RESEARCH ARTICLE

Acutely ill psychiatric inpatients and antimicrobial exposure

Kaitlin P. Kehoe, BS
Medical College of Georgia
Augusta University
Augusta, Georgia, USA

Brian J. Miller, MD, PhD, MPH
Department of Psychiatry and
    Health Behavior
Augusta University
Augusta, Georgia, USA

BACKGROUND: Patients with schizophrenia, bipolar disorder, and major depressive disorder (MDD) have increased infections. We explored the association between recent antimicrobial exposure and acute psychiatric illness.

METHODS: We performed a retrospective chart review of 267 acutely ill patients age 18 to 65. There were 92 patients with schizophrenia, 42 with bipolar disorder, 61 with MDD, and 72 with alcohol use disorders (hospitalized controls). Recent antimicrobial exposure was defined as occurring within 3 days of psychiatric hospitalization.

RESULTS: The prevalence of recent antimicrobial exposure was significantly increased in acutely ill patients with schizophrenia (16%), bipolar disorder (21%), and MDD (18%) compared with patients who had alcohol use disorders (4%, $P \leq .01$ for each). After controlling for potential confounders, participants with schizophrenia or mood disorders were 5 to 7 times more likely to have recent antimicrobial exposure than participants with alcohol use disorders (schizophrenia: odds ratio [OR] = 4.5, 95% confidence interval [CI] 1.0-21.0, $P = .053$; bipolar disorder: OR = 6.9, 95% CI 1.3-35.7, $P = .022$; MDD: OR = 5.7, 95% CI 1.2-28.3, $P = .032$). Among participants with mood disorders, the association was stronger for participants with depression and affective psychosis compared with participants with alcohol use disorders.

CONCLUSIONS: We found an increased prevalence of recent antimicrobial exposure in acutely ill patients with schizophrenia and mood disorders. The findings provide additional evidence that infections are relevant to acute psychiatric illness.

CORRESPONDENCE
Brian J. Miller, MD, PhD, MPH
Department of Psychiatry and
    Health Behavior
Augusta University
997 Saint Sebastian Way
Augusta, GA 30912 USA

E-MAIL
brmiller@augusta.edu

INTRODUCTION

Schizophrenia and mood disorders are associated with an increased prevalence of infections throughout the lifespan. Prenatal exposure to a variety of infectious agents, including bacteria, viruses, and the parasite *Toxoplasma gondii,* is associated with an increased risk of schizophrenia in offspring.[1,2] Less consistent evidence also links exposure to perinatal infections and risk of bipolar disorder.[3] In a nationwide Danish cohort, infections treated with anti-infective agents, including in the ambulatory care setting, were associated with a 1.4-fold increased risk of having a diagnosis of any mental disorder.[4] In that study, the risk was higher for infections treated with antibiotics, and there was evidence for dose-dependent increased risks of schizophrenia and affective disorders. Childhood hospitalizations for more severe infections are also associated with an increased risk of schizophrenia and mood disorders in adulthood.[5-8]

Patients with first-episode psychosis have a 2.5-fold increased risk of exposure to *T. gondii* (as measured by antibodies) compared with controls.[9] There is also evidence for increased risk of *T. gondii* infection in individuals with bipolar disorder.[10] Another Danish cohort study found that patients with severe mental illness, including schizophrenia and bipolar disorder, are at increased risk of hospitalization (and re-hospitalization) for respiratory and urinary tract infections (UTIs).[11] Patients with schizophrenia and bipolar disorder also have increased infectious disease mortality, including death from pneumonia and influenza.[12-14] Polymorphisms in immune genes are associated with both schizophrenia and bipolar disorder.[15] There is evidence for alterations in blood levels of cytokines—key regulators of the immune system—in patients with schizophrenia, bipolar disorder, and major depressive disorder (MDD).[16] Some studies have reported decreased numbers of natural killer cells in patients with schizophrenia and bipolar disorder, although there are failures to replicate.[17-19] Furthermore, patients with schizophrenia may have abnormal function of neutrophils[20,21] and natural killer cells,[22] which may increase susceptibility to infections via impaired host defense.

Infections and acute psychiatric illness

Along these lines, infections are also associated with acute psychiatric illness. Previous studies have found an association between UTIs and acute episodes of psychosis and mood disorders,[23] which may be a recurrent phenomenon.[24,25] However, recent evidence suggests that other types of infections may also be associated with acute psychiatric illness episodes. Among 602 acutely ill (inpatient or day hospital patient) patients with schizophrenia, bipolar disorder, or MDD and 55 healthy controls without current or past psychiatric disorders, Yolken et al[26] found a significant 3.7-fold increased odds of antimicrobial exposure (defined as an antibiotic prescription within 3 days of hospitalization) in patients with psychiatric disorders compared with controls. The most common sites of infection included the urinary tract, skin/soft tissue, respiratory tract, and oral infections. In this study, we aimed to further explore associations between recent antimicrobial exposure and acute illness episodes in patients with schizophrenia and mood disorders.

