BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, September 2020. Vol. **17**(3), p. 443-457

Escherichia coli in Saudi Arabia: An Overview of Antibiotic-Resistant Strains

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http://dx.doi.org/10.13005/bbra/2848

(Received: 06 February 2020; accepted: 17 August 2020)

Escherichia coli (E. coli) **bacterial strains are considered as the most important human pathogens. Health issues are increasing in complexity owing to the persistent emergence of antibiotic resistant *E. coli* strains, which have been isolated and detected worldwide, including Saudi Arabia. A review of the prevalent strains resistant to the standard antibiotics used in a local region is critical and may be beneficial at the national and international levels. Treatment for *E. coli* infection has been highly difficult by the rise of resistance to most first-line antibiotics. The present study aimed to update the scientific information regarding *E. coli* strains, which have the ability to resist the standard drugs used to treat bacterial infections in Saudi Arabia. The data retrieved from https://scholar.google.com and Saudi Digital Library (https://sdl.edu.sa/) indicate that *E. coli* strains isolated from several sources in Saudi Arabia show resistance to almost all antibiotics, except 5th generation cephalosporins (ceftraolin and ceftobiprole), which no isolate in Saudi Arabia has been recorded to resist. Based on the results of the present study, we conclude and recommend that integrated monitoring and management of the antibiotics may reduce the health risks associated with antibiotic resistant *E. coli* strains.**

Keywords: Antibiotic; *Escherichia coli*; Resistance; Saudi Arabia.

Escherichia coli(*E. coli*)is a coliform rod-shaped, Gram-negative, facultative, non-spore forming bacteriumof the genus *Escherichia* and family *Enterobacteriaceae,*which includes over 53 genera and 210 species (Jenkins *et al*., 2017; Tenaillon *et al*., 2010).According to a study on drug resistances it is predicted that ten million people may die from antibiotic-resistant diseases each year by 2050 if no precautions are taken to tackle the issue, among that more than three million will lose their lives to one bacterial infection by antibiotic resistant *E. coli* (O'Neill J., 2016).The*E. coli* strains are considered as one of the few microbes that have the skill to be adapted to numerous biofunctions. These bacteria can colonize the healthy intestinal tract of several mammals including humans. They are used as an important bio-tool in several biotechnological applications. Furthermore, they have virulence factors which cause numerous diseases in humans and animals, and affect a wide range of bio-cellular processes (Kaper *et al*., 2004). Although *E. coli* strains inhabit the gastrointestinal tract of healthy humans, it is considered as one of the most pathogenic microorganisms isolated from humans. *E. coli* is a very versatile bacterium that can modify easily from one bio-activity to another.

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Highly variable mutation rates have been reported in commensal and pathogenic *E. coli* strains (Matic *et al*., 1997).

Some strains of *E. coli* cause infections in the urinary, intestinal,and respiratory tractsalong with other diseases. The sources of pathogenic *E. coli* strains include contaminated water and food, and itmay be transmitted through direct contact with infected people and animals or non-direct contact. Pathogenic *E. coli* strains may cause enteric/diarrheal illness, urinary tract diseases (UTDs) or sepsis/meningitis(Kaper *et al*., 2004). According to the Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/ecoli/general/index.html, December 1, 2014), pathogenic *E. coli* strains can be classified into six pathotypic strains as follows: Shiga toxin-producing *E. coli* (STEC), enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroaggregative *E. coli* (EAEC), enter invasive*E. coli* (EIEC), and diffusely adherent *E. coli* (DAEC). Illnesses resulting from bacterial infections caused by pathogenic *E. coli* strains involve diarrhea, inflammation of the kidney (pyelonephritis), inflammation of the colon (dysentery), and hemolytic-uremic syndrome. Extreme response to such infectionsmay lead to tissue damage, organ failure, and death (Donnenberg, 2013). These bacterial strains may develop resistance mechanisms to inhibit the effects of antibiotics and there are confirmed scientific evidences reporting that these bacterial strains can also disseminate the resistance genes to other bacteria (Morris *et al*., 1998).

The treatment for infectious diseases caused by *E. coli* strains must not include antibiotics that can replicate the risk of severe complications such as hemolytic uremia. The misdiagnosis of *E. coli* infection and misuse of antibiotics for treatment, may lead to the emergence of antibiotic resistant *E. coli* strains. A number of pathogenic and non-pathogenic *E. coli* strains have developed the ability to resist the standard antibiotics through numerous mechanisms,whichwe have discussed in this study. In Saudi Arabia, antimicrobial drug resistance genes, including β-lactam (bla_{SHV}), gentamicin (aac(3)-IV), streptomycin (*aadA1*), tetracyclines (*tet*(A),*tet*(B)), chloramphenicol (*catA*1,*cmlA*), erythromycin (*ere*(A)), and sulfonamide (*sul*1) resistance genes, have been detected among *E. coli* isolates(Abo-Amer *et al*., 2018). The present review aimed to update several scientific concepts related to antibiotic resistant *E. coli* strains.

Antibiotic resistant *E. coli* strains.

