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Authors

Graham, Jay P
Amato, Heather K
Mendizabal-Cabrera, Renata
et al.

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Review Article

Waterborne Urinary Tract Infections: Have We Overlooked an Important Source of Exposure?

Jay P. Graham,^{1*} Heather K. Amato,¹ Renata Mendizabal-Cabrera,² Danilo Alvarez,² and Brooke M. Ramay^{2,3}

¹Berkeley School of Public Health, University of California Berkeley, Berkeley, California; ²Center for Health Studies, Universidad del Valle de Guatemala, Guatemala City, Guatemala; ³Paul G. Allen School for Global Animal Health, Washington State University Pullman, Pullman, Washington

Abstract. The presence of intestinal pathogenic *Escherichia coli* in drinking water is well recognized as a risk for diarrhea. The role of drinking water in extraintestinal infections caused by *E. coli*—such as urinary tract infections (UTIs)—remains poorly understood. Urinary tract infections are a leading cause of outpatient infections globally, with a lifetime incidence of 50–60% in adult women. We reviewed the scientific literature on the occurrence of uropathogenic *E. coli* (UPEC) in water supplies to determine whether the waterborne route may be an important, overlooked, source of UPEC. A limited number of studies have assessed whether UPEC isolates are present in drinking water supplies, but no studies have measured whether their presence in water may increase UPEC colonization or the risk of UTIs in humans. Given the prevalence of drinking water supplies contaminated with *E. coli* across the globe, efforts should be made to characterize UTI-related risks associated with drinking water, as well as other pathways of exposure.

INTRODUCTION

Urinary tract infections (UTIs) are the second most common infection globally, and an estimated 150 million people are diagnosed with UTIs each year, costing more than six billion U.S. dollars in treatment.^{1,2} In the United States, the CDC estimates that UTIs are responsible for nearly 13,000 deaths every year.³ In addition, uropathogens producing extended spectrum beta-lactamases (ESBLs), and showing resistance to most antimicrobials, are steadily increasing.^{4,5}

Exposure to *Escherichia coli*—a fecal indicator and a key member of the normal intestinal microflora of humans and other mammals—in drinking water, as well as recreational water, has been linked to an elevated risk of carrying enteric pathogens and diarrhea.^{6–8} Much less research, however, has been carried out to identify whether the presence of *E. coli* in water supplies, or the environment where human exposures occur (e.g., recreational water exposures like swimming), may increase the risk for extraintestinal infections, including UTIs. Some highly adapted *E. coli* strains have acquired specific virulence factors that confer an increased capacity to cause a spectrum of intestinal and extraintestinal diseases.⁹

Escherichia coli has the potential to cause three broad categories of infection: enteric infections, UTIs, and sepsis/meningitis.⁹ Infections can be further categorized as intestinal pathogenic *E. coli* (IPEC), and extraintestinal pathogenic *E. coli* (ExPEC), which includes uropathogenic *E. coli* (UPEC) and meningitis-associated *E. coli* (Figure 1).^{10,11} Uropathogenic *E. coli* is the most common etiologic agent of UTIs and causes 68–77% of recurrent UTI infections.¹² There are differences in virulence factors between UPEC and commensal *E. coli*, which make up most of the *E. coli* that populate the gut.

DEFINING UPEC

The features used to classify *E. coli* as UPEC vary significantly. There are likely diverse, complementary groups of

genetic factors that allow *E. coli* to interact with the host, resulting in UTIs. Progress in determining these mechanisms, however, is being made. *Escherichia coli* is often identified by serological typing: H (flagellar), O (lipopolysaccharide), and K (capsular) surface antigens. The O serogroup appears to influence pathogenicity, and it has been identified as a causal agent in most UTIs.¹³ Uropathogenic *E. coli* isolates are typically found in phylogenetic group B2, and to a lesser extent in group D.¹⁴ Although the *E. coli* isolates that cause UTIs are often clonal, there is no single phenotypic profile that defines UPEC isolates, which are completely distinct for their lack of a defined set of genes that distinguish them from non-UPEC isolates.^{15,16} Uropathogenic *E. coli* isolates typically have virulence factors, including adhesins, siderophore systems, toxins, and lipopolysaccharides that enhance their ability to survive outside of the host, colonize humans, and cause infection.¹⁷ Most potential UPEC strains carry these virulence genes, but are able to remain as commensals in our gut.¹⁶ Johnson et al.¹⁵ assessed a diverse set of predictors of virulence in a murine sepsis model and found that various factors—phylogenetic group, clonal complexes, and accessory genes—were important. Studies of putative uropathogenic *E. coli* (pUPEC) in water have typically classified the isolates based on the presence of specific genes or by their sequence type (ST).^{18–22}

