A Prevalence Study of Urinary Tract Infections in Acute Relapse of Schizophrenia

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ABSTRACT

Objective: Schizophrenia is associated with immune abnormalities and increased mortality from infectious diseases. The aim of this study was to examine whether acute relapse of schizophrenia was associated with urinary tract infection (UTI), in comparison with controls, after controlling for potential confounding factors.

Method: In a prevalence study conducted from January 2010 to April 2012 at Georgia Health Sciences University Medical Center, Augusta, we recruited 136 adult subjects (mean age = 42.8 years): 57 inpatients with an acute relapse of *DSM-IV* schizophrenia, 40 stable outpatients with *DSM-IV* schizophrenia, and 39 healthy controls from the community. *Urinary tract infection* was defined as having positive leukocyte esterase and/or positive nitrites on urinalysis and having ≥ 5 leukocytes per high-powered field (implies 5–10 or more) on urine microscopy. Determination of UTI status was made for each subject, and analyses were performed to examine the association between UTI and acute relapse of schizophrenia.

Results: 35% of acutely relapsed subjects, versus 5% of stable outpatients and 3% of controls, had a UTI ($P < .001$). Only 40% of subjects in the acute relapse group classified as having a UTI were treated with antibiotics during hospitalization. After analyses were controlled for gender and smoking status, subjects in the acute relapse group were almost 29 times more likely to have a UTI than controls (odds ratio = 28.97; 95% CI, 3.44–243.85; $P = .002$). There was no statistically significant association with UTI among the stable outpatients versus controls.

Conclusions: Our finding of an association between an increased prevalence of UTI and acute psychotic relapse warrants replication in other samples. The mechanism of this association remains unclear. The results also highlight the potential importance of monitoring for comorbid UTI in acutely relapsed patients with schizophrenia.

J Clin Psychiatry 2013;74(3):271–277

Submitted: *July 25, 2012; accepted September 28, 2012. (doi:10.4088/JCP.12m08050).*

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Schizophrenia is associated with dramatically increased premature mortality. Standardized mortality rates are 2 to 3 times those of the general population, with an increase in almost every leading cause of death, and the average decrease in lifespan is 15 to 25 years.[1,2] In particular, patients with schizophrenia have increased infectious disease mortality: 1 study found a greater than 8-fold increased risk of death from pneumonia,[1] and a meta-analysis found a 4.5-fold increased risk of death from all infectious diseases.[2]

Cystitis, or lower urinary tract infection (UTI), is the most common bacterial infection. Approximately 50% of women will experience at least 1 UTI in their lifetime.[3] Although UTIs occur less frequently in men than in women, a National Ambulatory Medical Care Survey[4] found that 0.6% of office visits among male patients (vs 1.2% among female patients) were for UTIs. Evidence from geropsychiatry supports an association between UTIs and worsening psychiatric symptoms, most often in patients with dementia or delirium. A study[5] of 551 nursing home residents found that a change in mental status—including newly altered perception, disorganized speech, and lethargy that was not present at baseline—was a predictor of UTI (relative risk = 1.38; 95% CI, 1.03–1.74; $P = .03$).[5] A retrospective study[6] involving 407 patients discharged from a geropsychiatric unit found that over 20% had a UTI at admission. Woo et al,[7] in a chart review of 79 consecutive admissions to an acute geropsychiatry unit, found that UTIs were the most common unrecognized medical condition on admission (n = 7; 9%). Of note, all 7 of these patients were experiencing psychosis (primary psychotic disorders, mood disorders with psychotic features, or dementia with psychosis) (Daniel D. Sewell, MD; University of California, San Diego; written communication, August 2010). However, another study[8] found that only 7 of 515 psychiatric inpatients (1.3%) were diagnosed with UTI following a routine dipstick urinalysis at admission.

