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Prevalence and Identification of Some Ocular Bacterial Infections in Baghdad City

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Abstract

The study included 176 patients attended to Iben AL-Haithem hospital of ophthalmology in Baghdad city, at age of (14-77) years from the period from September 2016-April 2017, there were 138(78%) patients having a positive culture of ocular bacterial infections. Men were representing 41% while women 59%, the patients with bacterial ocular infection from Baghdad were55% while the internally displaced were 45%, the patients with ocular bacterial infections were representing 20% at mean age of 21.6±0.3y, 26% at 37.5±0.21y , 24% at53.5±0.23 y and 30% at69.5±0.10 y. The results showed 37% of the patients with ocular bacterial infections were having a history of diabetes mellitus and 44% with high blood pressure at mean age of 69.5±0.10 y. Gram positive bacteria represented 58% from the total isolates ,while gram negative were 42% . S.aureus was the common dominant isolates 29% followed by S.pneumoniae 21%, P.areuginosa 16%, E coli 11%, Klibseilla spp 7% S.epidermidis 6%, Enterobacter spp6%, S.pyogenes 2%, Citrobacter freundii and Proteus spp 1% each of them , the mix infection was found in three samples including (E. coli and P. aeruginosa), (E. coli and S. aureus) and (P. aeruginosa and S. aureus). S. aureus isolates were susceptible to Amikacin 88%, Doxycycline 84% and they were highly resistance to Clindamycin 76%, while *S.epidermidis* isolates were susceptible to each of Amikacin, Cloramphenicol, Clindamycin and Doxycycline at a percentage of 80% and they were resistance to tetracycline 60% . S.pneumoniae isolates were susceptible to Clarithromycin 94%, Ceftriaxone 88%, S.pyogenes isolates were susceptible 100% to the most types of antibiotics such as Erythromycin , Clarithromycin , Cloramphenicol, Clindamycin and Ceftriaxone. P.areuginosa isolates were susceptible to Gentamicin 100%., Ciprofloxacin, Doxycycline, Amikacin 72% for each antibiotic , while E.coli isolates were susceptible to Cloramphenicol 90%, Ciprofloxacin and Gentamicin 80%. Klibseilla spp isolates were susceptible to Ciprofloxacin and Gentamicin 100%, Ceftriaxone 83% while Proteus spp isolate were susceptible to all types of antibiotics 100% Enterobacter spp isolates were susceptible to Ciprofloxacin 100%, both of Gentamicin and Cloramphenicol 80%, Citrobacter freundii isolate were susceptible to Ceftriaxone, Cloramphenicol, Ciprofloxacin, Gentamicin 100%.

Keywords: Ocular, bacterial infections, Baghdad.

انتشار وتحديد بعض اصابات العيون البكتيرية في مدينة بغداد زينة قاسم خليل¹، ايمان خضير ديوان¹، ذكرى محمود علي ²، سيف سعد كامل¹ المعهد الطبى النقنى ، المنصور ، بغداد، العراق. ²المعهد الطبى النقنى ، باب المعظم ، بغداد، العراق.

الخلاصة

شمات الدراسة 176 مريض مراجع لمستشفى ابن الهيثم للعيون في مدينة بغداد للأعمار ما بين (14-شمات الدراسة 176 مريض مراجع لمستشفى ابن الهيثم للعيون في مدينة بغداد للأعمار ما بين (14-(77) سنة للفترة من ايلول 2016-نيسان 2017 ، وجد ان 188(78%) مريض لديهم نتائج موجبة لإصابات بكتيرية في العين ، نسبة الرجال كانت41% والنساء 25% وكانت نسبة المرضى المصابين بالتهابات العيون البكتيرية 55% من بغداد و45% من النازحين . مثل المرضى المصابين بالتهابات العيون بالتهابات العيون البكتيرية 25% من بغداد و45% من النازحين . مثل المرضى المصابين بالتهابات العيون البكتيرية نسبة 20% للفئة العمرية 20.6 سنة، 26% للاعمار 27,5±2,10 سنة ،24% للاعمار و53, 53%

