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MAJOR ARTICLE

The Pandemic *H*30 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

James R. Johnson,[1,2] Paul Thuras,[1,2] Brian D. Johnston,[1,2] Scott J. Weissman,[3,4] Ajit P. Limaye,[3] Kim Riddell,[5] Delia Scholes,[3,5] Veronika Tchesnokova,[3] and Evgeni Sokurenko[3]

[1]Veterans Affairs Medical Center, and [2]University of Minnesota, Minneapolis; [3]University of Washington, [4]Seattle Children's Hospital, and [5]Group Health Cooperative, Seattle, Washington

Background. The *H*30 subclone within *Escherichia coli* sequence type 131 (ST131-*H*30) has emerged rapidly to become the leading antibiotic-resistant *E. coli* strain. Hypervirulence, multidrug resistance, and opportunism have been proposed as explanations for its epidemic success.

Methods. We assessed 1133 consecutive unique *E. coli* clinical isolates from 5 medical centers (2010–2011) for *H*30 genotype, which we compared with epidemiological and clinical data extracted from medical records by blinded reviewers. Using univariable and multivariable logistic regression analysis, we explored associations of *H*30 with underlying host characteristics, clinical presentations, management, and outcomes, adjusting for host characteristics.

Results. The *H*30 (n = 107) isolates were associated with hosts who were older, male, locally and systemically compromised, and healthcare and antibiotic exposed. With multivariable adjustment for host factors, *H*30 lost its numerous significant univariable associations with initial clinical presentation, but remained strongly associated with clinical persistence (odds ratio [OR], 3.47; 95% confidence interval [CI], 1.89–6.37), microbiological persistence (OR, 4.46; 95% CI, 2.38–8.38), subsequent hospital admission (OR, 2.68; 95% CI, 1.35–5.33), and subsequent new infection (OR, 1.73; 95% CI, 1.01–3.00). These host-adjusted associations remained strong even with added adjustment for resistance to the initially prescribed antibiotics, and the adverse outcome associations (subsequent hospital admission, new infection) were independent of clinical and microbiological persistence.

Conclusions. In addition to targeting compromised hosts and resisting multiple antibiotics, *H*30 isolates may have an intrinsic ability to cause highly persistent infections and later adverse outcomes. The basis for these host- and resistance-independent associations is unclear, but they should be considered when managing patients with *H*30 infections.

Keywords. *Escherichia coli* infections; ST131; host compromise; long-term care; antimicrobial resistance.

Escherichia coli is a major cause of extraintestinal infections, mainly of the urinary tract, but also of the bloodstream and diverse other body sites [1]. Extraintestinal *E. coli* infections have become increasingly difficult to manage due to the rising prevalence of resistance to first-line antibiotics [2–6], especially in elderly individuals [7]. The main driver of this trend is *E. coli* sequence type 131 (ST131), particularly its fluoroquinolone resistance–associated *H*30 subclone (hereafter, *H*30) [8–11]. *H*30 also is associated with resistance to trimethoprim-sulfamethoxazole and multiple other antibiotics, and with extended-spectrum β-lactamase production [10, 11]. Following its first appearance around the year 2000, *H*30 has expanded globally to become the dominant antimicrobial-resistant *E. coli* strain in many populations [8, 12–14].

The basis for *H*30's unprecedented worldwide expansion is unknown. Limited data from animal models, and some epidemiological data, have suggested that *H*30 strains are more virulent than other *E. coli* strains [10, 15–18]. However, most animal studies have failed to confirm such a virulence advantage [19, 20]. Alternatively, in this era of increasing broad-spectrum antibiotic use, especially of fluoroquinolones, *H*30's multidrug resistance and exceptionally intense fluoroquinolone resistance [21, 22] could underlie its dominance. Increasing epidemiological evidence also associates *H*30 with elderly and functionally dependent hosts [23–26], a characteristic of opportunists. Because such individuals represent the fastest-growing population segment, an opportunistic phenotype could provide *H*30 with another fitness advantage. However, detailed studies of the clinical and epidemiological correlates of infections caused by *H*30 have not been undertaken, leaving in question the relative contributions of virulence,

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Correspondence: J. R. Johnson, Infectious Diseases (111F), Veterans Affairs Medical Center, 1 Veterans Dr, Minneapolis, MN 55417 (johns007@umn.edu).

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resistance, opportunism, and possible as-yet-undefined phenotypes to the dominance of *H*30.

