Exploring potential risk factors for the asymptomatic intestinal carriage of ciprofloxacin-resistant uropathogenic *Escherichia coli*

Victoria Bowers

A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington
2022

Committee:
Paul A. Fishman
Evgeni V. Sokurenko

Program Authorized to Offer Degree:
Health Systems and Population Health

©Copyright 2022
Victoria Bowers

University of Washington

Abstract

Exploring potential risk factors for the asymptomatic intestinal carriage of ciprofloxacin-resistant uropathogenic *Escherichia coli*

Victoria Bowers

Chair of the Supervisory Committee:

Paul A. Fishman

Department of Health Systems and Population Health

This retrospective cohort study analyzed data collected under a larger parent study, the CLUE study in the Sokurenko laboratory at the University of Washington, to explore risk factors for the asymptomatic intestinal carriage of ciprofloxacin-resistant *Escherichia coli* (*E.coli*) (CipRE). This study included 1719 women aged 50 and older within the Kaiser Permanente Washington health system. Odds ratios (OR) and confidence intervals (CIs) from unadjusted and age-adjusted logistic regression models were used to explore the relationship between CipRE carriage and metabolic conditions, mood disorders and gastrointestinal conditions. Metabolic conditions were associated with CipRE carriage in the unadjusted (OR 1.42, 95% CI 1.07-1.89) and adjusted (OR 1.42, 95% CI 1.05-1.92) model. Gastrointestinal conditions were also associated with CipRE carriage in the unadjusted (OR 1.48, 95% CI 1.05-2.06) and adjusted (OR 1.47, 95% CI 1.04-2.06) model. Metabolic conditions were associated with two virulent CipRE sequence types, ST131-H30 and ST1193, in the unadjusted (OR 1.51, 95% CI 1.04-2.22) and adjusted (OR 1.50, 95% CI 1.01-2.26) model.

Abstract

Intro: This retrospective cohort study analyzed data collected under a larger parent study, the CLUE study in the Sokurenko laboratory at the University of Washington, to explore potential risk factors for the asymptomatic intestinal carriage of ciprofloxacin-resistant uropathogenic *Escherichia coli* (*E.coli*) (CipRE), as this carriage may increase the risk for acquiring ciprofloxacin-resistant urinary tract infections. This study included 1719 women aged 50 and older within the Kaiser Permanente Washington (KPWA) health system.

Methods: Odds ratios (OR) and confidence intervals (CIs) from unadjusted and age-adjusted logistic regression models were used to explore the relationship between CipRE carriage and clinical status groups which were mood disorders, metabolic conditions and gastrointestinal conditions. The two outcomes explored were the carriage of any type of CipRE (AnyCipRE), and the carriage of either of two CipRE sequence types (ST) known to be associated with high extraintestinal virulence, ST131-H30 and ST1193 (STCipRE).

Results: The average age of participants was 67.3 ± 9.8 years (range = 50-98). The prevalence of AnyCipRE carriage was 13.7% (236 cases, 1483 non-cases) and the prevalence of STCipRE carriage was 7.3% (125 cases, 1594 non-cases). Among all participants, 30%, 53% and 18% had a clinical status relating to mood, metabolic and gastrointestinal conditions, respectively. Among those with AnyCipRE, the average age of participants was 67.9 ± 9.8 years (range = 50-98), and 30%, 61% and 23% of participants had a clinical status relating to mood, metabolic and gastrointestinal conditions, respectively. A clinical status relating to metabolic conditions was associated with AnyCipRE carriage in both the unadjusted (OR 1.42, 95% CI 1.07-1.89; *P* = .015) and age-adjusted (OR 1.42, 95% CI 1.05-1.92; *P* = .022) model. A clinical status relating to gastrointestinal conditions was also associated with AnyCipRE carriage in both the unadjusted (OR 1.48, 95% CI 1.05-2.06; *P* = .024) and age-adjusted (OR 1.47, 95% CI 1.04-

2.06; *P* = .025) model. Among those with STCipRE carriage, the average age of participants was 68.1 ± 9.9 years (range = 50-98), and 30%, 62% and 22% of participants had a clinical status relating to mood, metabolic and gastrointestinal conditions, respectively. A clinical status relating to metabolic conditions was associated with STCipRE carriage in both the unadjusted (OR 1.51, 95% CI 1.04-2.22; *P* = .032) and age-adjusted (OR 1.50, 95% CI 1.01-2.26; *P* = .046) model.

