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### RESEARCH ARTICLE

#### BACTERIAL SPECTRUM OF EXTERNAL OCULAR INFECTIONS: PREVALENCE AND ASSOCIATED *IN VITRO* ANTIMICROBIAL SUSCEPTIBILITY AND RESISTANCE IN A TERTIARY CARE HOSPITAL.

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#### Abstract

**Background:** External ocular infections (EOI) can affect the lids, conjunctiva or cornea and may carry serious consequences including visual impairment if not correctly identified and treated. Empirical treatment is usually initiated using broad-spectrum antibiotics before concluding culture and susceptibility testing, this along with casual prescriptions, ineffective dosing and poor patient compliance have contributed to increasing bacterial resistance to commonly used topical antibiotics.

**Aims:** Through this study we aim to establish the prevalence of bacterial EOI and their associated *in vitro* antimicrobial susceptibility and resistance profiles.

**Materials and Methods:** This cross-sectional study reviewed consecutive microbiological reports of EOI from January 2015 to December 2016. Demographic data and bacterial organisms isolated as well as their susceptibility and resistance results to routine antibiotics used in culture testing were obtained and analyzed.

**Results:** A total of 218 reports of bacterial EOI were attained from 165 patients. Gram-negative organisms represented 71% of all culture reports. *H. influenza* was the most common etiologic agent representing 26% of all organisms, followed by *S. aureus* (12%) and *P. aeruginosa* (10%). Gram-negative isolates had the highest *In vitro* susceptibility to Amikacin, Colistin and Meropenem. Gram-positive isolates had the highest *In vitro* susceptibility to Vancomycin. Resistance to multiple antibiotic classes was seen in 39% of cultures.

**Conclusion:** The antimicrobials used in routine culture testing including topical antibiotics commonly used by ophthalmologists had high susceptibility rates overall, but *In vitro* resistance was encountered for various bacterial organisms. Susceptibility testing allows physician to choose the best antibiotic to avoid inadequate treatment and potential complications including visual impairment and blindness.

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## Introduction:-

External ocular infections (EOI) are common occurrences with bacteria representing one of the main infectious etiologies along with viruses and fungi. EOI due to bacteria can affect the lids, conjunctiva or cornea.[1,2] They lead to conjunctivitis more than keratitis, with blepharitis being the least common. Variables affecting the development of bacterial EOI include poor hygiene, socio-economic status, living conditions, contact lens use, previous ocular trauma, chronic epithelial defects and immune status.[2]

In the United States, bacterial conjunctivitis has an incidence of 135 cases per 100,000, while bacterial keratitis has an incidence of 11 cases per 100,000 of the population.[3,4] Based on estimations, the number of people who suffer from blepharitis in the United States may be 25 million, however bacterial blepharitis is less common than bacterial conjunctivitis and keratitis.[2, 5] This is due to multiple factors underlying the pathogenesis of blepharitis, not all of which are infectious.[6]

Like bacterial infections elsewhere, growth and identification of causative organisms, along with antibiotic susceptibility testing is paramount in aiding physicians in choosing suitable antimicrobial agents for treatment.[1, 7, 8] Empirical treatment is usually initiated using broad-spectrum antibiotics before culture and susceptibility testing has been concluded when treating EOI, this along with indiscriminate prescriptions has contributed to increasing bacterial resistance to commonly used topical antibiotics.[9-11]

Since bacterial EOI can affect large numbers of people and may carry serious consequences if not correctly identified and treated, we aim to establish the spectrum and prevalence of bacterial organisms causing EOI, and to assess their *in vitro* susceptibility and resistance to minimal inhibitory concentration (MIC) testing of antibiotics in a tertiary care hospital in Saudi Arabia.

## Materials and Methods:-

This cross-sectional study was conducted by reviewing consecutive microbiological reports of EOI specimens obtained from the eyelids, conjunctiva or the cornea during the study period of January 2015 to December 2016. Reports where the same bacterial organism was grown during the study period and susceptibility testing was not performed were excluded (24 reports). In total 218 culture reports and their susceptibility to antimicrobial testing were reviewed.

