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Prevalence of Some Extended Spectrum β- Lactamase Producing *Enterobacteriaceae* in Human: A Retrospective Study

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ABSTRACT

Extended spectrum beta lactamase producing *Enterobacteriaceae* (ESBL PE) bacteria represent an important public health concern as these organisms are resistant to multiple antimicrobial agents. A retrospective study was conducted to determine the prevalence of ESBL PE isolated from different samples of human patients and study the effect of age and sex on the estimated prevalence. Archival records of 320 patients with ESBL PE results were available for reviewing at the time of this study. Demographic data obtained included age, gender, type of examined samples and results of antibiotic sensitivity. It was found that the prevalence of ESBL PE in females (54.1%) was higher than in males (45.9%). The effect of age on the prevalence of ESBL PE clarified that the highest prevalence was observed in the age group > 65 years (49.1%) followed by the age group 45 < 65 years (25%) and finally the age group and 1 < 13 years (4.9%). Concerning the type of sample, the highest frequency of *E.coli* was reported in urine samples followed by wound swabs, blood, sputum, vaginal swabs and laryngeal swabs with prevalence while in *Klebsiella* spp., the highest frequency was observed in urine samples followed by sputum, wound, blood, vaginal swabs and laryngeal swabs. The results of antibiotic sensitivity was recorded as follow; *E.coli* displayed the highest resistance to penicillin followed by extended spectrum cephalosporin with higher susceptibility to carbapenems and relative high resistance to other antibiotics as aminoglycosides followed by fluoroquinolones, tetracycline, chloramphenicol, Nitrofurantoin and Cotrimoxazole. Regarding *Klebsiella* spp. isolates, they exhibited higher resistance to Penicillins followed by extended spectrum cephalosporin, then carbapenems. For the other antibiotic classes, they revealed higher resistance to chloramphenicol followed by fluoroquinolones, aminoglycosides, Cotrimoxazole, tetracycline and Nitrofurantoin. This retrospective study revealed higher antimicrobial resistance among *E. coli* and *Klebsiella* spp. to commonly used antimicrobial medications. These resistance levels could be attributed to ESBL production by these isolates obtained from both the hospital and the community.

1. INTRODUCTION

ESBLs were firstly reported in the year of 1980s, they were thought to be originated from point mutations of the TEM and SHV enzymes, which result in resistance to the β-lactam antibiotic. Many species have economic importance due to their pathogenic effects on agriculture and livestock.

Extended spectrum beta lactamase producing *Enterobacteriaceae* (ESBL PE) are gram-negative, facultative anaerobic, rod- shaped bacteria which are distributed worldwide. The plurality of the *Enterobacteriaceae* strains are living in the intestine of human and animals and few species are found in water and soil (Giske et al., 2009). In addition, ESBLs genes are plasmid-encoded and can be transmitted by conjugation to other bacteria, even across species barriers, these genes encoded enzymes destroy beta lactam antibiotic group. Beta-Lactams are commonly used for the treatment of several infections such as pneumonia, urinary tract infections (UTI), and severe life-threatening

infection and bloodstream infections (BSI) (Giske et al., 2009).

ESBLs are classified according to molecular sequence to class A,B, C and D with other classification put them in three main groups; $ESBL_A$, $ESBL_M$ and $ESBL_{CARBA}$. $ESBL_A$ includes CTX-M enzymes besides SHV and TEM enzymes that are inhibited by clavulanic acid. $ESBL_M$ includes miscellaneous and ESBLs acquired AmpC plasmid. $ESBL_{CARBA}$ are enzymes responsible for carbapenemase activity as metallo β-lactamases and KPC (Giske et al., 2009).

Human and animals usually got colonized before infection; the risk factors of colonization are traveling to endemic countries with high prevalence rates for ESBL PE. Human to human contact play an important role in the dissemination of ESBL PE among humans. Livestock derived foods are also considered sources for the colonization of humans with ESBL PE as ESBLs can be transferred from animals to humans through direct contact. Intestinal carriage of ESBL PE in food producing animals and contamination of retail meat and animal's product may be contributed to increase incidence of infections with ESBL PE in human population. The same ESBL genes could be detected in animals and the farmers who take care for them representing an occupational risk of its transmission (Leverstein et al., 2011).

