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Rates of Hospitalized Bacterial Infection Associated with Juvenile Idiopathic Arthritis and Its Treatment

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Abstract

Objective—Compare the incidence of hospitalized bacterial infections among children with and without juvenile idiopathic arthritis (JIA) and examine the effects of selected medications

Methods—Using national U.S. Medicaid data from 2000–2005, we identified a JIA cohort and a comparator cohort of children with attention-deficit hyperactivity disorder (ADHD). Exposures to methotrexate (MTX), TNF inhibitors, and oral glucocorticoids were determined using pharmacy

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claims. Hospitalized bacterial infections were identified using coded discharge diagnoses. We calculated adjusted hazard ratios (aHR) to compare infection incidence rates while adjusting for relevant covariates.

Results—We identified 8,479 JIA patients with 13,003 person-years of follow-up; 42% used MTX and 17% used TNF inhibitors. Compared with ADHD patients, JIA patients without current MTX or TNF inhibitor use had an increased rate of infection (aHR 2.0; 95%CI 1.5–2.5). Among JIA patients not using TNF inhibitor therapy, MTX users had a similar rate of infection compared with those without current MTX use (aHR 1.2; 95%CI 0.9–1.7). TNF inhibitor use (irrespective of MTX) resulted in a similar rate of infection compared to MTX without TNF inhibitor (aHR 1.2; 95%CI 0.8–1.8). With adjustment for MTX and TNF inhibitor use, high-dose glucocorticoid use (≥10 mg of prednisone daily) increased the rate of infection compared with no glucocorticoid use (aHR 3.1; 95%CI 2.0–4.7).

Conclusions—Children with JIA had an increased rate of infection compared to children with ADHD. Among children with JIA, the rate of infection was not increased with MTX or TNF inhibitor use, but was significantly increased with high-dose glucocorticoid use.

INTRODUCTION

The relationship between juvenile idiopathic arthritis (JIA) and serious bacterial infections has not been extensively studied. The relatively recent introduction of biologic agents for the treatment of JIA, including tumor necrosis factor alpha inhibitors (TNF inhibitors) (1, 2), has focused attention on the risks of infection. In adults with rheumatoid arthritis (RA), the most commonly reported serious adverse effect associated with TNF inhibitor therapy has been an increased rate of bacterial infections (3, 4). However, numerous studies of the association of TNF inhibitors and infection in adults with RA have reported seemingly conflicting results, most likely owing to fundamental differences in study populations and study designs (5). Among children with JIA, questions persist about a possible increased risk of serious infections associated with the use of TNF inhibitors (6–8).

The study of serious infections among children with JIA is complicated by the unclear role of the underlying disease processes. Studies in adult patients have shown an increased risk of infection associated with RA compared to the general population (9, 10) and a positive association between infection risk and RA disease activity and severity (11, 12). However, it is not known if a similar infection risk increase exists among children with JIA.

Reports from cohorts of children with JIA treated with the TNF inhibitor etanercept reveal a crude rate of serious infection (defined as requiring hospitalization or intravenous antibiotics) of approximately 2 to 3 per 100 person-years of TNF inhibitor use (6–8). Although methotrexate has been used for decades in the treatment of JIA, there are few estimates of the associated incidence of infection in clinical practice. One cohort of methotrexate users experienced a serious infection rate of 1.3 per 100 person-years, which the authors found to be similar to the infection rate observed with TNF inhibitors (8). Systemic glucocorticoids have been shown to significantly increase the risk of infection among adults with RA (9, 11, 13), but similar studies among children with JIA have not been published. There are no published reports of the overall infection rate of children with JIA in general or of children with JIA not receiving systemic immunosuppressant therapy.

Therefore, it is difficult to interpret the rate of infection associated with TNF inhibitors in children with JIA since few data exist on background rates of infection among these children, many of whom are also exposed to methotrexate or systemic glucocorticoids. We used national Medicaid data to determine incidence rates of hospitalized bacterial infection among children with JIA in clinical practice and among children without JIA. We sought to

answer several questions: What is the rate of infection among children with JIA who are not treated with methotrexate or TNF inhibitors? How does this rate compare to children without JIA? What are the rates of infection among children treated with methotrexate or TNF inhibitors? How do these rates compare? What role do oral glucocorticoids play in the risk of infection?