Acute psychotic relapse is common, and relapse prevention represents an important treatment issue in schizophrenia. Robinson et al[9] found that 82% of patients had an illness relapse within 5 years after recovery from a first episode of psychosis, and a majority had more than 1 relapse. Illness relapse is associated with adverse outcomes, including increased treatment resistance, cognitive decline, and functional disability.[10–12] An etiopathophysiologic role for immune abnormalities in schizophrenia has been one of the more enduring findings in the field. Prenatal maternal infection with a variety of viral and bacterial agents is a replicated risk factor for schizophrenia.[13] There is evidence for immune abnormalities, including abnormal blood levels of cytokines[14] and C-reactive protein,[15] in acute psychotic relapse. Immune cell function is also abnormal in acute psychosis. Neutrophils, part of the innate immune system, serve as a first-line response to inflammation, particularly bacterial infection. McAdams and Leonard[16] found evidence of reduced neutrophil phagocytosis during the active phase of psychotic illness that normalized upon recovery.

Despite these immune abnormalities and increased mortality from infectious diseases, there are no studies of the prevalence of infections at the time of hospitalization for acute illness relapse in patients with

Clinical Points

- Subjects with an acute relapse of schizophrenia have a significantly increased prevalence of urinary tract infection.
- Clinicians should monitor for comorbid urinary tract infection in patients with schizophrenia; such infections often go unrecognized and untreated.

schizophrenia and related disorders. In our clinical experience, we have observed, anecdotally, an apparent increase in prevalence of UTI on admission for patients with an acute psychotic relapse, but this finding has not been quantified. In this study, we tested the hypothesis that subjects with an acute relapse of schizophrenia and related disorders have an increased prevalence of UTI as compared to stable outpatients with schizophrenia and related disorders and to healthy controls, after controlling for potential confounding factors.

METHOD

Subjects

Fifty-seven subjects with an acute relapse of schizophrenia and related disorders, with *relapse* defined as requiring inpatient care for an exacerbation of psychosis, were identified by chart review of consecutive inpatient admissions to the Georgia Health Sciences University Medical Center Adult Inpatient Psychiatry Unit beginning in January 2010. Forty stable outpatients with schizophrenia and related disorders and 40 healthy controls were recruited in the Augusta, Georgia, area between July 2010 and April 2012. One control subject gave informed consent but withdrew from the study before any assessments were completed, leaving 39 subjects in the control group. Thus, a total of 136 subjects completed the study.

Inclusion criteria for all subjects were male or female gender, aged 18–70 years, with the capacity to give informed consent. Subjects with schizophrenia were administered the Evaluation to Sign Consent[17] by a physician, mental health nurse, or research coordinator not involved in the study. For subjects in the acute relapse group, urine samples were obtained within 48 hours of admission. Stable outpatients were deemed clinically stable on the basis of clinical judgment. Subjects in the acute relapse and stable outpatient groups met *DSM-IV* criteria for schizophrenia, schizophreniform disorder, delusional disorder, psychosis not otherwise specified, or schizoaffective disorder. Controls had no lifetime or current *DSM-IV* diagnosis of schizophrenia or related psychotic disorder; no lifetime or current manic, depressed, or mixed affective episode; and no history of exposure to any antipsychotic, antidepressant, valproate, divalproex, lithium, or gabapentin.

Exclusion criteria for all subjects were pregnancy; history of exposure to an antibiotic, urinary catheterization, or other urologic procedure in the past 2 weeks; gross hematuria; chronic renal or urologic abnormalities (other than stress urinary incontinence); and any of the following medical conditions: spinal cord injury, human immunodeficiency virus/acquired immunodeficiency syndrome, or multiple sclerosis. An additional exclusion criterion in the stable outpatient and control groups was evidence of imminent danger to self or others (ie, suicidal intent or recent history of violence or threats of violence). No subjects in the acute relapse and stable outpatient groups were receiving their first clinical contact for schizophrenia or related disorders.