كما بينت النتائج ان نسبة المصابين بالتهابات العيون البكتيرية ويعانون من مرض السكري كانت 37% بينما 44% كانوا يعانون من ارتفاع ضغط الدم للاعمار 0,10±69,5 سنة ، البكتيريا الموجبة لصبغة كرام مثلت 58% من مجموع العزلات الكلية بينما البكتيريا السالبة لصبغة كرام مثلت 42%. جرائيم المكورات العنقودية الذهبية كانت الاكثر شيوعا وبنسبة 29% ثم المسبحيات الرثوية 21% و الزوائف الزنجارية 16% و الاشريشيا القولونية 11% والكلبسيلا 7% والمكورات البشروية 6% والبكتيريا المعوية 6% والمسبحيات القيحية 2% و الليمونيات فريندى 1% والمتقلبلت 1% ، الاصابات المزدوجة لوحظت في ثلاثة نماذج وشملت الاشريشيا القولونية +الزوائف الزنجارية ، الاشريشيا القولونية + المكورات العنقودية الذهبية و الزوائف الزنجارية + المكورات العنقودية الذهبية . وبينت النتائج ان المكورات العنفودية الذهبية كانت حساسة لمعظم المضادات الحيوية التي استخدمت مثل الاميكاسين 88%و الدي اوكسيسايكلين 84% وكانت مقاومة للكلندمايسين 76% اما المكورات البشروية فكانت حساسة للاميكاسين والكلورمغينيكول والكلندمايسين والدى اوكسيسايكلين بنسبة 80% كما كانت مقاومة للتتراسايكلين 60% ، المسبحيات الرئوية كانت حساسة للكلااريرومايسين 94%والسيفترايكسون 88% ، المسبحيات القيحية كانت حساسة 100%لمعظم المضادات الحيوية المستخدمة مثل الارثرومايسين والكلاارثرومايسين و الكلورمفينيكول والكلندمايسين والسيفاترايكزون ،الزوائف الزنجارية كانت حساسة للجنتمايسين 100%والسايبروفلوكساسين والدياوكسيسايكلين والاميكاسين 72% لكل منهم بينما الاشريشيا القولونية كانت حساسة للكلورمفينيكول 90% والسايبروفلوكساسين والجنتمايسين 80% اما الكلبسيلا فكانت حساسة للسايبروفلوكساسين والجنتمايسين 100% السيفاترايكزون 83% بينما المتقلبات كانت حساسة لكل انواع المضادات الحيوية بنسبة 100% اما البكتيريا المعوية فكانت حساسة السايبروفلوكساسين 100% وكلا من الجنتمايسين والكلورمغينيكول 80% اما الليمونيات فريندى فكانت حساسة للسيفلترايكزون والكلورمفينيكول والسايبروفلوكساسين والجنتمايسين 100% الكلارارثرومايسين (94%) والجنتمايسين (. (%100

Introduction

Ocular bacterial infections contribute to 32 to 74% mainly gram positive and negative and causing external infections, such as, blepharitis, keratitis, dacryocystitis and orbital cellulitis [1]. It may cause many complications such as the presence of pus and conjunctival hyperemia or visual impairment [2]. The causative agents either come from the environment by airborne fomites and hand to eye contact or contact with upper respiratory tract infection secretions [3].

Infection may spread to the conjunctiva from the eyelids and sometimes from lacrimal drainage instrument or face but rarely, or due to systemic infections in the body [4].

The untreated ocular infections can lead to damage of eye structures which may be result in permanent loss of vision [5]. The conjunctival sac is colonized by microbial flora which are mainly *Staphylococcus epidermidis, S. aureus, Corynebacterium spp* and *Propionibacterium acnes* by age, Gram negative bacteria may become part of the flora, the changes in the flora could happened due to various factors [6].

Recently, many bacterial agents are encountered in ocular infections due to wide using of topical and systemic immunosuppressive therapy in cases of organ transplants, the dreaded infections endophthalmitis after cataract extraction and lens implantation and increased using of contact lens [7]. Thus, this study aimed to determine the prevalence some of the bacterial infection of eyes, some of the affecting risk factors and the antimicrobial susceptibility of the isolated types of bacteria to the most common antibiotics that were used in the study.

Patients and methods

A total of 176 patients attended to Iben AL-Haithem hospital of ophthalmology in Baghdad, from the period from September 2016-April 2017. The information was collected directly and the patient's agreement was taken for the research accomplishment, the questions parameters included the sociodemographic characters, age, and history of any disease.