Because of the tremendous and still-emerging public health significance of *H*30, we sought to further clarify *H*30's epidemiological and clinical correlates. Here, we extensively analyzed an existing epidemiological dataset based on 1133 consecutive clinical *E. coli* isolates from 5 different US medical centers [10, 17]. We focused especially on underlying host characteristics and antibiotic resistance as modifiers of the clinical presentation, evaluation, management, and outcomes associated with *H*30, as compared with other *E. coli* strains.

PATIENTS AND METHODS

Study Isolates

The 1133 *E. coli* study isolates were consecutive, unique (by patient) clinical isolates that had been collected in 2010–2011, with their susceptibility results, from the clinical microbiology laboratories of 5 medical centers, in Seattle, Washington (University of Washington Medical Center, Harborview King County Medical Center, Group Health Cooperative, and Seattle Children's Hospital) and Minneapolis, Minnesota (Veterans Affairs Medical Center [VAMC]) [10, 17]. Isolates were selected without regard for specimen type, susceptibility profile, or host characteristics. In the research laboratory, *H*30 subclone members were identified via *fumC*/*fimH*-based clonal typing, followed by full or partial multilocus sequence typing [10, 17] and subclone-specific polymerase chain reaction assays [12, 27].

Medical Records Review

Study personnel at each center who were blinded to the typing results used a standardized instrument to extract from each source patient's medical records relevant data regarding the index encounter (ie, the encounter associated with the index culture) and the subsequent 30-day period (Table 1). Data included index encounter setting, host demographics (sex, age), antibiotics used within the prior 30 days, and presence of predisposing conditions. These were subdivided as systemic (diabetes, chronic renal failure, cirrhosis, immunosuppression, neutropenia, prematurity, and pregnancy) and local, based on the primary site of infection. For urine isolates, local compromising conditions included urinary obstruction or instrumentation, neurogenic bladder, urologic surgery, urolithiasis, and high-grade vesicoureteral reflux. For wound isolates they included skin ulcer, trauma, surgery, vascular insufficiency, edema, dermatitis, and foreign body. For respiratory isolates they included chronic lung disease, intubation, and smoking. Healthcare exposures during the year preceding the index encounter included hospitalization, long-term care facility (LTCF) residence, and dialysis.

Presenting clinical manifestations included vital signs, symptoms and physical findings suggestive of infection (both systemic and localized to the site of infection), selected laboratory results (white blood cell count, maximum band form count, minimum neutrophil count), and provider documentation of a sepsis diagnosis or concern for infection. The systemic inflammatory response syndrome (SIRS) was defined using standard criteria [28].

Initial management data from the index encounter included imaging studies, invasive procedures, new antibiotic therapy (any, and specific agent[s]), hospital admission, and escalation of level of care (eg, intensive care transfer). Outcome data for the 30 days following the index encounter included resistance to the initially prescribed antibiotic(s), clinical or microbiological persistence, clinical or microbiological recurrence, new infections (ie, different organism and/or site), adverse drug reactions, imaging studies, invasive procedures, subsequent admission to hospital or intensification of care, subsequent sepsis diagnosis, and death. Given the difficulty of determining causal relationships, no inferences were made regarding whether the index *E. coli* strain was responsible for the observed clinical phenomena. The few missing data, which were distributed sporadically across the dataset, were imputed as having the consensus value for that variable.

Statistical Analysis

Comparisons involving categorical or continuous variables were tested using Fisher exact test and the Mann–Whitney *U* test, respectively. Spearman correlation was used to assess for correlation among epidemiological variables. Univariable and multivariable logistic regression analysis was used to characterize associations among the clinical and epidemiological variables and associations of *H*30 with the clinical and epidemiological variables. In different multivariable models, prior hospital stay and LTCF residence were assessed as predictors either individually or combined with dialysis as a composite "healthcare exposure" variable. Local institutional review boards approved the study protocol.

RESULTS

Study Population

The 1133 study subjects were mainly from Group Health Cooperative, followed by Seattle Children's Hospital, University of Washington Medical Center, Harborview, and the VAMC (Table 1). Median age was 49 years (range, 0–98 years). Approximately 20% of subjects were male, roughly one-third had local or systemic compromising conditions, 22% had past-year healthcare exposure, and 22% had used 1 or more antibiotics within 30 days before the index encounter (Table 1). These host variables were all highly collinear, yielding $P \leq .001$ for each pairwise comparison excepting recent antibiotic exposure vs age ($P = .02$) or systemic compromise ($P = .006$).

