Antimicrobial resistance of bacterial isolates from the clinical and hospital environment in Gaza Strip, Palestine: A review over 20-year

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Abstract

Background: Antimicrobial resistance is a serious threatening problem worldwide, associated with high morbidity and mortality. The dissemination and spread of antibiotic-resistant bacteria is influenced by several factors like inappropriate and unwise use of antibiotics as well as the un-regulated discharge of these antibiotics to the environment. A critical high rates of pathogenic bacteria isolates in Palestine are showing multiple drug resistance patterns. This fact will complicate treatment of patients suffering from bacterial infections.

Method: The study performed a review of most published articles on antibiotic resistant bacteria isolates from patients and hospital environment in Gaza strip/Palestine over the period 2002-2021 using Google scholar, Research gate, and PubMed search engines.

Results: Out of the 51 articles screened, 29 studies were met the eligibility criteria to be included in this review. The overall results of these studies have shown a high rates of multidrug-resistant gram-negative bacteria especially *E. coli*, *Enterobacter* spp., *Kebsiella* spp., *Acinetobacter* spp. and *Pseudomonas aeruginosa* over the study period. Also, vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* were also commonly reported among Gram-positive bacteria.

Conclusions: The high occurrence rates of multidrug resistant bacteria isolates from patients and hospital environment in Gaza/Palestine is alarming. Therefore, there is an urgent need to develop a local plan for containment of antimicrobial resistance by implement antimicrobial stewardship.

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Introduction

Bacterial ability to resist and overcome antimicrobial agents has been noticed since the development of these agents and their approval for use in the clinical field [1]. Antimicrobial resistance is a worldwide growing problem, leading to morbidity, mortality, and financial burden to the health-care system [2]. It is estimated that in the United States, at least 2 million patients develop serious infections due to antibiotic resistant bacteria annually [3]. It has been reported that antimicrobial resistance is one of the major public health concerns, particularly in developing countries, where the relative ease of medication availability and higher consumption rates, that have resulted in a disproportionately higher incidence of improper use of antibiotics and greater rates of resistance compared to more developed countries [4]. Additional factors contributing to the increased burden of bacterial resistance in developing countries are the weakened health infrastructure, behind scheduled presentations, the limited access to diagnostics (especially microbiology), and the reduced availability of second-line antibiotics [5]. Moreover, this alarming phenomenon may also be caused by antibiotics use in animal feed, inappropriate prescribing of antibiotics, and poor infection control strategies [6]. Wastewater from homes, industries and hospitals containing antibiotic residue are the main sources of antibiotic resistant bacteria in the environment. Additionally, the unwise use of antibiotics in clinical, agricultural, and veterinary medicine lead to the selective pressure on widely used antibiotics [3]. The hospital-acquired infections have become increasingly a major problem. It represents about 1.4 million infections worldwide each year. It is often reported that those infections caused by antibiotic-resistant bacteria originated from the hospital environment [7].

In short, bacteria exhibit resistance to antimicrobial agents through several mechanisms, including:

1. Harboring a drug efflux pump that expels (or decreases entry) antibiotics outside the cell via membrane-linked pumping proteins. It has been indicated that the multidrug efflux system is a primary determinant of aminoglycoside resistance in *Pseudomonas aeruginosa* [8, 9].
2. The production of specific enzymes that directed to nullify the effect of antibiotics. These enzymes are released through the expression of either chromosomal genes or through plasmid genes. These genes are capable of transfer through bacterial species by either horizontal gene or vertical gene transfer [10]. In this context, it is known that the production of β -lactamases is a serious threatening mechanism for β -lactam antibiotics resistance [10, 11]. An epidemiological study by Chuma *et al.* (2013), reported a recent emergence of cefotaxime resistance mediated by β -lactamase in *Salmonella enterica*/Seroovar infantis [12].
3. Mutation of key binding elements such as ribosomal RNA or reprogramming of biosynthetic pathways [10].
4. Bacterial harboring of resistant genes within integrons or transposons, which are able to integrate and translocate to other bacterial chromosomes or plasmid, facilitate the acquiring and transferring of those genes [13, 14].
5. The chemical modification of the compound or the drug target [15, 16].

Gaza strip is a region of poor resources suffering from years of negligence and no clear data about the epidemiological aspects of antimicrobial resistance. Despite the contribution of weakened health service system to the antimicrobial resistance burden, it is important to look at the existing situational and attempt to analyze existing data. Thus, appropriate interventions and measures can be implemented at the community level to tackle the problem. With this background, this study aims to evaluate, investigate, and discuss the situation

of antimicrobial resistance in the bacteria isolated from clinical samples and hospital environment in Gaza/Palestine.