Procedures

After providing written informed consent, stable outpatient and control groups underwent a laboratory, physical, and psychiatric diagnostic evaluation. The laboratory evaluation included a nonfasting blood draw for a complete blood count with differential and comprehensive metabolic panel. Subjects also provided a midstream clean-catch urine sample for urinalysis with microscopy and urine culture, a urine drug screen, and a urine pregnancy test in female subjects. The physical evaluation consisted of measuring height, weight, blood pressure, and pulse. These subjects (stable outpatients and controls) were also administered the Dartmouth Assessment of Lifestyle Inventory,[18] which quantifies use of drugs of abuse; a brief medical history was taken; and the Structured Clinical Interview for *DSM-IV* Axis 1 Disorders (SCID) psychosis and affective disorders modules[19] were administered to verify the psychiatric diagnosis in the stable outpatients (or absence of a diagnosis in the controls). Four trained raters performed the SCID interviews, although 1 rater (study author and principal investigator B.J.M.) performed the majority of the interviews (n = 44; 56%). Interrater reliability with the principal investigator (B.J.M.) was well established, with 100% concordance on a series of 10 vignettes. The study was approved by the institutional review boards of both Georgia Health Sciences University, Augusta, and the Georgia Department of Community Health, Atlanta.

Data for subjects in the acute relapse group were reviewed and extracted from the electronic medical records by 3 study authors (K.L.G., C.M.B., and N.H.C.). A total of 87 inpatient records were screened, of which 57 met the study inclusion/exclusion criteria. A complete blood count with differential and comprehensive metabolic panel and a midstream clean-catch urine sample for urinalysis with microscopy, urine drug screen, and urine pregnancy test in female subjects were part of routine admission orders for all subjects. However, urine cultures were not part of routine admission orders. Height, weight, smoking status, and medical history were also recorded at the time of admission. The psychiatric diagnosis for subjects in the acute relapse group was verified from the hospital discharge summary, which reflects the final diagnosis given by the attending inpatient psychiatrist.

UTI Determination

The gold standard for diagnosis of UTI is > 100,000 colony-forming units (CFU) per mL of a single bacterial species in a symptomatic patient. Urinalyses positive for leukocyte esterase and/or nitrite have a 67%–100% sensitivity and

Table 1. Descriptive Statistics for the Total Sample and by Urinary Tract Infection (UTI) Status

Variable	Total Sample (N = 136)	UTI (n = 23; 17%)	No UTI (n = 113; 83%)	*P* Value[a]
Subject group, n (%)				**< .001**
Acute relapse	57 (42)	20 (87)	37 (33)	
Stable outpatient	40 (29)	2 (9)	38 (34)	
Control	39 (29)	1 (4)	38 (34)	
SCID diagnosis, n (%)[b]				.565
Schizophrenia	60 (62)	14 (64)	46 (61)	
Schizoaffective disorder, bipolar type	29 (30)	7 (32)	22 (29)	
Schizoaffective disorder, depressed type	5 (5)	0 (0)	5 (7)	
Psychosis not otherwise specified	2 (2)	1 (5)	1 (1)	
Delusional disorder	1 (1)	0 (0)	1 (1)	
Gender, n (%)				**.010**
Male	69 (51)	6 (26)	63 (56)	
Female	67 (49)	17 (74)	50 (44)	
Race, n (%)				.632
African American	62 (46)	12 (52)	50 (44)	
White	62 (46)	10 (44)	52 (46)	
Other	12 (9)	1 (4)	11 (10)	
Highest education, n (%)[c]				.141
Advanced degree	13 (10)	0 (0)	13 (12)	
Some postgraduate studies	5 (4)	0 (0)	5 (5)	
College degree	10 (8)	0 (0)	10 (9)	
Some college	24 (19)	5 (25)	19 (18)	
High school graduate	36 (28)	7 (35)	29 (27)	
Some high school	27 (21)	8 (40)	19 (18)	
Completed eighth grade	6 (5)	0 (0)	6 (6)	
Some grade school	5 (4)	0 (0)	5 (5)	
No education	1 (1)	0 (0)	1 (1)	
Ever married, n (%)[c]				.960
Yes	69 (52)	11 (52)	58 (52)	
No	64 (48)	10 (48)	54 (48)	
Smoker, n (%)				.417
Yes	47 (35)	6 (27)	41 (36)	
No	89 (65)	16 (73)	73 (64)	
Diabetes, n (%)				.968
Yes	30 (22)	5 (22)	25 (22)	
No	106 (78)	18 (78)	88 (78)	
Age, mean (SD), y	42.8 (13.0)	44.1 (13.6)	42.5 (12.9)	.596
Body mass index (kg/m^2), mean (SD)	30.9 (8.6)	33.2 (8.5)	30.4 (8.6)	.159

[a]Bolded *P* values are significant at the α = .05 level.
[b]Among the acute relapse and stable outpatient groups only (n = 97; UTI = 22; non-UTI = 75).
[c]Data were missing for 9 subjects for education (n = 127; UTI = 20; non-UTI = 107) and for 3 subjects for marriage status (n = 133; UTI = 21; non-UTI = 112).
Abbreviation: SCID = Structured Clinical Interview for *DSM-IV* Axis I Disorders.

