Urinary Tract Infections in Acute Psychosis

Krystle L. Graham, DO; Chelsea M. Carson, MD; Amaka Ezeoke, MD; Peter F. Buckley, MD; and Brian J. Miller, MD, PhD, MPH

ABSTRACT

Objective: Schizophrenia is associated with increased infections across the lifespan. We previously found an association between urinary tract infection (UTI) and acute nonaffective psychosis. The aims of this study were to explore further the relationship between UTI and acute psychosis, including associated clinical features.

Method: We identified by chart review subjects aged 18–64 years who were hospitalized between January 2010 and April 2012 for an acute episode of *DSM-IV* nonaffective psychosis (schizophrenia, schizoaffective disorder, psychosis not otherwise specified, or delusional disorder; n = 134), affective psychosis (bipolar or major depressive disorder with psychotic features; n = 101), or alcohol detoxification (n = 105), and we recruited healthy controls (n = 39). *Urinary tract infection* was defined as positive leukocyte esterase and/or positive nitrites on urinalysis and ≥ 5–10 leukocytes/high-powered field on urine microscopy.

Results: The prevalence of UTI was 21% in nonaffective psychosis, 18% in affective psychosis, 12% in alcohol use disorders, and 3% in controls. After controlling for potential confounders, UTI was almost 11 times more likely in subjects with nonaffective psychosis than controls (OR = 10.7; 95% CI, 1.4–83.2; *P* = .02) and almost 9 times more likely in subjects with major depressive disorder with psychotic features than controls (OR = 8.9; 95% CI, 1.1–71.4; *P* = .04). There were no associations between clinical characteristics and UTI in acute psychosis.

Conclusions: We replicated and extended an association between an UTI and acute psychosis. Findings suggest that infections appear relevant to the etiopathophysiology of relapse and increased premature mortality risk in the psychoses. The results also highlight the potential importance of monitoring for comorbid UTI in relevant patient populations.

J Clin Psychiatry 2014;75(4):379–385

Submitted: *March 13, 2013; accepted October 24, 2013.*
Online ahead of print: *January 21, 2014 (doi:10.4088/JCP.13m08469).*
Corresponding author: *Brian J. Miller, MD, PhD, MPH, Department of Psychiatry and Health Behavior, Georgia Regents University, 997 Saint Sebastian Way, Augusta, GA 30912 (brmiller@gru.edu).*

Schizophrenia is associated with increased infections across the lifespan, and an etiopathophysiological 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[1] and may act synergistically with family history of psychosis.[2] Childhood central nervous system viral infections were associated with a 2-fold increased risk of schizophrenia in adulthood in a meta-analysis.[3] Another meta-analysis found that subjects with first-episode psychosis have a 2.5-fold increased risk of infection with *Toxoplasma gondii* (as measured by antibodies) compared to controls.[4] Patients with schizophrenia also have increased mortality,[5] including mortality from potentially preventable infectious diseases, such as pneumonia and influenza.[6,7] There is also evidence that the mortality gap in schizophrenia may be increasing over time.[8] Increased urbanicity, a replicated risk factor for schizophrenia, may be associated with increased exposure to infections.[9] Polymorphisms in major histocompatibility complex genes, which are critical to immune function, are associated with increased risk of schizophrenia.[10] There is evidence for abnormalities in immune cell numbers[11] and cytokine levels[12] in first-episode psychosis, suggesting a role for immune dysfunction that may be independent of antipsychotic medications. Furthermore, patients with schizophrenia may have abnormal function of neutrophils[13,14] and natural killer cells,[15] and the resulting impaired host defense may increase susceptibility to infections.

Along these lines, infections are also associated with acute psychosis. The most well known association is geriatric patients with psychosis and a comorbid urinary tract infection (UTI) in the context of either dementia or delirium.[16,17] Acute psychotic relapse is common, and relapse prevention represents an important treatment issue in schizophrenia. Robinson et al[18] 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-resistant symptoms, cognitive decline, and functional disability.[19–21]

The association between UTI and acute psychosis may also extend to patients with primary psychotic disorders. We previously reported a 35% prevalence of UTI on admission in a sample of 57 acutely relapsed inpatients with *DSM-IV* schizophrenia.[22] In that study, after data were controlled for gender and smoking status, acutely relapsed subjects with schizophrenia were almost 29 times more likely to have a UTI than controls. By contrast, there was no statistically significant association with UTI among the stable outpatients versus controls. In this study, we aimed to explore further the association between UTI and acute psychosis, including associated clinical features.