We hypothesize that drinking water represents an important source of UPEC (Figure 1), especially in low- and middle-income countries (LMICs), where fecally contaminated drinking water is more prevalent. The application of advanced genotyping methods in these countries is often more limited, and research has likely missed this important pathway of exposure, in contrast to high- and upper-middle-income countries. A growing body of research, primarily in high-income countries, is rapidly building on foodborne UTIs (FUTIs).^{23–28}

To find relevant documents describing the evidence of pUPEC in waters used as sources for drinking or recreation that may cause UTIs or potentially other extraintestinal infections, we searched PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) using the following search terms: (“urinary tract infection” OR “Extraintestinal pathogenic *E. coli*” OR “ExPEC” OR

* Address correspondence to Jay P. Graham, Division of Environmental Health Sciences, University of California, Berkeley School of Public Health, 2121 Berkeley Way West, Rm. 5302, Berkeley, CA 94720. E-mail: jay.graham@berkeley.edu

FIGURE 1. Conceptual illustration of the exposure pathway for waterborne urinary tract infections (WUTIs). *E. coli* includes commensals, intestinal pathogenic *E. coli* (IPEC), and extraintestinal pathogenic *E. coli* (ExPEC), which include meningitis/sepsis-associated *E. coli* (MNEC) and uropathogenic *E. coli* (UPEC), the most common infecting agent in the urinary tract. This figure appears in color at www.ajtmh.org.

“uropathogenic *E. coli*” OR “UPEC”) AND “water.” We also searched the resulting reference lists to identify additional articles.

EVIDENCE OF PUTATIVE UPEC IN WATER

We identified 20 studies of 394 search results that assessed the role of water, or wastewater, as a reservoir of ExPEC or UPEC. The studies which used genotyping methods are summarized in Table 1, and they indicate that fecally contaminated water—mainly surface waters and wastewater—are an important source of UPEC.^{20,29–37} Zhi et al.^{38,39} identified pUPEC by screening wastewater samples from treatment plants in Alberta, Canada, for *E. coli* containing at least three of five UPEC virulence genes. When the researchers compared pUPEC with known UPEC from UTIs from international databases, they found > 96% whole genome similarity; one isolate demonstrated 99.5% genome similarity. In a study of 308 *E. coli* isolates from surface water samples collected from diverse aquatic ecosystems in the United States, researchers used DNA microarray technology and found that most *E. coli* isolates were putative ExPEC pathotypes and belonged to phylogenetic groups B2 and D.²¹ Johnson and others¹⁸ characterized 280 *E. coli* isolates from seven surface water sites and found that 5% of isolates were pExPEC strains. In Japan, researchers studied 531 *E. coli* isolates from the Yamato River and found 58 pExPEC isolates that belonged to lineages of human UPEC (ST95, ST127, ST12, ST14, and ST131).^{40,41} A study of household drinking water in India applied multi-locus sequence typing (MLST) to identify pUPEC; they found four *E. coli* STs, ST648, ST92, STc23, and ST58, that are often found to cause UTIs.²⁰ Similarly, a study of surface water in Georgia used MLST to identify ST131, a common ST associated with UTIs globally, in surface waters.²² In Southeast Queensland, Australia, researchers tested 200 *E. coli* isolates from 22 rainwater tank samples for 20 virulence factors associated with ExPEC; the researchers also classified *E. coli* by their phylogenetic groups. Putative ExPEC were identified in 15 of the 22 tanks based on the prevalence of ExPEC-associated virulence genes.⁴² In a study of constructed wetlands in the United States, researchers examined whether crows were carriers of ExPEC and if wetland roost areas contribute to their spread. The study found that 11.2% of the *E. coli* isolates identified in impacted waters were pExPEC.¹⁹ In India, researchers have studied *E. coli* from coastal estuaries and found that ~16% were pExPEC, and approximately one-third of isolates contained antimicrobial resistance genes.^{43,44} In France, researchers evaluated the prevalence of ExPEC in effluents of a municipal wastewater treatment plant receiving wastewater from a slaughterhouse; ExPEC was more prevalent in city wastewater (8.4%) than in slaughterhouse wastewater (1.2%).⁴⁵ A few studies have used serotyping to identify pUPEC in drinking water and environmental water sources.^{46–48}