At the index encounter, most subjects were outpatients (88%) or had been in hospital ≤2 days (6%), whereas 6% had been hospitalized >2 days. The most common culture source was

Table 1. Epidemiological Variables in Relation to *H*30 Status Among 1133 *Escherichia coli* Clinical Isolates

Variable	Prevalence, No. (Column %)			
	Total (N = 1133)	Non-*H*30 (n = 1026)	*H*30 (n = 107)	*P* Value[a]
Location				
Children's Hospital (Seattle)	269 (24)	254 (25)	15 (14)	**.01**
Group Health Cooperative (Seattle)	471 (42)	436 (43)	35 (33)	.06
Harborview Medical Center (Seattle)	135 (12)	114 (11)	21 (20)	**.02**
UWMC (Seattle)	158 (14)	141 (14)	17 (16)	
Minneapolis VAMC	100 (9)	81 (8)	19 (18)	**.002**
Latter 3 (Harborview, UWMC, VAMC)	393 (35)	336 (33)	57 (53)	**<.001**
Host factors				
Male	250 (22)	212 (21)	38 (36)	**.001**
Local compromise[b]	428 (38)	363 (35)	65 (61)	**<.001**
Systemic compromise[c]	351 (31)	300 (29)	51 (48)	**<.001**
Hospital stay (past year)	235 (21)	196 (19)	39 (37)	**<.001**
Long-term care facility stay (past year)	71 (6)	46 (5)	25 (24)	**<.001**
Any healthcare risk factor	257 (23)	213 (21)	44 (42)	**<.001**
Prior antibiotics[d]				
Any	244 (22)	199 (20)	45 (41)	**<.001**
Penicillin, cephalosporin, or carbapenem	111 (10)	98 (10)	13 (12)	
Fluoroquinolone	48 (4)	33 (3)	15 (14)	**<.001**
Trimethoprim-sulfamethoxazole	65 (6)	53 (5)	12 (11)	**.02**
Nitrofurantoin	29 (3)	23 (2)	6 (6)	**.047**
Vancomycin	24 (2)	19 (2)	5 (5)	.07
Presentation				
Local manifestations[b]	705 (62)	643 (63)	62 (58)	
Systemic manifestations[c]	338 (30)	307 (30)	31 (29)	
Any clinical manifestations	879 (77)	806 (79)	73 (68)	**.02**
Suspected infection	973 (86)	889 (87)	84 (79)	**.03**
SIRS	147 (13)	126 (12)	21 (20)	**.048**
Sepsis diagnosis	40 (4)	34 (3)	6 (6)	
Bacteremia	27 (2.4)	26 (2.5)	1 (0.9)	
Management				
Imaging	254 (22)	219 (21)	35 (33)	**.01**
Procedure	373 (33)	322 (31)	51 (48)	**.001**
Escalation in level of care	33 (4)	31 (4)	2 (3)	
Admission to intensive care unit	55 (8)	50 (8)	5 (7)	
Antibiotic therapy	838 (74)	779 (76)	59 (55)	**<.001**
Outcome				
Resistant to chosen antibiotic	99 (9)	79 (8)	20 (19)	**<.001**
Clinical persistence[e]	86 (8)	67 (7)	19 (18)	**<.001**
Microbiological persistence[e]	61 (5)	41 (4)	20 (19)	**<.001**
Clinical and/or microbiological persistence	110 (10)	82 (8)	28 (26)	**<.001**
Clinical recurrence[f]	36 (3)	31 (3)	5 (5)	
Microbiological recurrence[f]	25 (2)	23 (2)	2 (2)	
Later sepsis diagnosis	28 (3)	22 (2)	6 (6)	**.04**
Later outpatient visit(s)	503 (44)	445 (43)	58 (54)	**.04**
Later escalation in level of care	36 (3)	31 (3)	5 (5)	
Later admission to hospital	59 (5)	44 (4)	15 (14)	**<.001**
Later antibiotics	478 (42)	410 (40)	68 (64)	**<.001**
Later imaging	309 (27)	265 (26)	44 (41)	**.001**
Later procedure	324 (29)	278 (27)	46 (43)	**.001**
New infection[g]	125 (11)	100 (10)	25 (24)	**<.001**
Later complication[h]	224 (20)	191 (19)	33 (31)	**.005**

Abbreviations: SIRS, systemic inflammatory response syndrome; UWMC, University of Washington Medical Center (Seattle); VAMC, Veterans Affairs Medical Center (Minneapolis).

[a] *P* values (Fisher exact test) are shown where $P < .10$. Boldface text indicates $P < .05$.

[b] Local compromise and local manifestations were specific to the site of infection.

[c] Systemic compromise: any of diabetes, chronic renal failure, cirrhosis, immunosuppression, neutropenia, prematurity, and pregnancy. Systemic manifestations: any of fever (subjective), chills, malaise, lethargy, irritability, unresponsiveness, and seizure.

