Open Access **Baghdad Science Journal** **P-ISSN: 2078-8665**
Published Online First: November 2021 **E-ISSN: 2411-7986**

DOI: http://dx.doi.org/10.21123/bsj.2022.19.3.0469

Evaluation of some Virulence Factors and Drug Resistance of Bacteria Isolated from the Urine of Patients with TCC-Bladder Cancer

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Received 17/11/2020, Accepted 3/3/2021, Published Online First 20/11/2021

Abstract:

Urinary tract infections (UTIs) mean microbial pathogens in the urethra or bladder (lower urinary tract). Important risk factors for recurrent UTI include obstruction of the urinary tract, use of a bladder catheter or a suppressed immune system. This study aims to isolate and identify bacteria from patients with TCC-bladder cancer or patients with a negative cystoscope and estimate antibiotic susceptibility patterns and evaluate some of the virulence factors. From a total of 62 patients with TCC-BC or negative cystoscope, only 35 favorable bacterial growths were obtained, including *Escherichia coli* (UPEC), a significant bacterial isolate, and *Stenotrophomonas maltophilia.* The percentage of multi drug-resistance bacteria (MDR) was identified in (62.8%) while the extended drug-resistance bacteria (XDR) was (28.5%). All isolates were producer for biofilm either moderately 18/35 (49%) or strongly 18/35 (51%). Only 25/35 (71%) isolates were produced for siderophore, while 10/35 (29%) isolates were non-produced. Inducing cytochrome P450 expression protein was seen in (14/35) 40% isolates. In conclusion**,** patients with TCC-BC or negative cystoscope who had a urinary catheter or immune-compromised were at high risk of infecting with nosocomial or opportunistic pathogens, which could be develop antibiotic resistance, the central problem in the cohort of patients undergoing chemotherapy or immune cancer therapy

Key words: Antibiotic susceptibility, CytochromeP450, Siderophore production, TCC-BC, Virulence factors.

Introduction:

Urinary tract infections (UTIs) mean microbial pathogens in the urethra or bladder (lower urinary tract), or ureter and pelvis of the kidney (upper urinary tract). In men, the prostate also may be involved [1]. Risk factors for recurrent UTI include obstruction of the urinary tract, use of a bladder catheter, a suppressed immune system, estrogen deficiency, genetic predisposition, and sexual intercourse [2]. Uropathogenic *E. coli* (UPEC) can invade bladder epithelial cells during UTI and form intracellular bacterial communities (IBC), which can be the cause of UTI recurrence [3].

Uropathogens bacterial have several virulence determinants necessary for initial adhesion and colonization of host mucosal surfaces, cell and tissue invasion, overcoming the host defense mechanisms, and causing persistent and chronic infections. These microbial virulence determinants include surface factors (fimbriae, adhesins, P pili and type-1 pili) and extracellular factors (toxins, siderophores, enzymes, and biofilm formation) [4]. Transient inflammation is considered part of the body's immune defense against pathogens, while persistent inflammation may promote cancer development [5]. This study was aimed to isolate and identify bacteria from urine samples obtained from patients with transitional cell carcinoma-bladder cancer and patients with negative cystoscope and to detect antibiotic

susceptibility patterns. Also, to evaluate some virulence factors in isolated bacteria.

Materials and Methods:

Methodology

Patients and sampling

In the present study, 62 urine samples were collected from patients with TCC—BC, and patients with negative cystoscope (as negative control for TCC-BC) from AL-Imamein AL-Kadhmain Medical City Hospital and Ghazi-AL-Hariri Specialized Surgery Hospital/ Medical City Hospital, Baghdad Iraq, in period extended for 10 months. These samples (50 from male and 10 from female) were cultured on MacConkey agar, nutrient agar, blood agar, and UTI medium for bacterial growth (incubated at 37°C for 24 hrs).

Identification of bacteria using VITEK 2compact system

Bacteria were subjected for identification by VITEK 2 compact system according to the instruction provided by the company. The turbidity was adjusted to 0.5 MacFarland turbidity range and measured using visible spectrophotometer DensiChekTM Plus. The bacterial suspension was used to inoculate the VITEK 2 system (bioMérieux/France). Interpretation of results was performed according to VITEK 2 compact system special software to identify bacterial species and strains**.**

Determination of antibiotic susceptibility using VITEK® 2 compact

Susceptibility to the following antimicrobial agents (depending on the bacterial genus) was determined using VITEK 2 compact system: antibiotic included: Ticarcillin, Ticarcillin/ clavulanic acid, Piperacillin, Piperacillin/Tazobactam, Imipenem, Meropenem, Amikacin, Trimethoprim/sulfamethoxazole, Gentamicin, Tobramycin, Ciprofloxacin, Ceftazidime, Minocycline, Cefepime, Azteronam, Colistin, Trimethoprim, GN.H.L.S Gentamicin High Level (synergy), Streptomycin High Level (synergy), linezolid, tetracycline, Erythromycin, Tigecycline, Levofloxacin, Vancomycin, Teicoplanin, Benzylpenicillin, Oxacillin, Clindamycin, Fusidic acid, Moxifloxacin and Rifampicin. The break point for each antimicrobial used was determined according to CLSI (2019) [6].

Identification of uropathic *E.coli* by detection of *pap E* using Conventional PCR

Uropathogenic *E.coli* was identified by detection of *pap E* using conventional PCR. Extraction of DNA was done using XIT™ Genomic DNA Purification Kit following manufacturer instructions. PCR was performed using a specific primer set for the detection of *pap E* in bacterial extracted DNA[7]. PCR products were electrophoresed in 1.5% agarose gel. The appearance of a band with a molecular size 321 bp referred to the amplification of *papE.*

Biofilm assay using Tissue culture plate method

Overnight Bacterial growth was grown on LB broth at 37 °C for 24hr. The culture was adjusted to 0.01 with McFarland solution. Of bacterial growth,50µl was added to 150 µl of LB broth on tissue culture plate wells and incubated at 37 °C for 24 hrs. The culture was removed carefully, and wells were washed two times with 250 µl distilled water. Then, 250 µl of (0.2%) of Crystal violet was added and incubated for 10 minutes at 25 °C. Wells were washed with distilled water 2-3 times and dried at room temperature. Finally, 200 µl of 95% ethanol was added to wells. Optical density (O.D) was measured at 630 nm. Interpretation producer of results was done [8].

