

# A Study of some Immune Factors in Patients with Bacterial Urinary Tract Infections Caused by Aerobic Bacteria.

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## ARTICLE INFO

Received: 19 / 5 /2022

Accepted: 28 / 5 /2022

Available online: 19/7/2022

DOI: 10.37652/juaps.2014.123987

## Keywords:

urinary tract infection,  
Tamm- horsfall Protein,  
Bacteriurea.

## ABSTRACT

One hundred and fifty seven (157) adult patients from both sexes were included in this study. Sixty(60) adult persons were presented as control groups . Patients were suffering from Urinary tract infections.Urine and serum specimens were taken from each patient to be used for IgG , IgM , IgA and complement C3 study . Tamm Horsfall protein , IgM and IgG were studied in urine . Bacteriological investigations were done for each urine specimen from patients and control groups. Sixty(60) patients were showing positive Urine culture , females were showing the highest ratio in all age groups particularly the first two groups(17-27) and (28-38) years old. Sera from patients of positive and negative Urine cultures were showing higher values of IgG, IgM, IgA and C3 than control . Higher values of THP were found in urine of patients with negative Urine culture and control groups . In conclusion,Tamm-Hors-fall protein,IgM, IgG and IgA are important to combat UTIs locally and systemic.

## Introduction:

Urinary tract infection ( UTI) is an inflammatory response of the urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria <sup>(1)</sup>. These infections usually result from the entry of periurethral microorganisms through the urethra into the bladder lumen ,the bacteria may ascend via the ureters into the kidney and even reach the kidney parenchyma to enter the lymphatic system or blood stream<sup>(2)</sup>. Therefore the manifestation of UTIs can range from asymptomatic bacteriuria to urthritis,cystitis , pyelonephritis, bacteraemia and sepsis <sup>(3)</sup>. Continuous flow of the urine and presence of antibacterial inhibitory Factors in the bladder wall play a defensive role by entrapping and flushing uropathogens out with the flow of urine <sup>(4)</sup>. Tamm-Horsfall Protein (THP) also known Uromoduline is the most abundant protein in the urine of all mammals, with approximately 50 mg released per day <sup>(5)</sup>. Tamm-Horsfall protein is defending the urinary tract against the bacterial infections <sup>(6)</sup>. Tamm-Horsfall protein facilitates organisms elimination from the urinary tract by coating the adhesions present in the surfaces<sup>(7)</sup>. Serum antibodies found in UTI positive patients have bactericidal activity<sup>(8)</sup>.

Antibodies in urine may resist UTI by preventing the adherence of bacteria to uroepithelial cells, the role of humoral immune response which increased IgG and IgA, IgM production were associated with UTI <sup>(9)</sup>. Also bacteria are killed by infected human serum through the lytic activity of the complement system. Complement 3 (C3) levels are significantly higher in the urine of UTI patients and uropathogenic *E. coli* may stimulate C3 production <sup>(10)</sup>.

## Patients and methods :

One hundred fifty seven (157) adult patients from both sexes were included in this study and sixty (60) adult individuals were presented as control group . Patients were suffering from Urinary tract infections were attending Ramadi Teaching Hospital during the period extended from 1st March 2013 to 30th August 2013 were included in this study. These patients were examined by senior urologists and all inclusion criteria recommended for cases of UTIs were applied. Midstream urine specimens were taken from each patient following WHO guidelines (11). Each specimen was examined macroscopic and microscopic and urine cultures were done within 60 minutes following Vandepitte et al (11). Also serum specimens were taken from each patient to be used for immunological tests. Quantitative urine culture was performed, urine samples obtained were cultured directly on to MacConkey and Blood agar plates using direct streaking method with calibrated bacteriological loop . The

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inoculated plates were incubated aerobically at 37°C for overnight then examined for growth, if no growth was detected, plates were re-incubated for another 24 hours before discarding as negative cultures (11). A single colony was taken from each primary positive culture and its identification depended on the morphological properties, Gram staining of the bacterial smear, specific biochemical tests were performed to reach final identification (12). Quantitative determination of immunoglobulins (IgG, IgA, IgM) and complement C3 in sera using Single Radial Immunodiffusion test kit (SRID). Quantitative detection of Tamm-Horsfall Protein, IgG and IgM in human urine were done using special kits for Enzyme Linked Immunosorbent Assay (ELISA).