Materials and Methods

This review was conducted during April 2021. Search was conducted through Google scholar, Researchgate, and PubMed (Public Medline by the National Center for Biotechnology Information) search engines. The key words used for the search included: Antimicrobial resistance, antibiotic resistance burden, antibiotic resistance, antimicrobial resistance mechanisms, resistance rate, prevalence, isolation, Gaza strip, and Palestine. The search was performed for the relevant information from Gaza strip about the antimicrobial/antibiotic resistance context since the year 2002 to 2021, which yielded 51 references. Out of these, 29 studies reported data about the antimicrobial resistance extent in Gaza Strip. Other studies were reviews, studying the antimicrobial resistance issue in different areas of interest, or considered microbes that recovered neither from clinical samples nor from hospital settings. Articles included in this review focused in the antimicrobial resistance of pathogens isolated in Gaza Strip, used Kirby-Bauer disk diffusion method, and measured antimicrobial susceptibility in adherence to Clinical and Laboratory Standards Institute (CLSI) recommendations. Excel 2010 was used to manipulate extracted data from selected studies and to draw illustrative figures and tables.

Results

Overview of studies characteristics

Fifty-one studies were screened, of these 29 were viewed and met the eligibility criteria to be included in this review. Among the 29 studies, two were retrospective in design and 27 were cross-sectional studies. Selected studies varied in their topic of in-

terest, types of bacteria discussed, and source of samples investigated. However, the 29 studies can be categorized according to their topic into five sections as illustrated in **Table 1**.

Table 1. Sample sources of the included studies.

Source of sample	No. of studies
Urinary tract infection (uropathogens)	7
Blood Stream infections, wound, ear, pus, vaginal discharge, cerebrospinal fluid, and sputum (with/without urine sampling)	6
Gastroenteritis	4
Burn infection, Burn units, Hospital settings	7
Health care workers, their belongings, surrounding environment	5
Total	29

Resistance pattern of bacteria recovered from urinary tract infections

Table 2 shows the prevalence of uropathogens in the selected studies, where **Table 3** demonstrated the resistance rates of uropathogens to various tested antibiotics. Amoxicillin resistance rates ranged from 72.9% to 100% [17-21]. One study published in 2018 revealed that the resistance rate to amoxicillin/clavulanic acid was reached 99% [20]. A study in 2006 investigated the presence of 131 *P. aeruginosa* in urine samples and found its resistance rates against amoxicillin (99%), doxycycline (96.2%), cephalexin (98.5%), nalidixic acid (93.5%), and cefaclor (97.4%) [22]. While another study in 2004 reported the overall antibiogram of *P. aeruginosa* isolated from other clinical samples (sputum, blood, and pus) besides urine showed the highest resistance rates among amoxicillin (95.4%), doxycycline (64.8%), cephalexin (89.1%), and nalidixic acid (58.8%) [18].

In this context, a study during 2017 looked for ESBL producing Gram-negative bacteria isolated from urine and pus samples. The study stated that 28% of *Escherichia coli* and *Klebsiella pneumonia*

Table 2. Prevalence of isolated uropathogens.

Year [Ref.]		2002 [17]		2004 [18]		2006 [19]		2014 [25]		2018 [20]		2002 [17]	
Isolate		No	%	No	%	No	%	No	%	No	%	No	%
Gram negative	<i>E. coli</i>	70	57.9	798	57	538	42	132	37	131	59.8	1743	59.9
	<i>Proteus spp.</i>	12	9.9	129	9.2	58	4.5	64	18	9	4.1	69	2.4
	<i>Klebsiella spp.</i>	8	6.6	168	12	157	12.2	-	-	50	22.8	725	24.9
	<i>P. aeruginosa</i>	7	5.8	81	5.8	131	10.2	57	16	16	7.3	123	4.2
	<i>Acinetobacter spp.</i>	3	2.5	27	1.9			-	-	-	-	-	-
	<i>Citrobacter spp.</i>	1	0.8	13	1.0	103	8.0	-	-	-	-	-	-
	<i>Enterobacter spp.</i>	9	7.4	54	3.9			11	3	-	-	12	0.4
Gram positive	<i>S. aureus</i>	1	0.8	5	0.4	27	2.1	-	-	-	-	41	1.4
	<i>Enterococcus spp.</i>	4	3.3	52	3.7	88	6.9	-	-	7	3.2	13	0.4
	<i>S. saprophyticus/CNS</i>	6	5.0	63	4.5	84	6.5	47	13	6	2.7	-	-
	<i>Streptococcus spp.</i>	-	-	-	-	97	7.6	47	13	-	-	98	3.4
	Positive samples	121	44.8	1399	49.2	1637	34	38	10.6	219	17.2	2910	24.5
Total samples		270	100	2844	100	4778	100	358	100	1276	100	11890	100
-: The organism was either not studied or not isolated													

Table 3. The resistance pattern of the most prevalent uropathogens.