In general, the pure bacterial isolates are considered resistant to a specific antibiotic if the minimum inhibitory concentration (MIC) (mg/L) of the antibiotics is greater than the breakpoint (mg/L). The standard assays define MIC as the lowest concentration of the antibiotic,which has the ability to inhibit the bacterial growth, using the standard methods such as two-fold macro-dilution serials, two-fold micro-dilution serials, or E-test protocol.

The MIC breakpoints are determined by several health organizations, such as the European Committee on Antimicrobial Susceptibility Test (EUCAST) and Clinical Laboratory and Standards Institute (CLSI), based on clinical and pharmacokinetic studies (Kuper *et al*., 2009; Reller *et al*., 2009). The bacterial strains, which show resistance to most standard antibiotics,are often known as superbugs.The MIC breakpoints (mg/L) and zone diameter breakpoints (mm) for most pathogenic microorganisms, including *E. coli,* are available in breakpoint tables for interpretation of MICs and zone diameters, Version 9.0, valid from 2019-01-01, http://www.eucast.org/clinical_breakpoints/). The breakpoints are alsoupdated regularly by CLSI (https://clsi.org/media/2270/clsi_astnewsupdate_june2018_final.pdf). The methods used to determine MICs and MIC breakpoints must adhere to the procedures approved by the international committees on antimicrobial susceptibility testing, such as performance standards for antimicrobial susceptibility testing. 28th ed. CLSI supplement M100.

Antibiotic resistance pattern among *E. coli* isolates in Saudi Arabia has been evaluated using a group of standard antibiotics listed in Table 1. Figure 1 shows the percentage of antibioticsused for the treatment of urinary tract infections caused by Gram-negative bacilli, including *E. coli* isolates, in Buraidah Central Hospital from 1/8/2016 to 1/1/2017.

β-lactam antibiotic resistant *E. coli* strains

Chemically, the presence of a β-lactam ring is sufficient to distinguish between the molecular

structures of β-lactam antibiotics and those of the others. The β-lactam antibiotics are considered as the most widely prescribed group among all antibiotics, and include a large group of antibiotics such as penicillins (penicillin G and penicillin V, ampicillin, carbenicillin, oxacillin, piperacillin, ticarcillin , dicloxacillin, nafcillin, amoxicillin, and ampicillin), cephalosporins (cephalothin, cefoxitin, cefuroxime, ceftriaxone, cefotaxime, cefepime, ceftaroline,fosamil, and ceftolozane), monobactams (aztreonam, tigemonam, nocardicin A, and tabtoxin), carbapenems (imipenem, ertapenem, doripenem, and meropenem), and carbacephems. The β-lactam antibiotics perform a specific biological activity to inhibit bacterial cell wall biosynthesis (Demain and Elander, 1999; Elander, 2003)

The β-lactam antibiotics act by penetrating the bacterial outer membrane through protein membrane channelscalled porins, to bind with penicillin-binding proteins (PBPs). Modifications in porinsmay reduce the permeability of bacterial cell membrane and β-lactam antibiotic resistance. The primary strategy followed by β-lactam antibiotic-resistant bacterial strains is the production of β-lactamase enzymes that biochemically disrupt the β-lactam ring, leading to the inactivation ofthe antibiotic (Bush and Bradford, 2016; Féria *et al*., 2002).

Ampicillin resistant *E. coli* strains

Ampicillin (aminobenzylpenicillin) is a â-lactam and broad-spectrum antibacterial agent that can be produced from penicillin using semi-synthetic methods. Ampicillin inhibits the cell wall biosynthesis of Gram-negative and Gram–positive bacteria as well as aerobic and anaerobic bacteria. The biochemical functions of specific proteins, called PBPs, located inside the bacterial cell wall are hampered by ampicillin. Ampicillin is considered as a bacteriolytic agent,which can interfere with autolytic enzyme inhibitors such as the autolysin inhibitor. The amino group present in the chemical structure of ampicillin facilitates the passage of ampicillin through the outer membrane

