Hospitalization for Varicella and Zoster in Children with Inflammatory Bowel Disease

Daniel J. Adams, MD, and Cade M. Nylund, MD

Objective To evaluate the association between inflammatory bowel disease (IBD) and varicella- and herpes zoster–related pediatric hospitalizations.

Study design We performed a cross-sectional inpatient study using the triennial Healthcare Cost and Utilization Project Kids' Inpatient Database for years 1997-2012 to evaluate the association between a secondary diagnosis of IBD and a primary diagnosis of varicella or herpes zoster for hospitalized children ages 5-20 years. Billing codes were used to identify varicella, herpes zoster, ulcerative colitis, Crohn's disease, and other immunocompromising conditions. A logistic regression model was fitted to quantify the odds of varicella or zoster between these categories.

Results There were 8 828 712 weighted admissions meeting the study criteria, 4434 with varicella and 4488 with herpes zoster. There was an association of IBD and immunocompromising conditions with hospitalization for varicella and herpes zoster. This association was stronger among children with Crohn's disease (varicella OR, 12.75; 95% CI, 8.30-19.59; zoster OR, 7.91; 95% CI, 5.60-11.18) compared with children with ulcerative colitis (varicella OR 4.25; 95% CI 1.98-9.12, zoster OR 3.90; 95% CI 1.98-7.67).

Conclusions IBD in children is associated with hospitalizations for varicella and herpes zoster. These results highlight the importance of efforts to vaccinate patients with IBD without varicella immunity, ideally before the initiation of immunosuppressive therapy. Furthermore, research is needed on the safety and efficacy of the varicella vaccine in children with IBD on immunomodulators or biologic therapy. *(J Pediatr 2016;171:140-5)*.

Varicella-zoster virus (VZV) is a member of the herpesvirus family. Primary VZV infection causes chickenpox, a highly contagious illness characterized by a diffuse vesicular rash, which can progress toward severe disease in children with immunocompromising conditions. VZV, like other herpes infections, establishes latency in the dorsal root ganglia. Reactivation of latent VZV causes herpes zoster, commonly called shingles, a painful clustering of vesicular lesions along a dermatome.[1] Hosts with immunocompromising conditions can develop severe complications from both primary varicella and herpes zoster, including pneumonia, hepatitis, and encephalitis.[2,3] Use of the live-attenuated varicella vaccine has led to a substantial reduction in both cases of, and mortality from, varicella infection.[4,5] VZV infection, however, remains a significant health threat for children with immunocompromising conditions.

Inflammatory bowel disease (IBD) is a chronic and relapsing inflammatory disease condition of the bowel that comprises 2 disorders: Crohn's disease and ulcerative colitis. The use of immunomodulators, such as azathioprine, methotrexate, corticosteroids, and 6-mercaptopurine, alone or in combination with newer biologic agents such as tumor necrosis factor alpha (TNF-α) inhibitors, has changed dramatically the management of IBD in the past 20 years. Although use of these agents has been beneficial for disease control, each of them has been associated with an increased risk of viral infections, including VZV.[3,6] Because of the increased risk of VZV among those with IBD, guidelines have been published that advise both an evaluation of VZV immunity in each new patient with IBD, and, when possible, varicella vaccination before immune suppression for those without immunity.[7-9] Despite efforts to advocate for improved VZV-preventive measures, both adults and children with IBD remain largely underimmunized, with only 77% of children with IBD demonstrating immunity in one study.[10-12]

An increased risk of herpes zoster infection among adults with IBD has been confirmed in one large controlled study.[6] Cases of severe varicella complicating IBD in children have been reported also; however, there are few data quantifying the association between VZV infections and children with IBD.[13-15] Our aim was to evaluate the association between IBD and hospitalization with a primary diagnosis of varicella and herpes zoster infections among children in the US. We hypothesized that

CCS	Clinical Classification Software
HCUP-KID	Healthcare Cost and Utilization Project Kids' Inpatient Database
IBD	Inflammatory bowel disease
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
LOS	Length of stay
TNF-α	Tumor necrosis factor alpha
VZV	Varicella-zoster virus

From the Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, MD

The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Air Force, Department of Defense, or the US Government. The authors declare no conflicts of interest.

Portions of the study were presented as a poster at the meeting of Digestive Disease Week, Washington, DC, May 16, 2015.

0022-3476/$ - see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.jpeds.2015.12.072

there would be a significant association between IBD and VZV-related pediatric hospitalizations. We anticipated the association would be comparatively stronger among children with Crohn's disease compared with children with ulcerative colitis, given the greater use of immunomodulators and biologic agents in children with Crohn's disease.