METHODS

Study populations

After obtaining Institutional Review Board approval, we performed this study using United States Medicaid Analytic eXtract (MAX) files from all 50 U.S. states and the District of Columbia. MAX files contain medical and pharmacy administrative claims records for low income children enrolled in Medicaid (government medical assistance). We identified a cohort of children with JIA and a comparator cohort of children without JIA who were diagnosed with attention-deficit hyperactivity disorder (ADHD). We chose a comparator cohort of children diagnosed with a chronic non-inflammatory disease in order to increase the proportion of children who had sustained interactions with the healthcare system and thus remained observable in the claims data during follow-up (see below). Children diagnosed with ADHD are not known to have a different rate of hospitalized bacterial infection compared to the general population. Data from the years 2000 through 2005 were used for the JIA cohort and from the years 1999 through 2002 for the ADHD comparator cohort. These were the most recent data available to us at the time of the study.

We used International Classification of Disease, Ninth Revision (ICD-9) codes and pharmacy claims to identify children with JIA. In order to include all categories of JIA (14), the following ICD-9 diagnosis codes were accepted: rheumatoid arthritis (714); psoriatic arthritis (696.0); ankylosing spondylitis (720); and inflammatory bowel disease-associated arthritis (713.1 with concurrent 555 or 556). Children who were less than 16 years old and who had 2 or more JIA ICD-9 coded physician claims that were at least 7 days but not more than 183 days apart were included. Additionally, children who had a single JIA ICD-9 coded physician claim followed by an outpatient pharmacy claim for TNF inhibitor or methotrexate or leflunomide within 183 days were included.

All children who were less than 19 years old and who had 2 or more physician claims with the ICD-9 code for ADHD (314.0) that were at least 7 days but not more than 183 days apart were included in the comparator cohort. Children were excluded from the ADHD comparator cohort if they had any physician ICD-9 codes for JIA at any time.

For all children, the start of follow-up (index date) was the first date when both of the following criteria were met: (1) accumulated 183 consecutive days of observable time within the MAX data and (2) satisfied the respective disease cohort definition. The 183 day baseline period immediately prior to index dates was used to apply cohort exclusion criteria and assess baseline covariates. All children with any physician ICD-9 code or hospital discharge diagnosis for malignancy, organ transplantation, or human immunodeficiency virus infection were excluded or censored, respectively, if the code occurred during the baseline period or follow-up. All children with 2 or more ICD-9 codes for other rheumatic diseases (systemic lupus erythematosus and other diffuse connective tissue diseases, vasculitis, or sarcoidosis) that were at least 7 days but not more than 183 days apart were excluded. All children less than 6 months of age at the time of disease diagnosis were excluded, due to the uncertainty of a diagnosis of JIA at this age (15). All children who were exposed to other immunomodulatory agents (abatacept, alefacept, anakinra, azathioprine, cyclophosphamide, cyclosporine, efalizumab, 6-mercaptopurine, mycophenolate mofetil, rituximab, and tacrolimus) were excluded or censored, respectively, if the exposure occurred

during the baseline period or during follow-up. Additionally, children in the ADHD comparator cohort who were exposed to methotrexate, leflunomide, or TNF inhibitors were excluded or censored, respectively, if the exposure occurred during the baseline period or follow-up. In order to ensure that children remained fully observable with respect to medication exposures and hospitalized infection outcomes in the MAX claims database, all children without at least 1 outpatient pharmacy claim every 6 months and full medical benefits every month were censored. Follow-up was also censored when a hospitalized infection outcome occurred or the study period ended.

