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

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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 (ceftriaxone and cefotibiprole), 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 bacterium of 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.
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 tracts along with other diseases. The sources of pathogenic E. coli strains include contaminated water and food, and it may 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), enterohemorrhagic E. coli (EHEC), enterinvasiveE. 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 infections may 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, which we have discussed in this study. In Saudi Arabia, antimicrobial drug resistance genes, including β-lactam (blaλsa), gentamicin (aac(3)-IV), streptomycin (aadA1), tetracyclines (tet(A), tet(B)), chloramphenicol (catA1, cmlA), erythromycin (ere(A)), and sulfonamide (sul1) 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 also updated 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 antibiotic used 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 channels called porins, to bind with penicillin-binding proteins (PBPs). Modifications in porins may 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 of the antibiotic (Bush and Bradford, 2016; Féria et al., 2002).

**Ampicillin resistant E. coli strains**

Ampicillin (aminobenzylpenicillin) is a β-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.](https://stock.adobe.com)

*Cross section of *Escherichia coli* bacteria obtained from https://stock.adobe.com.*

[Source of data: http://www.textbook 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 with a 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 a 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 3rd 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 ampC 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
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 *ampC* β-lactamase-producing Gram-negative bacteria (Ibrahim et al., 2019).

**Imipenem-resistant *E. coli***

Imipenem (C₁₉H₁₇N₃O₄S) 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 Arabia (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) with UTIs (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., cephalexin, cefoxitin, cefuroxime, cefazidime, ceftriaxone, cefotaxime, and cefepime) (Alharbi et al., 2018; Ali, 2018). Ceftobiprole (fifth generation of cephalosporins) has been approved to treat pneumonia infections in 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.
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

<table>
<thead>
<tr>
<th>Chemical group</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams</td>
<td>Penicillin G, Ampicillin, Augmentin, Oxacillin, Piperacillin, Aztreonam.</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Cephalothin, Cefoxitin, Cefuroxime, Ceftazidime, Ceftriaxone, Cefotaxime, Cefepime.</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Amikacin, Gentamicin, Neomycin, Tobramycin</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Nalidixic acid, Ciprofloxacin</td>
</tr>
<tr>
<td>Flouroquiolones</td>
<td>Norflaxacin</td>
</tr>
</tbody>
</table>
Nitrofurans  
Nitrofurantoin

Sulfonamides  
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 the tet 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 strains can 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 (C₁₉H₂₅N₄O₆) is a secondary metabolite produced by *Micromonospora purpurea* (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>
<thead>
<tr>
<th>Number of isolates (N)</th>
<th>Percentage (%) of ampicillin resistant <em>E. coli</em> strains.</th>
<th>Source of samples</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>115</td>
<td>88.7%</td>
<td>Chicken</td>
<td>(Al Ghamdi et al., 1999)</td>
</tr>
<tr>
<td>99</td>
<td>70.7%</td>
<td>Patients</td>
<td>(Al Ghamdi et al., 1999)</td>
</tr>
<tr>
<td>117</td>
<td>53.8%</td>
<td>poultry industry workers</td>
<td>(Al Ghamdi et al., 1999)</td>
</tr>
<tr>
<td>392</td>
<td>In 2004 (75%)</td>
<td>Patients</td>
<td>(Al Johani et al., 2010)</td>
</tr>
<tr>
<td></td>
<td>In 2005 (80%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In 2006 (60%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In 2007 (70%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In 2008 (&gt;80%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>In 2009 (&gt;80%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>78.4%</td>
<td>Chicken meat</td>
<td>(Altalhi et al., 2010)</td>
</tr>
<tr>
<td>202</td>
<td>75.7%</td>
<td>Patients (urinary tract infection)</td>
<td>(Alghoribi et al., 2015)</td>
</tr>
<tr>
<td>227</td>
<td>84.8%</td>
<td>Patients (wound infections)</td>
<td>(Alharbi et al., 2018)</td>
</tr>
<tr>
<td>240</td>
<td>9.1%</td>
<td>Raw milk</td>
<td>(Alharbi et al., 2018)</td>
</tr>
<tr>
<td>182</td>
<td>44%</td>
<td>(Camel, Beef, Lamb, Poultry)</td>
<td>(Greeson et al., 2013)</td>
</tr>
<tr>
<td>150</td>
<td>51%</td>
<td>Chickens</td>
<td>(Abo-Amer et al., 2018)</td>
</tr>
<tr>
<td>683</td>
<td>85%</td>
<td>Patients</td>
<td>(Ali, 2018)</td>
</tr>
<tr>
<td>157</td>
<td>83</td>
<td>Outpatient</td>
<td>(Al Wutayd et al., 2018)</td>
</tr>
<tr>
<td>82</td>
<td>70% (migratory birds)</td>
<td>Birds</td>
<td>(Shobrak and Abo-Amer, 2014)</td>
</tr>
<tr>
<td></td>
<td>40% (non-migratory birds)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Percentage (%) of Cephalosporin-resistant *E. coli* strains isolated from several sources in Saudi Arabia