Discussion: Within this study population, there is evidence to suggest a potential association between the carriage of ciprofloxacin-resistant *E.coli* and a clinical status relating to metabolic and gastrointestinal conditions. There is also evidence to suggest a potential association between a clinical status relating to metabolic conditions and the carriage of two ciprofloxacin-resistant *E.coli* sequence types known to be associated with high extraintestinal virulence, ST131-H30 and ST1193. More large-scale studies are needed to explore the asymptomatic carriage of multidrug-resistant *E.coli* so we may be more proactive in the prevention, prediction and treatment of multidrug-resistant urinary tract infections.

Background

Uropathogenic *Escherichia coli* (*E.coli*) are the primary causative agents of urinary tract infections (UTIs), one of the most common infections found in both the inpatient and outpatient setting.[1,2] If left untreated, or if initial antibiotic therapies fail, UTIs can become complicated by spreading to the kidneys (pyelonephritis) and bloodstream (urosepsis), generally requiring hospital admission.[3-5] UTIs cost the U.S. healthcare system between 3-6 billion dollars per year,[6,7] with costs rising as antibiotic resistance increases.[8] UTIs place a particular burden on women, with 50-60% of all women experiencing at least one UTI in their lifetime, and nearly 30% experiencing more than one UTI per year.[9] Pregnant and elderly women are at increased risk for complications, as UTIs are associated with preterm birth[10-12] and increase in incidence

after menopause.[13] In addition to medical concerns, UTIs significantly reduce the emotional and mental wellbeing of women suffering from them.[14-17]

First-line antibiotic treatment for UTIs includes nitrofurantoin, fosfomycin and trimethoprim-sulfamethoxazole.[18] Ciprofloxacin, a fluoroquinolone, is reserved for more complicated UTIs due to increasing levels of ciprofloxacin resistance, as well as concern over its risks, which include tendon rupture, aortic aneurysm and increased risk for *Clostridioides difficile* infection.[19] Despite concerns, research indicates ciprofloxacin is still overprescribed for the treatment of uncomplicated UTIs.[20]

Since the late 1990s and early 2010's, two sequence types (ST) of fluoroquinolone-resistant *E.coli* have emerged at pandemic levels, ST131-H30 and ST1193, respectively.[21] These sequence types are particularly uropathogenic as they possess extraintestinal virulence factors, which enable them to colonize the urinary tract more easily than other ciprofloxacin-resistant *E.coli* sequence types.[22-24] Importantly, ST131-H30 is associated with older age and immunocompromised status.[25,26] Compared to other fluoroquinolone-resistant clones, both have been shown to persist in the intestinal tract for longer periods of time and have been shown to colonize the urinary tract at much higher rates.[27,28]

Recent research indicates nearly 9% of women within the Kaiser Permanente Washington (KPWA) health system are asymptomatic intestinal carriers of ciprofloxacin-resistant *E.coli,* with a significant proportion of that *E.coli* belonging to the ST131-H30 and ST1193 groups.[25] This carriage may increase the risk for acquiring a ciprofloxacin-resistant UTI, which poses a few questions: Who is at risk for this carriage? How should the health system address this? To add to the limited knowledge base, we explore this issue as our health system works to be more

proactive in the prevention, prediction and treatment of multidrug-resistant urinary tract infections.

Methods

Study Setting and Study Design:

This retrospective cohort study was conducted under a larger parent study, the CLUE study, which was a collaboration between the Kaiser Permanente Washington Research Institute and the Sokurenko laboratory in the Department of Microbiology at the University of Washington. Electronic health record (EHR) data from women within the Kaiser Permanente Washington (KPWA) health system were analyzed. The CLUE study was approved by the Institutional Review Boards of the University of Washington and Kaiser Permanente Washington Research Institute, and this study was approved by the Institutional Review Boards of the University of Washington.

Study Population:

This study explored EHR data obtained from 1719 women aged 50 and older within the KPWA health system. For inclusion, participants had to be enrolled at KPWA for at least one year, could not have been diagnosed with a urinary tract infection, or taken oral antibiotics one year prior to sample submission.