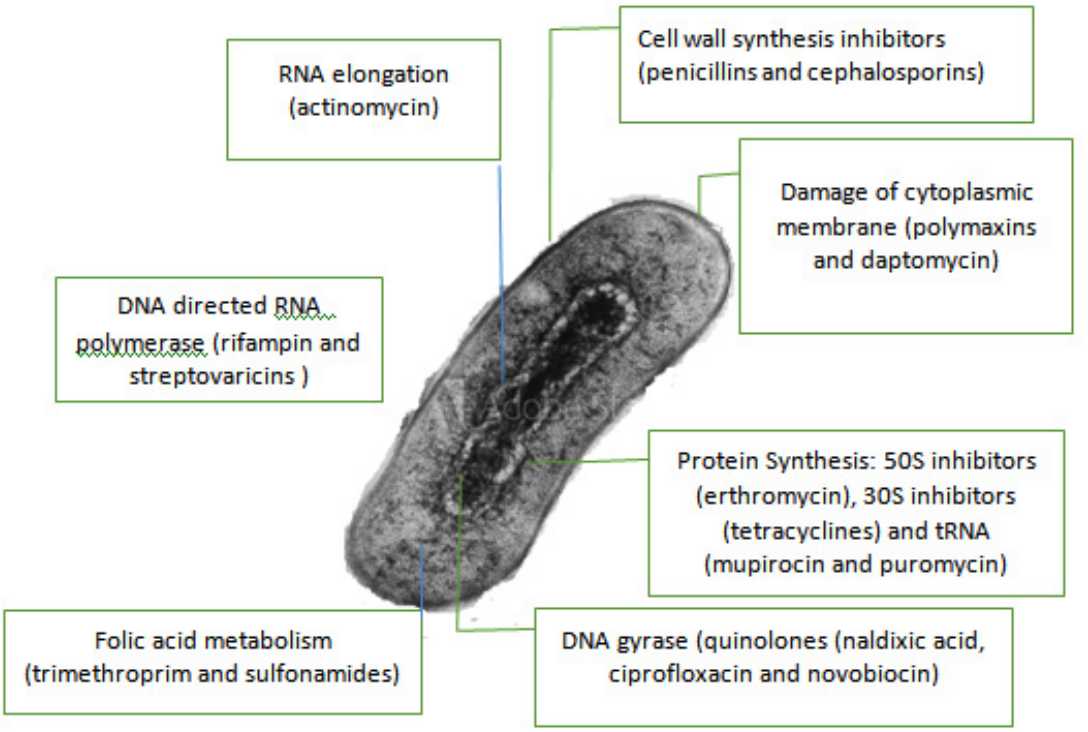


Fig. 1. Biological microbial sites affected by several standard antibiotics.
*Cross section of *Escherichia coli* bacteria obtained from https://stock.adobe.com.[Source of data:http:// www.text book of Brook biology of microorganisms org.com]

of pathogenic Gram-negative bacteria causing irreversible inhibition of transpeptidase enzyme, leading to bacterial lysis during the binary fission stage.

The major mechanism of resistance to β-lactam antibiotics depends on the disruption of these compounds by the β-lactamases, which destroy the amide bond of the lactam ring(Munita and Arias, 2016). Although TEM, SHV, and OXA-type β-lactamases have been detected in *E. coli* strains resistant to ampicillin, TEM is considered as a major β-lactamase enzyme responsible for resistance to ampicillin (Briñas *et al*., 2002).

Ampicillin resistant *E. coli* strains have been isolated and identified from patients and several environmental sources over the last 20 years in Saudi Arabia. The following table summarizes the most important findings.

Oxacillin-resistant *E. coli*

Oxacillin is a β-lactam antibiotic witha narrow-spectrum activity against penicillin- and methicillin-resistant bacterial strains. It generally is described as β-lactam antibiotic resistance to penicillinase enzyme. Oxacillin may obstruct chemical transpeptidation reaction in bacterial cell walls, leading to the inhibition of peptidoglycan synthesis, which in turn causes bacterial cell autolysis (Nadarajah *et al*., 2006). One of the studies carried out in Saudi Arabia has reported that *E. coli* isolates are the most predominant among uropathogenic bacteria (N=632) and concluded that all *E. coli* strains have no ability to resist oxacillin (Ali, 2018).

These findings were confirmed in a study (Alharbi *et al*., 2018), which showed that *E. coli* strains (N=227) isolated from wounds did not resist oxacillin. In 2004, Shobrak and Abo-Amer reported that all *E. coli strains* (N=82) isolated from migratory and non-migratory wild birds were resistant strains to oxacillin (Shobrak and Abo-Amer, 2014).

Piperacillin-resistant *E. coli*

Piperacillin is β-lactam antibiotic with broad-spectrum activity, classified as ureidopenicillin antibiotics, which are a class of penicillins used to treat *Pseudomonas aeruginosa*. Piperacillin prohibits the 3ed and final phase of the synthesis of the microbial cell wall, and is believed to inhibit autolysin inhibitors in microbial cell lysis stages. The *E. coli* strains can hydrolyze piperacillin via *amp*C and TEM-1 β-lactamase mediated in the chromosome or plasmid (Kadima and Weiner, 1997; Schechter *et al*., 2018). Combinations of piperacillin-tazobactam are often used to avoid these problems; nevertheless, piperacillin-tazobactam resistant *E. coli* strains

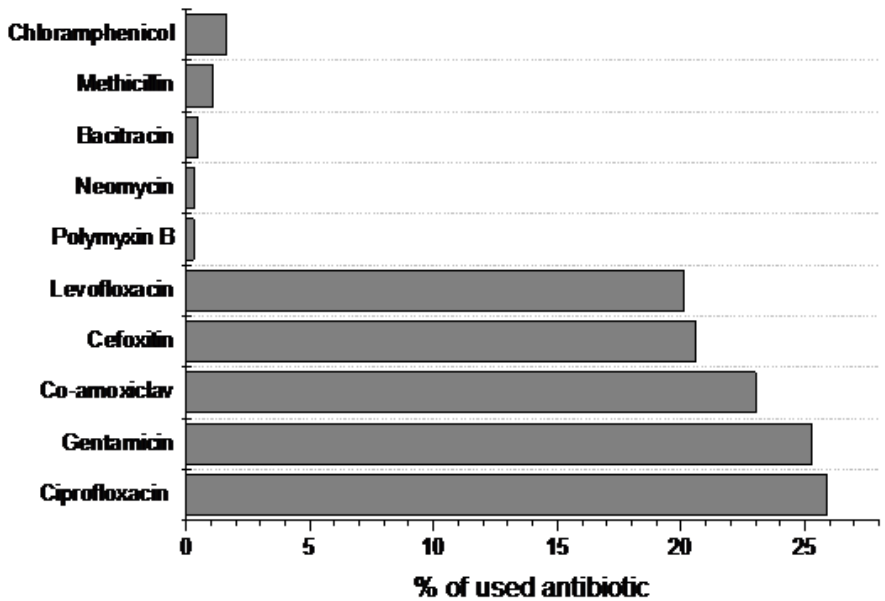


Fig. 2. The percentage (%) of the antibiotics used for treatment of urinary tract infections caused by Gram-negative bacilli. [Source of data:(Alsohaim et al., 2019)

