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A Review of Antimicrobial Resistance (AMR) of *Escherichia coli* on Livestock and Animal Products: Public Health Importance

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ABSTRACT

Antimicrobial resistance (AMR) has become a major challenge for the world of health in this century. This resistance event is closely related to the use of antibiotics that are not in accordance with the rules in both the hospital sector and the livestock sector. Antibiotics have an important role in treating infectious diseases. The role of antibiotics is expanding not only as a treatment but also to prevent disease and as a growth promoter in livestock. Escherichia coli has been widely used to monitor resistance in livestock and food of animal origin because these microbes can be found in the digestive tracts of warm-blooded animals. Several strains of Escherichia coli are potential sources of resistant genes that can be transmitted to humans. Livestock and food of animal origin such as poultry, pigs, cattle, sheep, eggs, and milk have become reservoirs for resistant Escherichia coli. It is not only resistant to one type of antibiotic but has also become multidrug resistant, and also become public health problem. Escherichia coli has different resistance mechanisms depending on the type of antibiotic. This resistance mechanism is also encoded by resistance genes which can be transmitted horizontally. Resistant bacteria encode different resistance genes for each antibiotic class. There needs to be strict regulations and supervision to limit the use of antibiotics in the livestock sector so that it can reduce cases of antibiotic recession in the world.

Keywords: Escherichia coli, Antimicrobial resistance, Livestock, Animal products, Public health

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INTRODUCTION

Antimicrobial resistance (AMR) was introduced more than fifty years ago and is the biggest challenge of this century. Resistance of pathogenic bacteria to antibiotics is one of the major public health problems of the 21st century (1). This resistance is a growing public health threat throughout the world (2). Microbes can simultaneously be resistant to several groups of antibiotics. This event is called multidrug-resistant, ie when the microbes are resistant to at least 3 types of antibiotics (3). This incident is associated with the use of antibiotics that are not according to the rules. Such as excessive use of antibiotics and errors in diagnosing diseases. Not only because of its use in humans but also on farm animals (4). The use of antibiotics is expected to continue to increase rapidly in the coming years due to the intensification of the livestock sector in many developing countries (5).

Animal husbandry is one of the sectors that has the potential as a reservoir for resistant microbes (4). The use of antibiotics in animal husbandry is directly related to the cases of resistant bacteria in food of animal origin (6, 7). In the poultry sector, breeders in various countries use antibiotics to raise poultry (8, 9). Antibiotics are given orally to treat livestock infected with pathogenic bacteria, prevent livestock from disease, and to increase productivity (10). The indiscriminate use of antimicrobials in livestock has the opportunity to accelerate the development of resistant pathogenic microbes as well as in commensal organisms (11). Apart from concerns about the emergence of AMR in bacteria from poultry production, there are also human health concerns about the presence of antimicrobial residues in foods of animal origin such as milk (11), meat (12), and eggs (13). In addition, AMR in poultry pathogens is likely to result in economic losses. Infectious diseases in livestock that are not handled and due to the purchase of antibiotics that are not effective in treating them (14).

The case of resistance to the gram-negative group of bacteria is very worrying because of the limited choice of antibiotics to treat infections caused by several organisms such as Enterobacteriaceae, Pseumonas aeruginosa, and Acinetobacter which have become resistant to almost all available antimicrobials, including carbapenems (4). The Enterobacteriaceae group is a microbe that is clinically fast growing agents to become resistant to available antimicrobials (15). Cases of microbial resistance to antibiotics that are widely reported in livestock and food of animal origin include Escherichia coli. Resistant Escherichia coli was found in chickens in Ghana (16), pork and beef in Mexico (17), chicken in Pakistan (18), chicken in France (19) and chicken in Indonesia (11).

OVERVIEW

Escherichia coli

Escherichia coli is a member of the Enterobacteriaceae family in the Gammaproteobacteria class (20) which is commonly found living in human and animal digestion as normal microflora (21). Escherichia coli includes Gram negative bacteria which are facultative anaerobes (22). These bacteria are Gram-negative bacteria with short rods, measuring 2.4 x 0.4-0.7 µm, motile with petritic flagella, and without spores and including opportunistic pathogens which always show increased resistance to various antibiotics. These bacteria have the highest incidence of urinary tract infections (UTIs) (23). Escherichia coli is able to reproduce itself in approximately twenty minutes (20).