Data Collection:

The CLUE study obtained urine and fecal samples from 1822 women between May 2021 and February 2022. These samples were analyzed for the presence of ciprofloxacin-resistant *E.coli*, including specific *E.coli* sequence types (ST). Only data from participant fecal samples were included in this study. Diagnosis and prescription data were obtained for each participant from KPWA's EHR. This data included any diagnosis or prescription recorded for each participant

within one year prior to their date of sample submission. Dummy variables were added for participants with a prescription record but no diagnosis record, and vice versa. Participants found to have neither record were excluded. These data were checked to ensure participants were not prescribed an oral antibiotic or diagnosed with a urinary tract infection or acute cystitis one year prior to sample submission. Participants with records indicating a violation of this criteria were excluded. The diagnosis data were synthesized based on the 10th revision of the International Classification of Disease (ICD-10) codes.

Statistical Analyses:

Summary statistics

Mean, standard deviation and range are reported for participant ages. Counts and percentages are reported for the prevalence of ciprofloxacin-resistant *E.coli* carriage among participants. Counts and percentages are also reported for the distribution of participants among age and clinical status groups. Chi-square tests were used to test for significance between ciprofloxacin-resistant *E.coli* carriage and age and clinical status groups. The Student's t-test was used to test for significance between the mean age of participants with and without ciprofloxacin-resistant *E.coli* carriage.

Logistic regression

Odds ratios (OR) and confidence intervals (CIs) from unadjusted and age-adjusted logistic regression models were used to explore the relationship between clinical status groups and CipRE carriage. Potential confounders were identified based on literature review and clinical relevance. Older age is associated with ciprofloxacin-resistant *E.coli* carriage, so it was included in the age-adjusted logistic regression model.[25] The predictor variables were three clinical status groups indicated by the literature to have an association with intestinal microbiome disruption, as this disruption may increase the likelihood of harboring antibiotic-resistant bacteria.[29-31]

These clinical status groups were metabolic conditions, mood disorders and gastrointestinal conditions (Supplementary Material, Table 1). Participants were included in a clinical status group if they were diagnosed with, or were prescribed a prescription relevant to, a condition contained within the group one year prior to sample submission (Supplementary Material, Table 2). Clinical status groups were conceptually evaluated for multicollinearity prior to model inclusion. The two outcomes of interest were the carriage of any type of CipRE (AnyCipRE) and the carriage of either of two CipRE sequence types known to be associated with extraintestinal virulence, ST131-H30 and ST1193 (STCipRE). Statistical significance was determined using a p-value threshold of $p<0.05$. All analyses were conducted using R-4.1.2 and Real Statistics Resource Pack for Excel Release 8.2.

Results

Summary statistics

Tables 1 and 2 report summary statistics. The average age of participants was 67.3 ± 9.8 years (range = 50-98). The prevalence of AnyCipRE carriage was 13.7% (236 cases, 1483 non-cases) and the prevalence of STCipRE carriage was 7.3% (125 cases, 1594 non-cases). Among all participants, 30%, 53% and 18% had a clinical status relating to mood, metabolic and gastrointestinal conditions, respectively. Among those with AnyCipRE carriage, the average age of participants was 67.9 ± 9.8 years (range = 50-98), and 30%, 61% and 23% of participants had a clinical status relating to mood, metabolic and gastrointestinal conditions, respectively. Among those with STCipRE carriage, the mean age was 68.1 ± 9.9 years (range =50-98), and 30%, 62% and 22% of participants had a clinical status relating to mood, metabolic and gastrointestinal conditions, respectively.

No statistically significant difference was found between the mean age of participants with and without AnyCipRE carriage (P = .251), nor between the mean age of participants with and

without STCipRE carriage (*P* = .334). Chi-square tests of independence indicated an association between CipRE carriage and clinical status groups relating to metabolic (P=.008) and gastrointestinal (*P* = .012) conditions, but not between CipRE carriage and the clinical status group relating to mood disorders (*P* = .897). Chi-square tests of independence also indicated an association between between STCipRE carriage and the clinical status group relating to metabolic conditions (*P* = .023), but not between STCipRE carriage and clinical status groups relating to mood disorders (*P* = .864) or gastrointestinal conditions (*P* = .135).