ESBL/AmpC-producing zoonotic pathogens contaminating food products constitute a direct risk for public health. In those bacteria, ESBL/AmpC encoding genes are usually acquired from the animal reservoir.In the case of poultry farming, this mainly concerns the farmers and slaughterhouse workers; the risk of intestinal colonization with ESBL PE of poultry farm workers depends on their tasks, if they have close and frequent contact to live animals, carcasses or organs. Those workers play important role to spread ESBL/ AmpC to human population (Dohmen et al., 2015). Exchanges of ESBL producing CTX-M15 K. pneumoniae clone is widely disseminated in humans and also recognized in pets and horses, while some E. coli lineages play an important role in the dissemination of ESBL/AmpC genes.

In humans, infections with ESBL PE are associated with high rate of diseases. Since the 1990s, there has been a shift in ESBL genes associated with nosocomial and health related infections from genes mainly of class A.

The Centers for Disease Control and Prevention (CDC) confirmed that more than 2.8 million people are infected annually in the US with antibiotic resistant bacteria and at least 35.000 die due to these infections. The calculated price tag is $20 billion in direct healthcare costs. Britain also predicts that the toll of global antimicrobial resistance will be 10 million deaths annually and up to $100 trillion lost to the global economy by 2050. It also estimates 150 million of urinary tract infection was annually reported worldwide and about 35% of those are suffering from nosocomial infection (CDC, 2021).

WHO reported very high rates of resistance both for health care associated (HCA) and community acquired (CA) infections. The data pointed out that fluoroquinolone resistance in E. coli was reported in 92 member states out of 194 and 5 out of 6 WHO global regions. Similarly, extended spectrum cephalosporin resistance was recorded in 86 member states and 5 regions (WHO, 2014).

In Africa, In Algerian hospitals, ESBLs reported in 16.4-31.4% of the samples in which Class A ESBLs were most common, but plasmid encoded AmpC was also present. In Egypt, ESBLs were reported in 11-42.9% of samples in both hospitals and communities; the genes involved were class A ESBLs, while In Guinea-Bissau and Libya, class A and D ESBLs and $ESBL_{CARBA}$ were reported in 32.6 and 16%, respectively, in rectal or stool samples. In Morocco, class A and D ESBLs, AmpC, and $ESBL_{CARBA}$ were reported in hospital settings,while in the community setting, class A and D ESBLs were reported in between 1.3 and 7.5% of acquired urine samples. In Tunisia, class A and D ESBLs, AmpC, and $ESBL_{CARBA}$ were ranged from 11.7 to 77.8% in hospitals and was 0.7 and 7.3% in two communities (Storberg, 2014). So the aim of the current work was to determine the prevalence of ESBL PE isolated from different samples of human patients and study the effect of age and sex on the estimated prevalence.

2. MARTIAL AND METHODS:

2.1. Study period and area:

A retrospective study was conducted on confirmed patients with ESBL PE infection during the period extended from January 2019 to August, 2020. Data was kindly obtained from two hospitals; the first was located in Kafr El- Zayat district, Gharbya Province, while the other was located in Alexandria Province. In addition, data was obtained from a private laboratory in Damanhur, Beheira Province.

2.2. Study population:

Archival records of 320 patients with ESBL PE results were available for reviewing at the time of this study. Demographic data obtained included

age, gender, type of examined samples and results of antibiotic sensitivity.

2.3. Ethical Issues:

The restored data was nameless and was not linked to any patient.

3. RESULTS AND DISCUSSION

In human population the unwise and random use of antibiotics especially extended spectrum beta lactam antibiotics increase the resistance of bacterial pathogens to the most commonly used antibiotic groups. High incidence of ESBL PE has resulted in limitation of therapeutic options, multidrug resistance which can disseminate even between different bacterial families, and increased mortality. ESBL PE become one of the most common nosocomial infections, so it is necessary to detect and treat them as early as possible (Soltani et al., 2014). Without control of antimicrobial resistance in hospitals, and wise treatment program in animal population, patients and animals can disseminate antibiotic residues and resistance genes in between and to community and environment.