METHODS

Study participants

Two hundred sixty-seven acutely ill participants were identified by chart review. Participants were from consecutive inpatient admissions to the Augusta University Adult Inpatient Psychiatry Unit from January 1, 2010, through December 31, 2016. One hundred seventy-two participants (64%) were included in a previous study of the prevalence of UTIs in acute psychosis.[27] Acute illness was defined as requiring inpatient psychiatric hospitalization. All participants were exposed to the same hospital environment, including staff, because our inpatient unit does not have separate wards for patients with different diagnoses. Participants were stratified into 4 groups: n = 92 with schizophrenia, n = 42 with bipolar disorder, n = 61 with MDD, and n = 72 with alcohol use disorders. We chose participants with alcohol use disorders as a hospitalized control group to 1) facilitate comparisons with our previous study of infections in acute psychosis,[23] and 2) decrease potential residual confounding factors that may be associated with both psychiatric hospitalization and infection, including self-care, hygiene, recent sexual activity, impulsive behaviors, or access to health care. Recent antimicrobial exposure was defined as occurring within 3 days of hospitalization, and stratified according to agents prescribed prior to admission, at the time of admission, or during the course of hospitalization. The study was approved by the Institutional Review Board of Augusta University, which granted a waiver of informed consent.

Inclusion criteria. Our study included men and women who were age 18 to 65. Participants in the schizophrenia group met DSM-IV or DSM-5 criteria for schizophrenia or schizoaffective disorder. Participants in the mood disorders groups met DSM-IV or DSM-5 criteria for bipolar disorder or MDD. Participants in the alcohol use disorders group met DSM-IV or DSM-5 criteria for alcohol abuse, alcohol dependence, or alcohol use disorder, and the primary reason for hospitalization was alcohol detoxification.

Exclusion criteria. Individuals were excluded from the study if they were pregnant, had an intellectual disability, had IV drug use in the past 2 weeks, or had a spinal cord injury, human immunodeficiency virus (HIV), or multiple sclerosis. Additional exclusion criteria for patients with alcohol use disorders were if alcohol detoxification was not the primary reason for psychiatric hospitalization, or if the patient had a comorbid diagnosis of a psychotic or mood disorder.

Measures

Data from the electronic medical record were reviewed and extracted for all participants, including the admission history and physical examination, as well as the hospital discharge summary, by both study authors. A total of 341 inpatient records were screened, of which 267 met the study inclusion criteria. The most common reasons for exclusion were psychiatric comorbidity in participants with alcohol use disorders, recent IV drug use, and HIV. Blood and urine tests, including a urine drug screen, and urine pregnancy test in females were part of routine admission orders for all participants. For all participants, demographic information (including age, sex, race, highest education, and marital status), psychiatric history, medical history, family psychiatric history, smoking and other substance use history, and admission laboratory results were recorded. The diagnosis for all participants was verified by the hospital discharge summary, which is based on clinician interview and judgment. For participants with schizophrenia, we extracted data from the medical record on the following psychotic symptoms (recorded as categorical yes/no variables):

- hallucinations
- delusions
- paranoia
- disorganized thinking and behavior
- catatonia.

For participants with schizophrenia or mood disorders, we also extracted data on:

- suicidal and homicidal ideation
- manic symptoms
- depressive symptoms.

Recent antimicrobial exposure was defined as occurring within 3 days of hospitalization (either before or after) and was determined based on the admission history and the electronic medication administration record. We chose 3 days as the definition of recent antimicrobial exposure, because: 1) data for a longer time frame prior to hospitalization were unavailable and/or unreliable based on chart review; 2) this definition would still capture participants taking a short course of antimicrobials prior to hospitalization (eg, 3 days of antibiotics for uncomplicated UTI in females); and 3) antimicrobials initiated >3 days after admission are likely less directly relevant to the hospitalization (eg, increased possibility of a nosocomial infection). Recent antimicrobial exposure was further stratified according to agents prescribed prior to admission, at the time of admission, or within the first 3 days of hospitalization.

Statistical analysis

Sample size was determined assuming a Pearson's Chi-square test, power of 0.80, and a significance level of .05. Rates of antimicrobial exposure assumed in each group were 0.01 in the alcohol use disorders group, and 0.05 in the schizophrenia, bipolar disorder, and MDD groups (based on Yolken et al[26]). Based on these assumptions, a sample size of 120 participants per group yields 80% power for detecting an odds ratio (OR) of 4.0 in the comparison of participant groups using a significance level of .05.