Methods

We performed a retrospective inpatient cross-sectional study using data from the triennial Healthcare Cost and Utilization Project Kids' Inpatient Database (HCUP-KID) to test our hypothesis that IBD is associated with VZV-related hospitalizations in children. HCUP-KID is an inpatient database of pediatric hospitalizations in the US with data available from the years 1997, 2000, 2003, 2006, 2009, and 2012. The database coverage has expanded over that time span, from initially including discharge data from 22 states in 1997, to including data from 44 states in 2012. The HCUP-KID database now represents approximately 95.6% of all US pediatric hospitalizations.[16] The database assigns an individual-level population weight that allows for estimation of national case rates and trends.[16]

We identified our population of interest by searching the HCUP-KID database for children and adolescents, ages 5-20 years, hospitalized with a secondary diagnosis of IBD. A secondary diagnosis included any diagnosis numbered 2-15 for the HCUP-KID years 1997-2006 or any diagnosis numbered 2-25 for years 2009-2012. IBD diagnoses were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 555.x for Crohn's disease and 556.x for ulcerative colitis. The use of these codes to represent Crohn's disease and ulcerative colitis has been validated in adults but not in children.[17] Several studies, however, have used these codes to identify IBD using the HCUP and HCUP-KID databases.[18-20] Any hospitalizations related to pregnancy were identified using procedure codes (72-74) and excluded, because pregnancy carries its own risk for severe VZV-related complications.[21]

The outcome of interest was hospitalization with a primary diagnosis of varicella or herpes zoster, which was identified with the use of ICD-9-CM codes 052.x and 053.x, respectively. We also sought to understand how IBD might compare with other disorders of immunity, which carry an increased risk of varicella or zoster. Therefore, VZV-related hospitalizations were compared between children with and without IBD, and to a third group of children with immunocompromising conditions. This group was defined by the use of HCUP Clinical Classification Software (CCS), a diagnostic software that groups diagnostic and procedure codes into clinically significant categories.[22] Children with immunocompromising conditions were defined as those hospitalized with a secondary diagnosis of malignancy (CCS code 2.x), HIV (CCS code 1.3.1), or a disorder of immunity (CCS code 3.10).

The HCUP-KID database includes demographic data on race/ethnicity (white, black, Hispanic, Asian or Pacific Islander, or other/not reported), sex, age, payer type (private insurance, public insurance, and uninsured), geographic region (Northeast, Midwest, South, or West), and geographic location (urban vs rural) of the hospital. We used population weights to provide a summary of hospitalizations and demographic data for children with Crohn's disease, ulcerative colitis, immunocompromising conditions, and for those without immunocompromising conditions or IBD. Rao-Scott χ^2 tests were used for comparisons among these 4 categories of patients for each of the demographic and geographic variables.

Multivariable logistic regression was used to generate aOR and 95% CI for the likelihood of hospitalization for varicella or zoster. Varicella or herpes zoster was the dependent variable and Crohn's disease, ulcerative colitis, or immunocompromising condition groups were independent variables. ORs also were adjusted for the covariates age, sex, race/ethnicity, payer status, and geographic region. Overall trend in varicella and zoster was evaluated by including the year of hospitalization in the logistic regression model and the Cochran-Armitage test for trend was used to analyze trends in hospitalization rates. An alpha of 0.05 was considered significant. All analyses were performed using SAS 9.3 (SAS Institute, Cary, North Carolina).

Results

The total weighted number of hospitalizations of children, ages 5-20 years during the 6 study periods, was 8 828 712. Children with a secondary diagnosis of Crohn's disease accounted for 19 920 (0.23%) of these hospitalizations, 11 367 (0.13%) were identified as having a secondary diagnosis of ulcerative colitis, and 535 147 (6.06%) had an immunocompromising condition (**Table I**). The numbers of children in each category admitted with a primary diagnosis of varicella or herpes zoster are listed in **Table I**. Compared with children without immunocompromising conditions or IBD, those with IBD were significantly older, more likely to be white, more likely to be living in the Northeast, and to have private health care insurance (**Table I**).

The multivariable logistic regression model identified a strong association between Crohn's disease and hospitalization for both varicella (OR 12.75, 95% CI 8.30-19.59) and herpes zoster (OR 7.91, 95% CI 5.60-11.18; **Table II**). There also was a significant association between ulcerative colitis and hospitalization for both varicella (OR 4.25, 95% CI 1.98-9.12) and herpes zoster (OR 3.90, 95% CI 1.98-7.67). The association between Crohn's disease and VZV-related hospitalization was comparatively stronger than in children with ulcerative colitis. Children with an immunocompromising condition had the greatest association with hospitalization for herpes zoster (**Table II**). Several other demographic variables were associated with VZV-related hospitalization, including age, Hispanic ethnicity, hospitalization in the Midwest, and insurance provider (**Table II**). Among those patients hospitalized with varicella or zoster, the length of stay