[d] Prior antibiotic use within 30 days of index episode. (Percentage values are based on number evaluable, which for some variables was less than total population.) Data are shown only for antibiotic classes used by >1% of subjects. For other antibiotic classes, the overall prevalence of use was nitrofurans, 0.9%; lincosamides, 0.7%; aminoglycosides, 0.6%; tetracyclines, 0.6%; and nitroimidazoles, 0.5% (no significant differences, *H*30 vs non-*H*30).

[e] Clinical persistence: initial symptoms present 5 days into therapy. Microbiological persistence: repeat positive culture (same site/organism as initially), without intervening negative culture.

[f] Clinical recurrence: return of initial symptoms after symptom resolution. Microbiological recurrence: repeat positive culture (same site/organism as initially) after negative culture.

[g] Different site and/or organism than index episode.

[h] Any of: adverse drug event, drug fever, drug rash, anaphylaxis, *Clostridium difficile* infection, nausea, vomiting, cytopenias, or acute renal failure.

urine (93%), followed by wound (4%), blood (2.2%; mostly from a urinary source), and sputum (1%). Of the 1133 *E. coli* isolates, 161 (14.2%) represented ST131 and 107 (9.6%; 66% of ST131 isolates) represented *H*30.

Clinical Presentation, Management, and Outcome

At the index visit, 77% of patients had documented clinical manifestations of infection (62% local, 30% systemic) and 86% were suspected of having an infection (Table 1). Less frequent were SIRS (13%), a sepsis diagnosis (4%), or bacteremia (2.4%). As part of the index visit, 22% patients underwent imaging, 33% had an invasive procedure, and 74% received new antibiotic therapy.

Overall, in relation to the index visit, 9% of patients received a new antibiotic regimen to which the *E. coli* isolate was resistant and 10% experienced clinical and/or microbiological persistence (Table 1); these variables were closely correlated ($P < .001$). In the subsequent 30 days, although only 2%–3% had clinical or microbiological recurrence, 11% had a new infection, 3% received a new sepsis diagnosis, 20% had some other complication, 44% had 1 or more outpatient visits, 5% were admitted to hospital, 42% received new antibiotics, and 27%–29% underwent imaging or a procedure (Table 1).

Associations With *H*30

*H*30 was associated positively with most of the host and clinical variables (Table 1). Of the 5 centers, *H*30 was associated positively with Harborview (county hospital) and the VAMC, but negatively with Seattle Children's Hospital and, with borderline significance, Group Health Cooperative (community clinics). *H*30 also was associated with local and systemic compromise, past-year healthcare exposures (including hospital stays and LTCF residence), and recent use of any antibiotic, including, specifically, fluoroquinolones, trimethoprim-sulfamethoxazole, and nitrofurantoin (Table 1). Host age was significantly greater in association with *H*30 (median, 60 vs 48 years; $P < .001$).

At the index visit, patients with an *H*30 isolate were significantly less likely than other patients to have clinical manifestations of infection, to be suspected of being infected, or to receive new antibiotic therapy (Table 1). Nonetheless, they were somewhat more likely to have the (comparatively infrequent) endpoints of SIRS or a sepsis diagnosis, albeit not bacteremia, and were more likely to undergo imaging or a procedure.

*H*30 patients also were more likely, in relation to the index visit, to receive a new antibiotic regimen to which their *E. coli* isolate was resistant and to have persistent clinical manifestations and/or positive cultures (Table 1). In the 30 days after the index visit, although *H*30 patients were no more likely to have clinical or microbiological recurrence, they were more likely to have 1 or more other adverse outcomes, including a new infection, a new sepsis diagnosis, some other complication, and new antimicrobial therapy, imaging, or a procedure (Table 1).

Logistic Regression

According to univariable logistic regression, *H*30 was significantly associated with all of the underlying host variables (Table 2). In multivariable models that included all these host-factor variables as candidate predictors of *H*30 status, strong associations with *H*30 persisted for local and systemic compromise, LTCF exposure, and any healthcare contact (Table 2).

Accordingly, we assessed *H*30 by logistic regression for its associations with the clinical variables, with and without adjustment for the host variables (Table 3). In the host factor-adjusted models, *H*30 was not associated with any of the initial clinical presentation variables. However, despite adjustment for host factors, *H*30 remained significantly associated with 7 clinical variables, including either no or only inactive initial antibiotic therapy, clinical and microbiological persistence after the index visit, and subsequent new infection, hospital admission, or antibiotic therapy. Notably, in these multivariable models, 1 or more host variables significantly predicted each of the clinical variables (Supplementary Table 1). The strongest and most consistently predictive host variables were LTCF exposure and recent antibiotic use (Supplementary Table 1).