Statistical analyses were performed using SPSS, version 24 (IBM SPSS, Chicago, Illinois), with significance assessed using an alpha level of .05. Descriptive statistics were calculated by participant group and by recent antimicrobial exposure status. The association of demographic and clinical variables—including age, sex, race, smoking status, diabetes mellitus, and illicit drug use—as potential confounders with participant group was determined using Pearson's Chi-square or one-way analysis of variance (ANOVA).

The association between the participant group and recent antimicrobial exposure was investigated using logistic regression. Separate regression analyses were performed for schizophrenia, bipolar disorder, and MDD

TABLE 1

Demographic characteristics by participant group

Variable	Level	Schizophrenia n = 92		Bipolar disorder n = 42		MDD n = 61		Alcohol use disorders n = 72		P^a
Sex (n, %)	Male	49	53%	15	36%	20	33%	48	67%	<.01
	Female	43	47%	27	64%	41	67%	24	33%	
Race (n, %)	African American	65	71%	12	29%	27	44%	23	32%	<.01
	Caucasian	26	28%	28	67%	32	53%	49	68%	
	Other	1	1%	2	4%	2	3%	0	0%	
Highest education (n, %)	High school graduate or higher	46	50%	30	81%	39	82%	54	75%	<.01
Ever married (n, %)	Yes	30	34%	23	56%	43	74%	48	68%	<.01
	No	58	66%	18	44%	15	26%	23	32%	
Smoker (n, %)	Yes	37	41%	17	41%	23	38%	36	50%	.49
	No	54	59%	25	59%	38	62%	36	50%	
Diabetes (n, %)	Yes	22	24%	10	24%	6	10%	4	6%	<.01
	No	70	76%	32	76%	55	90%	68	94%	
Positive UDS (cocaine)	Yes	11	13%	3	7%	6	10%	10	14%	.70
	No	81	87%	39	93%	55	90%	62	86%	
Positive UDS (marijuana)	Yes	12	14%	9	22%	8	13%	5	7%	.15
	No	80	86%	33	78%	53	87%	67	93%	
Positive UDS (opiates)	Yes	2	2%	2	5%	2	3%	2	4%	.89
	No	90	98%	40	95%	59	97%	70	96%	
Age (mean [SD])		40.8 (11.2)		39.6 (13.6)		43.1 (12.6)		44.1 (11.0)		.16

[a]Age was compared between participant groups using analysis of variance. All other variables were compared using Pearson's Chi-square test.

MDD: major depressive disorder; SD: standard deviation; UDS: urine drug screen.

(each vs alcohol use disorders). Among patients with mood disorders, additional regression analyses were performed for participants hospitalized for depression as well as participants with affective psychosis. A model-building strategy was used to arrive at a final model controlling for potential confounders utilizing the same approach as in several previous papers on this topic.[27,28] First, each individual potential confounder including age, sex, race, smoking, diabetes, and illicit drug use (cocaine, marijuana, and opiates were each considered separately) was assessed for its association with antimicrobial exposure in simple logistic regression models. A backward model-building strategy was then used. All potential confounders and participant group were included in a full logistic regression model. The least significant potential confounder was removed from the model and a −2 log likelihood ratio test was performed to examine whether the variable was needed in the model.

Additionally, the effect of removing the potential confounder on the estimated OR between participant group and antimicrobial exposure was assessed. Variables that did not result in a significant −2 log likelihood ratio test or did not change the estimated OR between participant group and antimicrobial exposure 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 ratio test.

RESULTS

TABLE 1 presents the demographic characteristics of the study sample. There were significant between-group differences for sex, race, highest education, marital status, and diabetes mellitus, but not age, smoking, or illicit drug

TABLE 2
Prevalence of antimicrobial exposure by participant group

Group	Antimicrobial exposure and timing									P^a (vs alcohol)
	Yes (n, %)							No (n, %)		
	Prior to admission		At admission		After admission		Total				
Schizophrenia	5	5%	7	8%	4	4%	15	16%	77	84%	.01
Bipolar disorder	0	0%	6	14%	4	10%	9	21%	33	79%	<.01
MDD	1	2%	5	8%	5	8%	11	18%	50	82%	<.01
Alcohol use disorders	0	0%	2	3%	1	1%	3	4%	69	96%	

[a]The prevalence of infections in the schizophrenia, bipolar disorder, and MDD groups—each vs the prevalence in the alcohol use disorders group—was compared using a Pearson's Chi-square test.

