A Review on Antibiotic Drug Resistance in Escherichia Coli

Archana Singh Sikarwar, Denishvaran Jaya Gopal

Abstract— Antibiotic drug resistance to Escherichia coli is an emerging issue for healthcare which causes public health problems and outbreak worldwide. Antibiotic resistant of E.coli can cause community and hospital acquired infections. Uses of broad spectrum antibiotics, inadequate aseptic techniques and improper infection control measures had worsen the emergence of antibiotic resistance of E.coli. Emergence of antibiotic resistant E.coli is a major challenge to healthcare provider to create newer, better and more efficient antibiotics. Infection control measures should be taken by healthcare provider to control emergence and spread of antibiotic resistant E.coli. Further researches are needed to evaluate the available antibiotic drugs, agent and identify new drugs that can solve the issue of antibiotic resistant emergence.

Index Terms— Antibiotic drug resistance, Escherichia coli, infections

I. INTRODUCTION

E.coli is a gram negative, bacilli bacteria in the Enterobacteriaceae family. There are hundreds of *E. coli* bacteria strains in the world. Most of them are harmless to human, however some strains can cause infection in human examples, bloody diarrhoea, UTI, hemolytic uremic syndrome, and kidney failure. In some cases these infections may lead to death. Since the scientist discovered antibiotic drugs such as penicillin, cephalosporin, monobactam, and carbapenems, this problem was resolved. Even the dangerous strain can be treated by using antibiotic drugs. However, few *E.coli* strains become resistance to the antibiotic drugs and becomes a big challenge for healthcare and healthcare providers. Use of broad spectrum antibiotics causes antibiotic drug resistant *E.coli* because they can develop and evolving constantly to adjust to their surroundings that asserts selective pressure on them. They are emerging drastically, thus possess great health threat to the public and challenges to the healthcare. Antibiotic resistant *E.coli* infections have been increased in the last few decades. Because of the antibiotic resistant ability, *E.coli* is untreatable and thus these infections have begun to occur as outbreak. There have been increased in morbidity, mortality, and healthcare costs because of antibiotic resistance in *E.coli*. In recent decades, the increase of *E.coli* resistance to the β-lactams antibiotics such as penicillin, cephalosporin, monobactam, and carbapenems has become more serious issue [1]. Extended spectrum β-lactamase (ESBL) is the major reason of *E.coli* resistance to the antibiotic drugs. ESBL producing *E.coli* has been reported increasingly in recent years which causes limitation to the treatment [2]. *E.coli* bacteria produces ESBLs enzymes which causes resistance to certain antibiotics. *E.coli* can spread by the faecal oral route and by contact with contaminated hand, objects or equipment. Contaminated food and water with *E.coli* have been responsible for disease outbreaks and deaths around the world in recent years. *E.coli* is the second most common source of infection behind *Staphylococcus aureus*. *E. coli* infection has been developed as a significant public health problem worldwide [3].

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II. B-LACTAM ANTIBIOTICS

The most commonly prescribed drugs for *E.coli* infection are β-lactam antibiotics drug. The β-lactams antibiotics are a broad class of antibiotics consisting of four main groups: penicillin, cephalosporin, monobactam, and carbapenems. These antibiotics drugs have a β-lactam ring. β-lactam antibiotics act on bacteria through two mechanisms where both mechanisms target the inhibition of bacterial cell wall synthesis. The first mechanism of action is to act on the bacterial cell wall and to inhibit the action of the transpeptidase enzyme which is responsible for completion of the cell wall. The second mechanism is attached to the penicillin binding proteins which suppress cell wall hydrolases and release hydrolases, which in turn act to lyse the bacterial cell wall. However, there are some *E.coli* strain that becomes resistant to antibiotic drugs. Bacteria resist by producing β-lactamase to avoid antibiotic mechanisms of action [4].