Medication exposures

Exposure status was determined using pharmacy and procedure claims for MTX (methotrexate or leflunomide), TNF inhibitor (etanercept, infliximab, or adalimumab), and oral glucocorticoids (GC). “Current medication use” ended 30 days after the days supplied by the last claim. We analyzed 3 medication exposure groups of primary interest: (1) no current MTX or TNF inhibitor use, (2) current MTX use without current TNF inhibitor use, and (3) current TNF inhibitor use irrespective of MTX use. The oral GC daily dose was determined by summing the total dosage of dispensed oral GC in prednisone-equivalents in the 60 days prior to the date of interest (e.g., the index date) and dividing by 60. The oral GC daily dose was categorized as none, low (> 0 and < 10 mg prednisone equivalents per day), or high (≥ 10 mg prednisone equivalents per day). All medication exposure episodes were included in the main analysis (prevalent-user design) and children could contribute follow-time to more than 1 medication exposure group sequentially based on their clinical treatment course.

Outcome identification

Hospitalized bacterial infections were identified by examining all ICD-9 codes in any position from inpatient hospital discharge diagnoses. We used an adapted list of ICD-9 codes that was previously validated in adult RA patients against medical record review to identify bacterial infections (16). It was not possible to determine if bacterial infection was the primary reason for hospital admission or if the infection developed during the hospitalization.

Statistical analysis

We determined crude infection rates for children with ADHD and for children with JIA with the 3 medication exposure groups of primary interest, with and without current oral GC use. We calculated absolute differences in the crude infection rates associated with TNF inhibitor and MTX use.

We used Cox proportional hazard regression models to compare the incidence of infections among the study exposure groups. We calculated adjusted hazard ratios (aHR) by adjusting for patient characteristics, including age, sex, race, and the presence of ICD-9 codes indicating hospitalized bacterial infections, outpatient bacterial infections, asthma, and diabetes mellitus during the baseline period. Because patients could contribute person-time to more than one episode of medication exposure, a sandwich variance estimator was applied to account for additional correlations in the data (17). To evaluate the possibility of statistical interaction between oral GC and TNF inhibitor and hospitalized infection among children with JIA, we evaluated separate hazard models for children with and without current oral GC use on the index date. We also evaluated hazard models that included the GC daily dose after the index date as a time-varying covariate by updating the oral GC daily dose for all study subjects each time an infection outcome occurred.

We performed a secondary analysis of JIA subjects restricted to new users of TNF inhibitor compared to new users of MTX without current or prior TNF inhibitor (new user design) (18), with new use defined as no prior pharmacy claims for the medication in the previous 6 months. In addition, we conducted sensitivity analyses to evaluate the robustness of our findings. First, the infection outcome identification was restricted to the primary hospital discharge diagnosis. Second, we repeated all analyses with current medication use extended to include 90 days after the days supplied by the last pharmacy claim. We also compared the duration of hospitalizations among the study exposure groups using the Wilcoxon rank-sum test. Owing to the known association between JIA and specific immunodeficiencies (19, 20), we excluded children with any diagnosis code for immunodeficiency at any time and repeated the analyses.

RESULTS

We identified 8,479 children with JIA with a total of 13,003 person-years of follow-up and 360,489 children with ADHD with a total of 454,698 person-years of follow-up (Table 1). There were significant differences in the sex and race distributions between the JIA and ADHD cohorts. The median follow-up time was comparable between the two cohorts. Greater proportions of children with JIA were receiving oral GC on their index dates and had hospitalized infections during the baseline period compared to children with ADHD. The proportion of children with asthma was similar in both cohorts. Treatment with methotrexate represented 96% of the MTX use and etanercept represented 90% of the TNF inhibitor use during follow-up.

We identified 365 and 4,398 hospitalized infection outcomes in the JIA and ADHD cohorts, respectively. The types of bacterial infections by disease cohort are shown in Table 2. Urinary tract infections were relatively more frequent in JIA (0.5 versus 0.1 per 100 person-years; $p < 0.0001$), and this may be attributed to the much higher proportion of females in this cohort compared to the ADHD cohort (64% female versus 24%).