We next assessed whether the observed clinical associations of *H*30 that remained after adjustment for host factors were mediated through resistance to the initially prescribed antibiotic(s). For this, we constructed multivariable models in which *H*30 and resistance to the initial antibiotic regimen (Table 4) were assessed both separately and jointly as predictors of *H*30-associated

Table 2. Univariable and Multivariable[a] Logistic Regression Analysis of Host Factors and Hospital as Predictors of ST131-*H*30[b] Among 1133 *Escherichia coli* Clinical Isolates

	Association of Variable With *H*30[b]					
	Univariable			Multivariable[a]		
Epidemiological Variable	OR	95% CI	*P* Value[b]	OR	95% CI	*P* Value[b]
Host factor						
Age (per year)	1.02	1.01–1.02	**<.001**	1.01	1.00–1.02	**.06**
Male	2.15	1.38–3.23	**.001**	1.22	.76–1.98	.41
Local compromise[c]	2.83	1.88–4.25	**<.001**	1.64	1.02–2.63	**.04**
Systemic compromise[c]	2.20	1.47–3.30	**<.001**	1.54	1.00–2.43	**.05**
Hospital stay (past year)	2.46	1.61–3.76	**<.001**	1.09	.66–1.82	.73
LTCF stay (past year)	6.56	3.84–11.23	**<.001**	3.30	1.74–6.26	**<.001**
Healthcare risk (past year)[d]	2.67	1.76–4.03	**<.001**	1.52	.96–2.39	**.07**
Antibiotic use (past 30 d)	3.02	1.98–4.59	**<.001**	2.18	1.39–3.41	**.001**
Hospital						
HMC/UWMC/VAMC	2.34	1.57–3.50	**<.001**	1.31	.82–2.09	.26

Abbreviations: CI, confidence interval; HMC, Harborview King County Medical Center (Seattle); LTCF, long-term care facility; OR, odds ratio; UWMC, University of Washington Medical Center (Seattle); VAMC, Veterans Affairs Medical Center (Minneapolis).

[a] Two multivariable models were constructed. The first had only 1 healthcare contact variable: "healthcare risk (past year)," which includes hospital stay, LTCF stay, and dialysis. The second had 2 healthcare contact variables: "hospital stay (past year)" and "LTCF stay (past year)." Results as shown are from the first model, excepting those for "hospital stay (past year)" and "LTCF stay (past year)," which are from the second model.

[b] Boldface text indicates associations yielding $P < .10$.

[c] Local compromise: any predisposing condition involving the primary site of infection. Systemic compromise: any of diabetes, chronic renal failure, cirrhosis, immunosuppression, neutropenia, prematurity, or pregnancy.

[d] Healthcare risk (past year) included any of the following: hospital stay, LTCF stay, or dialysis.

Table 3. Univariable and Multivariable Logistic Regression Analysis of ST131-*H30* as a Predictor of Clinical Presentation, Management, and Outcomes Among 1133 *Escherichia coli* Isolates

	Association of Clinical Variable With *H30*[a]					
	Univariable Analysis			Multivariable Analysis[b]		
Clinical Variable	OR	95% CI	*P* Value[a]	OR	95% CI	*P* Value[a]
Presentation						
Local manifestations	0.82	.55–1.23	.34	1.06	.68–1.65	.93
Systemic manifestations	0.96	.62–1.48	.84	0.97	.60–1.55	.89
Any clinical manifestation	0.59	.38–.90	**.02**	0.87	.54–1.40	.57
Suspected infection	0.56	.34–.92	**.02**	0.81	.47–1.37	.43
SIRS	1.74	1.05–2.91	**.03**	1.17	.66–2.07	.58
Sepsis diagnosis	1.8	.72–4.29	.22	1.16	.43–3.08	.77
Bacteremia	0.37	.05–2.73	.31	0.41	.14–1.13	.40
Management						
Imaging	1.79	1.17–2.76	**.009**	1.14	.70–1.86	.58
Procedure	1.99	1.33–2.98	**.001**	0.89	.41–1.73	.63
Admission to hospital	2.28	1.36–3.84	.002	0.73	.38–1.41	.34
Antibiotic therapy	0.39	.26–.59	**<.001**	0.47	.31–.72	**.001**
Outcome						
Resistant to antibiotic	2.76	1.61–4.72	**<.001**	2.42	1.35–4.37	**.003**
Clinical persistence	3.17	1.82–5.52	**<.001**	3.47	1.89–6.37	**<.001**
Microbiological persistence	5.54	3.11–9.98	**<.001**	4.46	2.38–8.38	**<.001**
Clinical recurrence	1.59	.60–4.14	.36	1.34	.48–3.77	.58
Microbiological recurrence	0.83	.19–3.57	.80	0.80	.17–3.69	.78
Later sepsis diagnosis	2.70	1.07–6.81	**.04**	0.99	.35–.78	.98
Outpatient visit(s)	1.54	1.03–2.30	**.03**	1.24	.79–1.93	.34
Escalation in level of care	1.57	.60–4.13	.36	0.64	.22–1.82	.40
Admission to hospital	3.63	1.94–6.77	**<.001**	2.68	1.35–5.33	**.005**
New antibiotics	2.62	1.73–3.96	**<.001**	2.04	1.32–3.16	**.001**
Imaging	2.01	1.33–3.02	**.001**	1.27	.81–2.01	.30
Procedure	2.03	1.35–3.05	**.001**	1.30	.75–2.24	.35
New infection	2.82	1.72–4.62	**<.001**	1.73	1.01–3.00	**.047**
Other complication	1.95	1.26–3.03	**.003**	1.28	.78–2.07	.34