METHOD

Subjects

Three hundred forty acutely ill subjects from 3 subject groups, including 134 with schizophrenia and related disorders (nonaffective psychosis group), 101 with psychotic mood disorders (affective psychosis group), and 105 with alcohol use disorders (alcohol use disorders group), were identified by chart review of consecutive inpatient admissions to the Georgia Regents University

Clinical Points

- Subjects with acute nonaffective psychosis and psychotic depression have a significantly increased prevalence of urinary tract infections.
- Clinicians should monitor for comorbid urinary tract infections in patients with acute psychosis, which often go unrecognized and untreated.

Medical Center Adult Inpatient Psychiatry Unit, beginning in January 2010. As described previously,[22] 40 healthy controls were recruited in the Augusta, Georgia, area between July 2010 and April 2012. One subject gave informed consent but withdrew before any assessments were completed, leaving 39 subjects in the control group. Thus, a total of 379 subjects completed the study. There was no overlap between subjects in the nonaffective psychosis group in this study and in our previous publication.[22] The study was approved by the institutional review board (IRB) of Georgia Regents University. A waiver of informed consent was granted by the IRB for the chart review.

Inclusion criteria for the study were subjects who were male and female and aged 18–64 years. For all inpatients, urine samples were obtained within 48 hours of admission. Subjects in the nonaffective psychosis group met *DSM-IV* criteria for schizophrenia, schizophreniform disorder, delusional disorder, psychosis not otherwise specified, or schizoaffective disorder. Subjects in the affective psychosis group met *DSM-IV* criteria for either bipolar disorder with psychotic features (n = 39) or major depressive disorder with psychotic features (n = 62). Subjects in the alcohol use disorders group met *DSM-IV* criteria for alcohol abuse or dependence. Controls had no lifetime or current *DSM-IV* diagnosis of schizophrenia or related psychotic disorder or manic, depressed, or mixed affective episode; and they had no history of exposure to an 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 immune deficiency syndrome (HIV/AIDS), or multiple sclerosis. An additional exclusion criterion in the control group was evidence of imminent danger to self or others (ie, suicidal intent, or recent history of violence or threats of violence).

Procedures

Data for inpatient subjects were reviewed and extracted from the electronic medical record by 4 study authors (C.C., A.E., K.L.G., and B.J.M.). A total of 537 inpatient records were screened, of which 340 met the study inclusion/exclusion criteria. A complete blood count with differential, comprehensive metabolic panel as well as midstream clean-catch urine sample for urinalysis with microscopy, urine drug screen, and urine pregnancy test in females were part of routine admission orders for all inpatient subjects. However, urine cultures were not part of routine admission orders. Height and weight, smoking status, and medical history were also recorded at the time of admission. The diagnosis for inpatient subjects was verified from the hospital discharge summary, which reflects the final diagnosis given by the attending inpatient psychiatrist. For subjects in the nonaffective and affective psychosis groups, we also extracted data from the hospital admission and progress notes on the following psychiatric symptoms (recorded as categorical yes/no variables): auditory hallucinations, visual hallucinations, other hallucinations, delusions, paranoia, disorganized thinking, disorganized behavior, catatonia, prominent negative symptoms, suicidal ideation, homicidal ideation, manic symptoms, and depressive symptoms. A description of the laboratory, physical, and psychiatric evaluation of the control group has been described previously.[10]

UTI Determination

The gold standard for diagnosis of UTI is > 100,000 colony-forming units (CFU)/mL of a single bacterial species in a symptomatic patient. Urinalyses positive for leukocyte esterase and/or nitrite have a 67%–100% sensitivity and 67%–98% specificity for bacteriuria of > 100,000 CFU/mL.[23] Subjects with bacterial concentrations of > 100,000 CFU/mL and symptoms of UTIs have urine leukocyte counts of ≥ 10 leukocytes/high-powered field (HPF).[24] In this study, a UTI was defined as positive leukocyte esterase and/or positive nitrites on urinalysis and ≥ 5–10 leukocytes/HPF on urine microscopy. One investigator (B.J.M.), made the determination of UTI status and contacted subjects in the healthy control group with a UTI to advise follow-up medical care.