Year	Isolates	Antibiotic	AMX	AMC	AN	GM	DOX	CF	CTX	CTZ	TMP-SMZ	CIP	NOR	OFX	NA
Ref			%	%	%	%	%	%	%	%	%	%	%	%	%
2002 [17]	Gram negative	<i>E. coli</i>	72.9	32.9	2.9	15.7	70	44.3	18.6	2.9	71.4	2.9	5.7	1.4	10
		<i>Proteus spp.</i>	83.3	33.3	8.3	33.3	83.3	66.7	41.7	0	50	8.3	8.3	25	33.3
	Gram positive	<i>S. saprophyticus</i>	66.7	16.7	0	66.7	83.3	83.3	50	33.3	83.3	16.7	33.3	16.7	100
		<i>Enterococcus</i>	0	0	50	50	50	50	50	25	75	0	25	25	100
2004* [18]	Gram negative	<i>E. coli</i>	80.1	-	3	13.4	59.7	20.8	15.2	-	58.5	9.1	-	-	17.6
		<i>Klebsiella spp.</i>	93.1	-	6.5	21.1	62.6	27.2	16.7	-	63	12.6	-	-	21.1
	Gram positive	<i>S. saprophyticus</i>	71.4	-	-	-	68.3	20.6	13.1	-	68.4	14.5	-	-	-
		<i>Enterococcus</i>	72.2	-	-	-	72.1	24.7	22.6	-	69.6	18.2	-	-	-
2006 [19]	Gram negative	<i>E. coli</i>	97.9	-	10.6	11	90	50.2	-	13.1	63.9	19.9	-	-	30.6
		<i>Klebsiella spp.</i>	100	-	16.7	19.2	93	58.8	-	25.3	64.3	22.3	-	-	39.2
	Gram positive	<i>Streptococcus</i>	48.4	-	67	45.2	53.4	58	-	-	100	27.9	-	-	-
		<i>Enterococcus</i>	56.3	-	76.1	59	63.9	81.6	-	-	100	31.6	-	-	-
		CNS	92	-	36.9	25.6	64.1	58.9	-	-	60	13.2	-	-	-
2014 [25]	Gram negative	<i>E. coli</i>	50	61.5	0	-	-	-	23.1	14.2	-	-	-	0	7.7
		<i>Proteus spp.</i>	85.7	50	0	-	-	-	0	14.3	-	-	-	0	42.9
	Gram positive	<i>S. saprophyticus</i>	75	25	-	0	-	0	0	-	-	-	-	0	-
		<i>Streptococcus</i>	0	-	-	100	-	100	0	-	-	-	-	0	-
2018 [20]	Gram negative		-	99	-	11.2	-	-	87.4	-	59.7	-	-	-	-
	Gram positive		-	-	15.4	15.4	30.8	-	-	-	38.5	-	38.5	-	-

Year	Isolates	Antibiotic	AMX	AMC	AN	GM	DOX	CF	CTX	CTZ	TMP-SMZ	CIP	NOR	OFX	NA
Ref			%	%	%	%	%	%	%	%	%	%	%	%	%
2021 [21]	Gram negative	<i>E. coli</i>	90	73	2	23	59	60	49	41	66	35	-	-	53
		<i>Klebsiella spp.</i>	95	68	4	29	66	73	62	49	69	38	-	-	50
	Gram positive	<i>S. aureus</i>	71	45	17	30	29	15	26	50	54	38	-	-	33
		<i>Streptococcus</i>	67	42	-	48	48	74	47	-	78	63	-	-	100
		<i>Enterococci</i>	100	50	63	54	-	67	64	100	67	70	-	-	100

AMX: amoxycillin; **AMC:** amoxycillin-clavulanate; **AN:** amikacin; **GM:** gentamycin; **DOX:** doxycycline; **CF:** cephalexin; **CTX:** cefuroxime; **CTZ:** ceftazidime; **TMP-SMZ:** trimethoprim sulfamethoxazole; **CIP:** ciprofloxacin; **NOR:** norfloxacin; **OFX:** ofloxacin; and **NA:** nalidixic acid. -: The antibiotic not used in the study. *: The study showed the overall resistance rates of pathogens isolated from pus, blood, CSF besides urine.

were ESBL producers, among ESBL producers, *E. coli* showed the higher percentage (80.3%), as well as 73.2% of the ESBL producers isolates were uropathogens [23].

Overall, the findings viewed in **Table 2** showed that the most prevalent uropathogen was *E. coli*. Uropathogens showed high levels of multiple drug resistance, including resistance against the first, second, and third generations of cephalosporins as well as amikacin. In compared to other used antibiotics, ciprofloxacin and gentamicin resistance rates were lower [17-21]. However, a study in 2005 reported that resistance rates to ciprofloxacin were increasing among commonly UTI isolates including: *Acinetobacter haemolyticus* (28.6%), *S. saprophyticus* (25.0%), *P. aeruginosa* (20.0%), *K. pneumonia* (17.6%), and *E. coli* (12.0%). Minimal inhibitory concentration (MIC) of ciprofloxacin among the mentioned uropathogens evenly ranged from 4 to 32 µg/mL with a mean of 25.0 µg/mL [24].

El-Astal (2004), reported the emergence of vancomycin resistance (3.2%) in *Enterococci spp.* [18]. While Elmanama *et al.* (2018) demonstrated a steady increase in the resistance rate of *Enterococci spp.* to vancomycin (85.7%) [20].

Uropathogens antimicrobial susceptibility results showed that *E. coli* were still susceptible for amikacin (100%), ceftazidime (85.8%), nalidixic acid (92.3%)

and ofloxacin (100%). Also, *Proteus spp.* were susceptible for amikacin (100%), ceftazidime (85.7%), ceftriaxone (100%), cefuroxime (100%), and ofloxacin (100%). However, *Streptococcus spp.* showed 100% resistance rate against cefazolin, cephalexin, and gentamicin [25].

