REVIEW

Escherichia coli and urinary tract infections: the role of poultry-meat

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Abstract

Extraintestinal pathogenic *Escherichia coli* (ExPEC) is the most common cause of community-acquired and hospital-acquired extraintestinal infections. The hypothesis that human ExPEC may have a food animal reservoir has been a topic of investigation by multiple groups around the world. Experimental studies showing the shared pathogenic potential of human ExPEC and avian pathogenic *E. coli* suggest that these extraintestinal *E. coli* may be derived from the same bacterial lineages or share common evolutionary roots. The consistent observation of specific human ExPEC lineages in poultry or poultry products, and rarely in other meat commodities, supports the hypothesis that there may be a poultry reservoir for human ExPEC. The time lag between human ExPEC acquisition (in the intestine) and infection is the fundamental challenge facing studies attempting to attribute ExPEC transmission to poultry or other environmental sources. Even whole genome sequencing efforts to address attribution will struggle with defining meaningful genetic relationships outside of a discrete food-borne outbreak setting. However, if even a fraction of all human ExPEC infections, especially antimicrobial-resistant ExPEC infections, is attributable to the introduction of multidrug-resistant ExPEC lineages through contaminated food product(s), the relevance to public health, food animal production and food safety will be significant.

Keywords: Chicken, *Escherichia coli*, extraintestinal infections, extraintestinal pathogenic *E. coli*, poultry, reservoir, retail meat, urinary tract infections

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Introduction

Extraintestinal pathogenic *E. coli* (ExPEC) is the most common cause of community-acquired and hospital-acquired extraintestinal infections, including urinary tract (UTI), kidney, bloodstream and other infections. The incidence of extraintestinal infections is thought to exceed 7 million medical visits, 1 million emergency room visits and 100 000 hospitalizations every year in the USA [1]. The costs associated with these infections are estimated to range from $1 billion per year [2] to $1.6 billion (including indirect costs) per year in the USA [1].

In contrast to enteric *E. coli* pathotypes, such as enterohaemorrhagic, enterotoxigenic, enteroaggregative or enteropathogenic *E. coli* (which are associated with diarrhoeal illnesses in humans, have been linked to a wide variety of contaminated foods, and have been implicated in outbreaks of human infections), ExPEC does not cause disease in the gut of colonized individuals, but rather persists in the intestine until an opportunity to cause infection presents itself (e.g. sexual intercourse in community-acquired infections or catheter use in hospital-acquired infections). It is this time lag between the acquisition and asymptomatic colonization of the intestine with an ExPEC organism and the development of an infection that presents the biggest difficulty in attributing ExPEC to specific environmental sources or reservoirs. The precise length of this lag is unclear, but it may exceed many months, making the detection of transmission events from food or environmental sources challenging. Hence, there is still some uncertainty over whether ExPEC have a food animal reservoir and are disseminated via food. Environmental *E. coli* that resemble the ExPEC causing human extraintestinal infections have been recovered from waterways, sewage, domestic and wild animals, soil and

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other environmental samples; suggesting multiple non-human reservoirs for human ExPEC [3–8]. The human-to-human transmission of genetically closely related or indistinguishable ExPEC between household members and sexual contacts [9,10] has also been demonstrated in several studies; indicating that humans definitely act as reservoirs for ExPEC. The fact that ExPEC may be disseminated along multiple transmission routes is not in dispute; however, the magnitude of the contribution of these various routes is not known. Given that the food-borne route is arguably the biggest contributor to the transmission of enteric *E. coli* pathotypes, defining the existence of food-borne transmission routes for ExPEC is an obvious research need [11,12].

The hypothesis that food, in particular poultry products, may act as a reservoir for human ExPEC is derived from multiple lines of evidence: genetic relationships between avian pathogenic *E. coli* (APEC) (the *E. coli* responsible for extraintestinal infections in birds) and human ExPEC; experimental studies showing the pathogenic potential of APEC in mammalian animal models and the pathogenic potential of human-derived ExPEC in avian animal models; molecular epidemiological data showing close genetic relationships between *E. coli* isolates recovered from human extraintestinal infections, poultry and retail poultry meat (and occasionally pork); and the observation that specific strains of *E. coli*, over short time periods and in specific communities, may cause a disproportionate number of infections (i.e. cryptic outbreaks).