<table>
<thead>
<tr>
<th>Year</th>
<th>Cephalothin</th>
<th>Cefoxitin</th>
<th>Cefuroxime</th>
<th>Ceftazidime</th>
<th>Ceftriaxone</th>
<th>Cefotaxime</th>
<th>Cefepime</th>
<th>Sources</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>4</td>
<td>15.25</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>Healthy neonates</td>
<td>(Elkersh et al., 2015)</td>
</tr>
<tr>
<td>2015</td>
<td>13</td>
<td>0.00</td>
<td>32.20</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>Patients</td>
<td>(Al-Mijalli, 2016)</td>
</tr>
<tr>
<td>2015</td>
<td>6</td>
<td>0.00</td>
<td>0.00</td>
<td>43.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>Patients</td>
<td>(Ali, 2018)</td>
</tr>
<tr>
<td>2016</td>
<td>91</td>
<td>0.00</td>
<td>0.00</td>
<td>10.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>Raw milk</td>
<td>(Alharbi et al., 2018)</td>
</tr>
<tr>
<td>2016</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>Farm chicken</td>
<td>(Abo-Amer et al., 2018)</td>
</tr>
<tr>
<td>2017</td>
<td>0</td>
<td>0.00</td>
<td>8.40</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>Patients</td>
<td>(Ineta et al., 2018)</td>
</tr>
<tr>
<td>2018</td>
<td>2</td>
<td>0.00</td>
<td>1.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>Patients</td>
<td>(Alam et al., 2017)</td>
</tr>
<tr>
<td>2018</td>
<td>85.7</td>
<td>92.90</td>
<td>78.57</td>
<td>85.71</td>
<td>85.7</td>
<td>85.7</td>
<td>85.7</td>
<td>Patients</td>
<td>(Altalhi et al., 2010; Mantilla-Calderon et al., 2016)</td>
</tr>
</tbody>
</table>

Streptomyumycin

Streptomycin ($C_{21}H_{39}N_{7}O_{12}$) 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 bind to the 30S ribosomal subunit proteins and 16S rRNA. The interaction between streptomycin and decoding area in 16S 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 acquired streptomycin 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 Lys42, Lys87, Pro90, and Gly9 (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 the feces 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_{5}O_{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 mechanism that 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

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

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

<table>
<thead>
<tr>
<th>Number of isolates (N)</th>
<th>Percentage (%) of gentamicin resistant E. coli strains</th>
<th>Source of samples</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>116</td>
<td>89.7</td>
<td>Chicken</td>
<td>(Al Ghamdi et al., 1999)</td>
</tr>
<tr>
<td>96</td>
<td>21.9</td>
<td>Patient</td>
<td>(Al Ghamdi et al., 1999)</td>
</tr>
<tr>
<td>768</td>
<td>47% (from 2006 to 2010)</td>
<td>Hospitalized patient and outpatient</td>
<td>(Somily et al., 2014)</td>
</tr>
<tr>
<td>683</td>
<td>27%</td>
<td>Patients</td>
<td>(Ali, 2018)</td>
</tr>
<tr>
<td>157</td>
<td>14</td>
<td>Outpatient</td>
<td>(Al Wutayd et al., 2018)</td>
</tr>
<tr>
<td>32</td>
<td>0% (migratory birds) 4% (non- migratory birds)</td>
<td>Birds</td>
<td>(Shobrak and Abo-Amer, 2014)</td>
</tr>
</tbody>
</table>
Table 6. Percentage (%) of E. coli strains resistant to antibiotics, causing urinary tract infections in Saudi Arabia, in 1985 and 2017

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>% in 2017</th>
<th>Antibiotic</th>
<th>% in 1985</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole</td>
<td>72</td>
<td>Trimethoprim</td>
<td>59</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>75</td>
<td>Sulfamethoxazole</td>
<td>87</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>76</td>
<td>Nalidixic acid</td>
<td>10</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>26</td>
<td>Nitrofurantoin</td>
<td>32</td>
</tr>
<tr>
<td>Cip/Norfloxacin</td>
<td>59</td>
<td>N.T</td>
<td>-</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>100</td>
<td>N.T</td>
<td>-</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>100</td>
<td>N.T</td>
<td>-</td>
</tr>
</tbody>
</table>

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

**Kanamycin**

Kanamycin (C₁₉H₂₅N₄O₄S) is a bactericidal antimicrobial agent grouped on the basis 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 as the 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 Streptomyces kanamyceticus. The E. coli strains with kanMX 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, which have 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 the Eastern Province of Saudi Arabia were kanamycin-susceptible E. coli isolates.

**Neomycin**

Neomycin is one of the aminoglycoside antimicrobial agents that have strong biological 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 by interacting with 30S subunit and 16S rRNA. The E. coli strains that harbor the 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⁺-ATPase and 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 isolates of 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 (nalidixic acid and ciprofloxacin), fluoroquinolones (norfloxacin), 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).

Both extended 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, fluoroquinolones, nitrofurans, sulfonamides, 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.

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REFERENCES

13. Alghoribi, M.F., Gibreel, T.M., Farnham, G., Al Johani, S.M., Balkhy, H.H., Upton, M., Antibiotic-resistant ST38, ST131 and ST405 strains are the leading uropathogenic Escherichia coli clones in Riyadh, Saudi Arabia. Journal of


35. Germovsek, E., Barker, C.I., Sharland, M., What do I need to know about aminoglycoside antibiotics? *Archives of Disease in Childhood*.