Table 1: β-lactam Groups and examples of β lactam antibiotic agents

β-lactam groups	**Examples of antibiotic agents**
Penicillin	Penicillin G, penicillin
	Penicillinase resistant penicillins: methicillin, nafcillin, oxacillin, cloxacillin
	Aminopenicillins: ampicillin, amoxicillin
	Carboxypenicillins: carbenicillin, ticarcillin
	Ureidopenicillins: mezlocillin, piperacillin
Cephalosporin	First generation: cefazolin, cephalothin, cephalexin
	Second generation: cefuroxime, cefaclor, cefamandole, cefamycins (cefotetan, cefoxitin)
	Third generation: cefotaxime, ceftriaxone, cefpodoxime, ceftizoxime, cefoperazone, ceftazidime
	Fourth generation: cefepime, cefpirome
Carbapenems	Imipenem, meropenem, ertapenem
Monobactams	Aztreonam

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Table 2: Antibiotic agents, their modes of action, and resistance mechanisms

Antibiotic agents	Mode of action	Resistance mechanisms
β lactams	Cell wall synthesis, cell division	β lactamase, altered penicillin binding proteins
Glycopeptides (azoles, cycloserine)	Cell wall division	Blocking of drug access to pentapeptide
Aminoglycosides (spectinomycin)	Inhibit protein synthesis (bind to 30S ribosome)	Enzymatic inactivation, altered target, impermeability
Macrolides	Inhibit protein synthesis (bind to 50S ribosome)	Altered target, enzymatic inactivation
Tetracycline	Inhibit protein synthesis (affect t-RNA binding to 30S)	Efflux, altered target, impermeability, enzymatic inactivation
Chloramphenicol (lincosamides, streptogramin)	Inhibit protein synthesis (bind to 50S ribosome)	Enzymatic inactivation, impermeability
Quinolones	Replication: inhibit DNA gyrase	Altered target enzymes, impermeability
Rifampin	Transcription: inhibit DNA dependent RNA polymerase	Altered target enzymes, impermeability
Sulfonamides	Folic acid synthesis	Altered target
Trimethoprim	Folic acid synthesis	Altered target, impermeability
Polyenes (nystatin, amphotericin B)	Cell membrane permeability	Ergosterol deficient mutants

ß-lactamase

Bacteria that produce ß-lactamase enzyme exhibit resistance to ß-lactam antibiotics. The peptide bond of β-lactam ring in the β-lactam antibiotics can be hydrolysed by β-lactamases enzyme and cause inactivation of the antibiotic [5]. There are four groups based on their substrate and inhibitor profiles. Group 1 are cephalosporinases which are poorly inhibited by clavulanic acid; group 2 penicillinases, cephalosporinases, and broad-spectrum ß-lactamases which are normally inhibited by active site-directed ß-lactamase inhibitors; group 3 metallo-ß-lactamases that hydrolyze penicillins, cephalosporins, and carbapenems and they also not well inhibited by almost all ß-lactam-containing molecules; group 4 penicillinases which are poorly inhibited by clavulanic acid [24]. The first plasmid mediated b-lactamase was discovered in an isolate of *E.coli* in 1960s in Greece from a patient named Temoniera thus it was named TEM after the patient [6].

Extended Spectrum B-lactamases (ESBLs)

Extended-spectrum ß-lactamases (ESBLs) are a group of these ß-lactamase enzymes that have the ability to inactivate ß-lactam antibiotics such as cephalosporin, monobactam, penicillins and carbapenems. Most of them also have the ability to hydrolyze fourth-generation cephalosporins such as cefepime and cefpirome. As a result, bacteria that produce ESBLs become resistant to most of the ß-lactams antibiotics. ESBLs does not activate against cephamycins and carbapenems [6]. There are two most common types of ESBLs found in E.coli; TEM and SHV enzyme types [10]. There are more than 130 TEM type and more than 50 SHV type b-lactamases, mainly in *E. coli, Klebsiella pneumoniae,* and *Proteus mirabilis* [11].