All collected specimens underwent Gram's staining and were inoculated onto blood, chocolate and MacConkey agars. Growth of the same organisms on more than two solid phase media or confluent growth on one solid medium signified a positive culture. Sensitivity testing was performed using the Vitek® machine (Vitek® 2, BioMérieux) according to the instructions of the manufacturer and interpreted using the Institute's Clinical Laboratory Standards. Routine antimicrobial agents and minimally inhibitory concentrations were used for susceptibility testing of EOI cultures.

Data was recorded and subjected to statistical analysis using SPSS. For the descriptive analysis, frequency and percentage were computed for categorical variables like age, gender and organisms grown from cultures. Mean and standard deviation was estimated for quantitative variables for parametric data or median & interquartile range for non-parametric variable. Frequencies/percentages were calculated and presented in tables and charts. Chi-square test for the comparison of categorical variables, p-values <0.05 were considered significant.

## Results:-

A total of 218 reports of culture and susceptibility for bacterial EOI (of the lids, conjunctiva and cornea) were obtained from 165 patients. This is due to either the growth of multiple organisms from a single specimen, or the same patient developing EOI more than once at different times during the study period.

Males outnumbered females accounting for 59% of all cultures (Figure 1). There was no statistical significance in the occurrence of EOI between genders (p-value=0.34). Specimens were obtained from a wide age distribution, the youngest patient was less than a week old and the eldest was 99 years of age. Most reports (77%) were for those with EOI from birth up to the age of 2 years, followed by children and adolescents between the ages of 3 and 18 (13%). Adults between the ages of 19 and 64 represented 4% and those aged 65 and above represented 6% (Figure 2). Despite the large proportion of EOI occurring in those from birth to those under the age of 2, no statistical

significance existed for the occurrence of EOI between the four different age groups (p-value=0.25).

Gram-negative bacteria represented the majority of organisms cultured from EOI specimens with 154 of 218 cultures (71%) showing their growth. The different causative Gram-positive and Gram-negative organisms and their prevalence in our study are shown in Table 1. *Haemophilus influenza* was the most frequently encountered organism overall representing 57 of 218 and 26% of all cases, as well as being the most common Gram-negative bacteria seen in EOI. It was routinely tested for susceptibility to Ampicillin and Amoxicillin/Clavulanate, with 44 of the 57 *H. influenza* isolates (77.1%) found to be susceptible to Ampicillin, while remaining isolates were resistant. 53 of 57 *H. influenza* isolates (92.9%) were susceptible to Amoxicillin/Clavulanate with only 4 resistant cases. When resistance to both antibiotics was encountered, which occurred in 4 cases (7%) they were additionally tested against Ciprofloxacin and were susceptible in all cases.

From other commonly encountered Gram-positive organisms (more than 10 reports), the highest resistance of *Staphylococcus aureus* was towards Penicillin (88%). For Methicillin Resistant *Staphylococcus aureus* (11 cases) the highest resistance was to Gentamicin (18%) while the highest resistance for *Streptococcus pneumoniae* were towards Oxacillin (62%) and Erythromycin (48%). Of the drugs used in testing of all Gram-positive bacteria Vancomycin had the highest susceptibility rate (100%). Gentamicin had susceptibility rates of 100% for *S. aureus* and 82% for MRSA. Erythromycin's susceptibility rate for *S. aureus* was 78%, 52% for *S. pneumoniae* and 91% for MRSA. Moxifloxacin had 100% susceptibility for *S. aureus* and MRSA (Table 2).

For the most commonly encountered Gram-negative organisms (more than 10 reports); *Pseudomonas aeruginosa* cultures were susceptible in 95% of cases when tested against Gentamicin, 91% when tested against ciprofloxacin and 82% when tested against ceftazidime. 85% of *Klebsiella pneumoniae* isolates were susceptible to ciprofloxacin, 70% to gentamicin and 50% to trimethoprim/ sulfamethoxazole (SXT). *Escherichia coli* susceptibility was 100% to gentamicin and 83% to ciprofloxacin (Table 3). Colistin (100%), Amikacin (96%) followed by Meropenem (93%) had the highest *In vitro* susceptibility rates among the three most commonly cultured Gram-negative organisms with the exception of *H. influenza* (Table 3).