Escherichia coli is one of the bacteria that has been studied in depth. Sequence analysis of the Escherichia coli genome was first reported in 1997. Since then, more than 4800 Escherichia coli genomes have been sequenced (23). Escherichia coli can replicate in every 20 minutes. This rapid growth makes it suitable for observations of the evolution of microorganisms and research on long-term experimental evolution of more than 50,000 generations (24).

Escherichia coli has been widely used to monitor AMR in livestock and food of animal origin. This is because Escherichia coli can be found in the digestive tracts of warm-blooded animals (25). In addition, several strains of Escherichia coli are potential sources of the AMR gene which can be transmitted to humans through various means (21, 22). Escherichia coli carried through feces or treatment of wastewater that is disposed of into waterways can pollute the environment (26). The concentration of Escherichia coli per gram of feces varies across host species, typically reaching 107–109 in humans and 104–106 in domestic animals (27).

VIRULENCE FACTORS OF ESWCHERICHIA COIL

Escherichia coli is a normal opportunistic flora in the digestive tract, that is, if the number is within normal limits, the bacteria can be beneficial, but if there is an increase in the number from normal, the bacteria will become pathogenic (28). Pathogenic Escherichia coli can cause disease in the intestinal tract as well as outside the intestine (29). There are six intestinal pathotypes of Escherichia coli including Shiga toxin-producing Escherichia coli (STEC), entero-toxigenic Escherichia coli (ETEC), enteropathogenic Escherichia coli (EPEC), diffusely adherent Escherichia coli, and enteroinvasive Escherichia coli. These strains are classified based on their virulence properties and pathogenicity mechanisms that cause gastrointestinal diseases such as diarrhea (30, 31).

Escherichia coli is the main cause of urinary tract infections (UTIs). Apart from being infected with Escherichia coli, UTIs can also be caused by Proteus spp., Staphylococcus saprophyticus, Klebsiella spp. and other Enterobacteriaceae. However, among UTIS-causing bacteria, Escherichia coli is considered to be the most dominant cause of community and nosocomial UTI. In addition, having a history of UTI in a patient increases the chance of infection (23). Therapeutic measures for UTI treatment use several antibiotic options including cotrimoxazole (trimethoprim / sulfamethoxazole), nitrofurantoin, ciprofoxacin and ampicillin (32, 33). However, studies of antibiotic resistance using urinary tract isolates from Escherichia coli have shown increased resistance to certain antibiotics, for example to ampicillin and cotrimoxazole (32).

Escherichia coli causes infection in the bloodstream which can cause morbidity, mortality, and health problems (34). These infections can increase the mortality rate in the hospital and lead to resistance to antibiotics, leading to longer hospital stays (35). Nosocomial bloodstream infections caused by resistant bacteria have been reported in Africa, especially in areas that are vulnerable and at high risk of developing nosocomial infections, such as in intensive care units and pediatric departments (36-38).

USE OF ANTIBIOTICS IN ANIMALS

Antibiotics have contributed greatly to human and animal health since their appearance in the 1940's. The development of antibiotics in today's era cannot be separated from the services of Alexander Fleming who discovered penicillin in 1928 (38). The use of antibiotics can be found in several sectors, such as hospitals (39), animal husbandry and agriculture (40), and fisheries (41) which have the impact of increasing AMR on livestock (42-46), pet (47-50), poultry (51-55), fisheries (56-59) and also obtained from animal products (60-65). The use of antibiotics is increasingly widespread, not only for treating infectious diseases (66), but also for disease prevention and as growth promoters in livestock. Unfortunately, the use of antibiotics in subtherapeutic doses for disease prevention and growth enhancement is higher than for the treatment of disease (67–69). This is one of the factors that triggers AMR in livestock (70).

For at least 50 years, farms in the United States and other developed countries have used antibiotics as Antimicrobial Growth Promoters (AGPs). AGP was first introduced in the mid-1950s. The use of antibiotics as AGP were streptomycin, sulfasuxidine, and streptothricin to pig and chicken feed which has been shown to have a beneficial effect on livestock production for first reported (71).