ESBL-producing *E.coli*

In recent years, prevalence of antibiotic resistance among ESBL-producing *E.coli* has been increased [7]. ESBL-producing *E.coli* creates a lot of challenges to doctors, microbiologist, clinicians, scientists and other healthcare provider because of their dynamic evolution and epidemiology, therapeutic limitation, challenges in diagnostic and their prevention and infection control measures [6, 8]. Outbreaks of infection have been reported worldwide caused by ESBL-producing E.*coli*. Thus infection control measures become challenging [9].

Detection Method for ESBL-producing *E.coli*

ESBL-producing *E.coli* causes outbreaks. Rapid and reliable detection test are required for detection of ESBL-producing *E.coli* [4]. To detect ESBLs tests are available, double disc test, combination disk method, Vitek ESBL test, E Tests, MIC broth dilution, microdilution test [12].

Table 3: Laboratory tests for detection of ESBL-producing *E.coli*

Tests	Method and interpretation
Double disk approximation or double disk synergy	Disk of third generation cephalosporin placed at 30 mm distance from amoxicillin-clavulanic acid. Enhanced inhibition indicates ESBL
Combination disk	Uses two discs of third generation cephalosporin alone and combined with clavulanic acid. An increase in the zone inhibition of >5 mm with the combination disk indicates ESBL
Microdilution test	Growth in a broth containing 1 µg/ml third generation cephalosporin indicates ESBL
MIC broth dilution	MIC of third generation cephalosporin alone or combined with clavulanic acid. A decrease in the MIC of the combination of ≥3 twofold dilutions indicates ESBL
E test (MIC ESBL strips)	Two sided strip containing ceftazidime on one side and ceftazidime-clavulanic acid on the other. The ratio of the MIC of the combination to that of ceftazidime alone of >8, or the presence of a phantom zone (or both) indicates ESBL
Automated instruments (Vitek)	Measures MICs and compares growth of bacteria in presence of ceftazidime *v* ceftazidime-clavulanic acid
Molecular (DNA probes, PCR, RFLP)	Targets specific nucleotide sequences to detect different variants of TEM and SHV genes

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III. EMERGENCE OF THE ANTIBIOTIC DRUG RESISTANT E.COLI

Evolution of antibiotic drug resistant *E.coli* is continued for their existence by resisting new antibiotic drug introduced into practice. Emergence of antibiotic drug resistant *E.coli* creates challenges to healthcare. The available antibiotic drug can only be used as short term treatment before they become resistant to it. Therefore, new drugs have to be constantly developed to treat it.Many researches were conducted showed statistical data that suggest the rapid emergence of antibiotic drug resistant *E.coli* especially ESBL-producing *E.coli*. Outbreak cases and deaths were reported caused by *E.coli* infection worldwide.

Table 4: Evidence and statistics of Antibiotic drug resistant *E.coli* emergence

Timeline	Evidence and statistics of emergence
1960	The first plasmid mediated b-lactamase was discovered in an isolate of *E.coli* in 1960 in Greece. It was named TEM after the patient from whom it was isolated (Temoniera)
1961-1970	*E.coli* developed early ß-lactam-resistant via production of broad spectrum lactamases such as TEM-1, TEM-2 and SHV-1 that hydrolyzed penicillins, aminopenicillins, carboxypencillins, ureidopenicillins, and narrow-spectrum cephalosporins.
1980s	E.coli developed mutation in TEM and SHV. Thus producing ß-lactamases leading to emergence of extended spectrum ß-lactamases (ESBL). They hydrolysed broad-spectrum lactam with addition of third generation cephalosporins and aztreonam.
1990s	ESBLs-producing bacteria treated with carbapenems developed resistant via production of carbapenemases.

