UTIs .Resistance to two antimicrobial drugs was reported in 38.5%, resistance to three antimicrobial drugs was reported in 19.2%, Resistance to four antimicrobial drugs was reported in 11.5%, resistance to five antimicrobial drugs was reported in 7.7%, Resistance to six antimicrobial drugs was reported in 28.6%.[70]. Current results come closely to [71],they reported 93.1 % MDR among UTIs pathogens including proteus and 4.4% were resist to eight antimicrobial drugs. The rate of multiple drug resistance is lower than [72] ,they reported MDR in 95% of UTIs pathogens and high as compared to other studies, in Ethiopia, [73] , found MDR for eight AMDs that included in current study was 82.6 % .In another study in Ethiopia,[74] ,reported MDR was 58.53% and *P.mirabilis* resist for four AMDs that enrolled in current study. on the other hand [75] reported 100% MDR among pathogens causing UTIs including *p. mirabilis* which have resistant to four AMD of penicillins , beta-lactamase inhibitors, TMP-SMX, third generation cephalosporins and aminoglycosides . While in Iran MDR was reported in range 7-35% among *P.mirabilis* isolated from preteen children [76].In Nepal [77],reported that *p. mirabilis* which have resistant to four AMDs (ampicillin, Cefotaxime; Ofloxacin and Cotrimoxazole),MDR range 57-86% .In Ethiopia,[78],reported 11.1% of MDR- *p. mirabilis* that resist five common AMD was recovered from patients with UTIs .

Surprisingly, we do not find any official registration about MDR in Iraq especially by veterinary authorities. In current study ,among *P.mirabilis* isolated from sheep with UTIs one of the most interesting points was the distribution of MDR .Current study reported MDR for four, five, seven and eight AMDs at the same time .MDR range from 40-80%. The most common feature was the absolute resistance for penicillins(Ampicillin, Amoxicillin-Clavulanic acid) ,while resistance for extended-spectrum cephalosporins (Ceftriaxone, Cefotaxime, Cefixime) and nitrofurans (nitofurantoin);was reported in 80% of isolates. This is usually attributed to several factors ,mainly the inappropriate usage of AMDs , mainly of broad spectrum activities by unauthorized individuals like farmers that will leads to development and distribution of MDR pathogens including *P.mirabilis* in environment which devel-

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oped a strategies for survival and transmission from animal to human and this include several mechanisms .

Bacteria usually override the activity of AMDs by genetic changes to enable resistance to AMDs . Resistance usually depends on acquisition of DNA from parents by the transfer of resistance genes that located on plasmids and transposons from one bacterium to another . Some plasmids encode for resistance to several antibiotics and can be transferred between bacterial species leading to high resistance gene pool among pathogens causing UTI[79]. Production of enzymes such as β-lactamase which inactivate or modify antibiotics may explain the absolute resistance for penicillins ; ultrastructural changes in the bacterial cell membrane, preventing the uptake of an AMDs , modification of the target leading to prevent interacts with the AMDs , development of metabolic pathways by bacteria which enable the site of AMDs action to be bypassed[80].

Other factors may facilitate distribution of MDR *P.mirabilis* such as gross misuse, this misuse over time, will lead to greater levels of mutation in bacteria, leading to high levels of bacterial resistance . Usage of the antimicrobial agents inappropriately, with low doses and for short time this enhance the development of resistant strains. Highly enforcement of AMDs with broad spectrum activity that are used as growth promoters as well as control infectious disease may lead to the development of MDR due to change in the genetic composition of bacteria.

Beside the possibility of incorrect administration of antimicrobial agents, lack of good controlling mechanism, which can increase the prevalence of multidrug resistant microorganisms [81] . Taken all together, these findings clearly show how resistant strains are expanding at an alarming rate in the area. With this trend, an AMDs which was effective a year ago might not be used next year. This creates great burden especially to people living in resource-poor countries where they couldn't ensure their daily bread let alone for medication. The cost of new antibiotics is also high which in turn poses great burden for poor countries. For these reason, species identification, surveillance and study of the epidemiology of antimicrobial resistance will assist in the therapeutic management of patients by reducing the prescription of large spectrum antibiotics to control of infections.

In conclusion : MDR represent a serious problem in clinical practice and required serious attention from clinicians and health authorities.

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