Overall, the crude infection rate was nearly 3-fold higher among children diagnosed with JIA (2.8 per 100 person-years) compared to children diagnosed with ADHD (1.0 per 100 person-years) (Table 3). Among children with JIA, the crude infection rates were approximately 2 to 3 per 100 person-years for all medication exposure groups. Compared with no current use of oral GC, current oral GC use was associated with an increased crude rate of infection among children in all groups.

The absolute increase in the crude infection rate between children with current TNF inhibitor use irrespective of MTX compared to MTX without current TNF inhibitor was not significant (rate difference 0.2 per 100 person-years; 95% CI −0.1 to 1.3). The rate difference between TNF inhibitor and MTX use was also not significant if the comparison was restricted to either children without current oral GC use (rate difference 0.5 per 100 person-years; 95% CI −0.7 to 1.6) or with current oral GC use (rate difference −1.4 per 100 person-years; 95% CI −4.9 to 2.2).

Children with JIA without current MTX or TNF inhibitor use had an approximate 2-fold increased rate of infection compared to children with ADHD after adjustment for patient characteristics including oral GC daily dose on the index date (Table 4). Current users of MTX without TNF inhibitor did not have a significantly increased rate of infections (aHR 1.2 (0.9–1.7)) compared to those without current MTX or TNF inhibitor use. Similarly, current users of TNF inhibitor irrespective of MTX did not have an increased rate of infections (aHR 1.2 (0.8–1.8)) compared to those with MTX use without current TNF

inhibitor. The comparison of concurrent TNF inhibitor and MTX use versus MTX use without TNF inhibitor produced similar results (aHR 1.2 (0.7–1.8)).

In contrast, GC use was significantly associated with an increased rate of infections. In the comparison of current TNF inhibitor use irrespective of MTX versus current MTX use without TNF inhibitor, the aHR for high-dose oral GC use on the index date (≥10 mg of prednisone equivalents daily) was 3.1 (2.0 – 4.7) and for low-dose oral GC was 1.3 (0.9 – 2.1) compared to no current oral GC use on the index date. Similar aHR estimates were observed for current oral GC use in the other medication exposure group comparisons (data not shown).

Due to the possibility of a statistical interaction between oral GC and TNF inhibitor in the risk of infection, separate hazard models were analyzed for children with and without oral GC use on their index dates. We did not find evidence of interaction when comparing TNF inhibitor irrespective of MTX versus MTX without TNF inhibitor. Among patients without current oral GC use on their index date, the aHR associated with TNF inhibitor was 1.3 (0.7 – 2.3), and among patients with current oral GC use on their index date, the aHR associated with TNF inhibitor was 1.1 (0.7 – 1.8).

To further explore the relationship between oral GC use and infection, we adjusted for current oral GC use after the index date as a time-varying covariate. The aHR for GC and TNF inhibitors were similar to those that only adjusted for current oral GC dose at baseline (data not shown). An interaction term between GC dose and TNF inhibitor use was not statistically significant in this time-varying GC dose model.

Results of the new user design analysis were similar to the primary results. New users of TNF inhibitor had an aHR of 1.2 (0.5 – 2.9) for infection compared to new users of MTX without current or prior TNF inhibitor use. The aHR for use of high-dose GC use compared to no GC use on the index date was 3.2 (1.1 – 8.8).

Restricting hospitalized infection outcomes to the primary discharge diagnosis produced similar results. In the comparison of JIA without current MTX or TNF inhibitor versus ADHD the aHR was 2.2 (1.7 – 3.0), and for TNF inhibitor irrespective of MTX versus MTX without TNF inhibitor the aHR was 1.0 (0.6 – 1.6). The median duration of hospitalization with infection was 4 days for children with ADHD, children with JIA without current MTX or TNF inhibitor, JIA with current MTX and without TNF inhibitor, and JIA with current TNF inhibitor ($p > 0.3$ for all comparisons among groups). Restricting the study period to the years of overlapping data for the JIA and ADHD cohorts (i.e., 2000 – 2002) produced similar results, albeit with wider confidence intervals (data not shown). We repeated all analyses after increasing the exposure risk window for current medication use from 30 days to 90 days after the last pharmacy claim and the results were similar (data not shown). There were 89 children (1.0%) with JIA and 372 children (0.1%) with ADHD who were diagnosed with immunodeficiencies. Exclusion of these children produced similar results (data not shown).