Abbreviations: CI, confidence interval; OR, odds ratio; SIRS, systemic inflammatory response syndrome.

[a] Boldface text indicates comparisons yielding $P < .10$.

[b] A separate multivariable model was constructed for each clinical outcome variable. Host-related covariates that were added to each multivariable model included age, sex, hospital stay in past year, long-term care facility stay in past year, systemic compromise, local compromise, antibiotic use in past 30 days, and hospital (Harborview King County Medical Center, University of Washington Medical Center, or Minneapolis Veterans Affairs Medical Center). Regression results for these covariates are shown in Supplementary Tables 1 and 2.

Table 4. Multivariable Models to Assess *H30* and Resistance to the Initial Antibiotic(s) as Predictors of Subsequent Adverse Clinical Outcomes

					Series 3 Models[a]			
	Series 1 Models[a,b]: *H30*		Series 2 Models[a]: Resistance		*H30*		Resistance	
Outcome Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Clinical persistence	3.47 (1.89–6.37)	<.001	3.01 (1.64–5.52)	.001	3.04 (1.62–5.70)	.001	2.65 (1.42–4.94)	.002
Microbiological persistence	4.46 (2.38–18.38)	<.001	1.94 (.92–4.06)	.08	4.15 (2.18–7.90)	<.001	1.65 (.77–3.55)	.20
Later hospital admission	2.68 (1.35–5.33)	.005	1.60 (.68–3.79)	.29	1.59 (1.28–5.23)	.008	1.41 (.59–3.41)	.44
New antibiotics	2.04 (1.32–3.16)	.001	4.90 (3.01–7.99)	<.001	1.84 (1.17–2.89)	.008	4.71 (2.89–7.70)	<.001
New infection	1.73 (1.01–3.00)	.047	1.01 (.52–1.97)	.98	1.72 (1.00–2.96)	.05	0.95 (.48–1.85)	.87

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] As the main predictor variable(s), series 1 models included *H30*, series 2 models included resistance to the index visit antimicrobial regimen, and series 3 models included both of these. All models included, in addition to the main predictor variable(s), the following host-related covariates: age, sex, hospital stay in past year, long-term care facility stay in past year, systemic compromise, local compromise, antibiotic use in past 30 days, and hospital (Harborview King County Medical Center, University of Washington Medical Center, or Minneapolis Veterans Affairs Medical Center).

[b] Results shown for series 1 models (with *H30*) are as shown in Table 3 and Supplementary Table 1.

Table 5. Multivariable Models to Assess *H30* and Clinical or Microbiological Persistence as Predictors of Later Adverse Outcomes

