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## Urinary tract infections in children and adolescents with acute psychosis

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### ABSTRACT

**Objective:** Schizophrenia is associated with increased infections. We previously found an association between urinary tract infection (UTI) and acute psychosis in adults. The aims of this study were to 1) evaluate the prevalence of UTI at the time of admission in children and adolescents with non-affective psychosis and psychotic depression versus those with non-psychotic major depressive disorder, and 2) compare demographic and clinical features between children and adolescents with acute psychosis with and without comorbid UTI.

**Method:** We performed a retrospective chart review of 227 subjects ages 10–18 who were hospitalized between 2005 and 2014 for an acute episode of DSM-IV non-affective psychosis (schizophrenia, schizoaffective disorder, psychosis NOS, or delusional disorder;  $n = 80$ ), major depressive disorder (MDD) with psychotic features ( $n = 47$ ); or MDD without psychotic features ( $n = 100$ ).

**Results:** The prevalence of UTI was 20% in non-affective psychosis, 9% in MDD with psychotic features, and 13% in non-psychotic MDD. After controlling for potential confounders, UTI was 3.5 times more likely in subjects with non-affective psychosis than non-psychotic MDD (OR = 3.5, 95% CI 1.3–9.2,  $p = 0.01$ ). Subjects with UTI had a higher prevalence of manic symptoms, but otherwise there were no associations between clinical characteristics and UTI in acute psychosis.

**Conclusions:** We found an association between UTIs and children and adolescents with acute non-affective psychosis. The results highlight the potential importance of screening for comorbid UTI in patients with acute psychosis.

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### 1. Introduction

Schizophrenia is associated with increased infections throughout the lifespan. Prenatal maternal infection, with a variety of different infectious agents, is a replicated risk factor for the development of schizophrenia in the offspring (Brown and Derkits, 2010) and may act synergistically with family history of psychosis on schizophrenia risk (Clarke et al., 2009). This association appears to be bidirectional: hospital contact for infection during childhood or adolescence is associated with an increased risk of schizophrenia in adulthood (Nielsen et al., 2014), and schizophrenia is also a risk factor for infections (Benros et al., 2014). Schizophrenia is also associated with increased mortality from infectious diseases, including pneumonia and influenza (Brown et al., 2010; Saha et al., 2007). An etiopathophysiological role for immune abnormalities in schizophrenia has been one of the more enduring findings in the field. Polymorphisms in major histocompatibility complex genes, which are critical to immune function, are associated

with increased risk of schizophrenia (Shi et al., 2009). There is evidence for abnormalities in immune cell numbers (Miller et al., 2013b) and cytokine levels (Miller et al., 2011) 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 (McAdams and Leonard, 1993; Rwegellera et al., 1982) and natural killer cells (Abdeljaber et al., 1994), and the resulting impaired host defense may increase susceptibility to infections. Several studies have also found altered levels of blood inflammatory markers (Falcone et al., 2015; Simsek et al., 2016) and autoantibodies in children and adolescents with psychosis (Pathmanandavel et al., 2015).

A number of different viral, bacterial, and parasitic infections are associated with acute psychosis, a notable example being geriatric patients with psychosis and a comorbid urinary tract infection (UTI) in the context of either dementia or delirium (Brendel and Stern, 2005; Webster and Grossberg, 1998). UTI is one of the most common bacterial infections. In three previous studies in adults, we found that more than one in four subjects with acute psychosis in the context of schizophrenia had a urinary tract infection (UTI) at the time of hospitalization (Graham et al., 2014; Laney et al., 2015; Miller et al., 2013a). We found a 35% prevalence of UTI on admission in a sample of 57 acutely ill inpatients with schizophrenia (Miller et al., 2013a). Subjects with

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acute psychosis were almost 29 times more likely to have a UTI than controls. By contrast, there was no difference in the prevalence of UTI between stable outpatients with schizophrenia and controls, suggesting an association that may be specific to acute psychosis. In a replication sample, we found a 21% prevalence of UTI among 134 acutely ill subjects with schizophrenia, and 18% among 101 subjects with affective psychosis (Graham et al., 2014). After controlling for potential confounders, UTI was almost 11 times more likely in subjects with non-affective psychosis than controls, and almost 9 times more likely in subjects with major depressive disorder (MDD) with psychotic features than controls, suggesting an association that extends to the psychosis phenotype. Lastly, in a sample of 152 subjects with at least two hospitalizations for non-affective psychosis over a six-year period, 25 subjects had 2 or more UTIs, and these subjects had a UTI during 60% of their admissions during the study period (Laney et al., 2015). The presence of a recurrent phenomenon supports the hypothesis that UTIs may be clinically relevant to acute psychosis in patients with schizophrenia.