Logistic regression

Tables 3 and 4 report results from the logistic regression models. A clinical status relating to mood disorders was not associated with AnyCipRE carriage in the unadjusted (OR 0.93, 95% CI 0.68-1.26; *P* = .644) or age-adjusted model (OR 0.93, 95% CI 0.68-1.26; *P* = .646). However, a clinical status relating to metabolic conditions was associated with AnyCipRE carriage in both the unadjusted (OR 1.42, 95% CI 1.07-1.89; *P* = .015) and age-adjusted (OR 1.42, 95% CI 1.05-1.92; *P* = .022) model. A clinical status relating to gastrointestinal conditions was also associated with AnyCipRE carriage in both the unadjusted (OR 1.48, 95% CI 1.05-2.06; *P* = .024) and age-adjusted (OR 1.47, 95% CI 1.04-2.06; *P* = .025) model.

A clinical status relating to mood disorders was not associated with STCipRE carriage in the unadjusted (OR 0.95, 95% CI 0.63-1.41; *P* = .804) or age-adjusted (OR 0.95, 95% CI 0.63-1.41; *P* = .808) model. A clinical status relating to gastrointestinal disorders was also not associated with STCipRE carriage in the unadjusted (OR 1.33, 95% CI 0.84-2.06; *P* = .208) or age-adjusted (OR 1.33, 95% CI 0.83-2.06; *P* = .215) model. However, a clinical status relating to metabolic conditions was associated with STCipRE carriage in both the unadjusted (OR 1.51, 95% CI 1.04-2.22; *P* = .032) and age-adjusted (OR 1.50, 95% CI 1.01-2.26; *P* = .046) model.

Discussion

Within this study population, there is evidence to suggest a potential association between ciprofloxacin-resistant *E.coli* carriage and a clinical status relating to metabolic and gastrointestinal conditions. There is also evidence to suggest a potential association between a clinical status relating to metabolic conditions and the carriage of two ciprofloxacin-resistant *E.coli* sequence types associated with extraintestinal virulence, ST131-H30 and ST1193.

Importantly, the clinical status groups explored in this study contained several prescriptions and diagnoses relevant to each clinical status. One limitation this poses is that participants may have been prescribed a medication that is relevant to a certain condition without actually having that condition. For example, the medication Tofacitinib is prescribed for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis. This prescription was included in the clinical status group for gastrointestinal conditions due to its use for ulcerative colitis. However, study participants may have been captured within this group despite being prescribed Tofacitinib for conditions other than ulcerative colitis. To address this, future research could explore the association between CipRE carriage and specific medications or diagnoses, or incorporate methods to ensure there is a one-to-one match between a patient being diagnosed with a condition and being prescribed a medication specifically for that condition.

Additionally, participants were included in a clinical status group if their EHR indicated they were prescribed a medication or diagnosed with a condition relevant to the clinical status group on a first-instance basis. Future research may consider taking a volumetric approach to explore if prescription dose, length of time taking a prescription, or length of time having a medical condition influences CipRE carriage.

While this study did not collect data on sociodemographic characteristics other than age, future research may also consider controlling for additional variables associated with increased exposure to antibiotics and antibiotic-resistant bacteria. One such variable could be occupational status, with research showing both health care and meat industry workers have a higher risk of being colonized with drug-resistant pathogens than the general population.[32-34]

Notably, prescription data provided by KPWA (Figure 1) reveals the percentage of fluoroquinolones prescribed within the KPWA health system has been decreasing over the last five years. Additional research is needed, but this phenomenon may corroborate research indicating the intestinal acquisition of fluoroquinolone-resistant *E.coli* may occur even in the absence of antibiotic consumption.[25] If so, this phenomenon may pose a threat to one of the primary levers we have in mitigating antibiotic resistance - that of reducing antibiotic consumption through antibiotic stewardship.