Table 5: Evidence of Antibiotic drug resistant *E.coli* emergence worldwide

Year	Evidence and statistics of emergence	Country
2001	An Outbreak of ESBL-producing *Escherichia coli* among patients in liver transplantation unit.	USA
2010	An outbreak of ESBL–producing *E. coli* in neonatal care unit. ESBL-producing *E. coli* transmitted from a mother to her newborn twins during vaginal delivery. One healthcare worker gets infected and the infection spread to other neonates.	Switzerland
2011	Emergence of Fluoroquinolone-Resistant and ESBL-Producing *Escherichia coli* at a Comprehensive Cancer Centre in the United States.	USA
2011	Outbreak of new mutant *E.coli* knows as *E.coli* O1040:H4.	Europe

IV. HEALTHCARE CHALLENGES

Emergence of antibiotic drug resistant of *E.coli* has become a challenge to healthcare. Antibiotic drug resistant gives challenges in area of diagnosis, treatment and containment of *E.coli* infection [17]. Because of antibiotic drug resistance, drastic increase in morbidity, mortality, and health-care costs was reported [1].Antibiotic resistance of *E.coli* causes fatal infection such as the haemolytic uremic syndrome which can lead to death thus increasing mortality rate [16]. Detection of ESBL is not easy because there is no simple marker for its presence, not all ESBL-producing *E.coli* are universally resistant to any one of ß-Lactams antibiotics. They vary in their substrate specificity and may not phenotypically express resistance to its own substrate. Other than that, ESBL-producing E.coli may produce multiple ESBLs or other different enzymes which may alter the antibiotic resistance phenotype [6]. Identifying the source of the infection also becomes a major challenge to the healthcare. Infection control measures should be taken by the healthcare provider to avoid emergence and spread of resistant *E.coli.* Infection control measures should include use of protective garment and glove, proper hand washing, increased barrier precautions [18].

V. OUTBREAK

Recently, there is a new mutant of *E.coli* was reported. *E.coli* O104:H4 has been invading the Europe since May 2011 [20]. Mutant *E.coli* is resistant to antibiotic drug. The outbreak began in Germany and since then this antibiotic resistant *E.coli* has been invading several countries in Europe including France, Denmark, Netherlands, Austria, Czech, Greece, Norway, Luxembourg, Poland, Spain, Sweden and United Kingdom. There also been cases reported in Canada, Switzerland and USA. On 7th July 2011, there were 3941 cases of *E. coli* O104:H4 infection, including 52 dead [21]. It has become one of the outbreaks of *E. coli* in modern history [19]. The outbreak was started on May 19, 2011, the Robert Koch Institute was informed about three cases of the haemolytic–uremic syndrome in children admitted to the university hospital. The team found out the number of cases was increases. An investigation of the outbreak involving all levels of public-health and food-safety authorities was initiated to identify the causative agent and the vehicle of infection in order to prevent further cases of disease [22]. The source of the *E. coli* O104:H4 outbreak is still unclear thus it is difficult for the healthcare provider to control the spread. However, cucumbers, tomatoes and lettuce are suspected as the source of infection. On July 26, 2011, RKI has been declared the outbreak in Germany to be over.

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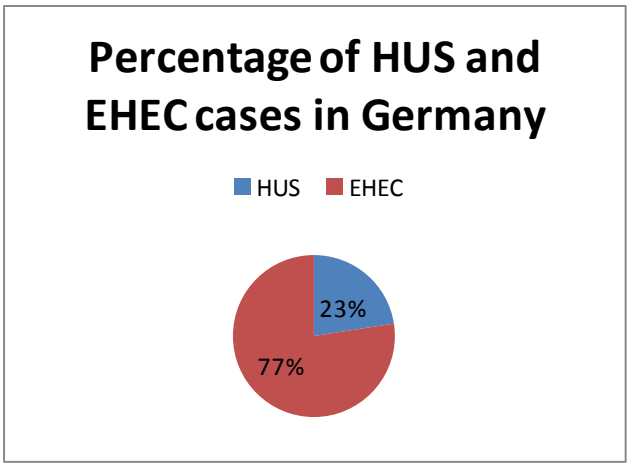