Statistical Analysis

Sample size was determined assuming a χ^2 test, a significance level of .05, and power of 0.80. Rates of UTI assumed in each group were 0.01 in controls, 0.08 in the psychotic mood disorders and alcohol use disorders group, and 0.20 for the schizophrenia (and related disorders) group. A total sample size of 318, or 106 per group, was needed to adequately test for difference in rates of UTI between the inpatient subject groups.

All statistical analysis was performed using SPSS, version 20 (IBM SPSS, Chicago, Illinois). Statistical significance was assessed using an α level of .05. Given the preliminary nature of this study, we did not correct *P* values for multiple comparisons. Descriptive statistics were calculated by subject group and by UTI status. Simple associations with UTI status of demographic, clinical, and the main independent variable subject group were determined using χ^2 and *t* tests. For the nonaffective and affective psychosis groups, simple associations with UTI status and psychiatric symptoms were determined using χ^2 tests. Additionally, the association of

Table 1. Prevalence of Urinary Tract Infection (UTI) by Subject Group

	UTI					
	Yes		No		*P* Value (vs alcohol	*P* Value[a]
Group	n	%	n	%	use disorder)	(vs control)
Nonaffective psychosis	28	21	106	79	.09	**<.01**
Affective psychosis	18	18	83	82	.33	**.03**
Alcohol use disorder	13	12	92	88		.11
Control	1	3	38	97		

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

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 on UTI was determined using logistic regression. A model building strategy was used to arrive at a final model controlling for potential confounders, utilizing the same approach as in our previous article on this topic.[22] 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 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 odds ratio between subject group and UTI were removed from the model. The final model resulted in those variables that were statistically significant confounders, changed the odds ratio significantly, or resulted in a significant −2 log likelihood test.

RESULTS

The prevalence of UTI by subject group is given in Table 1. Twenty-one percent of subjects with nonaffective psychosis, 18% with affective psychosis, 12% with alcohol use disorders, and 3% of controls had a UTI. Among subjects with affective psychosis, there was no difference in the prevalence of UTI between subjects with bipolar versus major depressive disorder (21% vs 18%, $P = .60$). There was a significant increased prevalence of UTI in subjects with nonaffective ($P < .01$) and affective ($P = .03$) psychosis, but not in alcohol use disorders ($P = .11$), compared to controls. There was a trend for an increased prevalence of UTI in subjects with nonaffective psychosis ($P = .09$), but not affective psychosis ($P = .33$), compared to subjects with alcohol use disorders.

Table 2 presents the descriptive statistics by UTI status for each subject group. Across all subject groups, a significant association with UTI status was found only for gender, with a significant increase in female subjects ($P < .01$). Otherwise, there was no difference in age, race, highest education, marital status, smoking status, diabetes, and BMI based on UTI status. Subjects in the acute relapse and stable outpatient groups were more likely to have less education, be smokers, have diabetes, and have higher BMIs than those in the control group ($P < .01$ for each). Female gender ($P < .01$) was significantly associated with UTI.

Table 3 describes the psychotropic medications by subject group. Nine subjects in the nonaffective psychosis group and 25 subjects in the affective psychosis group were not prescribed antipsychotics. Within each subject group, there was no difference in the prevalence of treatment with mood stabilizers, antidepressants, benzodiazepines, hypnotics, and medications for extrapyramidal symptoms based on UTI status.

Table 4 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. After controlling for potential confounding factors, we found that subjects with nonaffective psychosis were almost 11 times more likely to have a UTI than controls (OR = 10.7; 95% CI, 1.4–83.2; $P = .02$). Affective psychosis and alcohol use disorders (vs controls) were predictors of UTI at the trend level. In a secondary analysis, major depressive disorder with psychotic features (vs controls) was a significant predictor of UTI (OR = 8.9; 95% CI, 1.1–71.4; $P = .04$).

Table 5 describes the clinical characteristics by UTI status in subjects with psychosis. There was a trend for an association between UTI and increased illicit drug use in the nonaffective psychosis group ($P = .10$). In the affective psychosis group, there was a trend for increased disorganized thinking in subjects with UTI ($P = .05$). Otherwise, with psychosis, there were no significant differences in diagnosis, number of previous psychiatric hospitalizations, family history of psychosis, the prevalence of specific psychotic or mood symptoms, alcohol use, discharge Global Assessment of Functioning score, and length of stay based on UTI status.