MDD: major depressive disorder.

use. Participants with bipolar disorder and MDD were more likely to be female than those with alcohol use disorders. Participants with schizophrenia were more likely to be of African descent, have less education, have never married, and have diabetes mellitus than those with alcohol use disorders. In all participants, a recent antimicrobial exposure was significantly associated with sex (increased in females, $P < .01$), as well as for opiate and marijuana use ($P < .01$ for each). Otherwise, there were no differences in age, race, smoking, education, marital status, diabetes, and cocaine use based on recent antimicrobial exposure status.

The prevalence of recent antimicrobial exposure was 16% (n = 15) in the schizophrenia group, 21% (n = 9) in the bipolar disorder group, 18% (n = 11) in the MDD group, and 4% (n = 3) in the alcohol use disorders group (**TABLE 2**). There was a significant increased prevalence of recent antimicrobial exposure in participants with schizophrenia, bipolar disorder, and MDD compared with participants with alcohol use disorders ($P \le .01$ for each). For participants with schizophrenia, the majority of recent antimicrobial exposures were either prior to or at the time of admission (83% of exposures, n = 12). For participants with bipolar disorder, all antimicrobial exposures were either at the time of or after admission (n = 9). For participants with MDD, the majority of exposures were either at the time of or after admission (91% of exposures, n = 10). Two participants—1 in the schizophrenia group and 1 in the bipolar disorder group—were treated for 2 separate infections, 1 at the time of admission and another during the hospitalization. As noted above, 172 of the participants (64%) in the present study were included in a previous study of infections in

acute psychosis.[28] There was no difference in the prevalence of recent antimicrobial exposure in participants who were or were not included in the previous study (13.4% vs 16.0%, $P = .59$).

TABLE 3 presents both the types/sites of infections as well as the class of prescribed antimicrobial agents by participant group. In the schizophrenia, bipolar disorder, and MDD groups, UTIs were the most common type of infection. Other commonly identified sites of infection included the respiratory tract, skin, mouth, and other genitourinary tract. Participants were treated with a broad range of different antimicrobial agents, including clindamycin, fluoroquinolones, macrolides, nitrofurantoin, penicillins, sulfonamides, and tetracyclines. All recent antimicrobial exposures were oral agents.

TABLE 4 gives the results of the final logistic regression models. After controlling for potential confounding factors, participants with mood disorders were 5 to 7 times more likely to have recent antimicrobial exposure than participants with alcohol use disorders (bipolar disorder: OR = 6.9, 95% confidence interval [CI] 1.3-35.7, $P = .022$); MDD: OR = 5.7, 95% CI 1.2-28.3, $P = .032$). However, after controlling for potential confounding factors, participants with schizophrenia had a nonsignificant increased odds of recent antimicrobial exposure compared with participants with alcohol use disorders (OR = 4.5, 95% CI 1.0-21.0, $P = .053$). For participants with mood disorders, those with depression (bipolar or unipolar, OR = 8.5, 95% CI 1.8-41.0, $P = .008$) but not mania (OR = 2.8, 95% CI 0.3-26.7, $P = .359$) were more likely to have recent antimicrobial exposure than participants with alcohol use disorders. Participants with affective psychosis (either bipolar disorder or MDD with psychotic features,

TABLE 3

Infections and antimicrobial agents by participant group and UTI status

Variable	Schizophrenia n = 92		Bipolar disorder n = 42		MDD n = 61		Alcohol use disorders n = 72	
Infection (n, %)								
Abscess	1	1%	1	2%	0	0%	0	0%
Cervicitis	1	1%	0	0%	0	0%	0	0%
Epididymitis	1	1%	0	0%	0	0%	0	0%
Not specified	2	2%	2	5%	3	5%	0	0%
Respiratory	1	1%	0	0%	1	2%	0	0%
Skin	1	1%	0	0%	0	0%	0	0%
Tongue	0	0%	0	0%	0	0%	1	1%
Trichomonas	1	1%	1	2%	1	2%	1	1%
UTI	8	9%	5	12%	6	10%	1	1%
None	76	84%	33	79%	50	82%	69	96%
Antimicrobial agent (n, %)								
Clindamycin	0	0%	0	0%	0	0%	1	1%
Fluoroquinolone	2	2%	1	2%	3	5%	0	0%
Macrolide	2	2%	1	2%	0	0%	0	0%
Metronidazole	1	1%	1	1%	2	3%	1	1%
Nitrofurantoin	2	2%	2	5%	0	0%	0	0%
Penicillin	1	1%	1	2%	0	0%	0	0%
Sulfonamides	5	5%	2	5%	6	10%	1	1%
Tetracycline	2	2%	1	2%	0	0%	0	0%
None	77	84%	33	79%	50	82%	69	96%

MDD: major depressive disorder; UTI: urinary tract infection.