67%–98% specificity for bacteriuria of > 100,000 CFU/mL.[20] Subjects with bacterial concentrations of > 100,000 CFU/mL and symptoms of UTI have urine leukocyte counts of ≥ 10 leukocytes per high-powered field.[21] In this study, a UTI was defined as having positive leukocyte esterase and/or positive nitrites on urinalysis and having ≥ 5 leukocytes per high-powered field (implies 5–10 or more) on urine microscopy. One investigator (B.J.M.) made the determination of UTI status and contacted all subjects with UTI in the stable outpatient and control groups to advise follow-up medical care.

Statistical Analysis

Sample size was determined assuming a χ^2 test, a significance level of $P = .05$, and statistical power of 0.80. Rates of UTI assumed were 1% in the control group, 1% in the stable outpatient group, and 15% in the acute relapse group (estimates based on clinical experience). A total sample size of 120, or 40 per group, was needed to adequately test for difference in rates of UTI between the subject groups.

All statistical analysis was performed using SAS statistical software, version 9.3 (SAS Institute Inc, Cary, North Carolina). Statistical significance was assessed using an α level of .05 unless otherwise noted. Descriptive statistics were calculated overall and by UTI status. Simple associations of UTI status with demographic characteristics, clinical characteristics, and the main independent variable of subject group were determined using χ^2 and *t* tests. Additionally, the association of demographic and clinical variables—including age, gender, race, body mass index, smoking status (yes/no), and diabetes mellitus (yes/no)—as potential confounders with subject group was determined using χ^2 or 1-way analysis of variance.

The association of subject group with UTI was determined using logistic regression. A model-building strategy was used to arrive at a final model controlling for potential confounders. First, each individual confounder was assessed for its association with UTI in simple logistic regression models. A backward model-building strategy was then used. All potential confounders—regardless of statistical significance—and subject group were included in a full logistic regression model. The least significant potential confounder was removed from the model, and a −2 log likelihood test was performed to examine whether the variable was needed in the model or not. Additionally, the effect of removing the potential confounder on the estimated odds ratio (OR) between subject group and UTI was assessed. Variables that did not result in a significant −2 log likelihood test or did not change the estimated OR between subject group and UTI were removed from the model. The final model resulted in those variables that were statistically significant confounders, changed the OR significantly, or resulted in a significant −2 log likelihood test.

RESULTS

Descriptive statistics for all subjects and by UTI status are given in Table 1. Among all subjects, subject group ($P < .001$) and female gender ($P = .010$) were significantly associated with UTI. Thirty-five percent of subjects in the acute relapse group (n = 20) versus 5% of stable outpatients (n = 2) and 3% of controls (n = 1) had a UTI. Seventy-four percent of subjects with laboratory evidence of UTI were female.

Table 2 presents the descriptive statistics by UTI status for each subject group. Significant associations with subject

Table 2. Descriptive Statistics by Urinary Tract Infection (UTI) Status for Each Subject Group (N = 136)