DISCUSSION

We replicated and extended our previous finding of an association between UTI and acute psychosis. After controlling for potential confounding factors, we found that subjects with nonaffective psychosis were almost 11 times more likely to have a UTI than controls. The association between UTI and acute psychosis may also extend to affective psychoses. After controlling for potential confounding factors, we found that subjects with major depressive disorder with psychotic features were almost 9 times more likely to have a UTI than controls. Greater than 1 in 5 subjects with nonaffective psychosis and almost 1 in 5 with affective psychosis had a UTI. We did not find any significant associations between UTI and clinical characteristics in acute psychosis.

There are several strengths of the present study. We replicated our previous finding in a larger sample of subjects with nonaffective psychosis, and there was no overlap in subjects between the 2 studies. We also explored both the prevalence of UTI in patients with affective psychosis and the relationships between UTI and clinical characteristics in acute psychosis. Another strength is that we controlled

Table 2. Demographic Characteristics by Subject Group and Urinary Tract Infection (UTI) Status

	Nonaffective Psychosis (n = 134)				Affective Psychosis (n = 101)				Alcohol Use Disorder (n = 105)				Control (n = 39)				
	UTI (n = 28)		No UTI (n = 106)		UTI (n = 18)		No UTI (n = 83)		UTI (n = 13)		No UTI (n = 92)		UTI (n = 1)		No UTI (n = 38)		*P*
Variable	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	Value[a]
Male gender	7	25	63	59	2	11	27	32	5	38	65	71	0	0	19	5	**<.01**
Race																	
African	18	64	73	69	8	39	34	41	6	46	30	33	1	100	12	32	
White	9	32	31	29	9	56	47	57	7	54	62	67	0	0	19	50	
Other	1	4	2	2	1	6	2	2	0	0	0	0	0	0	7	18	
Highest education: high school graduate or higher	19	68	57	54	14	78	57	69	11	92	73	84	1	100	36	95	.79
Ever married: yes	16	54	34	32	13	72	42	52	10	77	61	67	0	0	26	68	.12
Smoker: yes	10	37	44	41	5	28	41	49	9	69	52	57	0	0	4	11	.67
Diabetes: yes	4	14	24	23	2	11	10	12	1	8	5	5	0	0	2	5	.84
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age, y	43.3	11.7	39.6	12.4	40.5	10.9	39.6	12.4	41.5	12.7	44.5	10.7	22.4		40.2	13.6	.71
Body mass index (kg/m^2)	30.3	11.3	29.3	8.2	29.2	7.8	30.3	8.1	23.7	4.0	27.6	6.2	39.6		26.5	5.3	.96

[a]Bolded *P* values are significant at the α = .05 level. *P* values are for the association of UTI status for all subject groups combined, with each variable.

Table 3. Psychotropic Medications by Subject Group and Urinary Tract Infection (UTI) Status