### Results:

Sixty (38.2%) urine samples showed positive bacterial culture results while 97 (61.8%) samples were showing negative results. Fourteen (14) (23.3%) of them were from male patients and 46 (76.7%) were from females. All Urine specimens from control group showed negative urine cultures. Sixty (60) patients of positive Urine culture were included into four age groups ranged from 17-60 years. Females were showing the highest ratio in all age groups particularly the first two of groups (17-27) and (28-38) years (Table-1).

#### Urine culture results :

*Escherichia coli* took the first rank of isolation (41.7%) from urine specimens of UTI patients followed by *Klebsiella pneumonia* (26.6%) while *Staphylococcus aureus* became next (20%) and other types of bacteria were showing lower rates of isolations percentage for each respectively were *Staphylococcus saprophyticus* (5%), *Pseudomonas aeruginosa* (3.3%), *Proteus mirabilis* (1.7%), *Streptococcus faecalis* (1.7%), ( $P < 0.01$ ) (Table -2).

#### Immune parameters in sera of patients and control group :

Sera from patients of positive and negative Urine cultures were showing higher values of IgG than control individuals. Patients with positive Urine culture were showing higher values than that of negative Urine cultures ( $p < 0.05$ ) except patients of age group (50-60). Non significant difference was found between IgM values in patients with positive Urine cultures and the values of negative Urine cultures ( $p > 0.05$ ). Both positive and negative Urine culture patients were showing more IgM mean values than control individuals. All individuals within age groups of negative Urine cultures were showing higher IgA values than that of the individuals of positive Urine cultures except patients with age groups 28-38 years old positive Urine culture were showing higher IgA values ( $p > 0.05$ ). Control group individuals were showing lower values of IgA in all age groups. Although positive Urine culture patients within age

groups were showing more C3 than patients with negative Urine culture but its non significant difference, except individuals in age groups (28-38) years old in urine showing higher C3 values ( $p > 0.05$ ) than that Negative urine culture. Control group individuals were showing lower C3 values than individuals of patients (Table-3).

#### Immune parameters in urine of patients and control group:

Higher values of THP were found in urine of patients with negative Urine culture and control groups in contrast to positive Urine culture ( $p < 0.01$ ). Patients within age group 50-60 years old were showing higher THP in urine followed by patients within age group 28-38 years old. Regarding IgM values, non significant differences were seen between different age groups of patients with positive Urine cultures ( $p < 0.05$ ). Patients within age groups 50-60 years old were showing higher IgG than others, followed by patients within age group 17-27 years old (Table-4). Urine specimens with positive culture isolates with *Escherichia coli* and *Pseudomonas aeruginosa* revealed high mean values of THP (334.25 ng/ml) and (230 ng/ml) respectively. Urine with *Streptococcus faecalis* became next with mean values (215 ng/ml), followed by *Staphylococcus aureus* and *Staphylococcus saprophyticus*, mean (192.55 ng/ml), (170.0 ng/ml) respectively, while *Klebsiella pneumonia* (161.13 ng/ml). Urine with *Proteus mirabilis* showed the lowest mean values of THP (50.0 ng/ml) (Fig-1). Males were showing higher mean values of THP in their Urine samples (229.08 ng/ml) than that of females (182.32 ng/ml) (Figure -2).

### Discussion:

#### Gender effect :

Regarding gender and number of patients and control, this study showed that UTI is more in females than males, this is due to the shorter urethra in females makes the exposed to ascending infection more than males (13,14). These results were in agreement with many pioneers (15,16,17). Young and adult females exposed to UTI more because of higher sexual activity which predispose infection due to hormones, contraceptives and contamination which may increase chance of UTI (18). A diaphragm was used with or without spermicide, changes the vaginal environment. The same occurs in menopause, disappearance of the previously predominant *Lactobacilli* from vaginal microflora and a rise in pH (19). These results are in accordance with the findings of (20,21,22).