Resistance to multiple antibiotic classes was seen in 85 of all 218 cultures (39%). Of the 20 cases of *K. pneumoniae*, 6 cases were Extended Spectrum Beta-Lactamase (ESBL) producing (30%), and 4 of 12 cases of *E. coli* were ESBL producing (33%). Thus, ESBL producing bacteria represented (4.6%) of all culture and susceptibility reports reviewed. The ratio of *S. aureus* to MRSA was almost 2.5 to 1 with MRSA representing 29% of all *S. aureus* isolates and 5% of all bacterial organisms examined.

Gentamicin had susceptibility rates of 100% and 82% when tested against *S. aureus* and MRSA respectively. For Gram-negative organisms Gentamicin had susceptibility of 100% when tested against *Serratia marcescens* and *E. coli*, 95% for *P. aeruginosa*, 89% for *Acinetobacter baumannii* and 70% for *K. pneumoniae* (Table 4). For the fluoroquinolones, Moxifloxacin, a fourth-generation fluoroquinolone had 100% susceptibility when tested against both *Staphylococcus aureus* and MRSA. Ciprofloxacin a second-generation fluoroquinolone was tested against Gram-negative organisms and had 100% susceptibility for *S. marcescens*, 90% for *P. aeruginosa*, 85% for *K. pneumoniae*, 83% *E. coli* and 78% for *A. baumannii* (Table 5).

## Discussion:-

Limitations for our study should be considered when interpreting results. The total number of cultures reviewed and our patient population's eligibility restrictions, with the exception of emergency cases make generalization of our results to the Western region of KSA challenging. Our study only included reports of positive cultures without looking at specimens obtained from EOI that had no growth and consequent antimicrobial testing. Literature review suggests that culture positivity in EOI specimens ranges from 65 to 75%. [1, 2, 12, 13] Isolating causative organism in EOI as with other infections varies according to the site from which specimens were taken, which medium was used, and whether the media was enriched or not, [14] the quantity of inoculum provided in specimens, [15] and whether topical antibiotics were used prior to specimen collection. [16]

A large number of all specimens (77%) were obtained from newborns to the age of 2 years and those between the ages of 3 and 18 years (13%), with resulting growth of *H. influenza* in 26% of the total cultures and in 37% of Gram-negative cultures. Studies on age-independent series and those exclusively on elderly populations show that Gram-positive cocci were the most frequently encountered organisms causing EOI and other ocular infections. [16-

24] However in our study we had a predominance of Gram-negative isolates (71%). Perhaps this is due to the number of those under the age of 2 seen in our study, less adults seeking medical attention for EOI, and the clinical practice of treating adult infections with a prophylactic approach without susceptibility testing while adopting a more guarded approach towards pediatric populations, including collection of specimens for culture and susceptibility testing. Regional and population based variants may also have contributed, and we acknowledge results may differ between studies.

Bacterial EOI such as blepharitis in any age group and conjunctivitis following the neonatal period do not usually disturb vision, however bacterial conjunctivitis in the neonatal period and bacterial keratitis in all age groups may lead to severe visual impairments if not correctly diagnosed and adequately treated.[25-27] Globally, corneal diseases including infections still represent one of the major causes of visual impairment and blindness.[26] Therefore serious bacterial EOI especially when keratitis is suspected, necessitate prompt diagnosis and precise treatment in order to preserve vision.[2] One possible cause of inadequate treatment of EOI is bacterial resistance to antimicrobials, which may have serious and undesirable consequences for patients.[7,8]

This concern is becoming more troubling especially when considering the worldwide increased resistance to topical antibiotics.[28] Multidrug resistance is also becoming more of a concern with prevalence rates as high as 77% reported.[12] Regular use of broad-spectrum antibiotics before culture and susceptibility testing along with increased antibiotic resistance makes choosing effective empirical agents more difficult.[7] In our study, multidrug resistance was encountered in 85 bacterial isolates (39%); this is significantly less than the number reported in a study from Ethiopia.[12] Perhaps this is due to virulence factors related to organisms, seriousness of an EOI prior to seeking medical attention, the use of over the counter medications, availability of medical care in both study areas and socio-economic circumstances of the populations, or any combination of these factors.