	Nonaffective Psychosis (n = 134)					Affective Psychosis (n = 101)					Alcohol Use Disorder (n = 105)				
	UTI (n = 28)		No UTI (n = 106)			UTI (n = 18)		No UTI (n = 83)			UTI (n = 13)		No UTI (n = 92)		
Medication	n	%	n	%		n	%	n	%		n	%	n	%	
Aripiprazole	3	11	1	1		4	22	12	14		0	0	0	0	
Clozapine	1	4	3	3		0	0	0	0		0	0	0	0	
Fluphenazine	0	0	0	0		0	0	1	1		0	0	0	0	
Haloperidol	1	4	2	2		0	0	0	0		0	0	0	0	
Haloperidol decanoate	0	0	1	1		0	0	0	0		0	0	0	0	
Loxapine	0	0	2	2		0	0	0	0		0	0	0	0	
Olanzapine	1	4	8	8		1	6	8	10		0	0	0	0	
Paliperidone	0	0	2	2		0	0	0	0		0	0	0	0	
Paliperidone palmitate	0	0	2	2		0	0	0	0		0	0	0	0	
Perphenazine	0	0	1	1		0	0	0	0		0	0	0	0	
Quetiapine	9	32	19	18		3	17	11	13		2	15	5	5	
Risperidone	7	25	31	29		3	17	24	29		0	0	1	1	
Thiothixene	0	0	0	0		0	0	1	1		0	0	0	0	
Ziprasidone	2	7	6	6		0	0	8	10		0	0	0	0	
Aripiprazole + quetiapine	0	0	2	2		0	0	0	0		0	0	0	0	
Aripiprazole + ziprasidone	0	0	0	0		0	0	0	0		0	0	1	1	
Chlorpromazine + trifluoperazine	1	4	1	1		0	0	0	0		0	0	0	0	
Haloperidol + quetiapine	0	0	1	1		0	0	0	0		0	0	0	0	
Olanzapine + quetiapine	0	0	1	1		0	0	0	0		0	0	0	0	
Risperidone + quetiapine	0	0	1	1		0	0	0	0		0	0	0	0	
Fluphenazine + fluphenazine decanoate	0	0	1	1		0	0	0	0		0	0	0	0	
Haloperidol + haloperidol decanoate	1	4	2	2		0	0	0	0		0	0	0	0	
Quetiapine + fluphenazine decanoate	0	0	1	1		0	0	0	0		0	0	0	0	
Quetiapine + haloperidol decanoate	0	0	1	1		0	0	0	0		0	0	0	0	
Quetiapine + paliperidone palmitate	0	0	1	1		0	0	0	0		0	0	0	0	
Quetiapine + risperidone LAI	0	0	1	1		0	0	0	0		0	0	0	0	
Risperidone + fluphenazine decanoate	0	0	1	1		0	0	0	0		0	0	0	0	
Risperidone + fluphenazine decanoate	0	0	1	1		0	0	0	0		0	0	0	0	
Risperidone + haloperidol decanoate	0	0	2	2		0	0	0	0		0	0	0	0	
Risperidone + paliperidone palmitate	0	0	1	1		0	0	0	0		0	0	0	0	
Ziprasidone + paliperidone palmitate	0	0	1	1		0	0	0	0		0	0	0	0	
Aripiprazole + quetiapine + haloperidol decanoate	1	4	0	0		0	0	0	0		0	0	0	0	
Olanzapine + risperidone + risperidone LAI	0	0	1	1		0	0	0	0		0	0	0	0	
None	1	4	8	8		7	39	18	22		11	85	85	92	
					P Value					*P* Value					*P* Value
Mood stabilizer	5	18	36	34	.11	6	33	30	36	1.00	0	0	5	5	> .99
Antidepressant	11	39	35	33	.66	11	61	56	67	.59	5	38	39	42	> .99
Benzodiazepines	4	14	18	17	1.00	4	22	17	20	1.00	0	0	3	3	> .99
Hypnotics	5	18	24	23	.80	6	33	28	34	1.00	6	46	25	27	.20
Medications for extrapyramidal symptoms	4	14	26	25	.31	0	0	5	6	.58	0	0	2	2	> .99

Abbreviation: LAI = long-acting injectable.

Table 4. Final Logistic Regression Model of Subject Group on Urinary Tract Infection Status

Variable	OR	95% CI	*P* Value[a]
Subject group			
Nonaffective psychosis	10.7	1.4–83.2	**.02**
Affective psychosis	6.5	0.8–51.6	.08
Bipolar disorder	8.1	0.9–69.3	.06
Major depressive disorder	8.9	1.1–71.4	**.04**
Alcohol use disorder	6.5	0.9–56.9	.07
Control	1.0		
Control			
Female	5.3	2.0–14.2	**<.01**
Male	1.0		

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

Table 5. Clinical Characteristics by Urinary Tract Infection (UTI) Status in Subjects With Psychosis