	Acute Relapse Group (n = 57)		Stable Outpatient Group (n = 40)		Control Group (n = 39)		
Variable	UTI (n = 20)	No UTI (n = 37)	UTI (n = 2)	No UTI (n = 38)	UTI (n = 1)	No UTI (n = 38)	*P* Value[a]
SCID diagnosis, n (%)[b]							.836
Schizophrenia	13 (65)	23 (62)	1 (50)	23 (61)			
Schizoaffective disorder, bipolar type	6 (30)	11 (30)	1 (50)	11 (29)			
Schizoaffective disorder, depressed type	0 (0)	1 (3)	0 (0)	4 (11)			
Psychosis not otherwise specified	1 (5)	1 (3)	0 (0)	0 (0)			
Delusional disorder	0 (0)	1 (3)	0 (0)	0 (0)			
Gender, n (%)							.945
Male	5 (25)	13 (35)	1 (50)	20 (53)	0 (0)	19 (50)	
Female	15 (75)	24 (65)	1 (50)	18 (47)	1 (100)	19 (50)	
Race, n (%)							.109
African American	10 (50)	19 (51)	1 (50)	19 (50)	1 (100)	12 (32)	
White	9 (45)	17 (46)	1 (50)	16 (42)	0 (0)	19 (50)	
Other	1 (5)	1 (3)	0 (0)	3 (8)	0 (0)	7 (18)	
Smoker, n (%)							**< .001**
Yes	4 (20)	16 (43)	2 (100)	21 (55)	0 (0)	4 (11)	
No	16 (80)	21 (57)	0 (0)	17 (45)	1 (100)	34 (89)	
Diabetes, n (%)							**.008**
Yes	5 (25)	13 (35)	0 (0)	10 (26)	0 (0)	2 (5)	
No	15 (75)	24 (65)	2 (100)	28 (74)	1 (100)	36 (95)	
Age, mean (SD), y	44.3 (13.5)	42.4 (13.4)	52.2 (3.2)	44.8 (11.7)	22.4	40.2 (13.6)	.177
Body mass index (kg/m^2), mean (SD)	32.6 (9.0)	32.0 (8.3)	35.8 (0.6)	32.6 (10.3)	39.6	26.5 (5.3)	**.003**

[a]*P* values are shown for the association with subject group; bolded *P* values are significant at the α = .05 level.
[b]Among the acute relapse and stable outpatient groups only.
Abbreviation: SCID = Structured Clinical Interview for *DSM-IV* Axis I Disorders.

group were found for smoking status, diabetes, and body mass index. Subjects in the acute relapse and stable outpatient groups were more likely to be smokers, have diabetes, and have a greater body mass index than those in the control group ($P < .01$ for each). Of the 2 subjects in the stable outpatient group with UTI, one was male with schizophrenia and the other was female with schizoaffective disorder, bipolar type. The control subject with a UTI was female.

Table 3 describes the psychotropic medications by subject group. Three subjects in the acute relapse group were not prescribed antipsychotics, and data on antipsychotics were missing for 2 subjects in the stable outpatient group. There was no difference in the prevalence of treatment with mood stabilizers, antidepressants, benzodiazepines, or medications for extrapyramidal symptoms between the acute relapse and stable outpatient groups. Table 4 describes the psychotropic medications by UTI status in the acute relapse group. There was no difference with respect to the prevalence of treatment with mood stabilizers, antidepressants, benzodiazepines, or medications for extrapyramidal symptoms for subjects with and without a UTI. Furthermore, there was no difference in the mean length of hospitalization in subjects with and without a UTI (8.0 ± 6.4 days vs 6.2 ± 3.2 days, respectively; $t = -1.16$; $P = .26$). Only 40% of subjects in the acute relapse group classified as having a UTI were treated with antibiotics during hospitalization.

Table 5 gives the results of the final logistic regression model. In both the simple and full models, subject group and gender were significant predictors of UTI status. In the simple model, the OR for subject group was 20.54 (95% CI, 2.62–160.96; $P < .001$), and the OR for female gender was 3.57 (95% CI, 1.31–9.72; $P = .013$). In the full model, the OR for subject group was 30.29 (95% CI, 3.22–285.40; $P < .001$), and the OR for female gender was 5.42 (95% CI, 1.52–19.28; $P = .009$). The final logistic regression model presents the association of subject group with UTI status, controlling for gender and smoking status. It should be noted that, while smoking status was not statistically significant in the model, it was needed in the model (according to the −2 log likelihood test), and removal of smoking status from the model lowered the OR significantly. When the analyses were controlled for gender and smoking status, subjects in the acute relapse group were almost 29 times more likely to have a UTI than those in the control group (OR = 28.97; 95% CI, 3.44–243.85; $P = .002$). There was no statistically significant association with UTI among the stable outpatients versus controls (OR = 2.68; 95% CI, 0.22–32.43).