We encountered 10 ESBL producing organisms (4.6% of the total), 6 cases due to *K. pneumoniae* and 4 cases due to *E. coli*. ESBL producing organisms have the ability to resist first-, second- and –third generation cephalosporins as well as aztreonam by hydrolyzing them, while also being inhibited by Beta-lactamase inhibitors such as clavulanic acid.[29] They may represent a diagnostic and therapeutic challenge especially when adequate resources for their detection or Beta-lactamase inhibiting antibiotics are not routinely available.

MRSA represented almost 5% of all organisms isolated with all 11 cases being susceptible to Vancomycin. MRSA comprised 29% of the total *S. aureus* isolates, which is similar to rates reported in a 20-year review of almost 400 cases of *S. aureus*. [30] MRSA susceptibility rates to SXT were generally reported to be more than 90% [17, 23, 31-36] which was consistent with our findings of 91%. However, other studies reported lower MRSA susceptibility rates to this drug ranging from 66.6% to 80%. [18, 32-35, 37] MRSA was susceptible to Gentamicin in 81% of cases, which was lower than previously reported in a seventeen-year review that included nine cases showing 100% susceptibility.[21] This may reflect increasing resistance of these organisms to commonly used antibiotics over time or may reveal geographic and population variations.

The majority of MRSA ocular infections are non-sight threatening.[32, 35] However MRSA ocular infections may have serious and destructive effects including cellulitis, corneal perforations and endophthalmitis.[23, 32-36, 38] The gold standard in treating MRSA keratitis is generally accepted to be Vancomycin.[18-21, 31, 32, 39] Exceptional reports concluded complete MRSA resistance to this medication.[40] However Vancomycin does have disadvantages including its short half-life, need for refrigerated storage and transport, expense and potential toxicity. In our study MRSA was also 100% susceptible to Linezolid, Colistin, Tigicycline and Moxifloxacin.

For Gram-positive organisms being tested against antimicrobials with topical preparations popular among ophthalmologists, Gentamicin had excellent susceptibility results of 100% and 82% when tested against *S. aureus* and MRSA respectively, while Moxifloxacin a fourth-generation fluoroquinolone was superior with 100% susceptibility when tested against both organisms. Erythromycin had susceptibility rates of 78% for *S. aureus*, 52% for *S. pneumoniae* and interestingly 91% for MRSA. Clindamycin also had 91% susceptibility rate for MRSA, but was inferior to Erythromycin for both *S. aureus* (78%) and *S. pneumoniae* (52%).

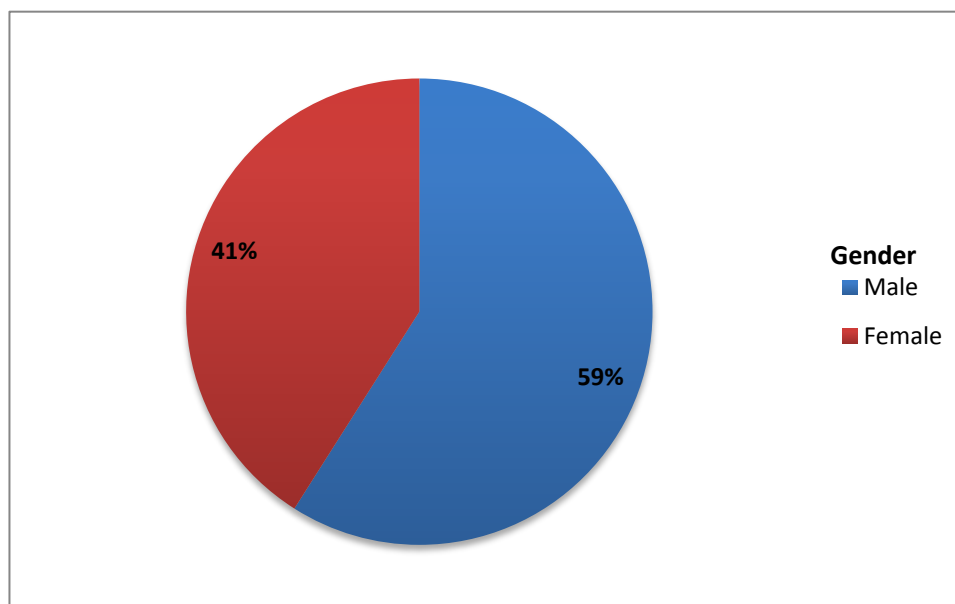
For Gram-negative organisms susceptibility to commonly used topical antibiotics, Gentamicin had susceptibility of 100% when tested for *S. marcescens* and *E. coli*, 95% for *P. aeruginosa*, 89% for *A. baumannii* and 70% for *K. pneumoniae*. Ciprofloxacin, a second-generation fluoroquinolone had 100% susceptibility for *Serratia marcescens*,