A study in 2019 investigated ESBL producing uropathogens, showed that 30 isolates (35.3%) out of total 85 were ESBL producers. Among ESBL-positive isolates, the bla_{CTX-M} gene that confer bacteria β-lactam-resistance was the most frequent, followed by the bla_{TEM} gene. ESBL producers were more resistant than non-ESBLs producers for almost all tested antibiotics [26].

Resistance pattern for pathogens recovered from Blood Stream infections (BSI), wound, pus, ear, vaginal discharge, cerebrospinal fluid (CSF), and sputum

Table 4 shows the prevalence of pathogens recovered from pus, blood, CSF, and/or Ear discharge. Whereas **Table 5** shows the overall antibiotic susceptibility of bacterial isolates from the different clinical specimens [18, 22, 23, 27]. According to a study in 2004, *E. coli* was the most frequent causative agent of blood stream infections; its resistance rate to amoxicillin was 80.1%, 58.5% to cotrimoxazole, 9.1% to ciprofloxacin and 3.0% to amikacin [18].

Table 4. Frequency of bacterial isolates isolated from different clinical samples.

Year [Ref.]		2004 [18]						2006 [22]*						2015 [27]		2017 [23]	
Isolate		Pus		Blood		CSF		PUS		Blood		Sputum		Ear swab or discharge		Urine & Pus	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Gram negative	<i>E. coli</i>	81	7.3	33	13.8	6	6.6	0	0	0	0	0	0	0	0	159	79.5
	<i>Proteus spp.</i>	109	9.8	5	2.1	0	0	0	0	0	0	0	0	24	20	0	0
	<i>K. pneumoniae</i>	60	5.4	13	5.4	0	0	0	0	0	0	0	0	2	1.7	41	20.5
	<i>P. aeruginosa</i>	168	15.1	6	2.5	9	9.9	348	23.3	25	5.95	37	49.3	39	32.5	0	0
	<i>Acinetobacter haemolyticus</i>	22	2.0	2	0.8	0	0	0	0	0	0	0	0	0	0	0	0
	<i>Citrobacter freundii</i>	5	0.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	<i>Enterobacter cloacae</i>	29	2.6	4	1.7	0	0	0	0	0	0	0	0	0	0	0	0
	<i>Neisseria meningitis</i>	0	0	3	1.2	18	19.8	0	0	0	0	0	0	0	0	0	0
	<i>Serratia marcescens</i>	7	0.6	5	2.1	0	0	0	0	0	0	0	0	0	0	0	0
	<i>H. Influenza</i>	14	1.2	10	4.2	32	35.2	0	0	0	0	0	0	0	0	0	0
	<i>Morganella morganii</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	<i>Moraxella spp.</i>	0	0	0	0	0	0	0	0	0	0	0	0	5	4.2	0	0
Gram positive	<i>S. aureus</i>	534	47.9	25	10.5	0	0	0	0	0	0	0	0	28	23.3	0	0
	<i>S. epidermidis</i>	0	0	114	47.7	0	0	0	0	0	0	0	0	0	0	0	0
	<i>S. saprophyticus/ CNS</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	<i>Enterococcus faecalis</i>	69	6.2	5	2.1	0	0	0	0	0	0	0	0	0	0	0	0
	<i>S. pneumoniae</i>	17	1.5	14	5.9	26	28.5	0	0	0	0	0	0	0	0	0	0
	<i>Streptococcus spp.</i>	0	0	0	0	0	0	0	0	0	0	0	0	11	9.2	0	0
	<i>Bacillus spp.</i>	0	0	0	0	0	0	0	0	0	0	0	0	8	6.7	0	0
Total samples		1115		239		91		1491		420		75		120		200	

*: The study screened *Pseudomonas aeruginosa* only. 0: means that the organism were not isolated or not studied.

Moreover, several studies have been revealed that *P. aeruginosa* were highly resistant to amoxicillin, cephalexin, cefaclor or cefadroxil [22, 27]. Gram negative bacteria (GNB) isolated from ear discharge showed susceptibility rates to ciprofloxacin (100%), gentamycin (87.5-100%) and ceftriaxone (100%) [27]. This was in exception for *P. aeruginosa* the most common GNB isolated from pus, sputum, and ear discharge samples, that showed resistance to many antimicrobial agents by means of multiple drug resistance (MDR) [22, 27].

Additionally, one study focused on assessing the antimicrobial resistance of *Acinetobacter spp.* recovered from pus samples collected with swabs or aspirated in syringes. A total of 152 isolates of *Acinetobacter spp.* were identified. The isolates showed high resistance to most of the commonly used drugs. The isolates showed almost complete resistance to cephalosporins (cephalexine 98%, cefuroxime 98.2%, cefotaxime 93.2%, ceftazidime 87.5%, ceftriaxone 93.3%, cefaclor 97.4%), while lower rates of resistance were shown against the aminoglycosides (amikacin 68.3%, and gentamicin 81.3%). However, data showed that the most

effective antibiotic with the least resistance rate (22.1%) was doxycycline [28]. According to the ESBL production among GNB that reported in a study by El Aila (2017), out of 200 GNB isolates recovered from urine and pus samples, 73.2% and 26.7% were ESBL producers, respectively [23] (Table 4).