DISCUSSION

We observed a 2-fold increase in hospitalized bacterial infection rates for children with JIA who were not currently treated with MTX or TNF inhibitors compared to children without JIA, while controlling for oral GC dose, sex, and other factors at the start of follow-up. This finding suggests that the inflammatory or autoimmune process of JIA may predispose children to infection irrespective of therapy. Similar results have been observed in adults with RA compared to the general population (9, 10). Among adults with RA, the risk of infection has been shown to increase with disease severity (11, 12), further supporting the

theory that inflammation may predispose to infection. Although immunodeficiency diagnoses were 10-fold more common among children with JIA compared to children without JIA, this difference did not explain the observed increased rate of infection.

The adjusted risk of infection associated with MTX use was similar to that for children not receiving MTX or TNF inhibitor. Though MTX has been used for decades in the treatment of JIA, there are few estimates of the associated relative infection risk in children. Our results are in agreement with the general impression of practicing pediatric rheumatologists that MTX does not significantly increase the risk of serious bacterial infections (21).

The adjusted risk of infection associated with TNF inhibitor use was similar that for MTX use without TNF inhibitor. There were few hospitalized infections which resulted in relatively wide 95% confidence intervals of the infection risk; nevertheless, based upon the upper bound of our 95% confidence interval, the possibility of a doubling of the risk of infection compared to MTX was statistically excluded.

Even after adjustment for TNF inhibitor and MTX use and other relevant covariates, the risk of infection increased 3-fold with the use of high-dose GC compared to no GC use. Similarly increased risks of infection with GC have been observed in studies of adults with RA (11, 13), including a dose-dependent increased risk (9). However, interpretation of these findings is complicated because oral GC use is likely associated with disease activity and severity. Assessing GC dose in a time-varying manner did not influence our results.

We restricted comparisons of infection rates for children receiving TNF inhibitors only to those children receiving MTX, because the accepted current clinical practice is to initiate TNF inhibitors in children who have failed to respond to MTX (22). Accordingly, most children without current MTX use are likely to have JIA that is less active and less severe compared to children receiving TNF inhibitors, and this may influence the risk of infection (5).

In addition to concerns about a possible overall increased risk of infection, there have been concerning uncontrolled reports of severe soft-tissue infections associated with TNF inhibitors (23, 24). In this large cohort, we did not observe enough soft-tissue infections (< 11) associated with TNF inhibitor use to perform an adjusted analysis, and the severity of soft-tissue infections cannot be accurately ascertained using the ICD-9 coding system. Nevertheless, the crude rates of hospitalized soft-tissue infections were not different between children treated with TNF inhibitors irrespective of MTX compared to MTX without TNF inhibitor (0.4 versus 0.3 per 100 person-years, respectively; $p > 0.6$).

Our study had limitations common to observational studies that use administrative claims data. We did not have access to medical records and could not directly verify the diagnoses of JIA or ADHD or of infection. However, we required 2 or more JIA ICD-9 codes separated in time, a methodology that has been commonly used in studies of adult RA (25). We used diagnosis codes for ADHD to identify comparator children without JIA who were likely to generate subsequent Medicaid claims observable in the MAX data; whether or not the diagnosis of ADHD was accurate is not material to this study. To identify hospitalized bacterial infections, we used an adapted list of ICD-9 codes that was previously validated against medical record review and found to demonstrate greater than 80% sensitivity and specificity (16). We could not directly measure or adjust for JIA disease activity or severity. Therefore, medication channeling by prescribers with resultant confounding between medication use and infection is possible (i.e., “sicker” patients received TNF inhibitors and were also more likely to develop infections). This confounding, if present, would have strengthened the association between medications and infection. Since we did not observe a strong association between TNF inhibitors and infection in our study, this is unlikely to have

created appreciable bias in these results. Nevertheless, this confounding may explain a portion of the association observed between oral GC use and infection. Similarly, if the clinical decision to admit a child with an infection to the hospital was influenced by the child's current medication regimen rather than the severity of the infection, then bias could result. If present, this bias would strengthen the association between immunosuppressant medications and hospitalized infection.