	Nonaffective Psychosis (n = 135)					Affective Psychosis (n = 101)				
	UTI (n = 29)		No UTI (n = 106)		*P*	UTI (n = 18)		No UTI (n = 83)		*P*
Variable	n	%	n	%	Value	n	%	n	%	Value
Schizophrenia	14	50	62	59						
Schizoaffective disorder	5	18	26	25						
Psychosis NOS	8	29	16	15	.13					
Delusional disorder	1	4	0	0						
Bipolar disorder w/psychotic features						8	44	31	37	
MDD w/psychotic features						10	56	52	63	.60
> 5 previous psychiatric hospitalizations	8	29	45	43	.43	2	11	22	27	.81
Family history of psychosis	6	21	18	18	.78	1	6	7	9	1.00
Auditory hallucinations	22	79	73	69	.36	13	72	58	70	1.00
Visual hallucinations	11	39	28	32	.24	7	39	31	37	1.00
Other hallucinations	1	4	1	1	.38	1	6	1	1	.33
Delusions	15	54	61	58	.83	6	33	40	48	.30
Paranoia	17	61	55	52	.52	3	17	28	34	.26
Disorganized thinking	9	32	26	24	.47	4	22	5	6	.05
Disorganized behavior	6	21	33	31	.36	2	11	7	8	.66
Catatonia	1	4	3	3	1.00	0	0	1	1	1.00
Prominent negative symptoms	3	11	6	6	.40	0	0	3	4	1.00
Suicidal ideation	14	50	45	42	.53	15	83	55	66	.26
Homicidal ideation	3	11	21	20	.41	3	17	11	13	.71
Manic symptoms	3	11	10	9	.73	4	22	18	22	1.00
Depressed mood	15	54	51	48	.67	14	78	70	84	.50
Current alcohol use	6	21	33	31	.36	4	22	24	29	.77
Current illicit drug use	12	43	26	25	.10	7	29	23	30	.40
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Discharge GAF score	48.5	9.2	47.8	8.5	.72	47.8	6.7	47.4	10.8	.88
Length of stay, d	8.0	6.0	7.6	4.5	.70	6.8	3.1	6.6	3.9	.83

Abbreviations: GAF = Global Assessment of Functioning, MDD = major depressive disorder, NOS = not otherwise specified.

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

Several potential limitations of the present study warrant further discussion. As noted in our previous study, while 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 inpatients in this study. Thus, our definition of UTI was based on urinalysis and urine microscopy only. In a previous study,[25] 8 of 14 patients (57%) with delirium and UTI were asymptomatic. Impairments due to acute psychosis could interfere with accurate reporting of urinary symptoms. It is also possible that some of the subjects with asymptomatic bacteriuria were misclassified as having a UTI. Another limitation of the present study is that clinical characteristics were determined by chart review, rather than by in-person interviews. Although we controlled for a number of important factors, the increased prevalence of UTI in psychiatric inpatients could be due to residual confounding: that is, confounded by an unknown or unmeasured factor. We were unable to assess or control for factors such as self-care/hygiene, frequency of recent sexual activity, poor access to care, or treatment nonadherence, which may have impact on this association.

We did not find significant differences in the prevalence of UTI among the inpatient subject groups. Our sample size calculations were based on an assumed 8% prevalence of UTI in the affective psychosis and alcohol use disorders groups. The higher observed prevalence in these groups suggests that our study was underpowered to detect a difference between these groups. Our study may have also lacked adequate statistical power to identify associations with clinical characteristics, given the relatively small number of subjects with UTI.

The potential mechanisms underlying the association between UTI and acute psychosis remain largely unknown. It is possible that a UTI precedes and is a precipitating factor for acute psychosis. Several case reports and case series support the plausibility of this hypothesis in that treatment of UTI was associated with amelioration of psychosis. Two case reports of first-episode psychosis in patients with a comorbid UTI described full remission of psychotic symptoms with treatment of the underlying infection.[26,27] Longitudinal follow-up of first-episode psychosis suggests that diagnoses may change between nonaffective and affective psychoses in a portion of subjects.[28] There are 3 case reports of patients with an acute exacerbation of chronic schizophrenia that resolved with treatment of comorbid UTI.[29–31] It is possible that the host inflammatory response to infection mediates the association with acute psychosis. We recently found that absolute blood monocyte counts were a significant predictor of UTI and that female subjects with comorbid UTI and acute nonaffective psychosis had significantly lower differential blood lymphocyte counts in our previous study.[32] Further studies are needed to investigate this potential mechanism.

Cystitis, or lower UTI, is the most common bacterial infection. Approximately 50% of women will experience at least 1 UTI in their lifetime.[33] Although UTIs occur less frequently in men than in women, a National Ambulatory Medical Care Survey found that 0.6% of male office visits (vs 1.2% among female visits) were for UTI.[34] Thus, our observed 3% prevalence of UTI in controls is comparable with the epidemiology of UTI in the general population. Although not the focus of the present study, we also found a trend for an association between UTI and alcohol use disorders, which has been described previously.[35] We found a 12% prevalence of UTI in subjects with alcohol use disorders, which is broadly consistent with a 7% prevalence of UTI among 382 inpatients with liver cirrhosis.[36] Interestingly, immune system dysfunction secondary to alcohol use has been posited to contribute to this association. Another possibility is that symptoms associated with alcohol use disorders may be associated with decreased self-care or other behaviors (eg, sexual activity) that could increase risk of UTI. This finding also highlights the potential importance of monitoring for comorbid UTI in acute psychiatric inpatients.