Females are more likely to develop urinary tract infections (UTIs) than males due to anatomical difference and this may be the cause of high prevalence of ESBL PE in females than males as shown in Table (1). It was observed that the prevalence of ESBL PE in females (54.1%) while in males (45.9%). This finding was similar to Mitu et al., (2019) who demonstrated a high prevalence of UTIs in females (83.5%) than in males (16.5%) and Abebe et al., (2018) who reported ESBL PE isolates with higher incidence in females (n=78) than males (n=52), while it differed with Ouedraogo et al., (2016) who recorded higher rate of ESBL PE in male than females patients.

Age plays an important role in distribution of antibiotic resistance as children and young adults are less susceptible to antibiotic treatment while elderly are more susceptible to admit to hospitals several times or for long times and to receive different antibiotic remedies and this make them more vulnerable for antibiotic resistance more than other age group and put them in risk to develop hospital acquired nosocomial infection and this may explain the highest prevalence of ESBL PE in age group > 65 (49.1%) as shown in Table (2) followed by 45 > 65 (25%) then age group 26 - < 45 (13.8%) and 13 - < 25 (7.7%), finally the lower prevalence was in age group 1 - < 13(4.4%) and this prevalence in children may be attributed to that children may acquire infections during health care, not from community.

It is also recommended to avoid unnecessary use of 3rd generation cephalosporin, carbapenems and fluoroquinolones in children treatment policy because that may lead to extended spectrum β-lactamase associated infection. This result is similar with Hu et al., (2019) and Toubiana et al., (2016) who reported prevalence of ESBL PE in children lower than that of adults.

Table (1): Prevalence of ESBL *PE* in human in relation to gender

Gender	Positive	
	No.	%
Males	147	45.9
Females	173	54.1
Total	**320**	**100.0**

Table (2): Prevalence of ESBL *PE* in human in relation to age groups

Age groups (Years)	Positive	
	No.	%
1 - < 13	14	4.4
13 - < 25	25	7.7
26 - < 45	44	13.8
45 - < 65	80	25.0
> 65	157	49.1
Total	**320**	**100.0**

Table (3): Frequency of isolation of ESBL PE in humans in relation to the type of examined samples

Type of the examined samples	*E. coli* isolates		*Klebsiella* spp. isolates	
	Frequency	**%**	**Frequency**	**%**
Urine	135	78.5	94	58.3
Blood	9	5.2	8	4.9
Sputum	8	4.6	41	25.4
Laryngeal swabs	1	0.6	1	0.6
Vaginal swabs	1	0.6	1	0.6
Wound swabs	18	10.4	16	9.9
Total number of isolates	**172**	**100.0**	**161**	**100.0**

Table (4): Results of sensitivity of *E.coli* isolates against β- lactams antibiotics and their derivatives

Families of antibiotics	Antibiotics	Resistant isolates	Not Inhibited by /or			Bash Jacoby type	Molecular type	Represented enzymes
			CA	TZB	SAM			
Cephalosporin	CEX	106 (76.8%)	86	35	106	1 & 1e	C	E. coli AmpC, p99, ACT-1, CMY-2, FOX-1 MIR-1, GCI, CMY-37 TEM-50
	CEF	31(91.1%)	31	31	31			
Extended spectrum cephalosporin	CAZ	116 (67.4%)	86	35	116			
	CPZ	126 (73.2%)	86	35	122			
	CXM	113 (81.8%)	86	35	113			
	CTX	122 (70.9%)	86	35	122			
	CTR	118 (68.6%)	86	35	118			
	FOX	38 (22%)	-	-	-			
	CPM	133 (77.3%)	86	35	122			
	CXM*	15 (44.1%)	15	15	15			
Extended spectrum cephalosporin with β-lactamase inhibitors	SCF	77 (44.7%)	86	35	77			
Penicillins	AMP	165 (95.9%)	86	35	122	2br	A	TEM-30, SHV-10
Carbapenems	MEM	21(12.2%)	21	21	21	3a , 3b	B (B1, B2, B3)	IMP-1, VIM-1 CcrA, IND-1 L1, CAU-1, GOB-1, FEZ-1 , CphA, Sfh-1
	ETP	24 (13.9%)	24	24	24			
	IPM	4 (2.3%)	4	4	4			
		Inhibited by SAM / TZB or CA						
Early Cephalosporin, Penicillins, extended spectrum cephalosporin	CEX	106 (76.8%)	20	71	-	2a, 2b 2be, 2e For CPM 2ce	A	PC1, TEM-1 TEM-2 SHV-2 CTX-M15 PER-1 VEB-1, CepA For CPM RTG-4
	CEF	31 (91.1%)	-	-	-			
	CAZ	116 (67.4%)	30	81	-			
	CPZ	126 (73.2%)	40	91	-			
	CXM	113 (81.8%)	27	78	-			
	CTX	122 (70.9%)	36	87	-			
	CTR	118 (68.6%)	32	83	-			
	FOX	38 (22%)	-	-	-			
	CPM	133 (77.3%)	47	98	10			
	CXM*	15 (44.1%)	-	-	-			
	AMP	165 (95.9%)	79	145	43			