Siderophore Production

Siderophore production using M9 medium supplemented with glucose 20% and casmino acid 20% was prepared [9].Bacterial growth turbidity was adjusted to 0.01 with McFarland solution, then cultured in M9 medium supplemented with casmino acid and glucose (2 gm/L each), and incubating at 37 °C for 48hrs. Appearing growth in medium indicates positive results.

Cytochrome P450 production

Detection of cytochrome P450 (P450)-producing bacteria was done using an M9 medium containing a P450-inducer as the sole carbon source 2-ethoxyphenol as a carbon source. Bacterial isolates were cultured in tubes contain M9medium incubated at 37C for seven days [10]. Quantification of cytochrome produced by bacteria was done using Modified microplate method [11].

Results:

Bacterial infection (Cystitis) in urine samples

From a total of 62 urine samples, only 32/62(51.6%) samples were positive for bacterial growth, including different species of bacteria. Three patients had co-infection (two bacterial species), so the total number of bacterial isolated was 35 isolates. The vast majority of bacteria isolated was Gram-negative bacteria 30/35(88.5%) while Gram-positive bacteria consisted 5/35 (11.5%).

Uropathic *Escherichia coli* is the most predominant bacteria isolated from patients with

TCC-BC, then *Stenotrophomonas maltophilia*, *Burkholderiacepacia*, *Pseudomonas spp.*, *Enterococcus faecalis*, *Ochrobactrum anthropi*, *Acinetobacter spp.*, *Sphingomonas paucimobilis*, *Bordetella bronchiseptica*, *Ralstonia mannitolilytica*, *Brevundimonas vesicularis* and *Kocuria rosea*, (Table 1).

Table 1. Bacterial identification in urine samples from patients with TCC and patients with negative cystoscopy

Bacterial species	Patient code	Number of patients
E.coli	5, 25,26, 31,35,40,94	7
Stenotrophomonas maltophilia	6,27,38,46,50, 30	6
E.faecalis	23a,31a,40a,43	4
Burkholderia spp	36,42,93,98	4
Pseudomonas spp	19,21,22	3
Ochrobactrum anthropi	8,39, 47	3
Acinetobacter spp	96,72	2
Sphingomonas spp	23,97	2
Bordetella spp	49	1
Brevundimonas vesicularis	44	1
Ralstonia mannitolilytica	92	1
Kocuria rosea	90	1

It is important to explain presence of *E.coli* and *E.faecalis* in patients with TCC-BC in different stage since TCC-BC patients under high risk to infected with nosocomial bacteria even before surgery. While infection with opportunistic bacteria such as *S. maltophilia, P.aeruginosa, B. bronchiseptica, R. mannitolilytica, B. vesicularis* and *K. rosea* may be introduced to urinary tract through urinary catheter.

Antibiotic Susceptibility

Antibiotic susceptibility of different bacterial isolates from urine samples using VITEK 2 compact system are shown in Table 2.

E. coli reveals highly sensitivity to imipenem and meropenem while resistance in percentage 100% (7/7) for Ticarcillin, Ticarcillin/Clavulanic Acid, piperacillin, piperacillin/tazobactam, Ceftazidime, Cefepime, aztreonam and Trimethoprim/Sulfamethoxazole

Table 2. Antibiotic susceptibility for *Escherichia coli*

Antibiotic classes according to the mode of action	Code of bacteria / Antibiotic	5	25	26	31	35	40	94
Cell wall inhibitor	Ticarcillin	R	R	R	R	R	R	R
	Ticarcillin/Clavulanic	R	R	R	R	R	R	R
	Piperacillin	R	R	R	R	R	R	R
	Piperacillin/ Tazobactam	R	R	R	R	R	R	R
	Ceftazidime	R	R	R	R	R	R	R
	Cefepime	R	R	R	R	R	R	R
	Imipenem	I	S	S	S	S	S	S
	Azteronam	R	R	R	R	R	R	R
	Meropenem	I	S	S	S	S	S	S
	Gentamycin	R	R	R	R	R	R	S
Protein synthesis inhibitor	Amikacin	R	S	R	I	S	S	S
	Tobramycin	R	R	R	R	R	R	S
	Minocycline	I	R	R	I	R	S	S
DNA synthesis inhibitor	Ciprofloxacin	R	R	R	R	R	R	S
Folic acid synthesis inhibitor	Trimethoprim/Sulfamethoxazole	R	R	R	R	R	R	S
phenotype		MDR ESBL^r Polypeptide^r Carbapenemase^r	MDR ESBL	MDR ESBL^r (ToB, NET, AMI)$^+$ aminoglycosides^r	MDR AmpC$^+$ Cephalosprinase$^+$ CARBA$^+$ Porins$^+$	MDR ESBL	MDR AmpC$^+$ Cephalosprinase$^+$, CARBA$^+$ Porins$^+$	MDR ESBL

ESBL: extend spectrum beta-lactamase, MDR:multi drug-resistance, R:Resistance, +: positive, S:Sensitive, I: Intermediate.

Antibiotic susceptibility of *P. aeruginosa* and *P. fluorescence* shown in Table 3. *P. fluorescence* differ from *P. aeruginosa* in three antibiotics, aztreonam, minocycline and Trimethoprim/sulfamethoxazole.

Table 3. Antibiotic susceptibility for *Pseudomonas spp*.