Questions remain as to how our health system should address the asymptomatic intestinal carriage of fluoroquinolone-resistant *E.coli*. Screening and treating patients for the asymptomatic carriage of pathogens is not a new practice within the U.S. health system. To reduce the risk of postoperative infection, it is common for hospitals to screen and treat patients for the asymptomatic carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) prior to certain procedures or surgeries.[35,36] Future studies are needed to explore if similar screening protocols may improve our ability to predict who may be at risk for acquiring fluoroquinolone-resistant UTIs. This may be of particular importance for patients undergoing procedures associated with UTIs, such as catheterization.[37] Ultimately, by improving our ability to predict fluoroquinolone-resistant UTIs, we may more promptly resolve acute UTIs and reduce unnecessary patient exposure to the risks associated with ciprofloxacin. This reduction in

inappropriate or unnecessary antibiotic prescriptions may also protect population health, as antibiotics are a societal medication - their prescription for one ultimately impacts all.

Tables and Figures

Table 1. CipRE carriage summary statistics

Age	**Have CipRE N=236 (14%)**	**Do not have CipRE N=483 (86%)**	**Total N=1719**	**P-value**
Age (continuous)	Mean = 67.9 SD = 9.8 Range = 50-98	Mean = 67.2 SD = 9.7 Range = 50-97	Mean = 67.3 SD = 9.8 Range = 50-98	0.2508
50-59	48 (20)	365 (25)	413 (24)	0.6173
60-69	82 (35)	520 (35)	602 (35)	
70-79	78 (33)	434 (29)	512 (30)	
80-89	24 (10)	140 (9)	164 (10)	
90-99	4 (2)	24 (2)	28 (2)	
<65	85 (36)	615 (41)	700 (41)	0.1133
≥65	151 (64)	868 (59)	1019 (59)	
Clinical status				
Mood disorder	71 (30)	440 (30)	511 (30)	0.8969
Metabolic condition	143 (61)	761 (51)	904 (53)	**0.0080**
Gastrointestinal condition	55 (23)	246 (17)	301 (18)	**0.0117**

P-value for Chi-square or Student's t-test
Bold values indicate statistical significance ($p < 0.05$)
SD = standard deviations

Table 2. STCipRE summary statistics

Age	**Have ST131-H30 or ST1193 N=125 (7%)**	**Do not have ST131-H30 or ST1193 N=1594 (93%)**	**Total N=1719**	**P-value**
Age (continuous)	Mean = 68.1 SD = 9.9 Range = 50-98	Mean = 67.2 SD = 9.7 Range = 50-97	Mean = 67.3 SD = 9.8 Range = 50-98	0.3340
50-59	27 (22)	386 (24)	413 (24)	0.8752
60-69	43 (34)	559 (35)	602 (35)	
70-79	38 (30)	474 (30)	512 (30)	
80-89	15 (12)	149 (9)	164 (10)	
90-99	2 (2)	26 (2)	28 (2)	
<65	43 (34)	657 (41)	700 (41)	0.1352
≥65	82 (66)	937 (59)	1019 (59)	
Clinical status				
Mood disorder	38 (30)	473 (30)	511 (30)	0.8642
Metabolic condition	78 (62)	826 (52)	904 (53)	**0.0225**
Gastrointestinal condition	28 (22)	273 (17)	301 (18)	0.1352

P-value for Chi-square test or Student's t-test
Bold values indicate statistical significance ($p < 0.05$)
SD = standard deviations

Table 3. Association between CipRE carriage and clinical status groups

Clinical status	Cases (N=236)	Non-cases (N=1483)	Unadjusted OR (95% CI)	P-value	Adjusted* OR (95% CI)	P-value
Mood disorder	71	440	0.93 (0.68 - 1.26)	0.6444	0.93 (0.68 - 1.26)	0.6456
Metabolic condition	143	761	1.42 (1.07 - 1.89)	**0.0151**	1.42 (1.05 - 1.92)	**0.0220**
Gastrointestinal condition	55	246	1.48 (1.05 - 2.06)	**0.0237**	1.47 (1.04 - 2.06)	**0.0248**