have also been isolated and detected (Schechter *et al*., 2018). In Saudi Arabia, piperacillin-resistant *E. coli* strains have been diagnosed in clinical and non-clinical samples. Approximately 70-80% of the clinical *E. coli* isolates have been found to be resistant to piperacillin (Alharbi *et al*., 2018; Ali, 2018; Shobrak and Abo-Amer, 2014). Piperacillin-tazobactam resistant *E. coli* strains have been isolated from a referral hospital in Saudi Arabia, among extended-spectrum β-lactamase- and *amp*C β-lactamase-producing Gram-negative bacteria (Ibrahim *et al*., 2019).

Imipenem-resistant *E. coli*

Imipenem ($C_{12}H_{17}N_3O_4S$) is one of the β-lactam carbapenem antibiotics with the ability to resist β-lactamase. It has wide spectrum activity against aerobic, anaerobic, Gram-positive, and Gram-negative pathogenic bacteria. It can be used as a combination (imipenem-cilastatin) or triple-antibiotic (imipenem-cilastatin-relebactam) product. It is reported that bacterial resistance to carbapenem antimicrobial agents (imipenem and meropenem) leads to limiting therapeutic choices.

There are generally two methods employed by *E. coli* strains to resist carbapenem antibiotics; producing β-lactamase enzyme or reducing the permeability of bacterial cells, and strains may sometimes use both these ways.

Resistance of *E. coli* strains to imipenem has been not detected in clinical and nonclinical samples in Saudi Araba(Alam *et al*., 2017; Alqasim *et al*., 2018; Saeed *et al*., 2018). Conversely, imipenem-resistant *E. coli* strains have been isolated and detected from patients (N=72) (Ali, 2018) withUTIs (N=189) (Ali, 2018) and wound infections (N=161) (Alharbi *et al*., 2018).

Cephalosporin-resistant *E. coli*

Cephalosporins are antibacterial agents classified as bactericidal β-lactam drugs. They show biological activity to inhibit the bacterial cell synthesis by blocking cell wall enzymes. Currently, there are five generations of cephalosporins, which have been produced and marketed worldwide(Shahid *et al*., 2009). Previous studies have reported that *E. coli* strains isolated from Saudi Arabia resist the first, second, third, and fourth generation of cephalosporins (i.e., cephalothin, cefoxitin, cefuroxime, ceftazidime, ceftriaxone, cefotaxime, and cefepime)(Alharbi *et al*., 2018; Ali, 2018). Ceftobiprole (fifth generation of cephalosporins) has been approved to treat pneumonia infectionsin several countries including Saudi Arabia(Pfaller *et al*., 2019).No evidence could be traced regarding isolation of *E. coli* strains resistant to ceftaroline and ceftobiprole, according to the information obtained by searching Google