Antibiotic classes according to the mode of action	Species	*P. aeruginosa*		*P.fluorescence*
	Code of bacteria Antibiotic	19	21	22
Cell wall inhibitor	Ticarcillin	R	R	S
	Ticarcillin/Clavulanic	R	R	S
	Piperacillin	R	R	R
	Piperacillin/Tazobactam	R	R	R
	Ceftazidime	R	R	I
	Cefepime	R	R	S
	Imipenem	R	R	S
	Aztreonam	-	-	R
	Meropenem	R	R	S
	Gentamycin	R	R	S
Protein synthesis inhibitor	Amikacin	R	R	S
	Tobramycin	R	R	S
	Minocycline	-	-	S
DNA synthesis inhibitor	Ciprofloxacin	R	R	S
Folic acid synthesis inhibitor	Trimethoprim/Sulfamethoxazole	-	-	S
	phenotype	Carbapenemase, HL CASE++ R - CARBAPENEMS (imp^r)-ESBL^r Polypeptides^r		

ESBL: extend spectrum beta lactamase, MDR: multi drug- resistance, R: Resistance, + positive, S: Sensitive, I: Intermediate.

Only two antibiotics included in VITEK 2 compact system depend on updating for *S. maltophilia*, which was showed Resistance to Trimethoprim and Trimethoprim/sulfamethoxazole (83%) isolates, Table 4.

Table 4. Antibiotic susceptibility for *Stenotrophomonas maltophilia*

Antibiotic classes according mode of action	Code of bacteria / Antibiotic	6	27	30	38	46	50
Inhibits folic acid synthesis	Trimethoprim	R	R	R	R	R	R
	Trimethoprim/Sulfamethoxazole	R	R	S	R	R	R
	phenotype	XDR	XDR	MDR	XDR	XDR	XDR

XDR: extended drug resistance, MDR: multi drug resistance, R: Resistance, S: Sensitive.

Bordetella bronchiseptica, *Ralstonia mannitolilytica*, *B.vesicularis*, *Burkholderia cepacia*, *Ochrobactrum anthropi*, *Acinetobacter spp*., *Sphingomonas paucimobilis* were showed variable patterns of antibiotic susceptibility, Tables 5 and 6.

Table 5. Antibiotic susceptibility of *B.bronchiseptica, R. mannitolilytica, B.vesicularis* and *O.anthropi*

Antibiotic classes according to the mode of action	Code of bacteria / Antibiotic	*B.bronchiseptica* 49	*R. mannitolilytica* 92	*B.vesicularis* 44	*O.anthropi* 8	39	47
Cell wall inhibitor	Ticarcillin	I	R	R	R	R	R
	Ticarcillin/Clavulanic	I	R	S	R	R	R
	Piperacillin	R	R	I	R	R	R
	Piperacillin/Tazobactam	R	R	S	R	R	R
	Ceftazidime	R	R	R	R	R	R
	Cefepime	R	R	I	R	R	R
	Imipenem	S	S	S	I	R	R
	Aztreonam	R	R	R	R	R	R
	Meropenem	R	I	S	I	R	R
	colistin	I	R	R	R	R	R
	Gentamycin	R	R	I	R	R	R
Protein synthesis inhibitor	Amikacin	R	R	S	R	R	R
	Tobramycin	R	R	R	R	R	R
	Minocycline	I	S	S	I	I	I
DNA synthesis inhibitor	Ciprofloxacin	R	S	R	R	R	R
Folic acid synthesis inhibitor	Trimethoprim/Sulfamethoxazole	R	S	R	R	R	R
	phenotype	MDR	MDR	MDR	MDR	XDR	XDR

MDR: multi drug-resistance, R: Resistance, S: Sensitive, I: Intermediate

Table 6. Antibiotic susceptibility for *Acinetobacter spp., Sphingomonas paucimobilis* and *B.cepacia*

Antibiotic classes according to the mode of action	Code of bacteria / Antibiotic	*S.paucimobilis*		*Acinetobacter*		*B.cepacia*			
		23	97	*A.lwoffii* 72	*A.haemolyticus* 96	36	42	93	98
Cell wall inhibitor	Ticarcillin	R	S	R	R	R	R	R	R
	Ticarcillin/Clavulanic	R	I	R	R	R	R	I	R
	Piperacillin	R	R	R	R	R	R	R	R
	Piperacillin/Tazobactam	R	R	R	R	I	R	R	R
	Ceftazidime	R	R	R	R	S	R	R	R
	Cefepime	R	R	I	R	S	R	R	R
	Imipenem	R	I	R	I	S	R	R	I
	Aztreonam	R	R	R	R	R	R	R	R
	Meropenem	R	I	R	I	I	I	R	I
	colistin	S	R	R	R	S	R	S	R
Inhibits Protein synthesis	Gentamycin	R	R	I	R	S	R	I	R
	Amikacin	R	R	R	R	S	R	I	R
	Tobramycin	R	R	R	R	S	R	S	R
	Minocycline	R	S	S	S	S	I	S	I
Inhibit DNA synthesis	Ciprofloxacin	R	S	R	R	S	R	R	R
Inhibits Folic acid synthesis	Trimethoprim/Sulfamethoxazole	R	R	R	S	R	S	R	S
	phenotype	XDR	MDR	MDR -BETA LACTAMS^r CARBAPENEMASE^r Polypeptides^r	MDR		MDR	MDR	MDR

ESBL: extend spectrum beta-lactamase, MDR: multi drug-resistance, R: Resistance, S: Sensitive, I: Intermediate

for *Kocuria rosea.* Antibiotic susceptibility patterns were shown in Tables 7 and 8.