Antibiotics commonly used in humans include penicillins, fluoroquinolones, and macrolides. Meanwhile, sulfonamides, penicillins, and tetracyclines are often used in animals (11). In a survey conducted in China in 2010, it was found that there were residues of ciprofloxacin, oxytetracycline, enrofloxacin and chlortetracycline in 143 manure samples (72). A survey in Chile suggested that antibiotic residues were also found in eggs produced on farms (73). Due to the high concentration of antibiotics in livestock manure, this manure is often used for fish use because it is believed to increase fish growth and maintain pond fertility (74).

Because the use of antibiotics has resulted in increasing cases of resistance, several countries have limited their use. As in the EU, the use of antibiotics as Antibiotic Growth Promotors (AGP) has been banned since 2006. While in the US it has been banned starting in 2017. In Europe, the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) recommend steps to reduce the use of antimicrobials in animal husbandry in the European Union (79). France also issued a policy of prohibiting the excessive use of antibiotics in chickens (19).

AMR OF ESWCHERICHIA COIL IN FOOD OF ANIMAL ORIGIN

Escherichia coli lives in both animals and humans as normal flora which has many uses (21). But on the other hand, it can also harm humans because it causes infectious diseases (28). To avoid these losses, breeders take precautions so that their livestock remain healthy and have high productivity (72, 75). Farmers give antibiotics to prevent infection and add antibiotics as additional feed to increase livestock productivity. The use of antibiotics without supervision can lead to resistance to one antibiotic or even more than 3 antibiotics called multidrug resistant (MDR). A total of 94.9% Escherichia coli in sheep isolates showed the presence of MDR during the antibiotic sensitivity test (76). This high percentage illustrates the potential for spreading resistant microbes through animal husbandry (16). The level of microbial resistance to antibiotics is called antimicrobial resistance (AMR) will continue to increase if farmers continue to use antibiotics excessively.

Cases of resistant Escherichia coli were found on farms, both in livestock and breeders (77). Livestock such as chicken, turkey, pig, cow, as well as food of animal origin such as eggs and milk are reported as reservoirs of resistant Escherichia coli. The majority of Escherichia coli isolated turned out to be resistant to penicillin class antibiotics such as penicillin, ampicillin and amoxicillin. Escherichia coli isolates isolated from milk isolates in India were reported to be 100% resistant to penicillin. Likewise in Indonesia, Escherichia coli isolates isolated from beef were also reported to be 100% resistant to ampicillin, which is a penicillin antibiotic class (12). For foods of other animal origin, microbial resistance to the penicillin class is also high, for example Escherichia coli in eggs in Pakistan reached 83.3% (78), chicken and turkey in Arizona (79).

Apart from livestock, cases of resistant Escherichia coli were also found in breeders. As Aworh reports, workers on Nigerian farms are also at risk of carrying Escherichia coli resistant to ampicillin, tetracycline, sulfamethoxazole-trimethoprim, and streptomycin. This resistant Escherichia coli can be transmitted from animals to humans via several transfer mechanisms (76). Transmission of Escherichia coli from animals into the human body can occur in at least two ways, namely (a) when humans eat food of animal origin that is contaminated with bacteria, the food is not washed and cooked properly and (b) through direct contact with existing Escherichia coli. Livestock is a reservoir of resistant Escherichia coli which has a resistance coding gene. The gene can reach humans via the food chain (76).

Antimicrobial resistance in chickens is a common problem in Bangladesh and other developing countries due to the indiscriminate use of antibiotics as feed additives and prophylactic treatment of infectious diseases. Commonly used antibiotic agents, such as ampicillin, tetracycline, streptomycin, ciprofloxacin, erythromycin, sulfamethoxazole-trimethoprim, cholistine sulfate, gentamicin, and levofloxacin have relatively high levels of resistance than previously reported. (80). The presence of MDR also cannot be separated from microbial resistance in animal husbandry. The Escherichia coli isolate showing very high resistance to multiple antibiotics and a high prevalence of MDR leads to an alarming situation that requires further investigation. There is a need for a framework to address these problems (81). Due to the lack of choice of antibiotics that are sensitive to bacteria, further research on alternative antimicrobial agents is currently urgently needed (80).