A recent study by Elmanama *et al.* [29] was performed to detect the resistance pattern among *Candida spp.* to antifungal drugs. A total of 100 samples of vaginal swabs were collected from pregnant women. *Candida spp.* were isolated from 43% of the collected samples. Amphotericin B was the most effective with 0% resistance rate, followed by itraconazole and nystatin with 9.4% resistance rates for both. Resistance rate to miconazole, ketoconazole, voriconazole, and fluconazole was 11.6%.

Resistance pattern for pathogens recovered from patients suffering gastroenteritis

Acute gastroenteritis is a widespread infection among children in Gaza Strip [30].

Table 5. The resistance rates of the most prevalent bacterial isolates isolated from different clinical samples.

Year	Isolates	Antibiotic	AMX	CP	AN	GM	DOX	CTZ	CRO	CIP	TMP-SMZ	NA	TZP	MET
Ref			%	%	%	%	%	%	%	%	%	%	%	%
2006 [22]	Gram negative	<i>P. aeruginosa</i>	99.0	98.5	34.9	31.4	96.2	35.8	-	26.1	94.7	93.5	61.8	-
2017 [23]	<i>E. coli</i> & <i>K. pneumoniae</i>	ESBL producers	100	94.6	34	38	-	98.2	96.4	-	-	-	-	-
		ESBL non producers	100	73	17.4	34.1	-	60	64	-	-	-	-	-
Year	Isolates	Antibiotic	AMC	CDX	CLR	GM	E	CTZ	CRO	CIP	P	NA	TZP\$	MET
Ref			%	%	%	%	%	%	%	%	%	%	%	%
2015 [27]	Gram negative	<i>P. aeruginosa</i>	79	97.4	100	43.6	-	11.3	19.1	5.2	-	-	-	-
		<i>Proteus spp.</i>	80	20	0	100	-	100	100	100	-	-	-	-
	Gram positive	<i>S. aureus</i>	25	46.4	46.4	-	35.7	-	0	-	64.3	-	-	25
		<i>Streptococcus spp.</i>	0	0	0	-	9.1	-	0	-	9.1	-	-	-

AMX: amoxicillin; AMC: amoxicillin-clavulanate, CP: cephalexin; CDX: cefadroxil; AN: amikacin; GM: gentamycin; CLR: clarithromycin; DOX: doxycycline; E: erythromycin; CTZ: ceftazidime; CRO: ceftriaxone; CIP: ciprofloxacin; TMP-SMZ: trimethoprim sulfamethoxazole; P: penicillin; NA: nalidixic acid, TZP: Piperacillin/Tazobactam, and MET: methicillin.

-: The antibiotic not used in the study data not clear.

Table 6. Antimicrobial resistance rates among isolated enteropathogenic.

Isolates	AM	E	CU	GM	TE	SXT	NA	CIP	Total resistance rate
	%	%	%	%	%	%	%	%	%
<i>Salmonella spp.</i>	0	-	0	0	33.3	0	33.3	0	9.5
<i>Shigella spp.</i>	50	-	0	0	50	50	50	0	28.5
<i>Campylobacter coli/jejuni</i>	75	75	-	-	-	-	-	33.3	61.1
<i>Aeromonas hydrophilia</i>	100	-	75	0	75	100	33.3	0	54.7
<i>Yersinia enterocolytica</i>	100	-	0	0	100	100	100	0	57.1
Total resistance rate	65	75	18.7	0	64.5	62.5	54.1	6.6	40.1

AM: Amoxicillin; **E:** Erythromycin; **CU:** Cefuroxime; **GM:** Gentamicin; **TE:** Tetracycline; **SXT:** Trimethoprim/sulfamethoxazole; **NA:** Nalidixic Acid; **CIP:** Ciprofloxacin. -: The antibiotic not used in the study.

A study in 2012 showed that out of 132 stool samples, 12 (9.1%) were containing enteropathogenic bacteria: *Salmonella spp.*, *Campylobacter coli/jejuni*, and *Aeromonas hydrophilia* were isolated in equal frequency (3/12; 25% each), *Shigella spp.* (2/12; 16.7%), and *Yersinia enterocolytica* (1/12; 8.3%). The isolates of *Campylobacter coli/jejuni* showed the highest antimicrobial resistance rates against both erythromycin and amoxicillin (75%) Both *Aeromonas hydrophilia* and *Yersinia enterocolytica* showed 100% resistance to amoxicillin, tetracycline, and trimethoprim/sulfamethoxazole. **Table 6** shows the resistance rates for the isolated enteric pathogens [30].

A study by Hijazi *et al.* (2009) estimated the prevalence of Vancomycin-Resistant Enterococcus (VRE) among hospitalized and non-hospitalized individuals. *Enterococci* were found in 94% and 89% of the hospitalized and non-hospitalized individuals, respectively. VRE were isolated from 69.1% of the hospitalized patients as well as 43.3% of the non-hospitalized individuals [31].