Gram-positive bacteria were included in four isolates of *Enterococcus faecalis* and one isolated

Table 7. Antibiotic Susceptibility for *Enterococcus faecalis*

Antibiotic classes according to the mode of action	Code of bacteria / Antibiotic	*Enterococcus faecalis* 23a	31a	40a	43
Cell wall inhibitor	Ampicillin	S	S	S	S
	Ceftazidime	R	R	R	R
	Cefepime	R	R	R	R
	Imipenem	R	R	R	R
	Vancomycin,	R	R	R	R
	Teicoplanin	R	R	R	R
Inhibits protein synthesis	GN.H.L. S Gentamicin High Level (synergy)	S	S	S	S
	Streptomycin High Level (synergy)	R	R	R	S
	Amikacin	R	R	R	R
	Tobramycin	R	R	R	R
	Lineozolid	I	S	S	S
	Tetracycline	R	R	R	R
	Erythromycin	R	R	R	R
	Tigecycline	S	S	S	S
Inhibits DNA synthesis	Ciprofloxacin	R	R	R	I
	Levofloxacin	R	R	R	R
phenotype		MDR	Glycopeptide^r (VAN A LIKE)		

MDR:multi drug-resistance, R: resistance, S:Sensitive, I: Intermediate

Note: Bacteria code with a symbol (a) referred to two species of bacteria (dull infection) were isolated from the urine of the same patient, such as 23a was *Enterococus faecalis* and 23 was *Sphingomonas paucimobilis* antibiotic pattern in the Table 6. Also, 31a and 40a was *Enterococus faecalis* while 31, 40 were *Escherichia coli* antibiotic pattern in Table 2.

Table 8. Antibiotic Susceptibility for *Kocuria rosea*

Antibiotic classes according to the mode of action	Code of bacteria / Antibiotic	*Kocuria rosea* 90
Cell wall inhibitor	Ceftazidime	R
	Cefepime	R
	Imipenem	R
	Vancomycin,	R
	Benzylpenicillin	R
	Oxacillin	R
	Meropenem	R
	Teicoplanin	R
Protein	Gentamicin	S
Synthesis inhibitor	Tetracycline	R
	Tigecycline	S
	Clindamycin	R
	Erythromycin	R
	Fusidic acid	R
DNA synthesis inhibitor	Ciprofloxacin	S
	Moxifloxacin	R
RNA synthesis inhibitor	Rifampicin	R
Folic acid synthesis inhibitor	Trimethoprim/Sulfamethoxazole	S
phenotype		MDR glycopeptidesviss Beta-lacam modification of PBP Oxazolidinone ^{r} Macrolides/lincosamides/streptogrami^{r} MLSB

- MDR:multi drug resistance, + positive , R: Resistance, S:Sensitive.

Identification of uro-pathogenic *E.coli* using *pap E*

Uro-pathogenic *E.coli* was first identified as *E.coli* using VITEK 2 Compact system, then at the molecular level using conventional PCR to detect the presence of *papE* and the results showed that 7/7 isolates had *papE*, Fig. 1.

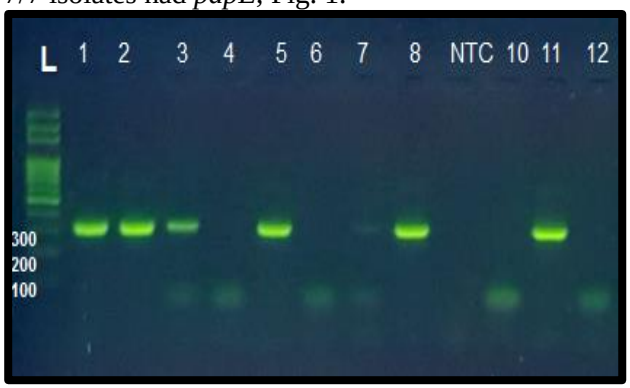

Figure 1. Identification of *pap E* in *Escherichia coli*. Lane 1,2,3,5,8, 11: isolates positive for *pap E*. Lane 4,6,7,10,12: isolates negative for *pap E*. Lane NTC: no template control. Lane L: DNA ladder molecular size control. Agarose concentration was 1.5%. Voltage used 45v and current used 100 Ampere for 1.30h.

Virulence Factors of Isolated Bacteria

Biofilm formation

The results of detection of biofilm formation of 35 isolates using TCP methods revealed that 17/35(49%) isolates were a strong producer for biofilm while 18/35 (51%) isolates were moderate producer for biofilm, Fig. 2.

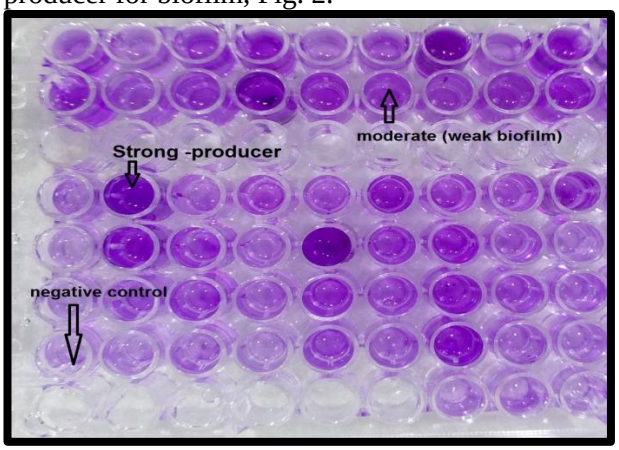

Figure 2. Identification of Biofilm formation using ELISA readers: (TCP) method.

Siderophore production

Siderophore production ability of 35isolates using M9 medium (Supplemented with vitamin B12 Casamino Acids and glucose) showed that 25/35

(71%) isolates were producer (growing on M9 medium) while 10/35 (29%) isolates were non-producer (no growth on M9 medium), Fig. 3.