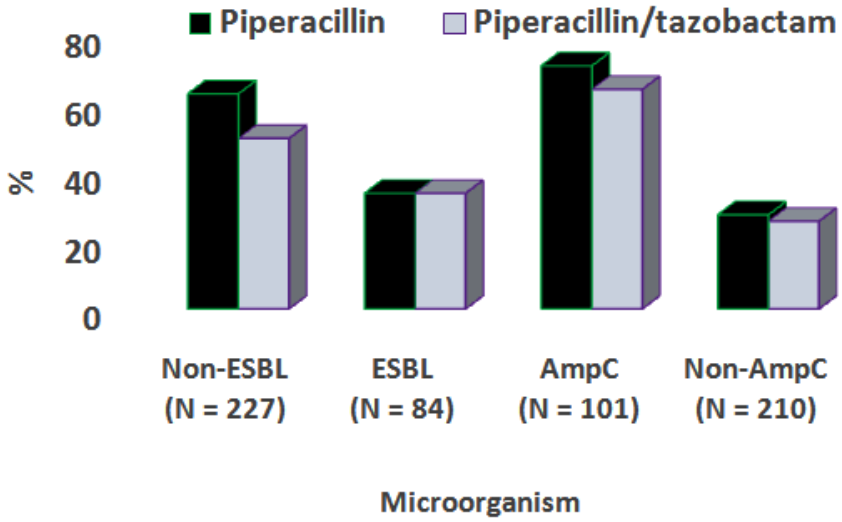
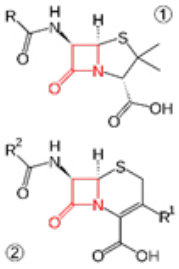
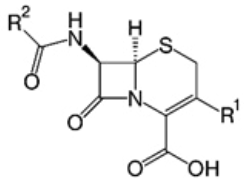
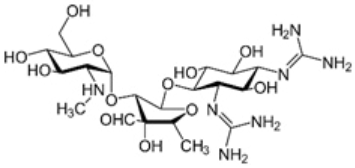
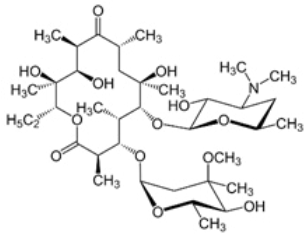
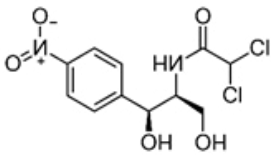
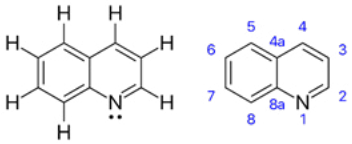
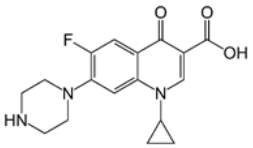
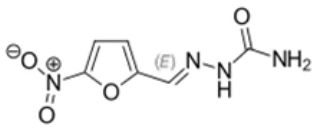
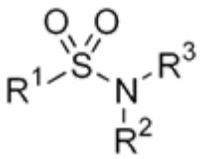
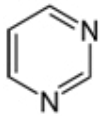
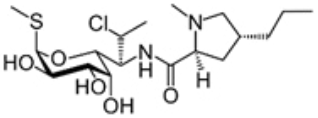
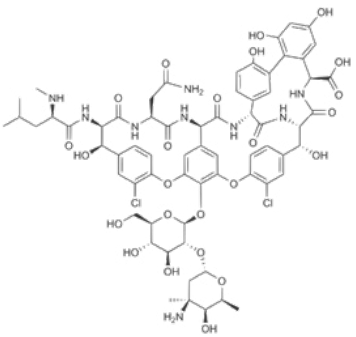
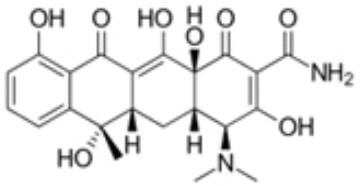


Fig. 3. Piperacillinand piperacillin/tazobactam resistant Gram-negative bacteria including *Escherichia coli,* detected in King Abdullah Hospital, Bisha Province, Saudi Arabia. ESBL=extended-spectrum β-lactamase, and AmpC=AmpC β-lactamases (Source of data: (Ibrahim et al., 2019)

Table 1. Grouping of standard antibiotics used to study antibiotic resistance patterns among *E. coli* strains isolated from Saudi Arabia,based on their chemical structures

Chemical group		Antibiotics
Beta-lactams		Penicillin G, Ampicillin, Augmentin, Oxacillin, Piperacillin, Aztreonam.
Cephalosporins		Cephalothin, Cefoxitin, Cefuroxime, Ceftazidime, Ceftriaxone, Cefotaxime, Cefepime.
Aminoglycosides		Amikacin, Gentamicin, Neomycin, Tobramycin
Macrolides		Erythromycin
Chloramphenicol		Chloramphenicol
Quinolones		Nalidixic acid, Ciprofloxacin
Flouroquiolones		Norflaxacin

Nitrofurans		Nitrofurantoin
Sulfonaides		Sulfamethoxazole
Pyrimidine analogues		Trimethoprim
Semisynthetic lincosamides		Clindamycin
Glycopeptides		Vancomycin
Tetracycline		Tetracycline
Synergic antibiotics		Cip/Norfloxacin (Ciprofloxacin/ Norflaxacin)Cotrimoxazole (Sulfamethoxazole /Trimethoprim)

*(Alharbi et al., 2018); (Ali, 2018), structural chemical groups from https://en.wikipedia.org/.

Scholar(https://scholar.google.com/) and (https://sdl.edu.sa/).

Tetracycline resistant *E. coli* strains

Tetracycline ($C_{22}H_{24}N_2O_8$), also known as anhydrotetracycline or deschlorobiomycin, is a bacteriostatic broad spectrum antibiotic that can act against an extensive range of pathogenic microbes including Gram-positive and Gram negative bacteria, chlamydiae, mycoplasmas, rickettsiae, and protozoan parasites (Chopra and Roberts, 2001). It is secondary metabolic products follows the polyketide antibiotics produced by some of the actinomycetes bacteria "*Streptomyces* spp.". In general, the tetracyclines can inhibit the biosynthesis of bacterial proteins by preventing the combination of aminoacyl-tRNA with the acceptor

site, in the bacterial ribosome. The biological activity of tetracycline may include the 30S, 50S bacterial ribosomal subunit, and the cytoplasmic membrane.

The outer membrane of Gram-negative bacteria is traversed by the tetracyclines through the OmpF and OmpC porin pathways (Chopra *et al*., 1992). The bacteria can resist the tetracyclines by exporting tetracycline from the bacterial cell by efflux proteins, which are encoded by thetet efflux genes, protection of bacterial ribosomes by cytoplasmic proteins, or inactivation of tetracycline through enzymatic modification (Ref.). The misuse of tetracycline compounds has been confirmed in Saudi Arabia. Several poultry products have been screened to detect the residues of tetracycline agents, the results indicate that the level of the tetracycline residues has reached over the maximum residue limit in some tested samples (Al-Ghamdi *et al*., 2000).