CXM*: Cefuroxime sodium

Among ESBL PE isolated worldwide, E. coli and K. pneumonia have the highest prevalence in both hospital, community acquired infections and animals population. E.coli is the most commonly isolated organism in the clinical laboratory. E coli are the major cause of urinary tract infections, including prostatitis and pyelonephritis. Klebsiella spp. is also common urinary tract pathogens.

K. pneumoniae causes a severe pneumonia. Both are major enteric pathogen, particularly in developing countries In normal condition they do not result in diseases, but the resistant nosocomial strains could colonize or overgrow when the normal intestinal flora are disturbed by antibiotic remedy. Skin trauma or wound and immunosuppressive remedy also increase the risk of infection (Abayneh et al., 2018 and Devi et al., 2020).

It was recorded that the prevalence of E.coli was higher than that of K. pneumoniae which could be attributed to occurrence of the infection after colonization. It was similar to Shakya et al., (2017), Kurz et al., (2017) and Mahamat et al. (2019) while, it did not agree with Feglo et al., (2016) and Ibrahim et al., (2019) who reported ESBL higher prevalence range in K. pneumoniae compared to that of E.coli.

Table (5): Results of sensitivity of *E.coli* isolates against several antibiotics families

Families of antibiotics	Antibiotics	No. of Isolates		Enzyme responsible for resistance
		Resistant	Sensitive	
Aminoglycosides	TOB	81 (47%)	51 (52.9%)	AAC, ANT, APH
	CN	65 (37.7%)	107 (62.2%)	
	AMK	20 (11.6%)	152 (88.3%)	
Quinolone Fluoroquinolones	CIP	113 (65.6%)	59 (34.3%)	GyrA, ParC (substitution mutation)
	LEV	111 (64.5%)	61 (35.4%)	
	OFX	117 (68%)	55 (31.9%)	
	NOR	93 (68.8%)	42 (31.3%)	
	NA	96 (71%)	39 (28.8%)	
	MXF	10 (29.4%)	24 (70.5%)	
Tetracycline	DOX	111 (64.5%)	61 (35.4%)	Tet(X)
	TE	100 (72.4%)	38 (27.5%)	
	TCG	5 (3.6%)	133 (96.3%)	
Semisynthetic broad spectrum	CL	114 (82.6%)	24 (17.3%)	CAT
Synthetic antimicrobial Nitrofurantoin	F	96 (71%)	39 (28.8%)	nfsA , nfsB
Co- trimoxazole	SXT	107 (62.2%)	65 (37.3%)	Sul1 , sul2, dfrA
Dihydrofolate reductase inhibitor	TMP	7 (20.5%)	27 (79.4%)	Over production of dihydrofolate reductase dfr genes
Antimycobacterials	RF	30 (88.2%)	4 (11.7%)	Mutation in RNA polymerase enzyme
Phosphonic acid antibiotic	FO	3 (0.8%)	31(91.1%)	FosA, FosB, FosX

Table (6): Results of sensitivity of *Klebsiella* spp. isolates against β- lactams antibiotics and their derivatives