#### Types of bacterial isolates:

Regarding types of bacteria isolated from urine, *Escherichia coli* is the predominant causative bacteria, this is due to easy contamination with fecal contents like *E. coli* which account about 105 cell/gram of stool (23-24). Uropathogenic *E. coli* serotypes are specific

subset of extraintestinal pathogenic *E. coli* causing UTI(25). These strains of *E. coli* show attraction to uroepithelium due to their virulence factors synthesized by pathogens including fimbriae, toxins, flagella, iron acquisition systems, and proteins that function in microbial invasion (26). Uropathogenic *E. coli* strains possess adhesions factors that enable them to aggregate and adhere to cellular surfaces (27), similar results were reported by (17,28,29). *Klebsiella pneumoniae* is the second important pathogen because these bacteria are among the intestinal flora like *E. coli*. The chance of infection of the urinary system increases because it possesses a protective capsule which makes it more resistant to body immune defences specially phagocytosis (30). Similar results were reported by (31). *Staphylococcus aureus* and *Staphylococcus saprophyticus* became next in isolation from urine of patients. It is well known that *Staphylococcus aureus* has a microcapsule which acts as anti phagocytic and predispose the adhesion to the host tissue, in addition to many other virulence factors (23,32). *Staphylococcus saprophyticus* was reported to be an important cause to UTI in sexual active young women (33). These results were in agreement with the findings of in this study (34,35,36). *Pseudomonas aeruginosa*, *Proteus mirabilis* were found to be the causative agents of few cases, the same result was reported by (37,38,39). This might be attributed to the nature of such organism as nosocomial pathogen (40).

#### Immune parameters in serum :

Patients were showing higher (IgG) values in their sera than control groups, at the same time more IgG values were seen in sera of patients with positive urine cultures within all age groups except age group (50-60) years old. This result was in agreement with the findings of (41). Higher values of IgG undergo increases to protect and to combat infection (42,43). Increased values of IgG of patients with negative urine culture within age group (50-60) years old might be due to frequent UTIs in males predisposed by prostatitis and in females due to menopause status (44). These findings were in agreement with the findings of (9,41). While it disagreed with the results of (45,46). This variation in results might be due to the difference in study conditions. Both positive and negative Urine culture patients were showing more IgM values in sera than control individuals. Increased IgM values in patients groups was attributed to the surveillance of immune system in the body and reaction against infection. The IgM undergo first release within the primary immune reaction in acute inflammation to combat infection (42,23). This result agreed with the findings of (9,41,47). While it disagreed with the results of (45,46). This was due to the difference in the study conditions and social status of studied patients. Increased IgM values in negative urine culture groups might be due to:

Other non infective inflammatory effects like rheumatic and inflammatory diseases (48,49).

B- UTI due to non cultivable detectable pathogens like *Chlamydia*, *Ureaplasma*, and *Mycoplasma* which can't be detected following routine cultivation methods (50). Increased values of IgA in sera of patients was due to immune reaction against causative agents of infection, this result agreed with the findings of (9,43,51). Higher IgA values in age group (28-38) years old might be due to pathogenic organism, which can be isolated from urine in low rate like gonococci, such organisms induce IgA release more in sexually active age groups (52). Nonsignificant difference between values of IgA between urine culture positive and urine culture negative patients might be attributed to infections caused by non cultivable organisms like *Chlamydia trachomatis* and other organisms which require special culture media and conditions like anaerobic bacteria, *Mycobacterium tuberculosis* and *Mycoplasma* spp. (50). Increased values of C3 in patients groups reflects the importance of complement against infections (53). Increased complement C3 in sera of patients with positive urine culture particularly in age group (28-38) years old supported the above mentioned facts and coped with the increased values of IgA in the same age group. This might be due to the effect of bacterial lectin pathway of complement activation (42). This result was agreed with findings of (53, 41).

#### Immune parameters in urine :

Lower values of IgG and IgM antibody values were found in urine patients with significant UTI. This might be attributed to antigens on mucosal surfaces bladder can induce a state of tolerance in the host by alimentary (9), or colonization with *E. coli* or repeated UTI may suppress host capacity to produce antibodies against bacterial antigens. Development of symptomatic UTI may partly be due to the poor production of IgG and IgM. (54). IgM low values in Urine of positive urine culture might be due to the higher molecular weight of IgM (pentameric molecules) which makes it difficult to pass through glomerular and thus to be excreted in to urine in low titer (42, 55). This result agreed with the findings of (9,56). In other hand it is possible that UTI susceptible individuals respond poorly to specific bacterial antigens because of a genetically determined restriction in antigen presentation or absence of gene coding for a specific antibody combining site (57). Negative urine culture of patients might be due to non cultivable organisms like *Chlamydia* or other organism which weren't studied there like *Mycoplasma* and anaerobic bacteria. Increased values of IgG in age group (17-27), might be due to infections like chronic gonorrhea or other inflammatory disease. Increased IgG values in age group (50-60) might be due to prostatitis, rheumatic infection in such age groups (42, 50,58). Tamm-Horsfall protein may inhibit the binding of microbial pathogens to epithelial cells within the urinary tract and may enhance their urinary clearance (59).