Ocular specimens were collected from the patients by an ophthalmologist , and were transported by using 2 ml of brain-heart broth tubes (Oxoid) to the laboratory in iced boxes within 2 hours and inoculated on" blood agar, chocolate agar, MacConkey agar, Mannitol salt agar and modified Thayer-Martin agar" (MTM) (Oxoid) .

The inoculated media were incubated at 37 °C for 24 h. Bacterial colonies were identified on the basis of Gram`s stain, morphology, cultured and further alternate identification systems used by the laboratory included API strips (bioMérieux).

Antibiotic susceptibility

Antibiotic susceptibility was monitored with the disk diffusion assay (Kirby–Bauer), the zone of inhibition was interpreted according to NCCLS guidelines [8].

The following antibiotics were tested Erythromycin (15 μ g), Clarithromycin (15 μ g), Chloramphenicol (30 μ g), Clindamycin (2 μ g), Tetracycline ,(30 μ g), Doxycycline (30 μ g), Amikacin (30 μ g), Gentamicin (10 μ g), Ciprofloxacin (5 μ g), Ceftriaxone (30 μ g) supplied by HiMedia Lab.(India), reference strains of "*Staphylococcus aureus* ATCC25923, *E. coli* ATCC25922 and *Pseudomonas aeruginosa* ATCC27853" were used as a control.

Statistical Analysis Statistical Analysis

Chi-square test for statistical analysis. A P value <0.05 was used for finding the significance difference between the groups and correlated t-test was used to find the relation between the variables within the same group by using spss program [9].

Results

From total 138 patients with ocular bacterial positive culture , men were representing 57(41%) while women 81(59%), and suffering from these following infections conjunctivitis 48 (35%), keratitis 39(28%), endophthalmitis 26(19%), blepharitis 11(8%), blepharoconjunctivitis 8(6%), dacryocystitis 6(3%) diagnosed cases as shown in Figure-1.

The results showed that the number of the patients with bacterial ocular infection from Baghdad were 76(55%) while the internally displaced were 62(45%), the differences between the two group were not significant as shown in Table-1

Table	1 -Distribution	of	the	patients	with	bacterial	ocular	infection	according	to	the	Socio-
demog	raphic character	s.										

Socio-demographic characters	patients with bacterial ocular infection	patients with non bacterial ocular infection
Baghdad	76(55%)	23(61%)
IDP	62(45%)	15(39%)
Total	138(100%)	38(100%)

IDP internally displaced persons, p value (< 0.05)

According to age there were 27(20%) at 21.5 \pm 0,3 y , 36(26%) at 37.5 \pm 0.21y, 34(24%) at 53.5 \pm 0.23 y and 41(30%) at 69.5 \pm 0.10y., there was a significant differences between the age groups as shown in Table-2.

The results found. that 72(52%) of the patients with ocular bacterial infection had a history of diabetes mellitus and 78(57%) with hypertension, there was no significant differences between the two groups shown in Table-3.

Age/years	Mean ± SD	Number of patients with ocular bacterial infections %	Number of patients with ocular non bacterial infections %
14-29	21.6±0.3	27(20%)	5(13%)
30-45	37.5±0.21	36(26%)	8(21%)
46-61	53.5±0.23	34(24%)	11(29%)
62-77	69.5±0.10	41(30%)	14(37%)

 Table 2- Distribution of ocular bacterial infection according to the age groups.

p value (< 0.05)

Table 3-Relation between the number of patients with ocular bacterial infection and disease history related to age groups.

Disease history	Age/years	Mean±SD	Number of patients with ocular bacterial infections %	Number of patients with ocular non bacterial infections %
	14-29	21.6±0.3	7(10%)	5(8%)
Diabetes mellitus	30-45	37.5±0.21	16(22%)	10(15%)
	46-61	53.5±0.23	22(31%)	21(32%)
	62-77	69.5±0.10	27(37%)	30(45%)
	14-29	21.6±0.3	3(4%)	4(7%)
	30-45	37.5±0.21	12(16%)	13(22%)
Hypertension	46-61	53.5±0.23	29(36%)	20(33%)
	62-77	69.5±0.10	34(44%)	23(38%)

p value (< 0.05)