DISCUSSION

We found that after the analyses were controlled for gender and smoking status, subjects in the acute relapse group were almost 29 times more likely to have a UTI than controls. Thirty-five percent of acutely relapsed inpatients with schizophrenia and related disorders, compared to 5% of stable outpatients and 3% of controls, had a UTI.

There are several strengths of the present study. To our knowledge, ours is the first study to explore the prevalence of UTI in patients with primary psychotic disorders. Another strength is that we controlled for multiple potential confounding factors in the analyses, including gender, smoking, and diabetes. Also, we excluded subjects with recent antibiotic-treated infections, recent urologic procedures, chronic renal or urologic abnormalities, and medical

Table 3. Psychotropic Medication Use by Acute Relapse and Stable Outpatient Groups (N = 97)

Medication	Acute Relapse Group (n = 57), n (%)	Stable Outpatient Group (n = 40), n (%)	*P* Value
Antipsychotic	54 (95)	38 (95)	1.00[a]
Aripiprazole	5 (9)	2 (5)	
Clozapine	2 (4)	5 (13)	
Fluphenazine	0 (0)	1 (3)	
Fluphenazine decanoate	0 (0)	1 (3)	
Haloperidol	0 (0)	1 (3)	
Haloperidol decanoate	2 (4)	0 (0)	
Olanzapine	5 (9)	1 (3)	
Paliperidone palmitate	0 (0)	1 (3)	
Paliperidone palmitate OR haloperidol decanoate[b]	0 (0)	3 (8)	
Quetiapine	6 (11)	0 (0)	
Risperidone	17 (30)	5 (13)	
Risperdal Consta	0 (0)	2 (5)	
Ziprasidone	3 (5)	4 (10)	
Aripiprazole + trifluoperazine	1 (2)	0 (0)	
Clozapine + aripiprazole	0 (0)	1 (3)	
Clozapine + risperidone	3 (5)	0 (0)	
Haloperidol + olanzapine	0 (0)	2 (5)	
Haloperidol + paliperidone palmitate	0 (0)	1 (3)	
Haloperidol + quetiapine	1 (2)	2 (5)	
Haloperidol + risperidone	0 (0)	1 (3)	
Olanzapine + risperidone	1 (2)	0 (0)	
Olanzapine + ziprasidone	1 (2)	0 (0)	
Paliperidone + quetiapine	1 (2)	0 (0)	
Risperidone + asenapine	1 (2)	0 (0)	
Risperidone + haloperidol decanoate	0 (0)	2 (5)	
Risperidone + quetiapine	2 (4)	2 (5)	
Risperidone + ziprasidone	1 (2)	0 (0)	
Risperdal Consta + haloperidol	0 (0)	1 (3)	
Risperdal Consta + quetiapine	2 (4)	0 (0)	
None	3 (5)	0 (0)	
Missing data	0 (0)	2 (5)	
Mood stabilizer	26 (46)	15 (38)	.53
Antidepressant	27 (47)	17 (43)	.68
Benzodiazepine	15 (26)	6 (15)	.22
Anti-EPS	18 (32)	11 (28)	.82

[a]*P* value not determined for specific antipsychotics due to lack of standardized treatment in the study.
[b]Subjects were enrolled in an ongoing randomized double-blind trial of these 2 agents.
Abbreviation: EPS = extrapyramidal syndrome.

Table 4. Use of Psychotropic Medications by UTI Status in the Acute Relapse Group (N = 57)