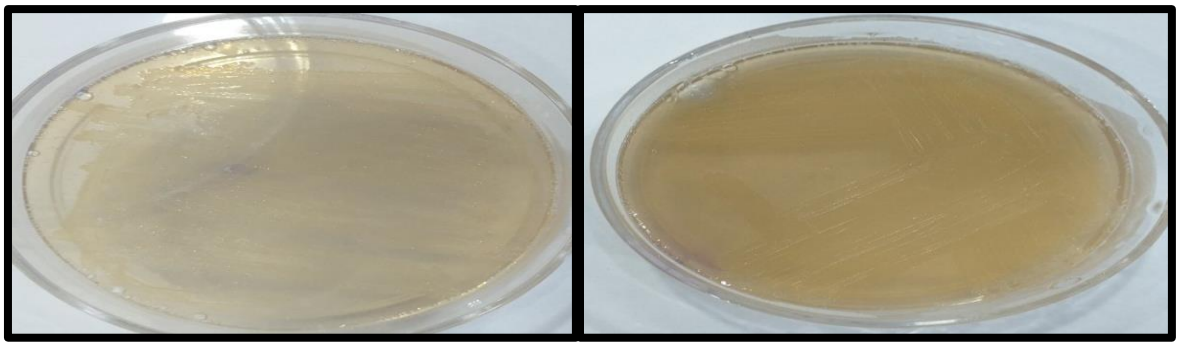

Figure 3. Identification of Siderophore production usingM9medium. Bacterial growth after incubation 37^{0}C for 24hr.

Escherichia coli (UPEC), *Stenotrophomonas maltophilia, Enterococcus faecalis, Pseudomonas aeruginosa, Brevundimonas vesicularis* and *Ralstonia mannitolilytica* isolates were showed ability for siderophore production, while species of *Burkholderia cepacia, Sphingomonas paucimobilis* and *Ochrobactrum anthropi* isolates were showed variable ability for Siderophore production, but species of *Pseudomonas fluorescence, Acinetobacter lwoffii, Acinetobacter haemolyticus, Bordetella bronchiseptica,* and *Kocuria* rosea isolates were not produced for siderophore.

Cytochrome P450

The ability of 35 isolates to grow on supplemented minimal medium for inducing cytochrome P450 expression protein was seen in 14/35 (40%) isolates as induced while (O.D reading => 0.2), while not induced in 21/35 (60%) isolates. *Sphingomonas paucimobilis, Ochrobactrum anthropi, Acinetobacter lwoffii* and *Acinetobacter haemolyticus* isolates were induced *Stenotrophomonas maltophilia, Enterococcus faecalis, Pseudomonas aeruginosa,* and *Burkholderia cepacia* isolates revealed variable ability for inducing. However, *Escherichia coli (UPEC) Brevundimonas vesicularis, Ralstonia mannitolilytica Bordetella bronchiseptica* and *Kocuria* rosea isolates showed no ability for inducing, Fig. 4.

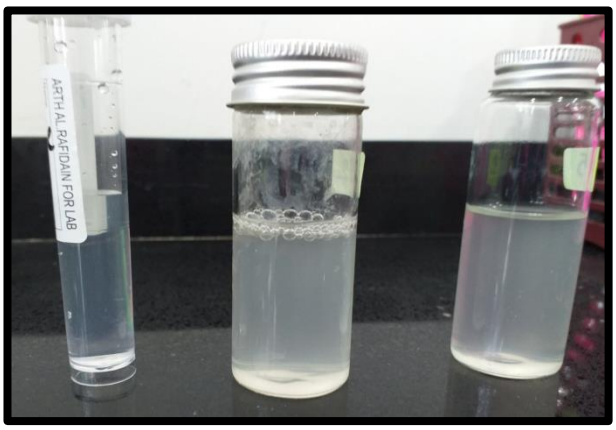

Figure 4. Turbidity in cytochrome induced medium after one week (incubation at 37C).

The range of O.D reading in ELISA reader for all isolates either producer or non-producer of cytochrome P450, in addition to negative control which contains only M9 medium, Fig. 5**.**

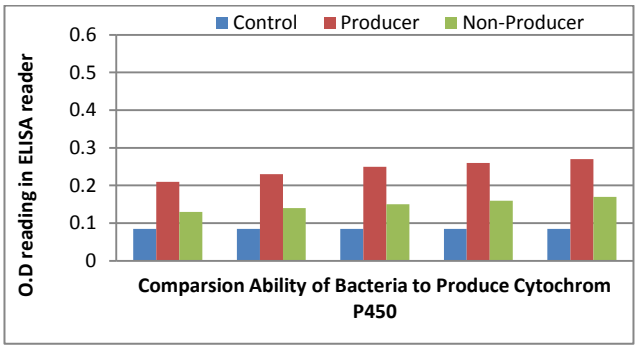

Figure 5. Diagram explains the ability of bacteria to produce cytochrome P450proteins (O.D reading).

Discussion:

Bacterial infection (Cystitis)

The infection of *S.maltophilia* and *P.aeruginosa* in patients with a negative cystoscope, may be related to those patients' bloody urine and the nature of these bacteria, especially

*S.maltophilia*which need iron as essential nutrients for bacterial survival. Iron was found to play a crucial role in the regulation of numerous virulence factors [12].

A study done in Egypt in 2015 found that, in 20 patients with TCC-BC, only 15 of them had urinary tract infection, and the most predominant organism isolated was *Escherichia coli*[13]. A study in the United States at (2013) referred to that endogenous bacteria, including cystitis, caused by bladder bacteria (bladder pathogens) and some intestinal opportunistic *Pseudomonas aeruginosa,* metabolically activate the bladder procarcinogens [14], while urinary bladder infection by *E. coli* plays a significant additive and synergistic roles during bladder carcinogenesis [15]. A study in China in 2019 from a total of 24 urine sample from patients with bladder cancer revealed the abundance of common core bacteria is significantly higher in bladder cancer urine samples, especially *Acinetobacter* which is much higher in bladder cancer urine samples because of bacterial ability for biofilm formation, adhesion and invasion of epithelial cells [16].