Figure 1: Percentage of HUS and EHEC cases in Germany

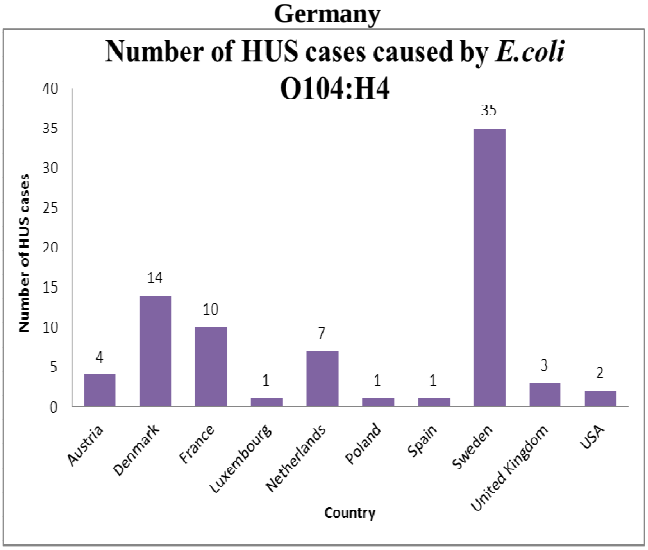

Figure 2: Number of HUS cases caused by *E.coli* O104:H4

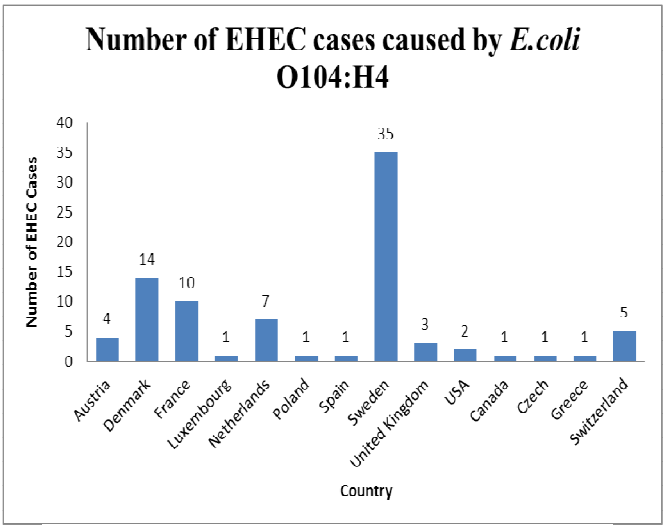

Figure 3: Number of EHEC cases caused by *E.coli* O104:H4

VI. CONCLUSION

Statistical data and evidences from researches prove that antibiotic resistant *E.coli* is emerging worldwide. It causes a public health problems and outbreak worldwide. Thus, it gives challenges to the healthcare. Antibiotic resistant *E.coli* can cause community and hospital acquired infections. Uses of broad spectrum antibiotics, inadequate aseptic techniques and improper infection control measures supported emergence of antibiotic resistant *E.coli*. Emergence of antibiotic resistant *E.coli is* a major challenge to healthcare provider. Healthcare providers are working in team to resolve this issue as soon as possible. Further researches are needed to limit and avoid the emergence and spread of antibiotic resistant *E.coli*. Healthcare provider need to evaluate the available antibiotic drugs and identify new drugs that can solve this antibiotic resistant emergence. Future research plans should focus on the re-evaluation of earlier-used antimicrobial agents, that had low clinical use in recent decades, for potential antimicrobial activity and clinical effectiveness against today's resistant micro-organisms may give a temporary solution to the problem of spreading and advancing bacterial drug resistance. Research should be conducted on development of new antibiotic drugs or advance agents that can be useful for the clinical therapeutic of antibiotic resistant E.coli infections. Clavulanic acid is a β-lactamase inhibitors combine with available cephalosporins could improve the effectiveness of the former agents against ESBL-associated infections [23].

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