Escherichia Coli

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Escherichia coli are facultative, anaerobic Gram-negative rods with many facets. Within resistant bacterial populations, they play an important ecological role and can be used as a bioindicator of antimicrobial resistance. All animal species used for food production, as well as humans, carry *E. coli* in their intestinal tracts; plus, the genetic flexibility and adaptability of this bacteria to constantly changing environments allows it to acquire a great number of antimicrobial resistance mechanisms. Thus, the prevalence of antimicrobial resistance in these commensal bacteria (or others, such as enterococci) can be a good indicator for the selective pressure caused by the use of antimicrobial agents, providing an early warning of the emergence of antimicrobial resistance in pathogens. As many as 90% of *E. coli* strains are commensals inhabiting the intestinal tracts of humans and warm-blooded animals. As a commensal, it lives in a mutually beneficial association with its hosts and rarely causes diseases. However, *E. coli* also remains as one of the most frequent causes of several common bacterial infections in humans and animals. In humans, it is the prominent cause of enteritis, community- and hospital-acquired urinary tract infection (UTI), septicemia, postsurgical peritonitis, and other clinical infections, such as neonatal meningitis, while, in farm animals, it is more prominently associated with diarrhea. On a global scale, *E. coli* can be considered the most important human pathogen, causing severe infection along with other major bacterial foodborne agents, such as *Salmonella spp.* and Campylobacter. Thus, the importance of resistance in *E. coli*, typically considered a benign commensal, should not be underestimated.

Escherichia coli ESBL food-producing animals antimicrobial resistance

1. Introduction

E. coli is a ubiquitous commensal of food-producing animals and humans. Most strains of this enterobacterial species are harmless commensals that live in a mutually beneficial association with their hosts and seldom cause disease. *E. coli* is, however, a particularly complex species, having diversified into pathogenic strains. Based on the type of virulence factor present, and the host's clinical symptoms, *E. coli* strains are classified into pathotypes of zoonotic intestinal pathogenic *E. coli* (IPEC) or extraintestinal pathogenic *E. coli* (ExPEC)[1].

Within the IPEC, the diarrheagenic *E. coli* (DEC) groups include enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enteroaggregative *E. coli* (EAggEC), diffusely adherent *E. coli* (DAEC), enterohemorrhagic *E. coli* (EHEC) and Vero cytotoxin-producing *E. coli* (VTEC) or Shiga toxin-producing *E. coli* (STEC)[2]. Food poisoning outbreaks have been particularly associated with VTEC and, to a lesser extent, EPEC, ETEC and EAggEC strains [3]. The *E. coli* O157:H7 VTEC strain has become widely recognized as a very important cause of foodborne illness [4]. Since 1982, outbreaks have been recorded in the U.S. and throughout

Europe. The source most often found to be contaminated was beef meat, often minced, but today, the organism is widespread in the guts of asymptomatic cattle, and their feces can potentially contaminate other products (like vegetables, sprouts, fruits, meat products, drinking water, juices and milk) [5][6].

The ExPEC group brings together the uropathogenic *E. coli* (UPEC), the neonatal meningitis *E. coli* (NMEC) and the avian pathogenic *E. coli* (APEC), which are frequently associated with nosocomial and community-associated infections[7]. Poultry meat is the food of the animal source most closely linked to human ExPEC. In addition to the overall highest levels of *E. coli* contamination found in poultry meat, virulence genes similar to those of human ExPEC are often found in poultry-associated *E. coli* strains[8]. Moreover, extensive genetic similarity has been documented between APEC and ExPEC strains, causing disease in poultry and humans, respectively [8][9]. Although beef and pork meats were also evaluated as potential reservoirs of ExPEC causing urinary tract infections (UTIs) in humans, the recovered ExPEC isolates were significantly less likely to be genetically related to isolates from humans with UTIs than those from poultry [10]. Some of the emerging ExPEC lineages associated with human outbreaks are known to be linked with food-producing animals. For example, *E. coli* O25:H4-B2-ST131 has a globally emerging lineage with an extensive antimicrobial resistance profile, including the CTX-M-15 enzyme, and fluoroquinolone resistance [10]. In addition, wild, companion and food-producing animals have been reported as carriers of this group [11]. Furthermore, *E. coli* (various serotypes)-A-ST10, a commonly encountered, antimicrobial susceptible, low-virulence, human intestinal colonizer has been associated with some human infections and extended spectrum β-lactamase (ESBL) production [11][12]. Moreover, the ESBL-producing *E. coli* ST10 has been recovered from chicken meat, other meat types, rectal swab samples from healthy humans and human blood cultures [13][14].