MECHANISM OF RESISTANCE ON ESWCHERICHIA COIL

Escherichia coli belongs to the Gram-negative bacteria group. Gram negative bacteria are more easily resistant because they have an outer membrane that is not owned by the Gram-positive bacteria group. The outer membrane of Gram negative is an essential structure in protection against antibiotics (81). The inner structure of this outer membrane is composed of phospholipids (PLs) and lipopolysaccharides (LPs) in the outer structure (82). PLs and LPs act as bacterial membrane defenses because they are composed of saturated chains so that they are hydrophobic (83). The molecules making up PLs and LPs each carry a negative charge which allows for intermolecular linking interactions through the binding of divalent cations (84) and the presence of porin as ion selective channels so as to limit the absorption of antibiotics (85)

Escherichia coli has the ability to modify antibiotic targets including the aminoglycoside class of antibiotics by modifying the ribosomal subunit through the acquisition of plasmids carrying 16S rRNA methyltransferases (86-87) against the fluoroquinolone group by means of mutations in the GyrA subunit which is chromosomally coded from gyrase (gyrA gene) or the ParC subunit of topoisomerase IV (parC gene) (88) and against penicillin by modifying penicillin-binding protein (PBP) (89, 90).

β-lactam is a class of antibiotics that has 3 carbon rings and 1 nitrogen ring which is responsible for the bacteriolytic mechanism of action against bacteria. β-lactam works by inhibiting the synthesis of peptidoglycan which is an important component of bacterial cell walls. Escherichia coli is able to be resistant to β-lactam by producing β-lactamase enzymes. The most widely used classification for the β-lactamase enzyme is the Ambler structural classification, which is based on the similarity of the sequence, so that this protein is divided into four classes, namely classes A, C, and D of serine-β-lactamase and class B of metalo-β- lactamase (91). Escherichia coli is capable of producing several types of enzymes such as broad-spectrum β-lactamase (ESBL), AmpC β-lactamase (AmpC) (92) and carbapenemase which have different hydrolytic activity against β-lactam antibiotics (93). ESBL is a major concern in the medical world because it has the highest level of causative factors for β-lactamase resistance (94). ESBL is predominantly class A in the Ambler classification and is resistant to penicillins, first, second, and third generation cephalosporins and monobactams (for example, aztreonam), but cannot hydrolyze cephamycins (cefoxitin) or carbapenems (imipenem, meropenem), and can be inhibited by β-lactamase inhibitors such as clavulanic acid, tazobactam and sulbactam (95).

AmpC has the ability to hydrolyze amino- and ureidopenicillins, oxyimino-β-lactams such as ceftazidime, ceftiofur, and aztreonam and deactivate cephalosporins such as cephamycins (cefoxitin) (96-97). AmpC-producing Escherichia coli strains ranging from 2.0% were isolated from patients in Portuguese hospitals (98) to 16.7% from three university hospitals in Iran (99) and 29.0% from five referral hospitals in Sudan (100) AmpC and ESBL may be owned by a strain of Escherichia coli simultaneously which causes the mechanism of action of antibiotics to be more complicated and resistance to increase (82, 101).

Carbapenems bind to penicillin-binding proteins and induce spheroplast formation and cell lysis. The Escherichia coli strain that produces carbapenemase has the ability to hydrolyze the antibiotic carpabenem (102). Increased resistance to carbapenem antibiotics has been reported in several countries, one of which is China, which in 2011 was 0% of cases then increased to 1.9% in 2017 (103).

Several types of efflux pumps found in E. coli are the ATP-binding cassette (ABC) family, the multidrug and toxic compound extrusion (MATE) family, the major facilitator superfamily (MFS), and the resistance-nodulation cell division (RND) family. . Escherichia coli has an ABC group efflux pump, namely the MacAB transporter which provides resistance to several macrolides (104); MATE which is capable of transporting fluoroquinolones (105, 106); MFS capable of transporting macrolides (MefB and MdfA pumps), fluoroquinolones (QepA2, EmrAB-TolC, and MdfA pumps), tetracyclines (EmrAB-TolC and MdfA pumps), trimethoprim (Fsr pumps), and chloramphenicol

(MdfA pumps) (107, 108); and RND which can release β-lactam, fluoroquinolone, tetracycline, chloramphenicol, and lincosamides (109-111).