OR = 10.1, 95% CI 2.2-46.0, *P* = .003) but not mania (OR = 2.8, 95% CI 0.3-26.7, *P* = .359) were more likely to have recent antimicrobial exposure than participants with alcohol use disorders.

For participants in the schizophrenia, bipolar disorder, and MDD groups, we also investigated associations between recent antimicrobial exposure, admission laboratory values, and psychiatric symptoms. Participants with schizophrenia and antimicrobial exposure were more likely to report depressive symptoms compared with those without this exposure (60% vs 48%, *P* = .020). Otherwise, there were no differences in laboratory values or other psychiatric symptoms for participants with schizophrenia. There were no differences in laboratory values or psychiatric symptoms in participants with mood disorders based on recent antimicrobial exposure status.

DISCUSSION

We found an increased prevalence of recent antimicrobial exposure in acutely ill patients with schizophrenia and mood disorders compared with a hospitalized control group. After controlling for potential confounders, participants with schizophrenia, bipolar disorder, and MDD were 5 to 7 times more likely to have recent antimicrobial exposure than participants with alcohol use disorders. For participants with mood disorders, associations with recent antimicrobial exposure were significant for participants with depression and affective psychosis. These participants presented with infections involving the respiratory tract, skin, mouth, and genitourinary tract that were treated with a broad range of oral antibiotics. Participants with schizophrenia and recent antimicrobial exposure were more likely to report

TABLE 4

Logistic regression models of participant group on antimicrobial exposure

Participant group	Final logistic regression model			
	OR (95% CI) for antimicrobial exposure		*P*	
Schizophrenia	4.5	(1.0-21.0)	.053	a
Bipolar disorder	6.9	(1.3-35.7)	.022	b
MDD	5.7	(1.2-28.3)	.032	c
Depression (bipolar or MDD)	8.5	(1.8-41.0)	.008	d
Mania	2.8	(0.3-26.7)	.359	
Affective psychosis (bipolar or MDD)	10.1	(2.2-46.0)	.003	e

[a]Adjusted for sex, smoking, opiate use, and marijuana use.
[b]Adjusted for age and opiate use.
[c]Adjusted for sex and opiate use.
[d]Adjusted for opiate use.
[e]Adjusted for opiate use.

CI: confidence interval; MDD: major depressive disorder; OR: odds ratio.

depressive symptoms compared with those without this exposure.

In the present study, we controlled for multiple potential confounding factors, including sex, smoking, diabetes mellitus, and illicit drug use. Our findings are broadly consistent with the previous study by Yolken et al,[26] who found a significant, 3.7-fold increased odds of antimicrobial exposure in patients with schizophrenia and mood disorders (combined). In that study, the strongest association was for participants with bipolar mania (OR = 6.1), whereas schizophrenia was associated with a 2.5-fold increased odds of antimicrobial exposure. However, the finding did not reach statistical significance.

We failed to find a significant association with bipolar mania in the present study, although the number of participants was small (n = 16). We highlight several differences between the 2 studies. First, Yolken et al[26] included both inpatients and day hospitalized patients, whereas we only included inpatients. Second, Yolken et al[26] used a healthy control group, whereas we used a hospitalized control group with alcohol use disorders. Last, we found a higher mean prevalence of recent antimicrobial exposure in patients with schizophrenia and mood disorders (16% vs 6%).

Limitations

Our findings are based on a relatively small number of patients with schizophrenia, bipolar disorder, and MDD with recent antimicrobial exposure. Furthermore, data were obtained by retrospective chart review of the electronic medical record. This raises a possible misclassification bias where some participants may have inappropriately received antibiotics (eg, misdiagnosis of asymptomatic bacteriuria as a UTI, or viral respiratory infections treated with antibiotics), although some infections may have gone undiagnosed. Therefore, replication of findings in larger cohorts, ideally prospective studies with data on inflammatory markers and registry-based data on infections and antimicrobial prescriptions, is warranted. We were not able to investigate potential effects of psychotropic medications, because data on medication adherence at admission were either unavailable or unreliable based on the chart review. Data on inflammatory markers, such as C-reactive protein or erythrocyte sedimentation rate, were not available for participants. Thus, we were unable to consider associations between recent antimicrobial exposure and inflammation in our sample. This association should be investigated in future studies. There is evidence for alterations in inflammatory markers in schizophrenia, bipolar disorder, and MDD.[16] While acute infections are associated with increased inflammation, it is also possible that altered inflammatory markers in psychiatric disorders might influence susceptibility to infections in these patients. The increased prevalence of recent antimicrobial exposure in acutely ill psychiatric patients could also be due to residual confounding by an unknown or unmeasured factor, such as self-care, hygiene, recent sexual activity, or access to health care, that might have impacted these associations.