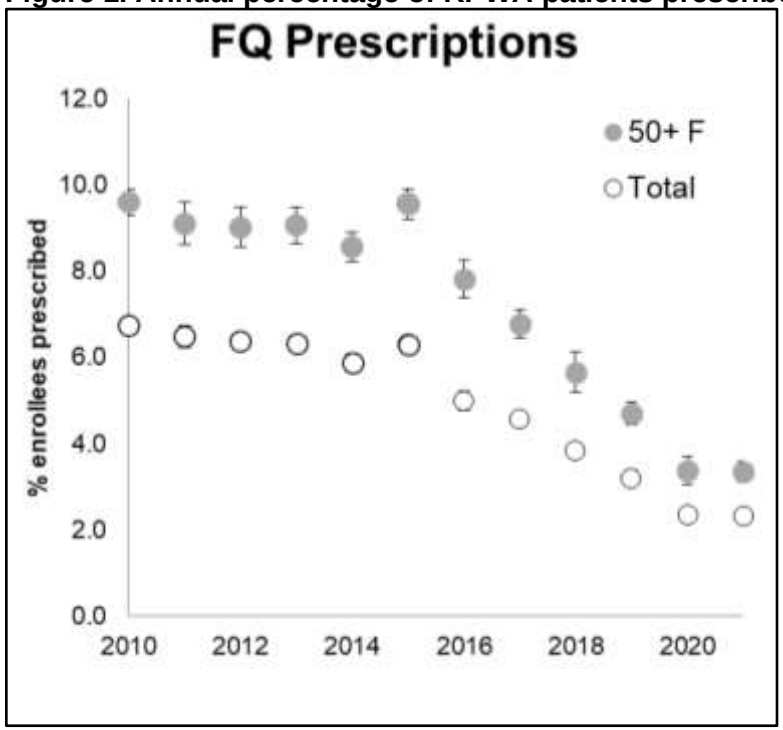
*Adjusted for age
Bold values indicate statistical significance ($p < 0.05$)

Table 4. Association between STCipRE carriage and clinical status groups

Clinical status	Cases (N=125)	Non-cases (N=1594)	Unadjusted OR (95% CI)	P-value	Adjusted* OR (95% CI)	P-value
Mood disorder	38	473	0.95 (0.63 - 1.41)	0.8044	0.95 (0.63 - 1.41)	0.8078
Metabolic condition	78	826	1.51 (1.04 - 2.22)	**0.0322**	1.50 (1.01 - 2.26)	**0.0456**
Gastrointestinal condition	28	273	1.33 (0.84 - 2.06)	0.2084	1.33 (0.83 - 2.06)	0.2151

*Adjusted for age
Bold values indicate statistical significance ($p < 0.05$)

Figure 1. Annual percentage of KPWA patients prescribed fluoroquinolones (2010-2021)



Per random annual sample of 10,000 KPWA patients
Data provided and analyzed by KPWA

References

1. Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. *Ther Adv Urol*. 2019;11:1756287219832172. Published 2019 May 2. doi:10.1177/1756287219832172

2. Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA; Healthcare Infection Control Practices Advisory Committee. Guideline for prevention of catheter-associated urinary tract infections 2009. *Infect Control Hosp Epidemiol.* 2010;31(4):319-326. doi:10.1086/651091

3. Zilberberg MD, Nathanson BH, Sulham K, Shorr AF. Descriptive Epidemiology and Outcomes of Hospitalizations With Complicated Urinary Tract Infections in the United States, 2018. *Open Forum Infect Dis.* 2022;9(1):ofab591. Published 2022 Jan 10. doi:10.1093/ofid/ofab591

4. Colgan R, Williams M, Johnson JR. Diagnosis and treatment of acute pyelonephritis in women. *Am Fam Physician*. 2011;84(5):519-526.

5. Simmering JE, Tang F, Cavanaugh JE, Polgreen LA, Polgreen PM. The Increase in Hospitalizations for Urinary Tract Infections and the Associated Costs in the United States, 1998-2011. *Open Forum Infect Dis*. 2017;4(1):ofw281. Published 2017 Feb 24. doi:10.1093/ofid/ofw281

6. McCann E, Sung AH, Ye G, Vankeepuram L, Tabak YP. Contributing Factors to the Clinical and Economic Burden of Patients with Laboratory-Confirmed Carbapenem-Nonsusceptible Gram-Negative Urinary Tract Infections. *Clinicoecon Outcomes Res*. 2020;12:191-200. Published 2020 Apr 8. doi:10.2147/CEOR.S234840

7. Carreno JJ, Tam IM, Meyers JL, Esterberg E, Candrilli SD, Lodise TP Jr. Corrigendum to: Longitudinal, Nationwide, Cohort Study to Assess Incidence, Outcomes, and Costs Associated With Complicated Urinary Tract Infection. *Open Forum Infect Dis*. 2020;7(1):ofz536. Published 2020 Jan 13. doi:10.1093/ofid/ofz536