Sanitation and hygiene likely play important roles in exposure to fecal pathogens such as UPEC. In some contexts, hands have been found to be a more important pathway of exposure to *E. coli* than water, although no study to date has looked at whether they are potentially UPEC isolates.⁴⁹ Access to improved sanitation and clean water also impact menstrual hygiene management practices, which may affect the risk of UTIs among women.^{50,51} Overall, however, there is a paucity of research investigating the impacts of sanitation and hygiene on exposures to UPEC or the risk of UTIs.

ANTIMICAROBIAL RESISTANCE IN UPEC

Antimicrobial-resistant *E. coli*—many harboring genes that allow them to produce ESBLs and avoid the effects of

TABLE 1

Examples of studies that identified putative uropathogenic *E. coli* (pUPEC) or extraintestinal pathogenic *E. coli* (pExPEC) in water samples based on multi-locus sequence typing or the presence of virulence genes¹⁷

Reference	Country	Source of samples	Virulence genes and their function used to identify pUPEC or pExPEC	Findings
Müller et al. ³⁷	Switzerland	207 <i>E. coli</i> from surface waters, freshwater fish, fresh vegetables, retail poultry meat, fecal samples of livestock, healthy humans, and primary care patients	Iron uptake (<i>fyuA</i> , <i>chuA</i> , and <i>yfcv</i>), toxin (<i>vat</i>), pathogenicity island (PAI), and protectins/serum resistance (<i>traT</i>)	Overlaps in <i>E. coli</i> genotypes were found for some pUPEC isolates from water and humans
Ahmed et al. ⁴²	Australia	200 <i>E. coli</i> from 22 rainwater tanks used for potable and non-potable purposes	Adhesins (<i>bmaE</i> , <i>papG</i> allele II, <i>papG</i> allele III, <i>papAH</i> , <i>papEF</i> , and <i>focG</i>), toxins (<i>cdtBa</i> and <i>cvaC</i>), invasins (<i>ibeA</i>), siderophores (<i>iutA</i>), capsule synthesis (<i>kpsMT</i> allele III and <i>kpsMT</i> allele K1), pathogenicity island (PAI), and protectins/serum resistance (<i>traT</i>)	Fifteen of 22 rainwater tanks were positive for pExPEC
Hamelin et al. ²¹	United States	308 <i>E. coli</i> from surface water collected from two large river systems	P pilus-encoding gene (<i>hlyA</i>); Iron uptake (<i>chuA</i> , <i>fepC</i> , <i>cnf1</i> , <i>irp1</i> , <i>irp2</i> , <i>fyuA</i> , <i>iroN</i> , and <i>usp</i>)	<i>E. coli</i> pathotypes were mostly pExPEC and belonged to phylogenetic groups B2 and D
Rayasam et al. ²⁰	India	104 <i>E. coli</i> from 51 drinking water samples collected from elevated storage reservoirs that are piped to households	STs known to cause UTIs in humans	Nineteen of the <i>E. coli</i> STs (18.3%) belonged to known lineages of human UPEC
Amato et al. ³⁵	United States	337 <i>E. coli</i> from streams draining 15 small watersheds of the Chesapeake Bay	Adhesins (<i>papA</i> , <i>papC</i> , and <i>afaC</i>), siderophores (<i>iutA</i>), and capsule synthesis (<i>kpsMII</i>)	Fifty-six isolates (17%) were pExPEC