From the total samples, there were 87 (63%) positive culture for bacterial isolates. Gram positive was (58%) from the total isolates while gram negative bacteria (42%). *S.aureus* was the common dominant isolates at (29%) followed by *S.pneumoniae* (21%), *P.areuginosa* (16%), *E coli* (11%), *Klibseilla spp*(7%), *S.epidermidis* (6%), *Enterobacter spp*(6%), *S.pyogenes* (2%), *Citrobacter freundii* and *Proteus spp* (1%) each of them , co – infection were found in the following three samples *E. coli* + *P. aeruginosa; E. coli* + *S. aureus* and *P. aeruginosa* + *S. aureus*. The most common bacterial isolates were in cases of conjunctivitis 40 (46%) and in keratitis 18(21%) while in endophthalmitis 11(13%) followed by 12(14%) in case of dacryocystitis then 3(3%) in both cases of blepharitis and blepharoconjunctivitis, there was no significant differences between the groups of isolates as shown in Table-4.

						-	
Type of isolates	Number (%)						
		conjunctivitis	keratitis	endophthalmiti s	blephari tis	blepharoconjuncti vitis	dacryocysti tis
S.aureus	25(29%)	11(44%)	8(32%)	2(8%)	2(8%)	1(4%)	1(4%)
S.pneumonia e	18(21%)	8(43%)	4(22%)	3(17%)	1(6%)	1(6%)	1(6%)
P.areuginosa	14(16%)	5(36%)	1(7%)	1(7%)	0	0	7(50%)

Table 4-The relation between the types of bacterial isolates and clinical diagnosis

E.coli	10(11%)	4(40%)	2(20%)	2(20%)	0	1(10%)	1(10%)
Klibseilla spp	6(7%)	3(50%)	0	2(33%)	0	0	1(17%)
S.epidermidis	5(6%)	3(60%)	1(20%)	1(20%)	0	0	0
Enterobacter spp	5(6%)	3(60%)	2(40%)	0	0	0	0
S.pyogenes	2(2%)	2(100%)	0	1	0	0	0
Citrobacter freundii	1(1%)	1(100%)	0	0	0	0	0
Proteus spp	1(1%)	1(100%)	0	0	0	0	0
Total	87(100%)	40(46%)	18(21%)	12(14%)	3(3%)	3(3%)	11(13%)

p value (< 0.05)

The results of antibiotic susceptibility showed that *S. aureus* isolates were susceptible to Amikacin 22(88%) followed by Doxycycline 21(84%) then Cloramphenicol and Tetracycline 20(80%) for each and they were highly resistance to Clindamycin 19(76%), while *S.epidermidis* isolates were susceptible to each of Amikacin, Cloramphenicol, Clindamycin and Doxycycline at a percentage of (80%) and they were resistance to tetracycline 3(60%) as shown in Table-5.

S.pneumoniae isolates were susceptible to Clarithromycin 17(94%), Ceftriaxone 16(88%) followed by Cloramphenicol, Tetracycline and Doxycycline 15(83%) for each one, *S.pyogenes* isolates were susceptible at (100%) to the most types of antibiotics such as Erythromycin, Clarithromycin, Cloramphenicol, Clindamycin and Ceftriaxone as shown in Table-6.

			S. aureus n	=25		S.epidermidis n=5					
Antibiotics	MIC (µg/ml)	S	Ι	R	MIC (µg/ml)		S	Ι	R FRR	
	50	90				50	90				
Erythromycin	0.25	64	15(60%)	1(4%)	9(36%)	0.25	64	3(60%)	1(20%)	1(20%)	
Cloramphenico l	0.25	64	20(80%)	2(8%)	3(12%)	0.12	64	4(80%)	1(20%)	0	
Clindamycin	0.06	64	5(20%)	1(4%)	19(76%)	0.06	32	4(80%)	1(20%)	0	
Tetracycline	1	4	20(80%)	1(4%)	4(16%)	1	4	1(20%)	1(20%)	3(60%)	
Amikacin	0.12	32	22(88%)	1(4%)	2(8%)	0.25	16	4(80%)	1(20%)	0	
Gentamycin	0,25	8	16(64%)	2(8%)	7(28%)	0.25	16	3(60%)	2(40%)	0	
Ciprofloxacin	8	8	18(72%)	1(4%)	6(24%)	8	8	3(60%)	2(40%)	0	
Doxycycline	0.12	16	21(84%)	1(4%)	3(12%)	0.12	16	4(80%)	1(20%)	0	

Table 5- Antibiotic sensitivity and resistance of S. aureus and S.epidermidis isolates.