Aminoglycosides resistant *E. coli*

The aminoglycosides are natural (gentamicin and tobramycin) or semisynthetic (derivatives of natural antibiotics such as amikacin), broad-spectrum, bactericidal antimicrobial agents which are generally introduced for the treatment of Gram-negative infections in humans(Germovsek *et al*., 2017; Krause *et al*., 2016). Aminoglycoside antibiotic-resistant bacterial strainscan fight the antibiotics derived from aminoglycosides,using various strategies including modification of target sites by biosynthesis of specific enzymes, as well as mutation in bacterial chromosome and efflux pump(Krause *et al*., 2016; Rosenberg *et al*., 2000). Aminoglycoside antibiotic-resistant *E. coli* strains have been detected in patients, individuals, and food products in Saudi Arabia (Al Ghamdi *et al*., 1999; Alharbi *et al*., 2018; Ali, 2018).

Gentamicin

Gentamicin ($C_{21}H_{43}N_5O_7$) is a secondary metabolite produced by *Micromonosporapurpurea* (a saprophytic, filamentous, aerobic, spore-forming, and Gram-positive bacterium, which can be isolated from the soil). In general, it is used for the treatment of bacterial infections caused by bacterial strains susceptible to antibiotics, including *E. coli* strains. Gentamicin is classified as an aminoglycoside antimicrobial agent with

Table 2. Percentage (%) of ampicillin resistant *E. coli* strains isolated from several sources in Saudi Arabia

Number of isolates (N)	Percentage (%) of ampicillin resistant *E. coli* strains.	Source of samples	Reference
115	88.7%	Chicken	(Al Ghamdi et al., 1999)
99	70.7%	Patients	(Al Ghamdi et al., 1999)
117	53.8%	poultry industry workers	(Al Ghamdi et al., 1999)
392	In 2004 (75%) In 2005 (80%) In 2006 (60%) In 2007 (70%) In 2008 (>80%) In 2009 (>80%)	Patients	(Al Johani et al., 2010)
	50% 63%	OutpatientsInpatients	(Al-Tawfiq, 2006)
37	78.4%	Chicken meat	(Altalhi et al., 2010)
202	75.7%	Patients (urinary tract infection)	(Alghoribi et al., 2015)
227	84.8%	Patients (wound infections)	(Alharbi et al., 2018)
240	9.1%	Raw milk	(Alharbi et al., 2018)
182	44%	(Camel, Beef, Lamb, Poultry)	(Greeson et al., 2013)
150	51%	Chickens	(Abo-Amer et al., 2018)
683	85%	Patients	(Ali, 2018)
157	83	Outpatient	(Al Wutayd et al., 2018)
82	70% (migratory birds) 40% (non- migratory birds)	Birds	(Shobrak and Abo-Amer, 2014)

Table 3. Percentage (%) of Cephalosporin-resistant *E. coli* strains isolated from several sources in Saudi Arabia

Year	Cephalothin	Cefoxitin	Cefuroxime	Ceftazidime	Ceftriaxone	Cefotaxime	Cefepime	Sources	Reference
2013	-	4	3	13	-	3	6	Healthy neonates	(Elkersh et al., 2015)
2015	-	15.25	-	81.36	-	76.27	75.58	Patients	(Alyamani et al., 2017)
2015	-	0	-	32.2	-	92.2	50	Patients	(Al-Mijalli, 2016)
2016	91	15	0	36	0	0	20	Patients	(Ali, 2018)
2017	69	24	52	33	43	100	27	Patients	(Ali, 2018)
2017	0	19	51.7	10.1	-	9	47.8	Patients	(Alharbi et al., 2018)
2017	0	0	8.4	0	-	0	0	Raw milk	(Alharbi et al., 2018)
2018	2	1	1	1	1	0	1	Farm chicken	(Abo-Amer et al., 2018)
2018	85.7	-	92.9	100	92.9	78.57	85.71	Patients	(Ineta et al., 2018)

broad-spectrum activity against Gram-positive and Gram-negative bacteria. It can obstruct the synthesis of bacterial proteins through interaction with the prokaryotic 30S ribosomal subunit, leading to misinterpretation of transfer ribonucleic acid (t-RNA) (Yoshizawa *et al*., 1998). In general, the bacteria acquire aminoglycoside resistance via three potential mechanisms: 1) alteration in bacterial cell permeability (reducing uptake), 2) modification at sites in the ribosomal subunit, and 3) synthesis of specific enzymes having the ability to modify the chemical structure of aminoglycosides (Yoshizawa *et al*., 1998). Aminoglycoside N(3)-acetyltransferase (aac(3)-IV) gene has been detected in numerous aminoglycoside-resistant *E. coli* isolates(Costa *et al*., 2008; Domínguez *et al*., 2002; Zhang *et al*., 2009).