	Series 1 Models:[a,b] *H30*		Series 2 Models:[a] Clinical or Microbiological Persistence			Series 3 Models[a]				
						H30		Clinical or Microbiological Persistence		
Outcome Variable	OR (95% CI)	*P* Value	Predictor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	Predictor	OR (95% CI)	*P* Value
Hospital admission	2.68 (1.35–5.33)	.005	Clinical persist.	2.17 (.89–5.28)	.09	2.56 (1.24–5.26)	.01	Clinical persist.	1.89 (.77–4.69)	.17
			Micro. persist.	1.31 (.47–3.61)	.61	2.68 (1.38–5.45)	.007	Micro. persist.	1.04 (.37–2.97)	.94
New antibiotics	2.04 (1.32–3.16)	.001	Clinical persist.	5.94 (3.40–10.38)	<.001	1.68 (1.06–2.67)	.03	Clinical persist.	5.62 (3.21–9.83)	<.001
			Micro. persist.	5.50 (2.81–10.85)	.001	1.70 (1.07–2.68)	.02	Micro. persist.	5.03 (2.54–9.93)	<.001
New infection	1.73 (1.01–3.00)	.047	Clinical persist.	2.81 (1.59–5.00)	<.001	1.43 (.81–2.53)	.22	Clinical persist.	2.69 (1.51–4.80)	.001
			Micro. persist.	2.95 (1.59–6.45)	<.001	1.39 (.79–2.46)	.25	Micro. persist.	2.75 (1.47–5.16)	.002

Abbreviations: CI, confidence interval; micro., microbiological; OR, odds ratio; persist., persistence.

[a] As the main predictor variable(s), series 1 models included *H30*, series 2 models included clinical or microbiological persistence, and series 3 models included both of these. All models included, in addition to the main predictor variable(s), the following host-related covariates: age, sex, hospital stay in past year, long-term care facility stay in past year, systemic compromise, local compromise, antibiotic use in past 30 days, and hospital (Harborview King County Medical Center, University of Washington Medical Center, or Minneapolis Veterans Affairs Medical Center).

[b] Results shown for series 1 models are as shown in Table 3 and Supplementary Table 1.

clinical variables (Table 3), incorporating in each instance all of the measured host-factor covariates (Table 2). In these models, the odds ratios (ORs) for *H30* were only slightly lower, and the corresponding *P* values only slightly higher, when *H30* and the resistance variable were entered as predictors jointly rather than separately (Table 4). This suggested that *H30* interacted minimally with resistance in predicting clinical or microbiological persistence, later hospital admission, use of new antibiotics, or new infection.

Using the same approach, we assessed whether clinical or microbiological persistence mediated the associations of *H30* with later hospital admission, new antibiotic use, or new infection (Table 5). Here again, the (host factor–adjusted) ORs and *P* values for *H30* changed only slightly when clinical or microbiological persistence was added as a covariate, suggesting that *H30* interacted minimally with these variables in predicting the later adverse outcomes.

DISCUSSION

The results of this study, the largest and most detailed to date of *H30*'s epidemiological and clinical correlates [8, 26], support 4 main conclusions. First, *H30*'s strong associations with multiple aspects of the initial clinical presentation can be explained by *H30*'s opportunist nature, that is, its preferential targeting of older, compromised, antibiotic-exposed, and functionally impaired hosts. Second, irrespective of host factors, *H30* is associated with recent antibiotic use and, at the index visit, either no antibiotic prescription or prescription of an antibiotic to which the organism is resistant. Third, irrespective of host variables and resistance to the initial antibiotic(s), *H30* infections tend to persist clinically and microbiologically. Finally, *H30* is associated with multiple subsequent adverse outcomes, including later hospital admission, new infections (different site or organism), and new antibiotic treatment, all of which appear to be independent of other *H30*-associated variables. If we wish to understand the reasons for *H30*'s recent pandemic emergence and to develop effective treatment strategies to improve outcomes for the patients that *H30* targets, these findings highlight the importance of taking into account *H30*'s seemingly intrinsic ability to colonize compromised hosts, resist multiple antibiotics, cause persistent infections, and result in adverse outcomes.

Regarding target populations, previous studies have associated ST131 and *H30* with advanced age, LTCF residence, and functional dependency [23–25, 29]. Our findings extend these associations to specific categories of host compromise that, to our knowledge, have not been examined previously with ST131 and its major subclone, *H30*. Notably, the strong univariable associations of *H30* with age, sex, and specific hospitals lost significance with multivariable adjustment for other host factors, suggesting that they were confounded by the other host characteristics. The subclone's strongest multivariable host associations were with compromising conditions, especially local factors (mainly involving the urinary tract); healthcare exposures (mainly LTCF residence); and recent prior antibiotic use.

The basis for these associations is unclear. Conceivably, *H30* is better able to colonize or infect the compromised urinary tract than other *E. coli* strains and, thus, becomes more prevalent clinically when local defenses are weakened—as proposed previously for other opportunistic uropathogens [30, 31]. Clarification of whether *H30*'s associations with prior hospitalization and LTCF residence reflect the accompanying exposures to an *H30*-rich institutional microbiota [23, 32], or identify especially vulnerable hosts (ie, who require hospitalization or LTCF placement), would clarify the possible need for intensified infection prevention efforts in such institutions.