Antibiotics			S.pneumonia	<i>e</i> n=18		S.pyogenes $n=2$					
	Μ (μg	IC /ml)	s	I	R	MIC (µg/ml)		S	I	R	
	50	90	נ	_	K	50	90		1		
Erythromycin	0.12	64	12(67%)	2(11%)	4(22%)	0.25	64	2(100%)	0	0	
Clarithromycin	0.25	64	17(94%)	1(6%)	0	0.12	64	2(100%)	0	0	
Cloramphenico l	0.25	64	15(83%)	1(6%)	2(11%)	0.12	64	2(100%)	0	0	
Clindamycin	0.12	64	16(88%)	1(6%)	1(6%)	0.12	64	2(100%)	0	0	
Tetracycline	0.12	64	15(83%)	2(11%)	1(6%)	0.25	64	1(50%)	0	1(50%)	
Doxycycline	0.25	64	15(83%)	2(11%)	1(6%)	0.12	64	1(50%)	1(50%)	0	
Ciprofloxacin	1	2	0	1(6%)	17(94%	1	1	0	0	2(100%	
Ceftriaxone	0.5	4	16(88%)	1(6%)	1(6%)	0.5	4	1(50%)	1(50%)	0	

Table 6- Antibiotic sensitivity and resistance of S. pneumoniae and S.pyogenes isolates.

Table 7- Antibiotic	sensitivity and	resistance of	of <i>P.areuginosa</i>	and E.coli isolates.
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Antibiotics			P.areuginosa	n=14		E.coli n= 10					
	MIC (µg/ml)		ç	T	D	MIC (µg/ml)		S	I	D	
	50	90	د	1	ĸ	50	90	5	1	K	
Amikacin	8	32	10(72%)	2(14%)	2(14%)	16	32	4(40%)	1(10%)	5(50%)	
Cloramphenico l	1	2	9(65%)	1(7%)	4(28%)	1	2	9(90%)	1(10%)	0	
Tetracycline	8	32	6(43%)	0	8(57%)	8	8	4(40%)	1(10%)	5(50%)	
Doxycycline	1	2	10(72%)	0	4(28%)	1	2	7(70%)	1(10%)	2(20%)	
Ciprofloxacin	1	16	10(72%)	3(21%)	1(7%)	64	64	8(80%)	2(20%)	0	
Gentamicin	2	8	14 (100%)	0	0	2	8	8(80%)	2(20%)	0	

			Klibseilla s	<i>pp</i> n=6		Proteus spp $n=1$					
Antibiotics	MIC (µg/ml)		C.	т	D	MIC (µg/ml)		c	т	D	
	50	90	3	1	К	50	90	3	1	К	
Ceftriaxone	0.25	64	5(83%)	1(17%)	0	0.12	64	1(100%)	0	0	
Cloramphenicol	0.25	64	4(67%)	2(33%)	0	0.25	64	1(100%)	0	0	
Tetracycline	8	8	2(33%)	0	4(67%)	8	8	0	1(100%)	0	
Ciprofloxacin	16	16	6(100%)	0	0	16	16	1(100%)	0	0	
Gentamicin	0.25	64	6(100%)	0	0	0.12	64	1(100%)	0	0	

The results revealed that *P.areuginosa* isolates were susceptible to Gentamicin 14(100%) followed by Ciprofloxacin, Doxycycline, Amikacin 10(72%) for each antibiotic, while *E.coli* isolates were susceptible to Cloramphenicol 9(90%) followed by Ciprofloxacin and Gentamicin 8(80%) as shown in Table-7. *Klibseilla spp* isolates were susceptible to Ciprofloxacin and Gentamicin (100%) followed by Ceftriaxone 5(83%) while *Proteus spp* isolate were susceptible to all types of antibiotics (100%) such as Ceftriaxone, Cloramphenicol, Ciprofloxacin 5(100%) then both of Gentamicin and Cloramphenicol 4(80%), *Citrobacter freundii* isolate were susceptible to Ceftriaxone, Cloramphenicol Ciprofloxacin, Gentamicin (100%) as shown in Table-9.