Streptomycin

Streptomycin ($C_{21}H_{39}N_7O_{12}$) is chemically classified as an aminoglycoside antimicrobial agent that can be produced by *Streptomyces griseus,*which is frequently isolated from the soil. Streptomycin has the ability to irreversibly bindto the 30S ribosomal subunit proteins and 16S rRNA. The interaction between streptomycin and decoding area in16S rRNA of the 30S ribosomal subunit (site near nucleotide 1400). The principle of interaction is the capacity of streptomycin to bind with a single amino acid of the 30S ribosomal protein S12 and four nucleotides of 16S rRNA, which lead to mRNA misreading. In bacteria, genetically acquiredstreptomycin resistance is frequently due to genetic alteration in *rpsL*gene,which encodes the ribosomal protein S12 (Springer *et al*., 2001).

In Saudi Arabia, *E. coli* strains resistant to gentamicin have been identified and isolated from inpatients, outpatients, animals, and foods. Spontaneous streptomycin resistant *E coli* strains have a genetic alteration in several sites in 30S ribosomal protein S12 including *Lys*42, *Lys*87, *Pro*90, and *Gly*9 (Chumpolkulwong *et al*., 2004). In Saudi Arabia, the *E coli* strains resistant to streptomycin have been characterized and streptomycin-resistance genes have been detected (Abo-Amer *et al*., 2018). Streptomycin-resistant *E. coli* strains have been isolated from numerous sources including raw chicken meat, wastewater, as well as in patient samples (skin, blood, urine, stool, and respiratory tract) (Alam *et al*., 2017; Altalhi *et al*., 2010; Mantilla-Calderon *et al.*, 2016). In a prior

study performed in Taif, Saudi Arabia, more than 48% of the streptomycin-resistant *E. coli* strains (N=119) were isolated from retail raw chicken meat (Al Johani *et al*., 2010).

In Riyadh, Saudi Arabia, it has been reported that all isolates of *E. coli*(N=200) detected in thefeces of broiler chickens are resistant to streptomycin (Al-Arfaj *et al.*, 2015). Streptomycin-resistant strains have been found to be the preponderant strains among enterotoxigenic *E. coli* isolates (N=181) collected from patients with diarrhea (Willshaw *et al.*, 1995).

Tobramycin

Tobramycin ($C_{18}H_{37}N_5O_9$) is a narrow spectrum aminoglycoside antimicrobial agent, which can interact with microbial 30S and 50S ribosome,thereby preventing the formation of 70S ribosome complex. It is widely used to treat microbial infections caused by Gram-negative bacteria. The intracellular concentration of tobramycin is critical for its action. Active transport of tobramycin through the bacterial membrane is a significant mechanismthat helps to increase tobramycin concentration inside the bacterial cell. The bacterial strains generally gain resistance to tobramycin through one or more of the three strategies mentioned above (physiological or genetic alteration in cell permeability, mutation at the ribosomal binding sites, or synthesis of enzymes having the ability to modify the aminoglycoside) (Islam *et al*., 2009). In Saudi Arabia, 67% of the *E. coli* strains (N=1116) isolated from patients were tobramycin-resistant strains (Kader and Kumar, 2004). In 2015,57% of *E. coli* strains (N=130) detected in pilgrims (patients) admitted in Makkah, Saudi Arabia were tobramycin-resistant(Haseeb *et al*., 2016).In King Fahd Hospital University, Clinical Microbiology Department, Al-Khobar, Saudi Arabia (Al-Zahrani and Akhtar, 2005), more than 75% of the *E. coli* strains (N=48) depicted the ability to resist tobramycin.

Table 4. Percentage (%) of tetracycline-resistant *E. coli* strains isolated from several sources in Saudi Arabia

Number of isolates (N)	Percentage (%) of ampicillin resistant *E. coli* strains.	Source of samples	Reference
116	99%	Chicken	(Al Ghamdi et al., 1999)
99	64.7%	Patients	(Al Ghamdi et al., 1999)
10	30	Pigeons	(Abulreesh, 2011)
150	97%	Chicken	(Abo-Amer et al., 2018)
100	49%	inpatients (urine samples)	(Alqasim et al., 2018)
683	85%	Patients	(Ali, 2018)
161	68%	Patients (wound infection)	(Alharbi et al., 2018)
32	100% (migratory birds) 84% (non- migratory birds)	Birds	(Shobrak and Abo-Amer, 2014)

Table 5. Percentage (%) of gentamicin-resistant E. coli strains isolated from several sources in Saudi Arabia

Number of isolates (N)	Percentage (%) of gentamicin resistant *E. coli* strains.	Source of samples	Reference
116	89.7	Chicken	(Al Ghamdi et al., 1999)
96	21.9	Patient	(Al Ghamdi et al., 1999)
768	47% (from 2006 to 2010)	Hospitalized patient and outpatient	(Somily et al., 2014)
683	27%	Patients	(Ali, 2018)
157	14	Outpatient	(Al Wutayd et al., 2018)
32	0% (migratory birds) 4% (non- migratory birds)	Birds	(Shobrak and Abo-Amer, 2014)

Table 6. Percentage (%) of *E. coli* strains resistant to antibiotics, causing urinary tract infections in Saudi Arabia, in 1985 and 2017