91% for *P. aeruginosa*, 85% for *K. pneumoniae*, 83% *E. coli* and 78% for *A. baumannii*. These results suggest that in EOI caused by Gram-negative organisms Gentamicin is superior to second-generation cephalosporins for the treatment of EOI caused by *P. aeruginosa*, *E. coli* and *A. baumannii* and only inferior for EOI caused by *K. pneumoniae*.

The overuse of topical antibiotics plays an important role in the development of bacterial resistance in EOI. However, incorrect selection of topical antimicrobials, insufficient dosing or poor compliance to medications may also play key parts in the increasing resistance. Due to the relative frequency of bacterial EOI and the number of people who develop them and seek medical attention, ophthalmologist and other physicians should be able to differentiate and manage EOI which may be sight threatening and those which are not, as well as knowing when to refer patients to specialists in diseases of the cornea and anterior segment of the eye. It is advisable for physicians and ophthalmologists to utilize bacterial cultures and susceptibility studies routinely to aid them in choosing the most effective antibiotic to give patients the best possible care, especially in cases where vision may be threatened. [7, 8, 41]

### Conclusion:-

The topical antibiotics commonly used by ophthalmologists did have high susceptibility results, but *In vitro* resistance to them was often encountered for various bacterial organisms causing EOI. Clinicians should utilize susceptibility testing to aid in justifiably utilizing the correct topical antibiotic medication to avoid inadequate treatment and avoid potential complications to patients including visual impairment and blindness. We recommend larger multi-center studies from different regions to help establish the most accurate bacterial spectrum and susceptibility results of EOI in KSA and elsewhere.



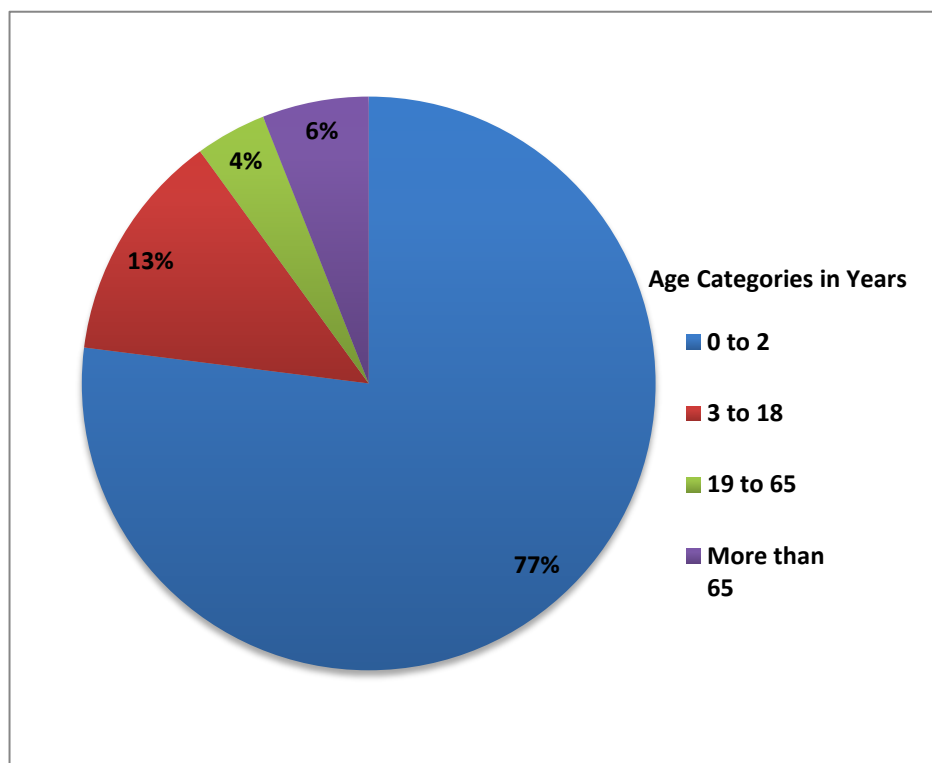
**Title:-** Percentage of EOI Culture Reports for each Gender