A hospital-based comparative cross-sectional study in Ethiopia in 2019 included 240 patients with any type of cancer; they found that *E. coli* (32.1%) was the most common bacteria isolated followed by *Klebsiella* species (25.0%), *Staphylococcus aureus* (21.4%), *Enterococcus* species (10.7%), *Serratia* species (7.1%), and *Enterobacter aerogenes*(3.6%) in the urine of patients with any type of cancer [17]. It is essential to focus on urinary tract infection (Inflammation or chronic Inflammation) since that chronic inflammation induced by biological factors associated with increased risk of human cancer at various sites due to Inflammation activates a variety of inflammatory cells, which induce and activate several oxidant-generating, by which these enzymes produce high concentrations of diverse free radicals and oxidants that react with each other to generate other more potent reactive oxygen and nitrogen species which can damage DNA, RNA, lipids, and proteins thus increased mutations and altered functions of enzymes and proteins (e.g., activation of oncogene-products and inhibition of tumor-suppressor proteins) [18].

Antibiotic Susceptibility

This study percentage of multi drug resistance bacteria MDR (62.8%) while extended drug resistance was XDR (28.5%). In Zakho city in Iraq 2016, a study included 106 UPEC isolates, resistance was (100%) to penicillin, ampicillin, and aztreonam. While (100%) were sensitive to imipenem and meropenem [19]. Another study in Iraq in Erbil 2018 included 25 isolates of UPEC, resistance percentage between 28 to 96 % to amikacin, amoxicillin, ampicillin, chloramphenicol, ciprofloxacin, erythromycin, nalidixic acid, penicillin, tetracycline, and trimethoprim [20]. A study in Iran in 2018 included 60 strains of *uropathicE.coli* was investigated antibiotic susceptibility using the Kirby Bauer disk diffusion method. They were found resistant to cefepime (100%) and cephalothin (74%) and while sensitive to imipenem (100%), vancomycin (100%), and doxycycline (100%) [21].

A study in Mexico in 2014 included 119 isolates of *Stenotrophomonas maltophilia* collected between 2006 to 2013, with a resistance rate above 75 % for imipenem, meropenem, ampicillin, aztreonam, gentamicin, and tobramycin, while resistance to trimethoprim-sulfamethoxazole was 32.8% [22]. While in Turkey, a study published in 2016 included 118 isolates of *Stenotrophomonas maltophilia* collected in a period extended from 2006 to 2012, they found that the resistance rate was 7.6% Levofloxacin. 18.2% chloramphenicol, 20.3% trimethoprim-sulfamethoxazole and 72% ceftazidime [23].

In 2019 a retrospective cohort study in Hungary extended from 2008 to 2017 included 579 isolates of *Stenotrophomonas maltophilia*, concluded 5.35% of isolates were multidrug-resistant (MDR) while 5.87% were extensively drug-resistant (XDR), that is, in addition to SMX/TMP, they were resistant to amikacin, colistin, Levofloxacin, and tigecycline [24]. In Nigeria 2018, a study included five isolated *Pseudomonas aeruginosa*, which were Resistance to Ampicillin and Amoxicillin/Clavulanic acid [25]. In Prague, a study extended from 2011 to 2019 included 6897 isolates from total *P.aeruginosa* form 180 (7.3%) of isolates, which were resistant to ofloxacin and sensitive to colistin [26].

A study in Duhok in Iraq in 2018 included 371 isolates from a total of 276 (74.4%) *E.coli*, 12 (2.8) *P.aeruginosa*, and 9 (2.4) *Acinetobacter* sp. Which were shows a varies pattern of antibiotic susceptibility also *Acinetobacter* sp showed resistance (100%) to Aztreonam, Augmentin and Nitrofurantoin while *P.aeruginosa* resistance (100%) to Augmentin [27]. A study in India in 2018 included 67 isolates of *Acinetobacter* sp were tested for sensitivity pattern using disk diffusion methods, which were 80.3% of isolates was multi drug resistance but (100%) sensitive to colistin [28]. Case report study in India in 2017 included isolate of *Ochrobactrum anthropi* from patients with septicemia; antibiotic susceptibility was done using VITEK® 2 Compact system, which was multidrug-

resistance, resistance to a wide range of antibiotics-ceftazidime, cefoperazone, cefepime, chloramphenicol, sulbactam, piperacillin /tazobactam, ciprofloxacin, imipenem, and meropenem while was susceptible to amikacin, tigecycline, cefepime–tazobactam, colistin, co-trimoxazole [29]. A study in Jordon 2017 included four isolates of *B.cepacia* complex isolates from the urine; antibiotic susceptibility was done using disk diffusion methods, which were resistant to lincomycin, nalidixic acid, oxacillin and penicillin G and sensitive to ceftazidime, ciprofloxacin, gentamicin, imipenem, and Levofloxacin [30]. One year prospective study in India 2018 included 43 isolates of *B.cepacia* complex isolates from blood and sputum, antibiotic susceptibility was done using VITEK 2 Compact system, showed Maximum Resistance with β–lactamase inhibitor drugs (83.7%) [31]. Case report study 2017 in Malaysia isolates *Ralstonia mannitolilytica* from the blood of 65 years female with underlying hypertension, diabetes mellitus and ischaemic heart disease as well as received regular renal dialysis culture showed sensitivity to ceftazidime and piperacillin/ tazobactam while resistant to amikacin, gentamicin, meropenem and polymyxin [32].