A recent study by Qadi *et al.* [32] investigated the colistin resistance among *Enterobacteriaceae* isolated from 100 clinical samples. Amikacin was the most effective antibiotic with susceptibility rate 74%, followed by chloramphenicol (48%), fosfomycin, and gentamicin (45%). High resistance was found to

trimethoprim (85%) and tetracycline (83%). About 41% of the isolates were considered as colistin resistant. The particular highest rates of resistance were found to be among the *Proteus spp.* (63.2%), followed by *Serratia spp.* (57.1%). About 39.0% of meropenem-resistant *Enterobacteriaceae* was susceptible to colistin, while 45.8% of imipenem-resistant *Enterobacteriaceae* was susceptible to colistin. Among isolates, 89% were MDR.

The study of Ayesh *et al.* [33] reported that clarithromycin resistance among *H. pylori* isolates from gastric biopsy samples was 58.6% (51 samples out of total 87). Among those isolates, (4/51) 7.8% were resistant to clarithromycin, 3.9% were positive for the 2143A>G mutation, 3.9% for 2144A>G, while none of the isolates were positive for the 2143A>C mutation.

Resistance pattern for pathogens isolated from burn patients, units, HCW, and hospital settings

One of the studies by Elmanama *et al.* (2013) evaluated the antibiogram of bacterial isolates from burn units. The study analyzed 118 wound samples from burn patients, 97 environmental samples, and 28 samples from health care workers (HCWs) (finger and nasal samples). Positive samples were 45.8% of the total. *Pseudomonas aeruginosa* was

the most common pathogen isolated (50%) from patients followed by *Enterobacter cloacae* (28.3%). From HCWs samples, the prevalence of coagulase negative *staphylococci* was 29% [34]. According to their antibiogram, *Pseudomonas spp.* isolates from patient samples were found to be resistant to most of the tested antibiotics including imipenem. The incidences of methicillin-resistant *Staphylococci* by means of oxacillin resistance were 60%, 77.8%, and 90% in patient's samples, HCWs samples, and environmental samples, respectively [34].

Furthermore, in a study detecting ESBL producers among GNB isolated from 40 burn wound patients, *P. aeruginosa* was the predominant isolate 15 (37.5%) followed by *K. pneumoniae* 10 (25%), *E. coli* 9 (22.5%), *E. cloacae* 4 (10%) and *A. baumannii* 2 (5%). ESBL was detected in 37.5% of the isolates. ESBL-producing isolates were 100% resistance against cefotaxime and ampicillin. *A. baumannii* isolates were resistant to all tested antibiotics [35]. Moreover, a previous study focused on *P. aeruginosa* ability to form biofilm and their antibiograms. Only 42 isolates were obtained from the hospital microbiology lab. Among them, 83.09% were strong biofilm formers. The isolates were 100% resistance to ceftazidime, piperacillin (97.6%), ciprofloxacin (28.57%), norfloxacin (9.5%), and both meropenem and aztreonam (2.38%) [36]. The resistance rates of *P. aeruginosa* to piperacillin in two different studies over few years indicated the emergence of piperacillin resistant strains (**Figure 1**) [34, 36]. Also, high resistance rates found in *A. Baumannii* isolates which were isolated from neonatal intensive care units (blood samples). Forty (6.9%) isolates from 579 samples were recovered. *A. baumannii* isolates were resistant to the most commonly available antibiotics. *A. baumannii* showed susceptibility to meropenem (92.5%), imipenem (90%), ciprofloxacin (75%), gentamicin (57.5%), and ceftriaxone (50%) [37].

A study by Al Laham [38] investigated the antimicrobial resistance profile of bacteria recovered from

Figure 1: Increasing resistance rate of *P. aeruginosa* to piperacillin over a 6-year period as reported in two studies [34, 36].

operation theaters, a total 243 swab samples were collected. About 24.7% were positive for bacterial contamination. Among the isolated GNB, the overall highest resistance was 93.9% to both ampicillin and amoxicillin, followed by cefazolin (81.8%). While Gram positive bacteria (that all belong to *Staphylococci*) showed 93.1% resistance to penicillin and 86.2% to ampicillin. Of GNB, 9.1% were ESBL producers. Among Gram-positive bacteria, 62.1% were methicillin resistance *Staphylococcus*. Methicillin resistance *Staphylococcus aureus* (MRSA) were 33.3%, while methicillin resistance coagulase negative Staph MR-CoNS were 65.4%.

The study of Rida *et al.* [39] focused on carbapenem resistance among GNB isolated from clinical and environmental hospital samples. The study tested 210 clinical samples, 150 environmental swabs, and 110 air samples. About 247 clinical isolates were recovered, 12.1% of them were carbapenem resistant. Resistance rate to imipenem was 8.1%, while to ertapenem and meropenem was 3.5% and 0.8%, respectively. Isolates recovered from intensive care units exhibited the highest resistance rate (52.9%). The resistance rate to carbapenem among *Enterobacteriaceae* was 13.2%, while none of the *Pseudomonas* isolates were resistant to this drug. Among *Enterobacteriaceae* isolates, *Klebsiella spp.* was the mostly resistant to carbapenems (14.4%),

followed by *E. coli* 9.8% in addition, 23.3% were positive for carbapenemases production. All *Enterobacteriaceae* isolates had MDR index higher than 0.2, while those of *Pseudomonas* had an average of 0.2 [39]. Another study detected the multi-resistance pattern of bacteria recovered from clinical samples in Palestine (Gaza Strip and the West Bank), Out of 248 GNB isolated, 21 (8%) were resistant to carbapenems and other antibiotics [40].