The association between UTI and acute psychosis, including affective psychoses, warrants replication in other samples. Given the high prevalence of medical comorbidity in patients with schizophrenia[37] and mood disorders,[38] the association between infection and acute psychosis could also be explored with other types of common infections, such as cellulitis and pneumonia. Regarding the association with UTI, future studies should obtain urine cultures and urinary symptoms to increase diagnostic accuracy. Future studies should also assess other potential confounding factors, such as self-care and access to care. Longitudinal studies with serial urinalyses/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 UTI as a routine part of health screening in relevant patient populations. Recognition and treatment of UTI in acute psychiatric inpatients may also decrease risks of other adverse events during hospitalization. Taken together, infections appear relevant to the etiopathophysiology of relapse and increased premature mortality risk in the psychoses.

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

Author affiliations: Department of Psychiatry and Health Behavior, Georgia Regents University (Drs Graham, Carson, Ezeoke, and Miller); and Medical College of Georgia, Georgia Regents University (Dr Buckley), Augusta.

Potential conflicts of interest: In the past 12 months, **Dr Buckley** has served as a consultant for the National Institute of Mental Health (NIMH), and has received grant/research support from Sunovion and NIMH. In the past 12 months, **Dr Miller** has received grant/research support from the NIMH and Georgia Regents University and has received honoraria from Medscape and Insight Consulting Group. **Drs Graham, Carson,** and **Ezeoke** have no financial or other conflicts of interest to disclose.

Funding/support: Direct funding for this research was provided by the Georgia Regents University Department of Psychiatry (Dr Miller).

Role of the sponsor: The Georgia Regents University Department of Psychiatry had no further role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Acknowledgment: The authors thank Courtney N. Caulder, BA, Department of Psychiatry and Health Behavior, Georgia Regents University, for assistance with and database entry. Ms Caulder reports no other financial or other potential conflicts of interest.

REFERENCES

1. Cannon M, Clarke MC. Risk for schizophrenia—broadening the concepts, pushing back the boundaries. *Schizophr Res*. 2005;79(1):5–13.
2. Clarke MC, Tanskanen A, Huttunen M, et al. Evidence for an interaction between familial liability and prenatal exposure to infection in the causation of schizophrenia. *Am J Psychiatry*. 2009;166(9):1025–1030.
3. Khandaker GM, Zimbron J, Dalman C, et al. Childhood infection and adult schizophrenia: a meta-analysis of population-based studies. *Schizophr Res*. 2012;139(1–3):161–168.
4. Torrey EF, Bartko JJ, Lun ZR, et al. Antibodies to Toxoplasma gondii in patients with schizophrenia: a meta-analysis. *Schizophr Bull*. 2007;33(3):729–736.
5. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia: antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. *Br J Psychiatry*. 1998;173(4):325–329.
6. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry*. 2007;64(10):1123–1131.
7. Brown S, Kim M, Mitchell C, et al. Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry*. 2010;196(2):116–121.
8. Miller BJ. Hospital admission for schizophrenia and bipolar disorder. *BMJ*. 2011;343(1):d5652.
9. van Os J. Does the urban environment cause psychosis? *Br J Psychiatry*.