**Explanation:-** Chart showing gender distribution for reports of positive bacterial cultures that underwent antimicrobial susceptibility testing.

**Numerical data chart in figure 1 is based on:-**

**Males:-** 129 culture reports

**Females:-** 89 culture reports



**Title:-** Percentage of Culture Reports for Different Age Categories in Years

**Explanation:-** Chart showing age distribution by age categories for reports of positive bacterial cultures that underwent antimicrobial susceptibility testing.

**Numerical data Figure 2 is based on:-**

Under the age of 2 = 168 culture reports

Between the ages of 3 and 18 = 28 culture reports

Between the ages of 19 and 64 = 9 culture reports

**Table 1:-** Bacterial Organism Reports Encountered.

Gram-Positive Bacterial Organisms	Number of Reports Tested
<i>Staphylococcus aureus</i>	27
<i>Streptococcus pneumoniae</i>	21
<i>Methicillin Resistant Staphylococcus aureus</i>	11
<i>Coagulase negative staphylococcus</i>	2
<i>Streptococcus pyogenes</i>	2
<i>Abiotrophia defectiva</i>	1
<b>Total</b>	<b>64</b>
Gram-Negative Bacterial Organisms	Number of Reports Tested
<i>Haemophilus influenza</i>	57
<i>Pseudomonas aeruginosa</i>	22
<i>Klebsiella pneumoniae</i>	20
<i>Escherichia coli</i>	12
<i>Acinetobacter baumannii</i>	9
<i>Serratia marcescens</i>	5
<i>Moraxella</i>	5
<i>Enterobacter cloacae</i>	3
<i>Citrobacter koseri</i>	2

<i>Acinetobacter lwoffii</i>	2
<i>Morganella morganii</i>	2
<i>Chryseobacterium indologenes</i>	2
<i>Enterobacter aerogenes</i>	2
<i>Klebsiella oxytoca</i>	1
<i>Citrobacter sedlakii</i>	1
<i>Pseudomonas luteola</i>	1
<i>Pseudomonas stutzeri</i>	1
<i>Enterobacter gergoviae</i>	1
<i>Acinetobacter radiorestens</i>	1
<i>Acinetobacter ursingii</i>	1
<i>Acinetobacter junii</i>	1
<i>Proteus mirabilis</i>	1
<i>Pantoea</i>	1
<i>Stenotrophomonas maltophilia</i>	1
<b>Totoal</b>	<b>154</b>

Aged 65 and over = 13 culture reports

**Table 1:-** Table showing the prevalence of bacterial organisms that underwent antimicrobial susceptibility testing during the study period.