Resistance pattern against methicillin among *Staphylococcus* spp. isolated from clinical and hospital setting samples.

Several studies focused on methicillin resistance *Staphylococcus*. Overall studies showed MRSA prevalence ranged from 22.6%-82.3% [41-44].

One study focused to detect MRSA and other antibiotic resistance pattern, MRSA were recovered from HCWs nares. The highest carriage rate of MRSA was among HCWs from surgery wards. All isolates were resistant (100%) to vancomycin and doxycycline. The multiple resistance pattern among MRSA (75%) were higher than MSSA (44.44%) and 61% of the isolates were MDR [41].

A second similar study showed that 62 out of 200 HCWs (31%) carried *S. aureus*, of which 51 (82.3%) were MRSA. Therefore, 25.5% of all HCWs were considered as MRSA carriers. The highest was

among nurses (30.4%) distributed in the internal medicine departments (41.3%) and surgical wards (35%). Penicillin has the highest resistant rates in both MRSA and MSSA (100%) [42].

Both studies adopted the phenotypic screening for MRSA using oxacillin disk diffusion and the genotypic analysis of the *mecA* gene (methicillin resistance gene). **Table 7** shows the resistance rate of *S. aureus* in these studies. Recent published studies in 2017 and 2020, have recorded a higher resistance rates when compared to a study reported in 2015 [41-43].

Furthermore, a recent study by Elmanama *et al.* [43] found that the majority of MRSA isolates (74-88.8%) were biofilm producers. In addition, the study reported the highest resistance rate to penicillin (92.9%), followed by cefoxitin (80.6%) and oxacillin (67.9%) (**Table 7**). About 71.4% of MRSA isolates were classified as MDR with a MAR index (≥ 0.2), and 90.5% of them were biofilm producers.

A second study investigated methicillin resistance and biofilm formation among CoNS recovered from clinical samples. The study showed the highest resistance rate to aminoglycosides, β -lactams, carbapenems, cephalosporins, fosfomycin fluoroquinolones and macrolides. MR-CoNS that constituted 60% of the isolates, showed higher MDR rates than MS-CoNS. About 88.9% of isolates

Table 7. Baseline data from studies focused on methicillin resistance of *Staphylococcus* spp.

Year [Ref.]		2015[41]	2017 [42]	2017 [44]	2020 [43]
No. of samples		140	200	1121	196
Sample source		HCWs nasal swabs		Pus, urine, blood, sputum, burn, and surgical swabs of inpatients	Different departments/ Different sites of infection
Prevalence of bacterial isolates	<i>S. aureus</i>	42.1%	31%	-	100%
	CoNS			100%	
	<i>S. haemolyticus</i>			42%	
	<i>S. epidermidis</i>	-	-	32.1%	-
	<i>S. saprophyticus</i>			16%	
	Methicillin resistance rate	22.6%	25.5%	MR-CoNS: 60%	80.6%

-: The organism not studied or isolated.

were MDR. Biofilm producers were mostly *S. epidermidis* (76.9%). There was a statistically significant association between methicillin resistance and biofilm formation. The study performed the phenotypic screening for methicillin resistance through oxacillin and ceftiofloxacin by disk diffusion method and the genotypic analysis of *mecA* [44]. Among swab samples from touchscreen Mobile Phones of HCWs and students. Out of the total 250 samples, 28.3% were MRSA, and 73.6% were penicillin-resistant [45].

Discussion

Most recent studies are reporting that resistance rates of bacteria isolates causing human infections are significantly increasing worldwide. The precise estimates of antimicrobial resistance burden is different from one country to other, and it would be difficult to evaluate this burden from current available studies carried out in our country [46]. Also, it has been found that antimicrobial resistance has potentially high impact on patient health through increasing patient mortality and cost of treatment [46] and this issues is not possible to be obtained from these studies. Therefore, the main objective of this review is limited to present overview and discuss the magnitude of antimicrobial resistance occurrence based on bacterial isolates from clinical samples and hospital settings in Gaza/Palestine. This review article couldn't perform statistical analysis to detect the actual significant of the antimicrobial resistance for each bacterial isolates. Based on our general observation there were increasing resistance rates during the period of 20-year, and those were varied over the study period, tested specimens, laboratory methods, types of antibiotics and local regions of Gaza.

We found that all studies carried out between 2002 to 2018, have reported that most uropathogens exhibited a noticeable increase in the resistance rates to several antibiotics including ciprofloxacin,

trimethoprim sulfamethoxazole, and nalidixic acid [17-21]. In particular, uropathogens were highly resistant to amoxicillin ranging from 72.9% to 100% [17-21]. One study reported that the resistance rate of uropathogens against amoxicillin/clavulanic acid was 99%. Also, multidrug resistance among uropathogens has been recorded to reach 99.5% in most of GNB, while lower percentage 92.3% has been detected in Gram-positive uropathogens [20]. Studies also reported the high occurrence of multidrug of *P. aeruginosa* recovered from UTIs especially to ciprofloxacin and gentamicin [21, 24]. These results are in line with data reported by the North American UTI Collaborative Alliance (NAUTICA), about the high incidence of resistance among uropathogens to ciprofloxacin and trimethoprim sulfamethoxazole [47].