Regarding clinical presentation, multivariable analysis showed that the contrasting ability of *H30* to have a lower likelihood of accompanying signs or symptoms of infection, but at

the same time a greater likelihood of severe manifestations [10, 17], is likely due to *H*30's associations with specific hosts. Indeed, associations of asymptomatic bacteriuria with elderly and compromised hosts, and the host's role in the development of sepsis, have been documented [30, 31]. *H*30 strains, however, deserve especially close attention (and hence, identification) as being potentially the most widespread cause of both asymptomatic bacteriuria and severe *E. coli* disease, especially in older patients.

Antibiotic–organism mismatch, and the associated treatment response delays, have been documented previously for ST131 [33] and, specifically, *H*30 [17]. Here, these associations remained strong even with adjustment for host factors. This reinforces the need for improved prescribing algorithms or rapid tests for antimicrobial resistance/susceptibility, to allow a more "individualized medicine" approach than does current antibiogram-based prescribing [17].

Because of *H*30 strains' multidrug resistance, they might be expected to persist despite empiric antimicrobial therapy, as confirmed here. Intriguingly, however, our multivariable models did not support the intuitive assumption that resistance to the initial regimen mediates clinical/microbiological persistence (Table 4). This suggests a seemingly distinctive capability of *H*30 to persist even when a correct antibiotic is used, which could be due to either *H*30's more intense drug resistance [21] or its possible ability to evade host defenses, leading to impaired pathogen clearance during treatment.

Two competing hypotheses might explain the greater risk of late-occurring adverse events among *H*30 patients despite no demonstrable increase in 30-day recurrence. First, the initial *H*30 infection may lead directly to later complications via delayed manifestations of infection-induced host damage or by predisposing to a subsequent infection involving a new site or organism, thereby leading to hospital admission and/or new antibiotic therapy. Alternatively, the initial episode may identify at-risk hosts who are predisposed to later complications, irrespective of the index infection/colonization episode. Indeed, compromised hosts are more likely to undergo procedures, be admitted to hospital, and experience later complications, creating associations of *H*30 with all these phenomena. Yet we observed associations of *H*30 with late complications despite adjustment for host characteristics, which supports a possible *H*30-specific effect. However, we cannot exclude that certain host variables were not adequately adjusted for, leaving residual confounding. Further study is needed to definitively separate the effects of the index episode (and, hence, *H*30) from those of underlying host characteristics and exposures.

Overall, the findings support a conceptual model whereby *H*30 strains are prevalent as minimally symptomatic or asymptomatic colonizers in older, functionally dependent hosts with compromised defenses. As discussed above, this could result from an ability of the pathogen to avoid host defenses, especially when these are weakened. Alternatively, *H*30 strains may be recovered incidentally as part of the broad evaluation such individuals commonly undergo when presenting with issues that might or might not involve infection. Additionally, such patients commonly have prior antibiotic use, increasing the chance that multidrug-resistant strains such as *H*30 [17, 21, 22] will persist in the urinary tract. Further studies are needed to determine whether *H*30 is indeed more likely than other strains to cause asymptomatic bacteriuria, and if so, why.

The study's limitations include its retrospective, observational nature, with reliance on medical records review and uncertain causality/temporal sequence. Additionally, the use of multiple comparisons risked finding associations by chance alone; follow-up was only for 30 days; and urinary tract infection history was not assessed. Its multiple strengths include the large, diverse, and recent study population, with both pediatric and adult patients; attention to host characteristics, clinical presentation, management, and outcomes; use of a standardized data collection tool, blinded data abstractors, and multivariable analysis; and classification of ST131 isolates as to *H*30 subclone.

In summary, we documented strong associations of *H*30 with older, compromised, antibiotic-exposed, and functionally impaired hosts, consistent with opportunism. Thus, *H*30 strains may be optimal opportunists for our times, with their predilection for the most rapidly growing segments of the host population [34] and ability to exploit the ever-increasing use of broad-spectrum antimicrobial therapy [35]. Nonetheless, with adjustment for host factors, although this lineage presented similarly to other *E. coli*, it was strongly associated with ineffective initial antimicrobial therapy, clinical and microbiological persistence, and diverse later-occurring adverse events. This suggests that *H*30 may have distinctive properties that allow it to act as a defenses-evading pathogen that, although often minimally apparent, is associated with delayed complications. These findings substantially advance our understanding of the host associations and clinical implications of *H*30. They also identify a need for improved antimicrobial prescribing that addresses *H*30's extensive resistance profile, and for clarification of the basis for *H*30's associated late complications.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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