In addition to these limitations, we used specific medication exposure definitions that may have influenced the results. The time window of potential increased risk of infection following initiation or cessation of MTX or TNF inhibitors is not precisely known. We considered current medication exposure up to 30 days after a missed prescription refill. We incorporated this refill grace period in order to maintain continuity within medication exposure episodes and to increase our ability to identify hospitalized infections that may have arisen after current medications were temporarily suspended owing to a minor infection that subsequently resulted in hospitalization. Increasing this refill grace period window to 90 days did not significantly affect the results. Sample size constraints limited our ability to perform a study restricted to new users of MTX and TNF inhibitors, which is typically regarded as the preferred study design (5, 18). Nevertheless, a secondary analysis restricted to new users of TNF inhibitors versus new users of MTX resulted in an infection risk estimate for TNF inhibitors that was very similar to our primary analysis of prevalent users, albeit with wider confidence intervals. We were unable to analyze agent-specific infection rates for the TNF inhibitors because etanercept was the only agent labeled for use by the U.S. Food and Drug Administration during the study period and consequently represented 90% of the TNF inhibitor use. We could not determine GC daily doses precisely from pharmacy claims, owing to several common behaviors, such as physician "as-needed" prescribing and patient non-adherence to the written prescription or self-administration from a cache of previously prescribed medication.

More recent data were not available to us at the time of this study owing to the lag time and financial cost inherent in the creation and release of national MAX files by CMS. Compared to the JIA cohort, we had access to fewer calendar years of data for the ADHD comparator cohort, but many more person-years of follow-up. Therefore, we allowed slightly older children to be included in the comparator cohort to ensure adequate overlap of children's ages with the JIA cohort and adjusted for age in our regression models. Furthermore, there was no anticipated calendar effect on infection rates. We formally tested this assumption by restricting our analyses to the calendar years common to both cohorts (2000 through 2002) and the results were similar.

In summary, children with JIA have higher rates of serious infection than children without JIA independent of the effect of treatment with GC, MTX, or TNF inhibitors. Among children with JIA, the rate of infection associated with MTX or TNF inhibitor use was similar. In contrast, compared with no use of GC, use of high-dose oral GC (≥ 10 mg prednisone daily) was consistently and independently associated with a more than doubling of the rate of subsequent infection. These data suggest the use of steroid-sparing treatment strategies may reduce the risk of serious infections in children with JIA.

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Table 1

Characteristics of the study patients

	JIA	ADHD
Number of patients	8,479	360,489
Mean age (SD)	9.7 (4.4)	9.8 (3.2)
% female	64	24
Race		
% white	52	64
% black	17	20
% latino	20	6
% other/unknown	11	10
Median follow-up time, years (IQR)	1.1 (0.5–2.2)	0.9 (0.4–1.9)
Hospitalized bacterial infection during baseline, n (%)	402 (4.7%)	2,941 (0.8%)
Outpatient bacterial infection during baseline, n (%)	4,004 (47%)	133,760 (37%)
Asthma, n (%)	669 (7.9%)	23,045 (6.4%)
Diabetes mellitus, n (%)	56 (0.7%)	842 (0.2%)
Current oral GC use on index date, n (%)	1,326 (16%)	6,973 (1.9%)
Oral GC daily dose among current users on index date, median (IQR)	10 mg (4–23)	6 mg (3–13)
Medication use during follow-up		
Oral GC use, n (%)	2,532 (30%)	33,388 (9.3%)
MTX use, n (%)	3,090 (36%)	
TNF inhibitor use, n (%)	1,315 (16%)	