Medication	UTI (n = 20), n (%)	No UTI (n = 37), n (%)	*P* Value
Antipsychotic	19 (95)	35 (95)	1.00[a]
Aripiprazole	3 (15)	2 (5)	
Clozapine	1 (5)	1 (3)	
Haloperidol decanoate	0 (0)	2 (5)	
Olanzapine	1 (5)	4 (11)	
Quetiapine	1 (5)	5 (14)	
Risperidone	7 (35)	10 (27)	
Ziprasidone	3 (15)	0 (0)	
Aripiprazole + trifluoperazine	1 (5)	0 (0)	
Clozapine + risperidone	2 (10)	1 (3)	
Haloperidol + quetiapine	0 (0)	1 (3)	
Olanzapine + risperidone	0 (0)	1 (3)	
Olanzapine + ziprasidone	0 (0)	1 (3)	
Paliperidone + quetiapine	0 (0)	1 (3)	
Risperidone + asenapine	0 (0)	1 (3)	
Risperidone + quetiapine	0 (0)	2 (5)	
Risperidone + ziprasidone	0 (0)	1 (3)	
Risperdal Consta + quetiapine	0 (0)	2 (5)	
None	1 (5)	2 (5)	
Mood stabilizer	7 (35)	19 (51)	.28
Antidepressant	8 (40)	19 (51)	.58
Benzodiazepine	6 (30)	9 (24)	.76
Anti-EPS	5 (25)	13 (35)	.56

[a]*P* value not determined for specific antipsychotics due to lack of standardized treatment in the study.
Abbreviations: EPS = extrapyramidal syndrome, UTI = urinary tract infection.

Table 5. Final Logistic Regression Model Showing the Associations of Subject Group and Potential Confounders With Urinary Tract Infection

Variable	Urinary Tract Infection, OR (95% CI)	*P* Value[a]
Subject group		**.002**
Acute relapse	28.97 (3.44–243.85)	
Stable outpatient	2.68 (0.22–32.43)	
Control[b]	1.00	
Gender		**.004**
Female	5.64 (1.75–18.23)	
Male[b]	1.00	
Smoker		.302
Yes	0.54 (0.17–1.75)	
No[b]	1.00	

[a]Bolded *P* values are significant at the α = .05 level.
[b]Reference group.

conditions associated with UTI, any of which might have confounded the results.

Several potential limitations of the present study warrant further discussion. Subjects with an acute psychotic relapse were identified by chart review, whereas stable outpatients and controls were prospectively recruited, a process which could have resulted in a selection bias. Nonetheless, the prevalence of laboratory evidence of UTI in the acute relapse group was strikingly high. Although the gold standard for diagnosis of UTI is > 100,000 CFU/mL of a single bacterial species in a symptomatic patient, urine cultures were generally not available for subjects in the acute relapse group, and we did not inquire about urinary symptoms at the time of assessment for stable outpatients and controls. This was an a priori decision, as data on the presence or absence of urinary symptoms in the acutely relapsed patients were inconsistently recorded. Thus, our definition of UTI was based on urinalysis and urine microscopy only. In the study by Manepalli et al,[6] however, 8 of the 14 patients with delirium and UTI (57%) were asymptomatic. It is possible that impairments due to acute psychosis could interfere with accurate reporting of urinary symptoms. Of the 2 subjects with a UTI in the stable outpatient group, one had a urine culture with > 100,000 CFU/mL of a single bacterial species, and the other had a negative urine culture. The control subject with a UTI had a urine culture with > 100,000 CFU/mL of a single bacterial species. An additional 5 subjects (2 stable outpatients and 3 controls) had a urine culture with > 100,000 CFU/mL of a single bacterial species in the absence of pyuria, leukocyte esterase, or nitrites, suggesting asymptomatic bacteriuria. Thus, it is possible that some of the subjects in the acute relapse group were misclassified as having a UTI.

The mechanisms underlying this association remain unclear. Antipsychotics, particularly high-potency first-generation agents, may be associated with urinary retention, which could increase the risk of UTI,[22] although the majority of subjects in our study were treated with second-generation agents. One possibility for this association is that acute psychosis precedes the UTI. Psychotic symptoms, including disorganization, delusions, and negative symptoms, as well as impulsivity, may be associated with decreased self-care or other behaviors that could increase the risk of UTI.