Another case report study (2019) in Italy studying Antibiotic susceptibility of *Ralstonia mannitolilytica* isolated from the blood of 46 years female with underlying diseases using the broth micro dilution method which resisted to a wide range of antibiotic including Amikacin, Aztreonam, cefepime, Ceftazidime, Ertapenem, gentamycin, imipenem, and meropenem [33]. While in China (2019) antibiotic susceptibility was studied using the VITEK 2 Compact system on two isolates of *Ralstonia mannitolilytica* isolated from blood indicated resistance to aminoglycosides, β-lactams, and polymyxin B [34]. Another case study in India 2014 included isolate of *Brevundimonas vesicularis* antibiotic susceptibility was done using disc diffusion methods, which was susceptible to piperacillin-tazobactam, minocycline, and co-trimoxazole, while resisting to amikacin, gentamicin, tobramycin, netilmicin, amoxicillin, amoxicillin-clavulanic acid, cefoxitin, cefotaxime, cefoperazone, ceftazidime, cefoperazone-sulbactam, imipenem, meropenem, ertapenem, aztreonam, norfloxacin, Levofloxacin and colistin [35].

A study in Kolkata in 2015 included 115 isolates of *Enterococcus faecalis*, which were resistant to ciprofloxacin (86.1%), amikacin (77.4%), cotrimoxazole (78.3%), and imipenem (52.2%) [36]. Case report study in China in 2020 included *E.faecalis* isolated from the urine of patients with underlying diseases, the drug of choice was Linezolid [37]. Case report study in India 2016 included *Kocuria* species isolated from urine, which was Resist to ampicillin, oxacillin, cefoxitin, ciprofloxacin, norfloxacin, nalidixic acid, piperacillin-tazobactam, amoxicillin-clavulanic acid, ceftriaxone, cefotaxime, cefepime and ceftazidime, while sensitive to vancomycin, linezolid, imipenem, amikacin, ofloxacin, trimethoprim-sulfamethoxazole, clindamycin, erythromycin, and tetracycline [38].

Identification of uropathogenic*E.coli* using *papE* gene

In this study, uropathogenic *Escherichia coli* (UPEC) is the most predominant bacteria isolated from bladder cancer patients. A study in Egypt in 2015 referred to that *E. coli* is the most common uropathogenic bacteria, which infects bladder cancer patients. Surface virulence factors (adhesins) are significance virulence factors of UPEC as the primary attachment factor, P fimbriae are associated with pyelonephritis and are encoded by *pap* genes(Pyelonephritis-Associated Pili), allowing them to colonize host mucosal surfaces and invade the normally sterile urinary tract [39].A study in Al-Kufa, Iraq (2015) investigated the severity of urinary tract infections in 48 patients with TCC and 20 patients with non-TCC as a negative control group. They obtained bacterial growth from 15 cultured urine samples. Among them, 41.67% were Gram-positive bacteria, and 27.78% was Gram-negative bacteria [40]. A prospective descriptive (cross-sectional) Iraqi study in 2020 included 170 specimens (100 urine and 70 stool specimens) screened for *papE* gene using conventional PCR. They indicated that (29/100) isolates were identified as UPEC [41].

In Iran, *Rahdar et al.* (2015) referred to that from 100 isolates of *E.coli* isolated from the urine of patients with UTI, only 57% was harbor *papE* detected using PCR[42]. In Egypt, a study in 2019 included 173 isolates of UPEC and diarrheagenic*E.coli*(DEC) investigated for phylogenetic typing and urovirulence genes using PCR, results 16.5% of UPEC was harbor *papE* but not present in DEC [43].

Virulence Factors of Isolated BacteriaBiofilm formation

In this study, all isolates were produced biofilm either moderate 17/35 (51%) or strong producer 17/35 (49%). The quantification test of biofilm was proved to be useful in detecting biofilm production by the clinical isolates (44). Urinary tract infections significantly associated with microbial biofilms, developed on catheters which conclude a high percentage of all nosocomial infections and are the most prevalent source of

Gram-negative bacteremia in hospitalized patients [45]. Biofilm formation is also considered a virulence determinant responsible for the long-lasting persistence of bacteria in the genitourinary tract [46]. *Escherichia coli* (UPEC) form biofilms on urinary catheters, as well as within bladder epithelial cells, which protects UPEC from environmental conditions, antimicrobial therapy, ultraviolet radiation, oxidizing biocides, and host immune defenses [47]. Iranian study in 2018 included 100 isolates of UPEC was screened ability for producing biofilm using microtiter plate methods (TCP) indicated 36/100 was strong producer, 48/100 was moderate producer, and 10/100 was the weak producer [48]. Another study in India in 2019 included 100 isolates of *E.coli* isolated from patients suffering from UTI, was studied the ability to produce biofilm their results indicated 69% of isolates were producers of biofilm [49]. Hungarian study in 2020 on 250 isolates of *E.coli* from patients with UTI screened ability for producing biofilm using crystal violet tube-adherence method their results indicated that 119 (47.6%) were positive for biofilm formation [50]. A study in Mexico in 2014 included 119 isolates of *Stenotrophomonas maltophilia* collected between 2006 to 2013, indicated that All *S. maltophilia* isolated were able to produce biofilms. Strains were classified as strong biofilm producers (13.4 %, 16/119) moderate, (38.7 %, 46/119), or weak (47.9 %, 57/119) [22].

Pseudomonas aeruginosa produce biofilm is an essential mechanism for survival, and its relationship with antimicrobial-resistance represents a challenge for patient therapeutics, especially in nosocomial infections of immune-compromised patients [51]. A study in Brazil in 2018 compromised 40 clinical isolates of *P.aeruginosa* has studied ability to produce biofilm using TCP method their results indicate 77.5% of isolates were biofilm producer [52]. A study in Belgium in 2014 in six isolates of *Burkholderiaspp* studied their ability to produce biofilm using TCP, indicated all isolates were able to produce biofilm but in different percentage [53]. Egyptian study in 2017 included 90 clinical isolates of *Enterococcus faecalis* studied their ability to produce biofilm using two methods Congo-Red agar (CRA) biofilm assay and TCP method. In (CRA) five potent biofilm-producing isolates 81 isolates ranged between moderate and weak, and 4 non-biofilm-producing isolates while in TCP methods only 5/90 (5.5%) were classified as strong biofilm-formers; 38/90 isolates (42%) were moderate; 43/90 were weak biofilm-formers (48%); and 4/90 (4.5%) could not form biofilm [54]. A study in china 2018 included 113 isolates of *E.faecalis* from urine of patients with UTI, studied the ability to produce biofilm using TCP methods, indicated that (59.7)% as a strong biofilm producer while (30.6%) as non-biofilm producer [55].