Antibiotic	% in 2017	Antibiotic	% in 1985
Cotrimoxazole	72	Trimethoprim	59
Chlormphenicol	75	Sulfamethoxazole	87
Nalidixic acid	76	Nalidixic acid	10
Nitrofurantoin	26	Nitrofurantoin	32
Cip/Norfloxacin	59	N.T	-
Erythromycin	100	N.T	-
Clindamycin	100	N.T	-

* References: (Ali, 2018); (Eltahawy and Khalaf, 1988); N.T= Not tested

Kanamycin

Kanamycin ($C_{18}H_{36}N_4O_{11}$) is a bactericidal antimicrobial agent grouped on thebasis of its chemical structure in the aminoglycoside antibiotics group. It has the ability to eliminate bacterial pathogens by inhibiting protein synthesis, using the same mechanism of action asthe aminoglycosides to cause irreversible damage in small ribosomal subunit and 16S ribosomal RNA. The pathogenic bacteria resistance to kanamycin. In industrial microbiology, kanamycin is produced using *Streptomyceskanamyceticus*. The *E. coli* strains withkanMX marker show resistance to kanamycin. In Kanamycin-resistant *E. coli* strains, efflux pumps may act to drive out kanamycin from *E. coli* cells. Resistance may be developed by a mutation in the ribosomal subunit target or by ribosome methyltransferases,whichhave gained increasing clinical importance(Garneau-Tsodikova and Labby, 2016). In Saudi Arabia, kanamycin-resistant *E. coli* strains have been isolated and detected in wastewater (Mantilla-Calderon *et al*., 2016), vegetable salads (Khiyami *et al*., 2011), and meat (Greeson *et al*., 2013). A study reported that all *E. coli* strains (N=60) isolated from frozen fish in Eastern Province of Saudi Arabia were kanamycin-susceptible *E. coli*isolates.

Neomycin

Neomycin is one of the aminoglycoside antimicrobial agents that have strongbiological activity against pathogenic Gram-negative bacteria. It can be produced by fermentation using *Streptomyces* spp. such as *S. fradiae*and*S. albogriseus*. Neomycin inhibits microbial protein synthesis byinteracting with 30S subunit and 16S rRNA.The *E. coli* strains that harborthe gene *neo* (coding for the 29-kDa phosphotransferase enzyme), have the biological ability to resist neomycin and kanamycin (Genilloud *et al*., 1988).

The neomycin-resistant *E. coli* mutants show significant alteration in the activity of membrane Mg2+-ATPaseand periplasmic alkaline phosphatase. Point mutations in rrsB 16S rRNA gene, especially at the 3' minor domain of helix 4 can lead to emergence of*E. coli* strains resistant to neomycin (Obaseiki-Ebor and Breeze, 1984) (https://card.mcmaster.ca/ontology/39986).In Saudi Arabia, *E. coli* strains resistant to neomycin have been reported by some previous studies (21% of 180 isolatesof *E. coli* were resistant)(Abo-Amer *et al*., 2018);however, many reports have confirmed that all *E. coli* strains were susceptible to neomycin (Ali, 2018).It has been reported that neomycin is one of the less-used drugs among the 44 antibiotic drugs used to treat urinary tract infections (N=339) (Alsohaim *et al*., 2019).

Other antibiotics

In Saudi Arabia, it has been reported that there are numerous *E. coli* strains that possess the ability to resist macrolides (erythromycin), chloramphenicol, quinolone (naldixic acid and ciprofloxacin), fluoroquinolones (norflaxacin), sulfonamide (sulfamethaxazole), glycopeptide (vancomycin), semisynthetic lincosamide (clindamycin), nitrofuran (nitrofurantoin), and pyrimidine (trimethoprim) antibiotics. Chloramphenicol, kanamycin, cefoxitin, and ceftiofur-resistant *E. coli* strains have been detected in Saudi Arabia from several sources of locally marketed meat(Greeson *et al*., 2013).

Bothextended spectrum β-lactamase (ESB) *E. coli* or non-ESB *E. coli* strains show resistance

to synergic action produced from sulfamethoxazole and trimethoprim (cotrimoxazole) among clinical isolates (Al-Otaibi and Bukhari, 2013). In fact, it is believed that the resistance to antibiotics is increasing continuously;however, sometimes the opposite occurs and the strains show susceptibility to the same antibiotics to which they were resistant in the past (Table).

CONCLUSION

Antibiotics are frequently used for therapy of infected humans and animals. Treatment for *E. coli* infection has been highly difficult by the rise of resistance to most first-line antibiotics. The data showed the prevalence of *E. coli* strains in Saudi Arabia, which can resist all antibiotic groups including β-lactams, cephalosporins, aminoglycosides (except fifth generation), macrolides, chloramphenicol, quinolones, flouroquiolones, nitrofurans, sulfonaides, pyrimidine analogues, semisynthetic lincosamides, glycopeptides, and tetracycline antibiotics. The integrated monitoring and management of the antibiotics used to treat infections caused by *E. coli* must be applied to reduce health hazards.

ACKNOWLEDGMENTS

The author wishes to thank Dr. Jamal M. Khaled and Dr. Shine Kadaikunnan for the helpful discussions on the topic. This project was funded by the King Abdulaziz City for Science and Technology (KACST), Kingdom of Saudi Arabia (Award number: LGP- 36-7).

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