This review has also found that all published studies over the period of 20-year reported high occurrence of resistance among certain Gram-negative bacteria recovered from various clinical specimens. For example, *Acinetobacter baumannii* infection was associated with high mortality rate among neonatal intensive care unit infants in Gaza, since all *A. baumannii* isolates were multidrug resistance [37]. Additionally, two studies from Western Saudi Arabia and Jordan have reported that *A. baumannii* isolated from pus samples, and respiratory and environmental samples (Jordan) were mostly MDR [48, 49].

P. aeruginosa recovered from pus, blood, sputum, and ear discharge showed a striking MDR pattern. It resistant to amoxicillin, cephalexin, cefaclor, and cefadroxil [22, 27]. Piperacillin-tazobactam-resistance in *P. aeruginosa* is an emerging problem. It may cause nosocomial infection. It can be isolated from clinical samples in hospitals, from the 127 intensive care units (ICUs) that participate in the Centers for Disease Control and Prevention's ICARE Project, about 6,917 *P. aeruginosa* isolates were investigated by means of susceptibility testing, and the rate of piperacillin resistance was 14.4% [50].

Piperacillin-tazobactam-resistant *P. aeruginosa* were found to be resistant to other antibiotics including carbapenems and aminoglycosides. Moreover, the isolation and detection of nosocomial piperacillin-tazobactam-resistant *P. aeruginosa* is challenging and may be affected by the exposure to multiple antibiotics such as: imipenem, aminoglycosides, vancomycin, and broad-spectrum [51].

Several studies showed nearly 100% resistance to β -lactam antibiotics, including carbapenem resistance in several pathogens [18-21, 27, 35, 37, 38, 42-44]. It has been explained that the resistance against β -lactam drugs can be facilitated by β -lactamase enzyme [52]. Genotyping of β -lactam resistant bacteria revealed that bacteria might possess genes of β -lactamase temoniera (bla_{TEM}), β -lactamase sulphydryl variable (bla_{SHV}), β -lactamase cefotaxime hydrolyzing capability ($\text{bla}_{\text{CTX-M}}$), and the β -lactamase oxacillin hydrolyzing capabilities (bla_{OXA}) [53]. These genes may participate in co-resistance to carbapenem.

Chromosomal carbapenemase is naturally co-transcribed with other nearby β -lactamases, which could be enhanced and actively expressed by the intake of β -lactam or carbapenem antibiotics [11, 21]. Thus, β -lactam resistance could be accompanied with carbapenem resistance. It is critical to investigate the antimicrobial resistance pattern along with the prevalence of resistance genes.

Furthermore, the expressing of New Delhi metallo-beta-lactamase-1 (NDM-1) gene provides resistance to a broad range of beta-lactam antibiotics [54]. This gene confers carbapenem resistance to bacteria. Several studies confirmed the emergence of carbapenem resistant strains of bacteria [32, 34, 36, 39]. One study showed that carbapenem resistant bacteria were having cabapenemase OXA-51 gene group in all isolates and one isolate from Gaza was positive for NDM-2 [40]. Further studies at the molecular level are needed to clarify the mechanisms of carbapenem resistance. For instance, Daoud *et al.* reported that the presence of carbape-

nem sensitive bacteria is positive for (NDM-1) gene that might be mutated, hence the enzyme is unable to work effectively [53].

H. pylori infections in Gaza Strip have higher resistance to clarithromycin compared to other studies from nearby populations [33]. The resistance of *H. pylori* to clarithromycin is often caused by point mutations at the domain V loop of the 23S rRNA gene [53]. *H. pylori* possesses two copies of that gene. A mutation in one of the two 23S rRNA copies can be enough to cause high resistance in a dominant pattern [55]. The resistance mechanism against clarithromycin may involve the decreased ribosome binding of the macrolide so that it fails to act by interrupting protein biosynthesis [56]. Among these mutations, the three most common mutations worldwide are 2143A>G, 2144A>G, and 2143A>C [57]. This important finding was confirmed by the study of Ayesh *et al.* [33] who has recently detected clarithromycin resistance genes in *H. pylori* isolates in Gaza.

Few studies has reported that Extended-Spectrum Beta-Lactamase (ESBL) production as well as colistin resistance among *Enterobacteriaceae* isolates in Gaza becomes more prevalent in recent years [23, 32, 35]. Additionally, MRSA was highly emerged either in clinical samples or hospital environment in Gaza strip [34, 41-45].

Few data are available about the antimicrobial resistance pattern among *Candida* species in Gaza, thus further studies are needed on this issue.

In conclusion, this review shows the widespread of antibiotic resistance of bacteria isolated from various clinical specimens and hospital environment in Gaza Strip, Palestine over a period 20-year. In particular, there is an increase in the frequency of ESBL producing Gram-negative bacteria with overall common occurrence of MDR including Vanomycin-resistance Enterococcus and MRSA. We hope that this current study will provide important information for health authorities and professionals to improve control of using antimicrobial agents. Future

research is required to assess the actual health and financial burden of antimicrobial resistance in our country.

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