8. Dadgostar P. Antimicrobial Resistance: Implications and Costs. *Infect Drug Resist*. 2019;12:3903-3910. Published 2019 Dec 20. doi:10.2147/IDR.S234610

9. Medina M, Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Ther Adv Urol. 2019;11:1756287219832172. Published 2019 May 2. doi:10.1177/1756287219832172

10. Baer RJ, Nidey N, Bandoli G, et al. Risk of Early Birth among Women with a Urinary Tract Infection: A Retrospective Cohort Study. *AJP Rep*. 2021;11(1):e5-e14. doi:10.1055/s-0040-1721668

11. Qobadi M, Dehghanifirouzabadi A. Urinary Tract Infection (UTI) and Its Association With Preterm Labor: Findings From the Mississippi Pregnancy Risk Assessment Monitoring System (PRAMS), 2009–2011, *Open Forum Infectious Diseases*, Volume 2, Issue suppl_1, December 2015, 1577, https://doi.org/10.1093/ofid/ofv133.1129
12. Werter DE, Schneeberger C, Mol BWJ, et al. The Risk of Preterm Birth in Low Risk Pregnant Women with Urinary Tract Infections [published online ahead of print, 2021 Nov 10]. *Am J Perinatol*. 2021;10.1055/s-0041-1739289. doi:10.1055/s-0041-1739289

13. Caretto M, Giannini A, Russo E, Simoncini T. Preventing urinary tract infections after menopause without antibiotics. *Maturitas*. 2017;99:43-46. doi:10.1016/j.maturitas.2017.02.004

14. Ellis AK, Verma S. Quality of life in women with urinary tract infections: is benign disease a misnomer?. *J Am Board Fam Pract*. 2000;13(6):392-397. doi:10.3122/15572625-13-6-392

15. Alanazi MQ. Evaluation of Health-Related Quality of Life in Women with Community-Acquired Urinary Tract Infections Using the EQ-5D-3L in Saudi Arabia. *Patient Prefer Adherence*. 2020;14:2419-2426. Published 2020 Dec 4. doi:10.2147/PPA.S277367

16. Eriksson I, Gustafson Y, Fagerström L, Olofsson B. Do urinary tract infections affect morale among very old women?. *Health Qual Life Outcomes*. 2010;8:73. Published 2010 Jul 22. doi:10.1186/1477-7525-8-73

17. Ernst EJ, Ernst ME, Hoehns JD, Bergus GR. Women's quality of life is decreased by acute cystitis and antibiotic adverse effects associated with treatment. *Health Qual Life Outcomes*. 2005;3:45. Published 2005 Jul 27. doi:10.1186/1477-7525-3-45

18. Chu CM, Lowder JL. Diagnosis and treatment of urinary tract infections across age groups. *Am J Obstet Gynecol*. 2018;219(1):40-51. doi:10.1016/j.ajog.2017.12.231

19. Baggio D, Ananda-Rajah MR. Fluoroquinolone antibiotics and adverse events. *Aust Prescr*. 2021;44(5):161-164. doi:10.18773/austprescr.2021.035

20. Durkin MJ, Keller M, Butler AM, et al. An Assessment of Inappropriate Antibiotic Use and Guideline Adherence for Uncomplicated Urinary Tract Infections. *Open Forum Infect Dis*. 2018;5(9):ofy198. Published 2018 Aug 10. doi:10.1093/ofid/ofy198

21. Tchesnokova VL, Rechkina E, Larson L, et al. Rapid and Extensive Expansion in the United States of a New Multidrug-resistant Escherichia coli Clonal Group, Sequence Type 1193. *Clin Infect Dis*. 2019;68(2):334-337. doi:10.1093/cid/ciy525

22. Kim B, Kim JH, Lee Y. Virulence Factors Associated With *Escherichia coli* Bacteremia and Urinary Tract Infection. *Ann Lab Med*. 2022;42(2):203-212. doi:10.3343/alm.2022.42.2.203

23. Can F, Kurt-Azap Ö, İspir P, et al. The clinical impact of ST131 H30-Rx subclone in urinary tract infections due to multidrug-resistant Escherichia coli. *J Glob Antimicrob Resist*. 2016;4:49-52. doi:10.1016/j.jgar.2015.10.006