To our knowledge, there have been few studies on infections in children and adolescent patients with acute psychosis. One case report describes an immune-competent female adolescent patient who experienced psychotic symptoms after receiving trimethoprim-sulfamethoxazole for the treatment of lower extremity cellulitis, which spontaneously resolved in 10 days after discontinuation of the antibiotic (Saidinejad et al., 2005). In the present study, we tested the hypothesis that acutely ill children and adolescents with non-affective psychosis and MDD with psychotic features have an increased prevalence of UTI as compared to subjects with non-psychotic MDD, after controlling for potential confounding factors. We also explored demographic and clinical features in pediatric subjects with psychosis with and without comorbid UTI.

## 2. Material and methods

### 2.1. Subjects

227 acutely ill subjects from 3 subject groups, including 80 with schizophrenia and related non-affective psychoses, 47 with MDD with psychotic features, and 100 with non-psychotic MDD (as a hospitalized control group) were identified by chart review of consecutive inpatient admissions to the Georgia Regents University Medical Center inpatient child and adolescent psychiatry unit, beginning in January 2005. The study was approved by the IRB of Georgia Regents University, and a waiver of informed consent was granted by the IRB for the chart review.

Inclusion criteria were male and female children and adolescents ages 10 to 18 who received psychiatric treatment at the Georgia Regents University Medical Center inpatient child and adolescent psychiatric unit from January 2005 through December 2014. The most common definition of early-onset psychosis is before age 18 (Clemmensen et al., 2012). The youngest identified case of non-affective psychosis in the study sample was age 10, and therefore for purposes of age matching, we set the lower limit of age inclusion as 10. Subjects in the psychosis groups met criteria for DSM-IV diagnosis of schizophrenia, schizophreniform disorder, brief psychotic disorder, delusional disorder, psychosis not otherwise specified, or schizoaffective disorder, or MDD with psychotic features. Hospitalized control subjects in met DSM-IV criteria for MDD without psychotic features.

Exclusion criteria were pregnancy, history of exposure to an antibiotic, urinary catheterization, urinary stone, or other urologic procedure in the past 2 weeks (based on review of the admission history and medical record), chronic renal or urologic abnormalities other than stress urinary incontinence, and any of the following neurologic conditions associated potential urologic dysfunction: spinal cord injury, HIV/AIDS, or multiple sclerosis.

### 2.2. Procedures

Data for inpatient subjects were reviewed and extracted from the electronic medical record by three study authors (CC, NP, and BJM). A total of 1112 inpatient records were screened, of which 227 met the study inclusion/exclusion criteria. The majority of records were excluded due to the absence of a primary diagnosis of non-affective psychosis or MDD. A complete blood count with differential, comprehensive metabolic panel, and mid-stream clean-catch urine sample for urinalysis with microscopy, urine drug screen, and urine pregnancy test in females, but not urine cultures, were part of routine admission orders for all subjects. 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 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.

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 (Wilson and Gaido, 2004). Subjects with bacterial concentrations of >100,000 CFU/mL and symptoms of UTIs have urine leukocyte counts of  $\geq 10$  leukocytes/HPF. In this study, as in our previous studies (Graham et al., 2014; Laney et al., 2015; Miller et al., 2013a), a UTI was defined as positive leukocyte esterase and/or positive nitrites on urinalysis and  $\geq 5$ –10 leukocytes/HPF on urine microscopy.

### 2.3. Data analysis

Sample size was determined assuming a chi-square test, a significance level of 0.05, and power of 0.80. Rates of UTI that were assumed in each group were 0.30 for the non-affective psychosis group (the weighted mean prevalence of UTI in our 3 previous studies in adults was 30%) and 0.05 in the major depressive disorder group. A total sample size of 129 or 43 per group was needed to adequately test for difference in rates of UTI.

All statistical analysis was performed using SPSS, version 22 (IBM SPSS, Chicago, Illinois). Statistical significance was assessed using an alpha level of 0.05. 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 chi-square and *t*-tests. In one logistic regression model, the main independent variable will be the group variable that has two levels: schizophrenia (and related disorders) and non-psychotic major depressive disorder. In a second logistic regression model, the main independent variable will be the group variable that has two levels: psychotic depression and non-psychotic major depressive disorder. For the non-affective and affective psychosis groups, simple associations with UTI status and psychiatric symptoms were determined using chi-square tests. Additionally, the association of demographic and clinical variables—including age, gender, race, body mass index, and smoking status (yes/no)—as potential confounders with subject group was determined using chi-square or one-way ANOVA.

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 paper on this topic. First, each individual confounder was assessed for its association with UTI in simple logistic regression models. A backward model building strategy was then

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