One systematic review has been conducted that addresses the question of potential food-borne transmission of ExPEC, but is focused on extended spectrum β-lactamase (ESBL) -producing ExPEC [13]. In this narrative review, the current evidence for the existence of a poultry reservoir for human ExPEC or food-borne transmission of ExPEC from poultry meat to humans is presented. The review does not focus on antimicrobial-resistant ExPEC *per se*; however, the majority of recent studies have focused on antimicrobial-resistant ExPEC, specifically ESBL-producing *E. coli*. Therefore studies of ESBL-positive ExPEC lineages tend to be over-represented in the literature. This review primarily focuses on the genetic evidence, specifically virulence genotyping, multilocus sequence typing (MLST) designation, pulsed-field gel electrophoresis (PFGE), or other molecular typing methods. The epidemiological challenges related to investigating the food–ExPEC hypothesis and limits to inferring attribution to poultry, are also described.

Extraintestinal pathogenic *E. coli*

Extraintestinal pathogenic *E. coli* are typically defined either by the presence of common virulence factors, including adhesins (e.g. P and S fimbriae), iron-acquisition systems, capsules, and toxins (e.g. haemolysin) [14] or by recovery of an *E. coli* isolate from clinical specimens associated with an extraintestinal infection. Multilocus sequence typing [15], which capitalizes on known sequence variation within a set of housekeeping genes to assign a sequence type (ST), has been the classification method of choice for ExPEC recently. Classification of MLST reflects evolutionary relatedness and *E. coli* population structure. Phylogenetic grouping is another common classification system, where *E. coli* are defined by the A, B1, B2 and D phylogroups [16]; this scheme has recently been expanded to include other pathogroups [17]. ExPEC generally fall into the B2 and D phylogroup categories, whereas groups A and B1 are more often associated with commensal *E. coli*. Finally, as a link to historical studies of *E. coli*, serotyping information is included as part of ExPEC classification, if known. A common nomenclature has emerged that describes ExPEC strains using a combination of Serotype—Phylogroup—Sequence Type, such as *E. coli* O25:H4-B2-ST131; this review will adhere to this ExPEC strain naming convention, or ST designations, whenever possible. Virulence gene profile-based genotyping has been performed in many studies, and is another common method of classifying *E. coli* into similar groups.

There are highly successful lineages or groups, many multidrug-resistant, which are responsible for the majority of human extraintestinal infections [18]. For example, *E. coli* O25:H4-ST131, a globally disseminated strain that has been shown to be responsible for up to 60% of all *E. coli* infections; and accounts for up to 78% of infections caused by fluoroquinolone-resistant and/or ESBL-producing ExPEC [13]. Common human ExPEC STs include: 10, 12, 38, 69, 73, 95, 117, 127, 131, 394, 405 and 1193 (Fig. 1; unpublished data), although the distribution of STs responsible for infections varies by geography [19].

Unlike many of the infections caused by enteric *E. coli* pathotypes, extraintestinal infections caused by *E. coli* are not usually recognized as being the result of a common-source epidemic or outbreak; however, potential community outbreaks of *E. coli* causing UTIs, in addition to other, more severe extraintestinal infections, have been identified in London, UK (O15:K52:H1-D-ST393) (1986), Copenhagen, Denmark (O78:H10-A-ST10) (1988), Berkeley, USA (O11:K52:H18-D-ST69) (1999), Calgary, Canada (2000) and elsewhere [20–24]. However, none of these outbreak investigations have identified the source for the ExPEC implicated in the outbreak.

Previous studies have identified indistinguishable PCR and PFGE patterns, suggesting that unrelated women were colonized and then infected by the same strain of ExPEC. This could occur through person-to-person contact or environmental exposures, but the more likely hypothesis was that there was a