Siderophore production

In the present study, 25/35 (71%) isolates were producer while 10/35 (29%) isolates were non producer. A study in India in 2017 included 200 isolates of UPEC isolated from patients with UTI, screened for siderophore production using Chrome azurol assay (CAZ) noticed that (95%) of isolates were siderophore production indicated that siderophores or Iron acquisition constitute a significance virulence factor requisite for Uropathogenic*E.coli* in the pathogenesis of UTI [56]. Another study in al-Kufa in Iraq in 2017 included 50 isolates of *E.coli* from different infections, screened for virulence factors including siderophore production using M9 medium supplemented with 2,2'-dipyridyl, their results indicated (100%) of isolates were siderophore producer [57]. A study in Argentina in 2012 included 31 clinical isolates of *S.maltophilia* screened for siderophore production using (CAZ) assay indicated that all isolated(100%) were siderophore production [58].

Cytochrome P450

In the present study, the inducing of cytochrome P450 expression protein was seen in (14/35) 40% isolates as induced, while not induced in (21/35) 60% isolates. Many types of research indicated that microorganisms such as Bacteria were shown to express cytochrome CYP-like genes (these genes in microbial organisms differ extensively even between species of the same genus) even though individual organisms having no *CYP* genes present (e.g., *Escherichia coli*), the considerable metabolic activity of the microbe is associated to its abundant collect of CYP enzymes [59]. This reason could explain the failure to induce (8) isolates of UPEC to express cytochrome P450. It was also reported that Bacterial cytochrome P450s were characterized in their high expression level in many microorganisms [60].

Microbial P450s have diverse catalytic functions. For example, in *Sphingomonas paucimobilis* had fatty acid α-hyroxylase (H2O2 dependent peroxygenase), and in *Pseudomonas sp* function as α-terpineol hydroxylase activity. Besides Microbial P450s have roles in the degradation of toxic compounds [61]. It is crucial to study microbes' ability to express cytochrome P450 proteins (specifically quantity) in the cell wall because *Pseudmonas aeruginosa* would metabolically activate the bladder procarcinogens, which is achieved by the presence of cytochrome P450 [14].

Conclusion:

Patients with TCC-BC or negative cystoscope who had a urinary catheter or immune-compromised were at high risk of infecting with nosocomial or opportunistic pathogens, which could develop resistance antibiotic the central problem in treating these patients before undergoing to chemotherapy or immune cancer therapy.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- The author has signed an animal welfare statement.
- Authors sign on ethical consideration's approval
- Ethical Clearance: The project was approved by the local ethical committee in Al-Nahrain University

Authors' contributions statement:

Sura Mouaid Abbas was contributed to sample collection samples and implementation of the research Maysaa Abdul Razzaq Dhahi was contributed to the design of the research, to the analysis of the results and to the writing of the manuscript. All authors discussed the results and contributed to the final manuscript

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Open Access **Baghdad Science Journal** **P-ISSN: 2078-8665**
Published Online First: November 2021 **E-ISSN: 2411-7986**

دراسة بعض عوامل الضراوة ومقاومة المضادات للبكتريا المعزولة من إدرار المرضى المصابين بسرطان المثانة

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فرع الإحياء المجهرية ،كلية الطب، جامعة النهرين، بغداد، العراق

الخلاصة :

التهاب المجاري البولية تعني وجود المكروبات الممرضة بالاحليل أو المثانة. أهم الأسباب لحدوث الأصابات المتكررة هو تخدش لمجرى البول نتيجة استعمال القسطرة البولية أو الأشخاص المكبوحين مناعيا. الدراسة الحالية ركزت على عزل وتشخيص المكروبات التي تسبب التهاب المجاري البولية ودراسة المقاومة الحيوية وبعض من عوامل الضراوة في الأشخاص المصابين بسرطان المثانة Transcial cell carcinoma نوع واشخاص تنظير المثانة سلبي لهم.تم جمع 62 عينة ادرار (50 مرضى سرطان المثانة و12 اشخاص تنظير المثانة سلبي) فقط 32 عينة كانت موجبة لوجود البكتريا وكانت النسبة الاعلى بالاصابة هي (uropathogenic*Escherichia coli* UPEC) تليها *Stenotrophomonasmaltophilia*. نسبة العزلات المقاومة للمضادات الحيوية كانت (62.8%) MDR بينما XDR كانت(28.5%) وكانت كل العزلات لها القابلية على انتاج الغشاء الحيوي اما بصورة متوسطة 17/35 (51%) او أنتاج قوي 17/35 (49%). أنتاج السيدروفور كان 25/35 (71%) منتجة و10/35 (29%) غير منتجة بينما قابلية لتحفيز لأنتاج السايتوكروم P450 كان (14/35) 40% لها القابلية و(21/35) 60% غير قادرة على الأنتاج.الاشخاص المصابين بسرطان المثانة اويخضعون لتنظير المثانة يكونوا عرضة للاصابة بالممرضات الانتهازية والعدوى من المستشفيات والتيمنال ممكنا نتطور المقاومة للمضادات الحيوية وهذه مشكلة اساسية لعلاج هذه الفئة من المرضى قبل اعطائهم العلاج الكيمياوي اوالمناعي .

الكلمات المفتاحية: حساسية للمضادات،سايتوكروم450، إنتاج السيدروفور، سرطان المثانة،عوامل الضراوة.