**Table 2:-** Susceptibility & Resistance Results of the Most Common Gram-Positive Bacteria in Percentages

Antibiotics Used	<i>Staphylococcus aureus</i> (N=27)		<i>Streptococcus pneumoniae</i> (N=21)		<i>Methicillin Resistant Staphylococcus aureus</i> (N=11)	
	Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant
<b>Clindamycin</b>	89	11	67	33	91	9
<b>Erythromycin</b>	78	22	52	48	91	9
<b>Gentamicin</b>	100	0	-	-	82	18
<b>Penicillin</b>	11	89	38	0	0	100
<b>Oxacillin</b>	100	0	38	62	0	100
<b>Ampicillin</b>	-	-	100	0	-	-
<b>Vancomycin</b>	100	0	100	0	100	0
<b>Linezolid</b>	100	0	-	-	100	0
<b>SXT</b>	100	0	-	-	91	9
<b>Cefazolin</b>	100	0	100	0	-	-
<b>Ceftriaxone</b>	-	-	100	0	-	-
<b>Moxifloxacin</b>	100	0	-	-	100	0
<b>Tigecycline</b>	100	0	-	-	100	0

**Table 2:-** Table showing susceptibility and resistance results of the most commonly encountered Gram-positive organisms. (More than 10 reports encountered) SXT = Trimethoprim/Sulfamethoxazole, (-) = Not tested.

**Table 3:-** Susceptibility & Resistance Results of the Most Common Gram-Negative Bacteria in Percentages

Antibiotics Used	<i>Pseudomonas aeruginosa</i> (N=22)		<i>Klebsiella pneumonia</i> (N=20)		<i>E.scherichia Coli</i> (N=12)	
	Susceptible	Resistant	Susceptible	Resistant	Susceptible	Resistant
<b>Gram-Negative Organisms (N=38)</b>						
<i>Pseudomonas aeruginosa</i> (N=22)	95	5	70	30	90	10
<i>Klebsiella pneumoniae</i> (N=20)	95	5	95	5	85	15
<i>Escherichia coli</i> (N=12)	-	-	0	100	83	17
<i>Acinetobacter baumannii</i> (N=9)	-	-	-	-	78	22
<i>Serratia marcescens</i> (N=5)	-	-	70	30	100	0
<b>Trimethoprim/Sulfamethoxazole</b>	-	-	85	15	42	58
<b>Cefazolin</b>	-	-	50	50	50	50
<b>Ceftriaxone</b>	-	-	-	-	58	42
<b>Ceftazidime</b>	82	18	-	-	-	-
<b>Cefepime</b>	86	14	-	-	50*	50*
<b>Ciprofloxacin</b>	91	9	85	15	83	17
<b>Meropenem</b>	82	18	100	0	100	0
<b>Imipenem</b>	73	27	100	0	100	0
<b>Colistin</b>	100	0	100	0	100*	0
<b>Piperacillin/Tazobactam</b>	91	9	65	35	67	33
<b>Tigecycline</b>	0	100	100*	*0	100*	*0

**Table 3:-** Table showing susceptibility and resistance results for Gram-negative organisms encountered 10 times or more. \*Only used for testing in ESBL producing organisms.

**Table 4:-** Gentamicin *In Vitro* Susceptibility and Resistance Results in Percentages

	Susceptible	Resistant
<b>Gram-Positive Organisms (N=38)</b>		
<i>Staphylococcus aureus</i> (N=27)	100	0
<i>Methicillin Resistant Staphylococcus aureus</i> (N=11)	82	18
<b>Gram-Negative Organisms (N=68)</b>		
<i>Pseudomonas aeruginosa</i> (N=22)	95	5
<i>Klebsiella pneumoniae</i> (N=20)	70	30
<i>Escherichia coli</i> (N=12)	100	0
<i>Acinetobacter baumannii</i> (N=9)	89	11
<i>Serratia marcescens</i> (N=5)	100	0

**Table 4:-** Table showing susceptibility and resistance results of the most commonly encountered Gram-positive and Gram-negative organisms towards Gentamicin.

**Table 5:-** Ciprofloxacin *In Vitro* Susceptibility and Resistance Results in Percentages

**Table 5:-** Table showing susceptibility and resistance results of the most commonly encountered Gram-positive and Gram-negative organisms towards Gentamicin.

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