Another important consideration is the use of participants with alcohol use disorders as a hospitalized control group. In a previous study,[27] we did not find a significantly

increased prevalence of UTIs in participants with alcohol use disorders compared with healthy controls. However, it is possible that participants with alcohol use disorders may have recently engaged in behaviors that increase the risk of infection, although this would be expected to bias the association towards the null hypothesis. It is also possible that alcohol use disorders might impair immune function, thereby increasing susceptibility to infection, although this would also bias findings towards the null hypothesis. Furthermore, participants with alcohol use disorders might be less likely than healthy controls to seek medical care for symptoms of infection. There is the potential for the introduction of another, unknown, selection bias with an alcohol use disorder (vs healthy) control group. The impact of these considerations on the odds of antimicrobial exposure between participant groups is unclear.

There was substantial overlap (64%) in participants included in the present study and our previous study of UTIs in acute psychosis.[27] However, there are several important distinctions between the 2 studies. Our previous study[27] investigated only UTIs, whereas the present study considered the prevalence of antimicrobial exposure for any type of infection, not just UTIs. Furthermore, the previous study did not investigate antibiotic treatment for UTI, only the prevalence of UTI based on urinalysis. We did not find a difference in the prevalence of recent antimicrobial exposure in participants who were or were not included in the previous study of UTIs (13.4% vs 16.0%, P = .59). Therefore, the present study replicates and extends previous findings, suggesting an increased prevalence of antimicrobial treatment for multiple, different types of infections in acutely ill patients with psychiatric disorders.

Although smoking was included in the final logistic regression model for schizophrenia, neither smoking nor diabetes mellitus—both of which are associated with increased infections—were predictors of recurrent infections in any of the other regression models. One possibility is that we were statistically underpowered to detect an association given the relatively small sample size of the present study.

Potential mechanisms

The potential mechanisms underlying the association between infections, recent antimicrobial exposure, and acute psychiatric illness remain largely unknown. Although the present study does not explicate these

mechanisms, several non-mutually exclusive theories may provide relevant insights.

First, it is possible that psychiatric disorders result in physiologic changes that predispose patients to certain infections. There is evidence for abnormal numbers and/or function of immune cells in patients with schizophrenia and mood disorders that may increase susceptibility to infections.[17,19-21] Conversely, behavioral disturbances associated with acute psychosis and mood disorders—such as decreased hygiene or increased impulsivity—may also modulate infection risk. Iatrogenic adverse effects of psychotropic medications may contribute to an increased risk of infection. For example, antipsychotic-associated urinary retention may increase the risk of UTI.[29]

Secondly, it is possible the host inflammatory response to infection may contribute to a worsening of psychiatric symptoms. We previously found that peripheral blood white blood cell counts predicted UTI in patients with acute psychosis.[24,30] Cytokines, which are involved in an acute inflammatory response and coordinate the immune response to infection, have altered levels in acutely ill patients with schizophrenia and mood disorders.[16] Interferon-gamma (IFN-gamma) may also worsen psychiatric symptoms by modulation of glutamatergic neurotransmission via the tryptophan catabolic pathway.[31,32] Epigenetic changes in DNA methylation may also contribute to immune activation in acute psychiatric disorders.[33]

The effects of antimicrobial agents on the host must be also considered. There is a very uncommon but reported incidence of psychiatric disorders induced by antibiotic treatment. One review reported 103 cases of antibiotic-induced mania during treatment of infection.[34] We previously reported 15 cases of antibiotic-induced psychosis, of which 60% were found to be "highly suggestive" of a causal relationship.[35] Therefore, it is possible but unlikely that a direct effect of antimicrobial usage contributed to the exacerbation of psychiatric symptoms. However, in a more subtle fashion than "antibiomania," antibiotics can alter the gut microbiome, which can modulate cognitive and mood states, or the pharmacokinetics of psychotropic medications.[36,37] There is evidence for alterations in the fecal microbiome in patients with MDD[34] and first-episode psychosis,[38,39] and antipsychotic treatment is associated with changes in the microbiome in patients with psychosis.[40] Indeed, outside of psychiatric disorders, there is evidence of bidirectional associations between infections and the microbiome: alterations

in the microbiome may increase susceptibility to infections, but infections are also associated with changes in microbial composition and function.[41-43] Future studies could therefore investigate the effects of antibiotic treatment on the microbiome in patients with schizophrenia and mood disorders.