JIA = juvenile idiopathic arthritis; ADHD = attention-deficit hyperactivity disorder; SD = standard deviation; IQR = inter-quartile range; E&M = evaluation and management; GC = glucocorticoids; MTX = methotrexate or leflunomide; TNF inhibitor = etanercept, infliximab, or adalimumab; mg = milligram in prednisone-equivalents

Table 2

Hospitalized bacterial infection types by cohort. Only infection outcome types containing 5% or more of infections are shown. Some hospitalized infections were associated with more than 1 discharge diagnosis (e.g., pneumonia and bacteremia). Percentages were calculated with the total number of hospitalizations as the denominator.

Infection Type	Number in JIA	Number in ADHD
Upper respiratory tract	110 (30%)	1544 (35%)
Pneumonia	87 (24%)	891 (20%)
Bacteremia/septicemia	67 (18%)	523 (12%)
Urinary tract/pyelonephritis	65 (18%)	402 (9%)
Skin and soft tissue	44 (12%)	616 (14%)
Abdominal abscess	20 (6%)	629 (14%)
Gastroenteritis	30 (8%)	331 (8%)
Total hospitalized infections	365	4,398

JIA = juvenile idiopathic arthritis; ADHD = attention-deficit hyperactivity disorder

Table 3

Crude rates of hospitalized bacterial infection by disease cohort and medication exposures. Current oral GC use refers to use during study follow-up.

	Person-years of observation	Number of hospitalized bacterial infections	Infection rate per 100 person-years (95% CI)	No current oral GC use: Infection rate per 100 person-years (95% CI)	During current oral GC use: Infection rate per 100 person-years (95% CI)
JIA: entire cohort	13,003	365	2.8 (2.5–3.1)	2.3 (2.1–2.6)	6.9 (5.6–8.5)
JIA: no current MTX, no current TNF inhibitor	8,777	222	2.5 (2.2–2.9)	2.2 (1.9–2.6)	7.3 (5.2–10.1)
JIA: current MTX, no current TNF inhibitor	2,646	88	3.3 (2.7–4.0)	2.4 (1.8–3.2)	7.1 (5.0–9.9)
JIA: current TNF inhibitor, irrespective of MTX	1,580	55	3.5 (2.6–4.5)	2.9 (2.1–4.0)	5.8 (3.4–9.1)
ADHD	454,698	4,398	1.0 (0.9–1.0)	0.9 (0.9–1.0)	5.0 (4.4–5.7)

JIA = juvenile idiopathic arthritis; ADHD = attention-deficit hyperactivity disorder; MTX = methotrexate or leflunomide; TNF inhibitor = etanercept, infliximab, or adalimumab; GC = glucocorticoids

Table 4

Relative hazard of hospitalized bacterial infection.

JIA medication exposure group	Referent Group	Unadjusted Relative Hazard (95% CI)	Adjusted* Relative Hazard (95% CI)
JIA: no current MTX, no current TNF inhibitor	ADHD	3.3 (2.6–4.1)	2.0 (1.5–2.5)
JIA: current MTX, no current TNF inhibitor	JIA: no current MTX, no current TNF inhibitor	1.3 (1.0–1.7)	1.2 (0.9–1.7)
JIA: current TNF inhibitor, irrespective of MTX	JIA: current MTX, no current TNF inhibitor	1.3 (0.9–1.9)	1.2 (0.8–1.8)

JIA = juvenile idiopathic arthritis; ADHD = attention-deficit hyperactivity disorder; MTX = methotrexate or leflunomide; TNF inhibitor = etanercept, infliximab, or adalimumab; GC = glucocorticoids

*Adjusted for patient age, sex, race, hospitalized bacterial infection during baseline, outpatient bacterial infection during baseline, asthma, diabetes mellitus, GC dose on index date (none, low (< 10 mg prednisone equivalents per day), or high (≥ 10 mg prednisone equivalents per day)).