In the present study, higher values of THP in urine specimens of patients with negative urine culture in contrast to that of positive urine culture and control groups, this was similar with previous studies (60). Lower THP values in urine of positive culture group was might be due to consumption of the THP urine content in defense against bacteria or fatigue of TAL cells due to higher bacterial numbers in urine (61,62). This result was agreed with the findings of (59,63). Regarding effect of age group on THP values in Urine of patients more values of THP were found in age groups (50-60),(28-38). This might be due to consumption of THP in other age groups to prevent infection. The amount of THP can be influenced by many physiological and pathological factors which include urine volume, pregnancy, diabetes mellitus, diet, exercise, stone formation, recurrent UTIs (64). In addition to the structural differences in THP also affected with Sialic acid residues may be important for this action of THP to prevent UTIS and to inhibit stone formation. About 30% of the THP/ uromodulin molecule consists of carbohydrates, comprising at least five N-glycosidically bound sugar chains. THP of healthy human contains large amounts of sialic acid (about 5% of total molecular Weight, so the lower sialic acid due to defect of THP function (65). These results were in accordance with the findings of (66). Non significant differences between Gram positive and Gram negative causative agents was might be the similarity in nature of THP constituents in both infections(sialic acid fragments) (65, 66,67). Thus the role of THP is the same in both types of infections(Gram positive and Gram Negative infections 68,69). In spite of similarity between the values in both Gram positive and Negative infection, it was found that higher values of in urine from positive urine culture patients (infected with *E. coli*, *Pseudomonas aeruginosa*, *Streptococcus faecalis*, *Staphylococcus aureus*, *Staphylococcus saprophyticus*, *Klebsiella pneumonia* and *Proteus* spp. receptivity). This was might be due to more requirement of THP to combat infection with high virulence adapted uropathogens (59,70). Regarding to THP values in urine of positive culture, in spite of the non significant difference in THP concentrations between genders, more values of THP in females than males, was attributed to the consumption of THP in females more than males due recurrent UTI, gallbladder stone and others. These results are in accordance with the findings of (66).

In conclusion, Females were showing high rates of UTIs, *Escherichia coli* and *Staphylococcus aureus* must be considered in UTI treatment and **follow up** through urine culture and sensitivity to antibiotics. Tamm-Horsfall protein, IgG and IgA are important to combat UTIs locally and systemic in urinary tract.

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**Table-1: Number and gender of patients and control groups.**

	Groups	Total No. %	Male No. %	Female No. %
1	Positive culture Growth	60(38.2)	14(23.3)	46(76.7)
2	Negative culture Growth	97(61.8)	35(36.1)	62(63.9)
	Total	157(100)		
3	Control	60(100)	24(40.0)	36(60.0)

**Table -2: Bacterial types in Urine positive culture specimens from patients.**

	Types of organisms	NO.	%
1-	Escherichia coli	25	41.7
2-	Klebsiella pneumonia	16	26.6
3-	Staphylococcus aureus	12	20.0
4-	Staphylococcus saprophyticus	3	5.0
5-	Proteus mirabilis	1	1.7
6-	Pseudomonas aeruginosa	2	3.3
7-	Streptococcus faecalis	1	1.7
	Totals	60	100%

**Table-3: IgG, IgM, IgA and Complement C3 mean values in sera of patients and controls groups.**

1	Culture groups	Immune factors			
		Age groups (years)	IgG values mg/dl M ± SD	IgM values mg/dl M ± SD	IgA values mg/dl M ± SD
Positive urine/culture groups		17-27	1475 ± 664	144 ± 65	166 ± 79
		28-38	1437 ± 418	151 ± 70	221 ± 147
		39-49	1724 ± 507	179 ± 78	212 ± 108
		50-60	840 ± 291	120 ± 34	178 ± 172
				116 ± 112	

2	negative urine/culture groups	Controls groups			
		Age groups (years)	IgG values mg/dl M ± SD	IgM values mg/dl M ± SD	IgA values mg/dl M ± SD
3	Controls groups	17-27	781 ± 669	72 ± 53	175 ± 125
		28-38	492 ± 341	63 ± 38	120 ± 75
		39-49	723 ± 640	95 ± 55	160 ± 85
		50-60	514 ± 249	61 ± 28	121 ± 76
				77 ± 36	