Sen et al. ¹⁹	United States	134 <i>E. coli</i> from wetlands contaminated by corvids	Siderophores (<i>iutA</i> , <i>iroN</i> , and <i>iutA</i>), capsule synthesis (<i>iss</i> , <i>kpsMTII</i> , and <i>traT</i>), adhesins (<i>papEF</i> , <i>papA/C</i> , <i>papG</i> , <i>sfa/foc</i> , and <i>afa/dra</i>), toxins and hemolysins (<i>cnf1</i> , <i>stx1</i> , <i>stx2</i> , <i>hlyA</i> , and <i>hlyF</i>), and invasion (<i>ibeA</i>)	Fifteen of 134 isolates (11.2%) were pExPEC
Cho et al. ²²	United States	34 Antimicrobial-resistant <i>E. coli</i> identified from a mixed-use watershed	STs known to cause UTIs in humans	Three of the 34 isolates were ST131, which are known lineages of human UPEC
Divya et al. ⁴³	India	300 <i>E. coli</i> from tropical estuarine water	Adhesins (<i>papAH</i> , <i>papC</i> , and <i>sfa/foc</i>), capsule synthesis (<i>kpsMT II</i>), and siderophore (<i>iutA</i>)	Forty-nine isolates (16.3%) were pExPEC, and approximately 34.6% of those isolates had antibiotic-resistant genes
Johnson et al. ¹⁸	United States	280 <i>E. coli</i> from seven surface water sites	Type 1 fimbriae (<i>fimA</i>), hemolysin (<i>hlyD</i>), P fimbriae (<i>papAH</i> and <i>papC</i>), S and F1C fimbriae (<i>sfa/focDE</i>), Dr-binding adhesins (<i>afa/draBC</i>), group 2 capsule (<i>kpsM II</i>), and aerobactin system (<i>iutA</i>)	Twenty-six isolates (5%) fulfilled the molecular criteria for pExPEC
Gomi et al. ⁴⁰	Japan	531 <i>E. coli</i> isolates obtained from Yamato River	STs known to cause UTIs in humans	Among 58 pExPEC isolates, several lineages of human UPEC were found (ST95, ST127, ST12, ST14, and ST131)
Franz et al. ⁵³	Netherlands	170 ESBL-producing <i>E. coli</i> from Dutch wastewater (<i>n</i> = 82) and surface water (<i>n</i> = 88)	Afimbril adhesion (<i>afa</i>), F1C fimbriae (<i>focG</i>), cytolytic protein toxin (<i>hlyD</i>), iron acquisition system (<i>iutA</i>), group 2 polysaccharide capsule (<i>kpsMII</i>), P fimbriae (<i>papA</i>), and S fimbriae (<i>sfaS</i>)	Fifteen of the ESBL-producing <i>E. coli</i> (8.8%) were pExPEC
Diallo et al. ⁴⁵	France	1,248 <i>E. coli</i> from effluents of a municipal wastewater treatment plant receiving wastewater from a slaughterhouse	S and F1C fimbriae (<i>sfa/focDE</i>), group 2 capsule (<i>kpsMT K10</i>), hemolysin (<i>hlyA</i>), P fimbriae (<i>papEF</i>), adhesins (<i>afa/draBC</i>), toxins, and hemolysins (<i>clbN</i> , <i>f17A</i> , and <i>cnf</i>)	ExPEC was significantly higher in city wastewater (8.4%) than in slaughterhouse wastewater (1.2%)
Anastasi et al. ³⁶	Australia	264 <i>E. coli</i> isolates collected from 129 receiving water sites in a 20-km radius surrounding sewage treatment plants	P fimbriae (<i>papAH</i> , <i>papEF</i> , and <i>papC</i>), siderophore (<i>iroN_{E.coli}</i>), toxins, and hemolysins (<i>cnf1</i> , <i>hlyA</i> , <i>eltA</i> , <i>estII</i> , <i>eaeA</i> , <i>stx1</i> , and <i>stx2</i>)	ExPEC virulence genes were found in 11% of the 15 most common <i>E. coli</i> types identified

E. coli = *Escherichia coli*; ESBL = extended spectrum beta-lactamases; ST = sequence type; UTI = urinary tract infections.