2004;184(4):287–288.
10. Irish Schizophrenia Genomics Consortium and the Wellcome Trust Case Control Consortium 2. Genome-wide association study implicates HLA-C*01:02 as a risk factor at the major histocompatibility complex locus in schizophrenia. *Biol Psychiatry*. 2012;72(8):620–628.
11. Miller B, Gassama B, Sebastian D, et al. Meta-analysis of lymphocytes in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry*. 2013;73(10):993–999.
12. Miller BJ, Buckley P, Seabolt W, et al. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effect. *Biol Psychiatry*. 2011;70(7):663–671.
13. McAdams C, Leonard BE. Neutrophil and monocyte phagocytosis in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 1993;17(6):971–984.
14. Rwegellera GG, Fernando KA, Okong'o O. Bactericidal activity of neutrophils of schizophrenic patients. *Med J Zambia*. 1982;16(2):21–22.
15. Abdeljaber MH, Nair MP, Schork MA, et al. Depressed natural killer cell activity in schizophrenic patients. *Immunol Invest*. 1994;23(4–5):259–268.
16. Brendel RW, Stern TA. Psychotic symptoms in the elderly. *Prim Care Companion J Clin Psychiatry*. 2005;7(5):238–241.
17. Webster J, Grossberg GT. Late-life onset of psychotic symptoms. *Am J Geriatr Psychiatry*. 1998;6(3):196–202.
18. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;56(3):241–247.
19. Müller N, Riedel M, Scheppach C, et al. Beneficial antipsychotic effects of celecoxib add-on therapy compared to risperidone alone in schizophrenia. *Am J Psychiatry*. 2002;159(6):1029–1034.
20. Shepherd M, Watt D, Falloon I, et al. The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. *Psychol Med Monogr suppl*. 1989;15:1–46.
21. Wyatt RJ. Early intervention with neuroleptics may decrease the long-term morbidity of schizophrenia. *Schizophr Res*. 1991;5(3):201–202.
22. Miller BJ, Graham KL, Bodenheimer CM, et al. A prevalence study of urinary tract infections in acute relapse of schizophrenia. *J Clin Psychiatry*. 2013;74(3):271–277.
23. Wilson ML, Gaido L. Laboratory diagnosis of urinary tract infections in adult patients. *Clin Infect Dis*. 2004;38(8):1150–1158.
24. Pappas PG. Laboratory in the diagnosis and management of urinary tract infections. *Med Clin North Am*. 1991;75(2):313–325.
25. Manepalli J, Grossberg GT, Mueller C. Prevalence of delirium and urinary tract infection in a psychogeriatric unit. *J Geriatr Psychiatry Neurol*. 1990;3(4):198–202.
26. Huber J, Huber CG, Lambert M, et al. 'Stoned': Schneiderian first-rank symptoms as a manifestation of bilateral obstructive urolithiasis. *Br J Psychiatry*. 2010;196(6):496–497.
27. Salviati M, Bersani FS, Macrì F, et al. Capgras-like syndrome in a patient with an acute urinary tract infection. *Neuropsychiatr Dis Treat*. 2013;9:139–142.
28. Salvatore P, Baldessarini RJ, Tohen M, et al. McLean-Harvard International First-Episode Project: two-year stability of *DSM-IV* diagnoses in 500 first-episode psychotic disorder patients. *J Clin Psychiatry*. 2009;70(4):458–466.
29. Rajagopalan M, Varma SL. Urinary tract infection and delusion of pregnancy. *Aust N Z J Psychiatry*. 1997;31(5):775–776.
30. Reeves RR. Exacerbation of psychotic symptoms associated with gatifloxacin. *Psychosomatics*. 2007;48(1):87.
31. Yeh YW, Kuo SC, Chen CY. Urinary tract infection complicated by urine retention presenting as pseudocyesis in a schizophrenic patient. *Gen Hosp Psychiatry*. 2012;34(1):101.e9–e101.e10.
32. Miller BJ, Bodenheimer CM, Culpepper NH, et al. Differential white blood cell counts may predict urinary tract infection in acute non-affective psychosis. *Schizophr Res*. 2013;147(2–3):400–401.
33. Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Am J Med*. 2002;113(suppl 1A):5S–13S.
34. Schapper SM. Ambulatory care visits to physician offices, hospital outpatients departments, and emergency departments. United States, 1997. *Vital Health Stat 13*. 1999;143:1–39.
35. Pitts TO, Van Thiel DH. Urinary tract infections and renal papillary necrosis in alcoholism. *Recent Dev Alcohol*. 1986;4:341–355.
36. Rosa H, Silvério AO, Perini RF, et al. Bacterial infection in cirrhotic patients and its relationship with alcohol. *Am J Gastroenterol*. 2000;95(5):1290–1293.
37. Goldman LS. Medical illness in patients with schizophrenia. *J Clin Psychiatry*. 1999;60(suppl 21):10–15.
38. McIntyre RS, Rosenbluth M, Ramasubbu R, et al; Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force. Managing medical and psychiatric comorbidity in individuals with major depressive disorder and bipolar disorder. *Ann Clin Psychiatry*. 2012;24(2):163–169.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.