Families of antibiotics	Antibiotics	Resistant isolates	Not Inhibited by /or			Bash Jacoby type	Molecular type	Represented enzymes
			CA	TZB	SAM			
Cephalosporin	CEX	137 (88.3%)	131	102	137	1 & 1e	C	AmpC, p99, ACT-1, CMY-2, FOX-1 MIR-1, GCI, CMY-37 TEM-50
	CEF	5 (83.3%)	5	5	5			
Extended spectrum cephalosporin	CAZ	136 (84.4%)	131	102	136			
	CPZ	141 (87.5%)	131	102	139			
	CXM	142 (91.6%)	131	102	139			
	CTX	143 (88.8%)	131	102	139			
	CTR	140 (86.9%)	131	102	139			
	FOX	108 (67%)	108	102	108			
	CPM	140 (86.9%)	131	102	139			
	CXM *	4 (66.6 %)	4	4	4			
Extended spectrum cephalosporin with β-lactamase inhibitors	SCF	129 (80.1%)	-	-	-			
Penicillins	AMP	155 (96.2%)	131	102	139	2br	A	TEM-30, SHV-10
Carbapenems	MEM	85 (54.8%)	85	85	85	3a , 3b	B (B1, B2, B3)	IMP-1, VIM-1, CcrA, IND-1, L1, CAU-1, GOB-1, FEZ-1 , CphA, Sfh-1
	ETP	97 (60.2%)	97	97	97			
	IPM	18 (11.6%)	18	18	18			
Inhibited by SAM / TZB or CA								
Early Cephalosporin, Penicillins, extended spectrum cephalosporin	CEX	137 (88.3%)	6	-	-	2a, 2b 2be, 2e For CPM 2ce	A	PC1, TEM-1, TEM-2, SHV-2, CTX-M15, PER-1, VEB-1, CepA For CPM RTG-4
	CEF	5 (83.3%)	-	-	-			
	CAZ	136 (84.4%)	5	-	-			
	CPZ	141 (87.5%)	10	-	2			
	CXM	142 (91.6%)	11	-	3			
	CTX	143 (88.8%)	12	-	4			
	CTR	140 (86.9%)	9	-	1			
	FOX	108 (67%)	-	-	-			
	CPM	140 (86.9%)	9	-	1			
	AMP	155 (96.2%)	24	-	16			
	CXM*	4 (66.6 %)	-	-	-			

Table (7): Results of sensitivity of *Klebsiella* spp. isolates against several antibiotics families

Families of antibiotics	Antibiotics	No. of Isolates		Enzyme responsible for resistance
		Resistant	Sensitive	
Aminoglycosides	TOB	118 (73.2%)	43 (26.7%)	AAC, ANT, APH
	CN	84 (52.1%)	77 (47.8%)	
	AMK	92 (57.1%)	69 (42.8%)	
Quinolone Fluoroquinolones	CIP	122 (75.7%)	39 (24.2%)	GyrA, ParC (substitution mutation)
	LEV	114 (70.8%)	47 (29%)	
	OFX	119 (73.9%)	42 (26%)	
	NOR	69 (73.4%)	25 (26.5%)	
	NA	68 (72.3%)	26 (27.6%)	
	MXF	3 (50%)	3 (50%)	
Tetracycline	DOX	98 (60.8%)	63 (39.1%)	Tet (X)
	TE	92 (59.3%)	63 (40.6%)	
	TCG	7 (4.5%)	148 (95.4%)	
Semisynthetic broad spectrum	CL	141 (90.9%)	14 (0.9 %)	CAT
Synthetic antimicrobial Nitrofurantoin	F	57 (60.6%)	37 (39.3%)	nfsA , nfsB
Co- trimoxazole	SXT	126 (78.3%)	35 (21.7%)	Sul1 , sul2, dfrA
Dihydrofolate reductase inhibitor	TMP	0 (0%)	6 (100%)	Over production of dihydrofolate reductase
Antimycobacterials	RF	5 (83.3%)	1 (16.6%)	Mutation in RNA polymerase enzyme
Phosphonic acid antibiotic	FO	2 (33.3%)	4 (66.6%)	FosA , FosB, FosX

Notes:

- Antibiotic; F, NA and NOR were used only for isolates obtained from urine samples.
- Antibiotics; CEX, CXM, MEM, CL, TGC and TE were used for 138 *E. coli* isolates while IPM was used for 155 *Klebsiella* spp. isolates.
- Antibiotic; moxifloxacin, fosfomycin, cefuroxime sodium, trimethoprim, cefadroxil and rifampicin were used for 34 *E. coli* isolates and 6 *Klebsiella* spp. isolates.