third-generation cephalosporins—have been identified in different sources of drinking water, including drinking water in high-income countries.^{30–32,52} In studies of pUPEC in environmental water samples, antimicrobial resistance genes, including ESBL genes, have been identified.³⁸ Rayasam et al.²⁰ found that six of 19 pUPEC were resistant to more than three classes of antimicrobial agents. Hamelin et al.²¹ found that the river sampling site most impacted by urban municipal wastewater also had a higher prevalence of pUPEC-carrying antimicrobial-resistant genes. A study of ESBL-producing *E. coli* from Dutch wastewater ($n = 82$) and surface water ($n = 88$) found that 8.8% of the 170 isolates studied were pExPEC.⁵³ A study of 22 environmental ESBL-producing *E. coli* found that six of the isolates were able to colonize bladder cells.⁵⁴

CONCLUSION

Defining the features that make up UPEC in a local geographic context or for a specific population will be an important step forward. Research that studies a combination of factors (e.g., phylogenetic group, clonal complex, and accessory genes) will be needed, and next-generation sequencing will be essential for assessing the role of fecally contaminated water, or fecally contaminated environments, in cases of human UTIs. Given rapid changes in circulating *E. coli* clones, human and nonhuman host factors, and resistance phenotypes, our ability to predict what features define UPEC will remain a challenge. As noted earlier, UPEC belongs to a wide variety of serogroups and STs, and may consist of a large variety of virulence factors. Future studies will need to identify the STs, serogroups, phylogenetic groups, and virulence genes associated with UTIs in local contexts to understand the full landscape of UPEC's defining features. Furthermore, a local set of multiplex panels could be used to understand the relationship between water quality and UTIs.

This report highlights a need to investigate the occurrence of pUPEC in drinking water sources to better understand the importance of waterborne UTIs (WUTIs). Given that antimicrobial resistance is predicted to reverse decades of progress in increasing longevity around the world,⁵⁵ research of WUTIs should test for susceptibility to antimicrobials in assessments of pUPEC. Research has shown the spread of clonal groups of multidrug-resistant *E. coli* linked to the food supply that cause UTIs in the United States.⁵⁶ Similar to research that is clarifying FUTIs,^{23,27,57} we suggest that a similar effort is needed for WUTIs. Drinking water across the globe is commonly contaminated with *E. coli*, and this pathway deserves more focused investigation. Studies that integrate spatiotemporally matched samples of drinking water and human fecal or urine carriage of pUPEC would provide initial evidence to estimate risks associated with exposures to contaminated drinking water. In addition, case-control studies of UTIs that assess UPEC isolates in both human cases (i.e., urine samples) and pUPEC in household drinking water will clarify the importance of UPEC in drinking water as a risk factor for UTIs in humans.⁵⁰ This study design has been used to characterize the role of domestic animals in pediatric enteric diseases.⁵⁸ Advanced molecular methods will be essential for characterizing the genotypic relationships of pUPEC in drinking water and UPEC in humans to elucidate mechanisms of transmission and host invasion pathways. Studies should also consider the effects of

sanitation and hygiene on UPEC in drinking water and UTIs. Conducting this research in areas where water supplies are unimproved or poorly managed, such as LMICs, will be important to understand the burden of disease and would likely facilitate gaining a better understanding of this exposure pathway. Even if a small fraction of UTIs or other extraintestinal infections—especially drug-resistant ones—are from contaminated drinking water, the relevance of this exposure to the global burden of disease will likely be substantial, and may generate additional support for efforts that aim to reduce exposures to fecal contamination from drinking water supplies and poor sanitation and hygiene.⁵⁹

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Authors' addresses: Jay P. Graham and Heather K. Amato, Division of Environmental Health Sciences, UC Berkeley School of Public Health, Berkeley, CA, E-mails: jay.graham@berkeley.edu and heather_amato@berkeley.edu. Renata Mendizabal-Cabrera, Centro de Estudios en Salud, Universidad del Valle de Guatemala, Guatemala City, Guatemala, E-mail: rmendizabal@ces.uvg.edu.gt. Danilo Alvarez, Centro de Estudios en Salud, Instituto de Investigaciones, Universidad del Valle de Guatemala, Guatemala City, Guatemala, E-mail: dalvarez@ces.uvg.edu.gt. Brooke M. Ramay, Instituto de Investigaciones Ciudad de Guatemala, Centro de Estudios en Salud, Universidad del Valle de Guatemala, Guatemala City, Guatemala, and The Paul G. Allen School for Global Animal Health, Washington State University Pullman, Center for Health Studies, Guatemala City, Guatemala, E-mail: bramay@uvg.edu.gt.

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