The presence of several putative virulence genes enables pathogenic ExPEC bacteria to cause infections. According to their phylogenetic classification, ExPECs typically belong to group B2 and, less commonly, to group D, whereas commensal intestinal strains belong to group A or B1 [15]. However, virulence-associated genes, in and of themselves, rarely make an organism virulent. Their levels of expression, which can vary between pathogenic and nonpathogenic isolates, can also be a determining factor [16]. Moreover, it seems that these putative virulence factors, rather than being directly involved in infection, also contribute to ExPEC fitness, increasing their adaptability, competitiveness and ability to colonize the human body [16]. ExPEC strains are characterized by virulence factors that may be present in various combinations, including adhesins (*papC*, F10*pap*A, *sfa*DE, *afa*BC III, *iha*, *fimH*, *clp*G, *tsh* and *hra*); invasin (*ibe*10); iron-sequestering systems (*iucD*, *irp*2 and *chuA*); toxins (*omp*T, *ehxA*, *espP*, *hlyA*, *hlyD*, *vat*, *sat* and *cnf*1); capsules (K1, K5, *kps*MT II and *kps*MT III); siderophores (*iro*N, *fyu*A and *ire*A) and various other factors (*iss*, *usp*, *tra*T, *mal*X, *cva*C and H7 *fli*C) [17].

2. Antimicrobial Resistance Trends in *E. coli*

The presence of mobile genetic elements such as plasmids, insertion sequences and transposons contributes to the plasticity of *E. coli*'s genome. Horizontal gene transfer has promoted the diffusion of antibiotic resistance genes among this species and other commensals [18], particularly in environments such as the intestinal tract, where the

species diversity and bacterial population density are large. Therefore, *E. coli* has been used as a sentinel microorganism for antimicrobial resistance surveillance, especially in the case of the β-lactams [19].

Antimicrobial-resistant *E. coli* strains are broadly distributed in Europe, both in humans and in food-producing animals. As reported in the 2018 Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net), more than half of the *E. coli* isolates in Europe were resistant to at least one class of antimicrobials. Aminopenicillin resistance, followed by a resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides, were the most prevalent [20]. Furthermore, the reduction of antimicrobial-resistant *E. coli* in Europe was very low or nonexistent between 2015 and 2018, with *E. coli* being the major burden of antimicrobial resistance both in the number of cases and number of deaths [20]. Meanwhile, among food-producing animals, the European Food Safety Authority (EFSA) reported that the high proportions of *Salmonella*, *Campylobacter* and indicator *E. coli* isolates exhibiting reduced susceptibility to fluoroquinolones remain of concern [21]. However, co-resistance to “clinically important antimicrobials”, such as a resistance to third-generation cephalosporins or fluoroquinolones, are generally reported at very low to low levels in commensal *E. coli* isolates from animals [21].

These trends among food-producing animals are also evidenced by several other reports. Resistance to third-generation cephalosporins and quinolones was found among clinical *E. coli*, already resistant to most antimicrobials available for poultry, in a study conducted in 200 industrial poultry farms in Italy [22]. Likewise, in Germany, animals from 60 beef cattle and 52 dairy cattle production units were sampled; third-generation cephalosporin-resistant *E. coli* were isolated from at least one sample in 70% of the beef cattle farms and 85% of the dairy farms [23]. Besides resistances to antimicrobial classes that have been extensively used for a long time (e.g., sulphonamides and tetracyclines), high resistance rates to ciprofloxacin were also found among isolates from food-producing animals, more often in broilers, chicken meat and turkey meat than in the cattle and pig production chains [24][25][26]. These reports notwithstanding, *E. coli* with resistance to “critically important” antibiotics (especially to quinolones but, also, to colistin) in food-producing animals has been increasingly reported by others, as well as multidrug resistance (MDR) in commensal *E. coli* [27][28][29][30][31][32][33][34]. Moreover, the worldwide dissemination of MDR *E. coli* strains is mainly due to the spread of genes located on mobilizable genetic elements, including integrons, plasmids and transposons [35][36][37][38][39]. Since quinolones, colistin and third-generation cephalosporins are priority antimicrobials in human antimicrobial therapy, the emergence of this resistance warrants special concern and requires close monitoring.

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