The term "para-infectious encephalopathy" describes a clinical pattern of global neurologic deterioration that can result from infections.[44] Patients with neurologic disorders, including dementia, multiple sclerosis, and Parkinson's disease, may have worsening of neurologic deficits after developing infections. By extension, it is plausible that patients with schizophrenia and mood disorders may experience similar acute exacerbation of psychiatric symptoms following an infection. However, given the mild nature of the infections among participants in the present study—which would have likely all been treated in an ambulatory setting if the patients were not hospitalized for psychiatric reasons—the relevance of this hypothesis is unclear. Another possibility is that increased stress associated with acute psychiatric illness may increase susceptibility to infections. Indeed, there is evidence that stress-related psychiatric disorders are associated with an increased risk of life-threatening infections.[45]

CONCLUSIONS

We found an increased prevalence of recent antimicrobial exposure in acutely ill patients with schizophrenia and mood disorders. The findings provide additional evidence that infections are relevant to acute psychiatric illness.

Associations between recent antimicrobial exposure and acute psychiatric illness warrant replication in larger, longitudinal samples, including prospective studies and registry-based data on infections and antimicrobial prescriptions (enabling a longer "look-back" period prior to hospitalization) as well as data on inflammatory markers, given the high prevalence of medical comorbidity in these patients.[5,29] Future studies could also investigate relationships between antimicrobial exposures and data on inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate. Our findings highlight the potential importance of routine clinical monitoring for infections in these patient populations. The present study provides additional evidence that infections are relevant to acute psychosis and mood disorders. ■

REFERENCES

1. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry. 2010;167:261-280.
2. Brown AS. Exposure to prenatal infection and risk of schizophrenia. Front Psychiatry. 2011;2:63.
3. Barichello T, Badawy M, Pitcher MR, et al. Exposure to perinatal infections and bipolar disorder: a systematic review. Curr Mol Med. 2016;16:106-118.
4. Köhler O, Petersen L, Mors O, et al. Infections and exposure to anti-infective agents and the risk of severe mental disorders: a nationwide study. Acta Psychiatr Scand. 2017;135: 97-105.
5. Benros ME, Waltoft BL, Nordentoft M, et al. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. JAMA Psychiatry. 2013;70:812-820.
6. Blomström Å, Karlsson H, Svensson A, et al. Hospital admission with infection during childhood and risk for psychotic illness--a population-based cohort study. Schizophr Bull. 2014;40:1518-1525.

7. Khandaker GM, Zimbron J, Dalman C, et al. Childhood infection and adult schizophrenia: a meta-analysis of population-based studies. Schizophr Res. 2012;139:161-168.
8. Nielsen PR, Benros ME, Mortensen PB. Hospital contacts with infection and risk of schizophrenia: a population-based cohort study with linkage of Danish national registers. Schizophr Bull. 2014;40:1526-1532.
9. Torrey EF, Bartko JJ, Lun ZR, et al. Antibodies to Toxoplasma gondii in patients with schizophrenia: a meta-analysis. Schizophr Bull. 2007;33:729-736.
10. de Barros JLVM, Barbosa IG, Salem H, et al. Is there any association between Toxoplasma gondii infection and bipolar disorder? A systematic review and meta-analysis. J Affect Disord. 2017;209:59-65.
11. Davydow DS, Ribe AR, Pedersen HS, et al. Serious mental illness and risk for hospitalizations and rehospitalizations for ambulatory care-sensitive conditions in Denmark: a nationwide population-based cohort study. Med Care. 2016;54:90-97.

12. Brown S, Kim M, Mitchell C, et al. Twenty-five year mortality of a community cohort with schizophrenia. Br J Psychiatry. 2010;196:116-121.
13. Hayes JF, Miles J, Walters K, et al. A systematic review and meta-analysis of premature mortality in bipolar affective disorder. Acta Psychiatr Scand. 2015;131:417-425.
14. 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; 64:1123-1131.
15. The International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia that overlaps with bipolar disorder. Nature. 2009;460:748-752.
16. Goldsmith D, Rapaport MH, Miller BJ. A meta-analysis of cytokine alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder, and depression. Mol Psychiatry. 2016;21:1696-1709.
17. Abeer, El-Sayed A, Ramy HA. Immunological changes in patients with mania: changes in cell mediated

immunity in a sample from Egyptian patients. Egypt J Immunol. 2006;13:79-85.

18. Fernandez-Egea E, Vértes PE, Flint SM, et al. Peripheral immune cell populations associated with cognitive deficits and negative symptoms of treatment-resistant schizophrenia. PLOS One. 2016;11:e0155631. doi: 10.1371/journal.pone.0155631.

19. Karpiński P, Frydecka D, Sąsiadek MM, et al. Reduced number of peripheral natural killer cells in schizophrenia but not in bipolar disorder. Brain Behav Immun. 2016;54:194-200.