FACTORS THAT INCREASE RESISTANCE ON ESWCHERICHIA COIL

High population density goes hand in hand with the increasing need for food derived from livestock. As a result, an intensive strategy is needed to prevent and control pathogenic infections by using antibiotics. The use of antibiotics in livestock requires a prescription from a doctor. However, farm managers often given antibiotics of their own accord even though it is in accordance with the guidelines given by veterinarians (112, 113). In addition, in some countries, antibiotics are available over the counter without a prescription. This absence of regulation makes antibiotics readily available, abundant and cheap, thus encouraging overuse. The ability to purchase such products online has also made them accessible in countries where antibiotics are regulated (114). Administration of antibiotics in livestock that is not in accordance with the needs (misused) which causes increased resistance to pathogens including Escherichia coli (115). Antibiotics used in livestock that induce resistance can enter the human body through the consumption of feed from livestock (116). Resistant bacteria that enter the human body will cause adverse health problems (34).

GENE CODE FOR RESISTANT TO ANTIBIOTICS ON ESWCHERICHIA COIL

Bacterial resistance to antibiotics is classified into two types, namely intrinsic resistance and acquired resistance (117). Intrinsic resistance is a congenital resistance due to the insensitivity of bacteria to certain antibiotic classes. This is due to the inability of the target structure for certain antibiotics, for example, vancomycin resistance in Gram negative bacteria due to the inability of vancomycin to penetrate the outer membrane (118). Conversely, acquired resistance is resistance caused by the acquisition of a foreign resistant gene or gene mutation (119). In bacteria, genes can be inherited from relatives or can be obtained from non-relatives of mobile elements such as plasmids. This horizontal gene transfer (HGT) may allow antibiotic resistance to be transmitted between different bacterial species (120). Resistance can also occur spontaneously via mutation (121).

Resistant bacteria encode different resistance genes for each antibiotic class. Gram negative bacteria that are resistant to the aminoglycoside antibiotic class have resistant coding genes, namely armA (122) npmA, rmtA, rmtB, rmtC, and rmtD (123,124). The rmt gene provides resistance to gentamicin and amikacin, while npmA provides resistance to gentamicin, neomycin, amikacin, and apramycin, but not to streptomycin (125). Meanwhile, the gene coding for Escherichia coli resistance can come from humans and animals. blaTEM-1 is an animal-derived Escherichia coli resistance gene to β-lactam that can inactivate penicillins and aminopenicillins. Meanwhile, the most common ESBL gene in Escherichia coli isolates of human origin is blaCTX-M-15 (126).

The target of the fluoroquinolone antibiotic against Escherichia coli is gyrase. Escherichia coli developed a fluoroquinolone resistance mechanism by carrying out mutations encoded by the gyrA and parC genes (127). Other genes at play are qnrS1, qnrB1, qnrB4, and qnrB10 (128). Escherichia coli resistance to tetracycline antibiotics is coded by tet (A), tet (B), tet (C), tet (D), tet (E), tet (G), tet (J), tet (L), and tet (Y) as the gene coding for the efflux pump and tet (M) and tet (W) as ribosome protectors (129). The coding genes for Escherichia coli resistance to phenicol antibiotics include paint, fluorine, and cfr (130). Escherichia coli of animal origin, is resistant to sulfonamide antibiotics mediated by sul1, sul2, or sul3. The sul2 gene is associated with the streptomycin strA-strB resistance gene whereas sul3 is associated with other resistance genes, such as the mef (B) macrolide resistance gene (131).

The dfr gene modulates resistance to trimethoprim antibiotics in Enterobacteriaceae and other Gram-negative bacteria. Based on its size and structure, the dfr gene is divided into two major groups, namely dfrA and dfrB (132-133). The dfrA gene encodes a protein from 152 to 189 amino acids, while dfrB encodes a protein of 78 amino acids. Most of the dfrA and dfrB genes are found in Escherichia coli of animal origin. Escherichia coli is also resistant to polymyxin antibiotics which are modulated by the pmrA, pmrB, mgrB, phoP, and phoQ genes isolated from pigs (134).

CONCLUSION

Microbial resistance to antibiotics is a health problem that continues to be a global challenge. One of them is Escherichia coli which is commonly found in livestock and humans as well as animal products that are resistant to several classes of antibiotics. Animals and food of animal origin such as poultry, pigs, cattle, sheep, eggs, and milk are reservoirs for resistant Escherichia coli that have the potential to cause disease in humans. Because there are fewer choices of antibiotics that are sensitive to microbes, it is necessary to look for new antibiotic alternatives that are more effective in treating pathogenic infections, especially Escherichia coli. In addition, there is a need for strict regulations governing the use of antibiotics in livestock and poultry to break the chain of antibiotic resistance.

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