An interesting alternative hypothesis is that the UTI precedes and is a precipitating factor for acute psychotic relapse. Uncomplicated UTI has been proposed as a sufficient cause for delirium in the elderly.[23] In the study by Manepalli et al,[6] delirium cleared in 9 of 14 subjects (64%) after treatment of UTI. In our clinical experience, we have observed improvement in psychotic symptoms following treatment of UTI in some patients with acute relapse of schizophrenia, without changes in psychotropic medications. Several case reports[24–26] support the plausibility of this observation. Huber et al[24] described a patient with a first episode of psychosis preceded by bilateral urolithiasis with urinary retention leading to a UTI. The patient had full remission of psychosis without antipsychotic treatment following relief of obstruction and treatment of infection. Rajagopalan and Varma[25] reported on a 57-year-old woman with an acute exacerbation of paranoid schizophrenia who presented with disorganized speech, loose associations, and multiple delusions, including a delusion of pregnancy. She had a UTI, and, within 1 week, the delusion of pregnancy resolved with treatment of the UTI. Reeves[26] described a clinically stable 62-year-old man with schizophrenia who developed a UTI and was started on gatifloxacin. He had worsening psychosis, including auditory hallucinations and delusions of reference, and a culture showed that the UTI was resistant to gatifloxacin. Following a change in antibiotics, his symptoms improved over the next 2 days, and he returned to his baseline status without changes in psychotropic medications. Although this case was reported as potential gatifloxacin-induced psychosis (a rare potential adverse effect of treatment with fluoroquinolone antibiotics[27]), it is also possible that the UTI precipitated the psychotic exacerbation, as evidenced by the rapid remission of psychotic symptoms following appropriate antibiotic treatment, without changes in psychotropic medications.

Our results are also broadly consistent with findings of impaired immune function in patients with schizophrenia.[16,28–31] The association between prenatal infection and increased risk of schizophrenia is 1 example of the concept of fetal origins of adult disease,[28] which posits that events at key time points during gestation impact development and the subsequent risk of adult disease. It has been hypothesized that infection and associated inflammation during critical periods of neurodevelopment may permanently alter the "set point" of the immune system,[29] which might confer increased susceptibility to infection or to adverse neuropsychiatric effects from infection in patients with schizophrenia. Patients with acute psychosis may have reduced neutrophil phagocytosis.[16] Another study[30] found lower neutrophil bactericidal reserve and a greater incidence of subclinical bacterial infection in patients with schizophrenia versus controls. Natural killer cells also function as first-line defenders against infections. Abdeljaber et al[31] found a significant decrease in natural killer-cell activity in patients with schizophrenia versus matched controls. These studies support the plausibility that UTI precedes and might precipitate an acute psychotic relapse.

The association between an increased prevalence of UTI and acute psychotic relapse warrants replication in other larger samples. Future studies should obtain urine cultures and information on urinary symptoms to increase diagnostic accuracy. Prospective studies with serial urinalyses and urine cultures, with relapse as an outcome, are also possible. Consistent replication of these associations in well-controlled studies would suggest that antibiotic prophylaxis for UTI might decrease relapse risk in some patients. Our findings also highlight the potential importance of monitoring for comorbid UTI in inpatients with acute schizophrenia and related disorders.

Drug names: aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote and others), gabapentin (Neurontin, Gralise, and others), gatifloxacin (Zymar, Zymaxid, and others), haloperidol (Haldol and others), lithium (Lithobid and others), olanzapine (Zyprexa and others), paliperidone (Invega), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

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Potential conflicts of interest: In the past 12 months, **Dr Miller** has received grant/research support from the National Institute of Mental Health (NIMH); Georgia Health Sciences University; and the University of Oulu, Oulu, Finland. In the past 12 months, **Dr Buckley** has served as a consultant for NIMH and has received grant/research support from NIMH and Sunovion. **Drs Graham**, **Bodenheimer**, and **Waller** and **Mr Culpepper** have no potential conflicts of interest to disclose.

Funding/support: Direct funding for this research was provided by the Georgia Health Sciences University Department of Psychiatry.

Acknowledgments: The authors thank the following individuals, all affiliated with the Department of Psychiatry and Health Behavior, Georgia Health Sciences University, Augusta, Georgia: Courtney N. Caulder, BA; Laura A. Meyer, MA; Christy L. Wise, BA (all of whom assisted with subject recruitment and assessment and with database entry); Dawn K. Montoya, BA, CCRC; Rebecca B. Nichols, BS, CCRC; and Edna M. Stirewalt, BS, CCRC (all of whom assisted with subject recruitment). These acknowledged individuals have no potential conflicts of interest to report.

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