24. Johnson TJ, Elnekave E, Miller EA, et al. Phylogenomic Analysis of Extraintestinal Pathogenic *Escherichia coli* Sequence Type 1193, an Emerging Multidrug-Resistant Clonal Group. *Antimicrob Agents Chemother*. 2018;63(1):e01913-18. Published 2018 Dec 21. doi:10.1128/AAC.01913-18

25. Tchesnokova VL, Rechkina E, Chan D, et al. Pandemic Uropathogenic Fluoroquinolone-resistant Escherichia coli Have Enhanced Ability to Persist in the Gut and Cause Bacteriuria in Healthy Women. *Clin Infect Dis*. 2020;70(5):937-939. doi:10.1093/cid/ciz547

26. Johnson JR, Thuras P, Johnston BD, et al. The Pandemic H30 Subclone of Escherichia coli Sequence Type 131 Is Associated With Persistent Infections and Adverse Outcomes Independent From Its Multidrug Resistance and Associations With Compromised Hosts. *Clin Infect Dis*. 2016;62(12):1529-1536. doi:10.1093/cid/ciw193

27. Johnson JR, Clabots C, Porter SB, Bender T, Johnston BD, Thuras P. Intestinal Persistence of Colonizing Escherichia coli Strains, Especially ST131-H30, in Relation to Bacterial and Host Factors [published online ahead of print, 2022 Jan 3]. J Infect Dis. 2022;jiab638. doi:10.1093/infdis/jiab638

28. Tchesnokova V, Radey M, Chattopadhyay S, et al. Pandemic fluoroquinolone resistant *Escherichia coli* clone ST1193 emerged via simultaneous homologous recombinations in 11 gene loci. *Proc Natl Acad Sci U S A*. 2019;116(29):14740-14748. doi:10.1073/pnas.1903002116

29. Francino MP. Antibiotics and the Human Gut Microbiome: Dysbioses and Accumulation of Resistances. *Front Microbiol*. 2016;6:1543. Published 2016 Jan 12. doi:10.3389/fmicb.2015.01543

30. Crits-Christoph A, Hallowell HA, Koutouvalis K, Suez J. Good microbes, bad genes? The dissemination of antimicrobial resistance in the human microbiome. *Gut Microbes*. 2022;14(1):2055944. doi:10.1080/19490976.2022.2055944

31. Langdon A, Schwartz DJ, Bulow C, et al. Microbiota restoration reduces antibiotic-resistant bacteria gut colonization in patients with recurrent Clostridioides difficile infection from the open-label PUNCH CD study. *Genome Med*. 2021;13(1):28. Published 2021 Feb 16. doi:10.1186/s13073-021-00843-9

32. Widerström M, Wiström J, Edebro H, et al. Colonization of patients, healthcare workers, and the environment with healthcare-associated Staphylococcus epidermidis genotypes in an intensive care unit: a prospective observational cohort study. *BMC Infect Dis*. 2016;16(1):743. Published 2016 Dec 9. doi:10.1186/s12879-016-2094-x

33. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications. *Molecules*. 2018;23(4):795. Published 2018 Mar 30. doi:10.3390/molecules23040795

34. Castillo Neyra R, Vegosen L, Davis MF, Price L, Silbergeld EK. Antimicrobial-resistant Bacteria: An Unrecognized Work-related Risk in Food Animal Production. *Saf Health Work*. 2012;3(2):85-91. doi:10.5491/SHAW.2012.3.2.85

35. Peterson LR, Diekema DJ. To screen or not to screen for methicillin-resistant Staphylococcus aureus. *J Clin Microbiol*. 2010;48(3):683-689. doi:10.1128/JCM.02516-09

36. Roth VR, Longpre T, Coyle D, et al. Cost Analysis of Universal Screening vs. Risk Factor-Based Screening for Methicillin-Resistant Staphylococcus aureus (MRSA). *PLoS One*. 2016;11(7):e0159667. Published 2016 Jul 27. doi:10.1371/journal.pone.0159667

37. Chuang L, Tambyah PA. Catheter-associated urinary tract infection. *J Infect Chemother*. 2021;27(10):1400-1406. doi:10.1016/j.jiac.2021.07.022