Antibiotics	Enterobacter spp n= 5					Citrobacter freundii $n=1$				
	MIC (µg/ml)		S	I	D	MIC (µg/ml)		S	T	D
	50	90	3	1	K	50	90	3	1	К
Ceftriaxone	0.25	64	3(60%)	1(20%)	1(20%)	0.25	64	1(100%)	0	0
Cloramphenico l	0.12	64	4(80%)	0	1(20%)	0.25	64	1(100%)	0	0
Tetracycline	1	2	2(40%)	0	3(60%)	1	2	0	1(100%)	0
Ciprofloxacin	0.25	64	5(100%)	0	0	0.12	64	1(100%)	0	0
Gentamicin	0.25	64	4(80%)	0	1(20%)	0.25	64	1(100%)	0	0

Table 9- Antibiotic sensitivity and resistance of Enterobacter spp and Citrobacter freundii isolates



Figure 1-Distribution of ocular infections among the patients

Discussion

The study revealed that a high bacterial infections (78%), the infections were (41%) between men, while non-pregnant women were (59%). According to age group, the patients with ocular infections was (30%) at age of 62-77 years followed by (26%) for age of 35-40 years this ratio is different in other studies in Basra (64%) and Erbil (51%), this might be due to choosing of i some ocular infection in the study [10,11].

These results were higher than found in India (34.5%), Japan (32.2%) and Iran (37.5%) might be due to sociodemographic and climatic differences [12-14]. Conjunctivitis was the most common infections (46%) then keratitis (18%) and these results agree with other findings in Baghdad (24.16%) and Mosel (96%) [15, 16].

The patients with bacterial ocular infection from Baghdad were (55%) while the internally displaced (45%) and this related to the bad healthy conditions and other life issues they had through.

The result reveled that gram-positive bacteria represented (57%) of the total bacterial isolates and the most predominant bacterial isolate was *S. aureus* (29%), also they were highest in conjunctivitis (44%), keratitis (32%), endophthalmitis (8%) and blepharitis (8%), *S.pneumoniae* isolates were (21%) .in conjunctivitis (43%), keratitis (4%) and endophthalmitis (17%), while *S.epidermidis* isolates were (6%) and in conjunctivitis (60%) followed by *S.pyogenes* (2%) as they were (100%) in conjunctivitis (35%) then *S.pneumoniae* (31%) followed by *S. epidermidis* (28%) and *S.pyogenes* (24%), while in Pakistan *S. aureus* was in the first class (41%) followed by *S.pneumoniae* (37%) [15, 16].

Among the gram-negative *P. aeruginosa* were (16%) then *E. coli* (11%) and *Klebsiella spp* (7%) as other study in Baghdad reported that *P. aeruginosa* (4.9%), *E. coli* (4.9%) and *Klebsiella spp* (3%), this might be due to the further isolates from endophthalmitis cases .[17]

P. aeruginosa was the predominant isolate in daryocystitis (50%) and this disagree with other findings in Turkey as *P. aeruginosa* isolates were (23.4%) in keratitis [18]

The results showed that both of gram –positive and gram-negative isolates were susceptible to the most tested antibiotics and resistance to few types of antibiotics. Amikacin (88%), Clarithromycin (94%) Gentamicin (100%) and Ciprofloxacin (100%) were revealed high efficacy towards the bacterial isolates, as these results were close to other studies in China and India but not in other studies in Gondar have reported lower susceptibility to Gentamicin (54.8%) and Ciprofloxacin (74.2%) ,this could be due to differences in the variety of bacterial isolates [19, 20] . *S. pyogenes* isolates were susceptible to Erythromycin and this is different from what has been reported in France and Canada, where most of isolates were resistance to Erythromycin , the hight resistance to Erythromycin was detected in many countries appears to be predominately associated with serotype M28 of *S. pyogenes* [21, 22]

The resistance to Tetracycline was high, and this agree with other study from Jordan and Kuwait might be due to the excessive use in treatment of patients that produce the drug resistant strains [23, 24].

Conclusions

Conjunctivitis was very clear followed by keratitis among the patients with ocular bacterial infections. *S. aureus* was the highest gram positive bacterial isolates followed by *S.pneumoniae* while gram negative dominant isolates were *P. aeruginosa*. Both gram positive and negative isolates were susceptible to the most common tested antibiotics which will support the treatment strategies and control the common practice of self-medication.

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