**Table-4: Values of THP, IgG and IgM in urine of different age groups of patients with negative urine culture**

1	THP	Immune factors			
		Age groups	No.	Mean (ng/ml)	±SD
2	IgM	(17-27)	12	1212	340.50
		(28-38)	10	1101.0	334.90
		(39-49)	3	266.67	136.13
		(50-60)	4	422.50	184.45



3	IgG	(39-49)		3	3	23.33	4.50
		(50-60)		4		22.00	2.16
		(17-27)		12	1212	547.33	1167.55
		(28-38)		10	11010	264.30	227.98
		(39-49)		3	3	326.67	410.41
		(50-60)		4		165.00	190.044

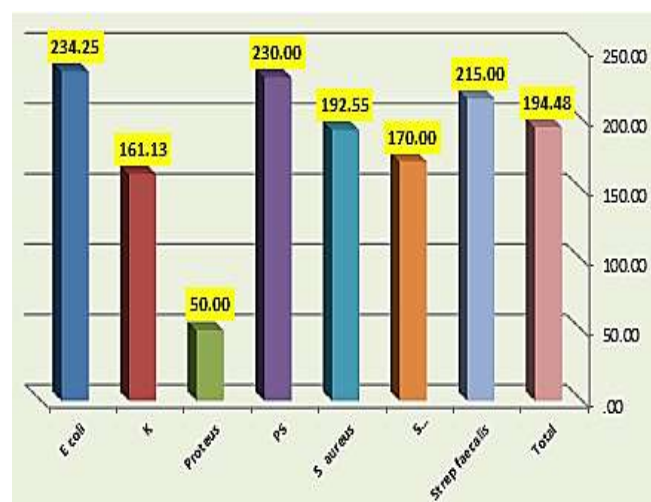


Fig-1: Tamm-Horsfall Protein values in urine regarding types of bacterial isolates.

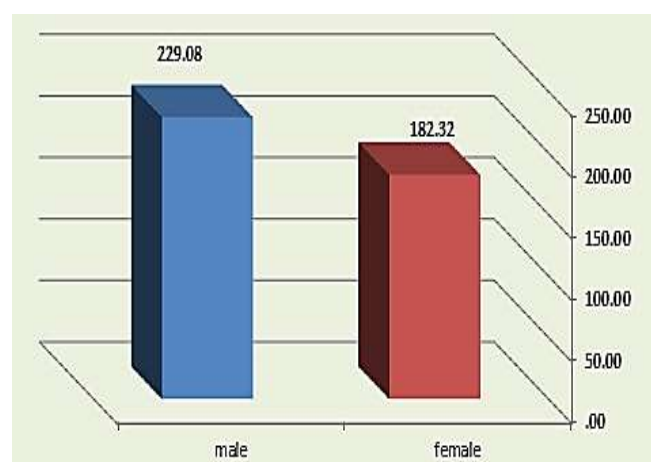


Fig.2: Tamm-Horsfall Protein values in urine regarding to gender of Patients.

## دراسة بعض العوامل المناعية في المرضى المصابين بخمج المجارى البولية

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### الخلاصة

تضمنت الدراسة مائة وسبعة وخمسين مريضاً بخمج المجارى البولية من الذكور والإناث البالغين إضافة إلى ستين شخصاً آخرين يمثلون المجموعة الضابطة للدراسة. وتم تقدير محتوى مصل دم المرضى والمجموعة الضابطة من الأضداد IgG, IgM, IgA والمتمم C3 وتم تقدير الأضداد IgG, IgM, IgA ومحتوى الإدرار من بروتين تام هورس بروتين. كان عدد عينات الإدرار الموجبة للزرع الجرثومي ستين عينة وكانت أعلى نسبة إصابة بخمج المجارى البولية في الإناث أكثر مما هي عليه في الذكور وخصوصاً الفئة العمرية 17-27 و28-38 عاماً. كان معيار الأضداد IgG, IgM, IgA عالياً في مصل المرضى مقارنة بمصل المجموعة الضابطة ولوحظت أعلى نسبة بروتين تام هورس في إدرار المرضى الذين كانت نتائج الزرع سالبة لنمو الجراثيم أكثر من غيرهم. نستنتج من هذه الدراسة إن بروتين تام هورس والأضداد مهمة للحد من خمج المجارى البولية موضعياً ومن خلال محتوى مصل الدم من عوامل المناعة.