20. McAdams C, Leonard BE. Neutrophil and monocyte phagocytosis in depressed patients. Prog Neuropsychopharmacol Biol Psychiatry. 1993;17:971-984.

21. Rwegellera GG, Fernando KA, Okong'o O. Bactericidal activity of neutrophils of schizophrenic patients. Med J Zambia. 1982;16:21-22.

22. Abdeljaber MH, Nair MP, Schork MA, et al. Depressed natural killer cell activity in schizophrenic patients. Immunol Invest. 1994;23:259-268.

23. Chae J, Miller B. Beyond urinary tract infections (UTIs) and delirium: a systematic review of urinary tract infections and neuropsychiatric disorders. J Psychiatr Pract. 2015;21:402-411.

24. Laney D, Philip N, Miller BJ. Recurrent urinary tract infections in acute psychosis. Schizophr Res. 2015;164:275-276.

25. Paletta N, Wang A, Miller BJ. Recurrent urinary tract infections in psychotic mood disorders. Schizophr Res. 2017;184:137-138.

26. Yolken R, Adamos M, Katsafanas E, et al. Individuals hospitalized with acute mania have increased exposure to antimicrobial medications. Bipolar Disord. 2016;18:404-409.

27. Graham KL, Carson CM, Ezeoke A, et al. Urinary tract infections in acute psychosis. J Clin Psychiatry. 2014;75:379-385.

28. Miller BJ, Graham KL, Bodenheimer CM, et al. A prevalence study of urinary tract infections in acute relapse of schizophrenia. J Clin Psychiatry. 2013;74:271-277.

29. Yeh YW, Kuo SC, Chen CY. Urinary tract infection complicated by urine retention presenting as pseudocyesis in a schizophrenic patient. Gen Hosp Psychiatry. 2012;34:101.

30. Miller BJ, Bodenheimer CM, Culpepper NH, et al. Differential white blood cell counts may predict urinary tract infection in acute relapse of schizophrenia. Schizophr Res. 2013;147:400-401.

31. Campbell B, Charych E, Lee A, et al. Kynurenines in CNS disease: regulation by inflammatory cytokines. Front Neurosci. 2014;8:1-22.

32. Myint A, Kim Y. Network beyond IDO in psychiatric disorders: revisiting the neurodegeneration hypothesis. Prog Neuropsychopharmacol Biol Psychiatry. 2014;48:304-313.

33. Sabunciyan S, Maher B, Bahn S, et al. Association of DNA methylation with acute mania and inflammatory markers. PLOS ONE. 2015;10:e0132001.

34. Aboesh A, Stone C, Hobbs W. Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. J Clin Psychopharmacol. 2002;22:71-81.

35. Mostafa S, Miller B. Antibiotic-associated psychosis during treatment of urinary tract infections: a systematic review. J Clin Psychopharmacol. 2014;34:483-490.

36. Borre YE, Moloney RD, Clarke G, et al. The impact of microbiota on brain and behavior: mechanisms & therapeutic potential. Adv Exp Med Biol. 2014;817:373-403.

37. Dickerson F, Severance E, Yolken R. The microbiome, immunity, and schizophrenia and bipolar disorder. Brain Behav Immun. 2017;62:46-52.

38. Jiang H, Ling Z, Zhang Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun. 2015;248:186-194.

39. Schwarz E, Maukonen J, Hyytiäinen T, et al. Analysis of microbiota in first episode psychosis identifies preliminary associations with symptom severity and treatment response. Schizophr Res. 2018;192:398-403.

40. Yuan X, Zhang P, Wang Y, et al. Changes in metabolism and microbiota after 24-week risperidone treatment in drug naïve, normal weight patients with first episode schizophrenia. Schizophr Res. 2018;201:299-306.

41. Lee KH, Gordon A, Shedden K, et al. The respiratory microbiome and susceptibility to influenza virus infection. PLoS One. 2019;14:e0207898.

42. Hanada S, Pirzadeh M, Carver KY, et al. Respiratory viral infection-induced microbiome alterations and secondary bacterial pneumonia. Front Immunol. 2018;9:2640.

43. Williams B, Landay A, Presti RM. Microbiome alterations in HIV infection a review. Cell Microbiol. 2016;18:645-651.

44. Hufschmidt A, Shabarin V, Rauer S, et al. Neurological symptoms accompanying urinary tract infections. Eur Neurol. 2010;63:180-183.

45. Song H, Fall K, Fang F, et al. Stress-related psychiatric disorders and increased risk of life-threatening infections: Swedish population-based sibling controlled cohort study. BMJ. 2019;367:l5784.