The recorded data in Table (3) showed the frequency of isolation of ESBL PE in humans in relation to the type of examined samples. Concerning E.coli isolates, the highest frequency was observed in urine samples (78.5%) then wound swab (10.4%), blood (5.2%), sputum (4.6%) followed by laryngeal (0.6%) and vaginal swabs (0.6%). This was similar to Chaudhary et al., (2020) who recorded increased frequency of E. coli in urine followed by sputum, pus, blood and vaginal swabs, while Feglo et al., (2016) recorded increased frequency of E. coli in urine followed by blood, wound, sputum and vagina. Also, Shashwatiet al., (2014) recorded higher frequency in urine samples.

Regarding K. pneumoniae isolates, the highest frequency was observed in urine (58.3%) followed by sputum (25.4%), wound swab (9.9%), blood (4.9%) while lower frequency was recorded in laryngeal and vaginal swabs (0.6% for each). The relative high frequency of k. pneumoniae in sputum may be attributed to that it is considered one of the most common causes of respiratory illness in human, it also one of the frequent isolated bacteria from ventilators in ICU. This result agreed with Feglo et al., (2016) who recorded increased frequency in urine samples followed by blood, wound, sputum and vaginal swabs. Also, Xercavins et al., (2020) observed increased frequency in urine samples (78%), followed by surgical wounds (10%), blood (10%) and lastly, respiratory samples (2%).

The recorded results in Table (4) represented the sensitivity of E. coli isolates against β- lactams and their derivatives which were classified according to Jacoby phenotypic classification (Bush and Jacoby, 2010). E. coli exhibited the highest resistance against penicillin followed by cephalosporin then extended spectrum cephalosporin while higher susceptibility to carbapenems representing class A , B and C. This was similar to Ahmed et al., (2013), Shashwati et al., (2014), Miao et al., (2017) and Jamil et al., (2018).

The recorded results in Table (5) represented the sensitivity of E.coli isolates against several antibiotics families; E.coli showed relative high resistance to aminoglycosides followed by fluoroquinolones, tetracycline, chloramphenicol, Nitrofurantoin and Cotrimoxazole. This was similar to Shashwati et al., (2014) and did not agree with Miao et al., (2017) and Jamil et al., (2018) who recorded relative lower resistance to amikacin (aminoglycosides).

The recorded results in Table (6) represented the sensitivity of Klebsiella spp. isolates

against β-lactams and their derivatives which were classified according to Jacoby phenotypic classifications. Klebsiella spp. displayed higher resistance to pencillins followed by extended spectrum cephalosporin. Also, it exhibited higher resistance to carbapenems in comparison to E.coli isolates. This was similar to Ahmed et al., (2013), Ghaffarian et al., (2018) and Sharma and Sharma, (2019) but they exhibited lower resistance to carbapenems.

The recorded results in Table (7) represented the sensitivity of Klebsiella spp. isolates against several antibiotics families. It revealed higher resistance to chloramphenicol followed by fluoroquinolones, aminoglycosides, Cotrimoxazole, tetracycline and Nitrofurantoin It was also noticed that resistance of Klebsiella spp. to these antibiotic groups was higher than that of E.coli.

This finding agreed with Ahmed et al., (2013) with higher resistance detected in our study and it may be attributed to the time interval which could be responsible for increasing the misuse of antibiotics and the sequential order of resistance, but it did not agree with Sharma and Sharma, (2019) who reported that 100% of Klebsiella spp. isolates were resistant to Cotrimoxazole and tetracycline and Ghaffarian et al., (2018) who reported increased susceptibility to carbapenems. Detection of carbapenems resistance in this study put pressure on common antibiotic treatment policy in intensive care units which select carbapenems as last drug of choice in treatment of ESBL PE.

5. CONCLUSION

This retrospective study revealed high antimicrobial resistance among E. coli and Klebsiella spp. to the commonly used antimicrobial medications. These resistance levels could be attributed to ESBL production by these isolates obtained from both the hospital and the community. These high levels of antimicrobial resistance and the widespread prevalence of ESBL producing E. coli and Klebsiella spp. emphasized the necessity to perform immediate intervention strategies to prevent severe hospital acquired infections and to continuously monitor ESBL dissemination into the community. This study also exhibited that ESBL producing microorganisms were not only resistant to β- lactam antibiotics but also to other group of antimicrobial agents which means that multiple mechanisms play a role in drug resistance among Gram-negative bacteria.

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