Hospitalizations for Respiratory Syncytial Virus and Vaccine-Preventable Infections in the First 2 Years After Pediatric Liver Transplant

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Objectives To examine in liver transplant recipients at centers participating in the Pediatric Health Information System dataset the number of hospitalizations for respiratory syncytial virus (RSV) and vaccine-preventable infections (VPIs) in the first 2 years after transplantation, morbidity and mortality associated with these hospitalizations, and costs associated with these hospitalizations.

Study design A retrospective cohort study of patients <18 years of age who underwent liver transplantation at a Pediatric Health Information System center between January 1, 2004, and December 31, 2012. Hospitalizations for RSV/VPIs during the first 2 years post-transplant were ascertained using *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes. Data were collected on clinical care, outcomes, and costs during these hospitalizations.

Results There were 2554 liver transplant recipients identified; 415 patients (16.3%) had 544 cases of RSV/VPIs. RSV, rotavirus, and influenza were the most common infections resulting in hospitalization. Ninety-two patients (3.6%) had RSV/VPI during their transplant hospitalization. Transplant hospitalizations complicated by RSV/VPI were longer (44 days vs. 21 days; $P < .001$), had higher rejection rates (37% vs. 26%; $P = .02$), and were more expensive ($259 697 vs. $190 860; $P < .001$). Multivariate analyses identified age <2 years at transplant ($P < .001$) and multivisceral recipient ($P = .04$) as predictors of a hospitalization for RSV.

Conclusions VPIs occurred in 1 of 6 liver transplant recipients in the first 2 years post-transplant, a significantly higher rate than in the general pediatric population. These hospitalizations had substantial morbidity, mortality, and costs, demonstrating the importance of vaccinating patients before transplantation. *(J Pediatr 2017;182:232-8).*

Infection is a recognized and potentially serious complication after solid organ transplantation. Transplant recipients are at increased risk for infection secondary to immunosuppression and exposure to sick contacts during medical visits. Pediatric recipients of a liver transplant are at unique risk for vaccine-preventable infections (VPIs) for a variety of reasons. First, many children undergo liver transplantation before their second birthday and are, therefore, unable to complete their full set of childhood immunizations before transplantation. Second, studies have shown that, despite the known importance of vaccination in preventing certain illnesses, many children still do not enter liver transplant fully up to date on their immunizations.[1,2] In 1 study from England, only 20%-30% of children were fully up to date on their vaccinations at the time of liver transplantation[2]; similarly, in another study from Switzerland, only 43% of patients were up to date for the diphtheria-tetanus-acellular pertussis-polio vaccines, 44% for the measles-mumps-rubella vaccine, 13% for hepatitis B, and 5% for hepatitis A at the time of liver transplantation.[3] Finally, recipients of a transplant may have suboptimal responses to vaccinations before transplantation and waning immunity after transplant.[3-7] Compared with healthy children, infections in recipients of an organ transplant are more likely to be complicated and even life threatening.[8-10] However, the true incidence, morbidity, mortality, and costs resulting from hospitalizations for these illnesses in the pediatric liver transplant population remain unknown.

To address this gap in knowledge, we used the Pediatric Health Information System (PHIS) database to investigate the impact of respiratory syncytial virus (RSV) and VPIs in the pediatric liver transplant population. Although RSV currently is not a VPI, we chose to include it in this study because RSV is one of the most common infectious causes of hospitalization in the pediatric population and there exists a monoclonal antibody (palivizumab) that has been shown to reduce risk of hospitalization in select populations.[11] For the purpose of this report, we refer to the collective group as R/VPIs. The goals of this study were to (1) examine the

CHA	Children's Hospital Association
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
ICU	Intensive care unit
PHIS	Pediatric Health Information System
RSV	Respiratory syncytial virus
R/VPI	Respiratory syncytial virus or a vaccine-preventable infection
VPI	Vaccine-preventable infection

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number of hospitalizations from R/VPIs during the first 2 years after liver transplantation (when children are most immunosuppressed); (2) describe morbidity (duration of hospitalization, need for intensive care unit [ICU] stay, need for mechanical ventilation, graft rejection) and mortality associated with these hospitalizations; and (3) compare the costs of transplant hospitalizations complicated by R/VPI with those without R/VPI. We hypothesize that R/VPIs in pediatric recipients of a liver transplant would be associated with significant morbidity, mortality, and costs.

Methods

A cohort of pediatric recipients of a liver transplant treated at hospitals contributing data to the PHIS database was identified retrospectively to investigate the impact of R/VPIs in the pediatric liver transplant population. The PHIS is an administrative database (Children's Hospital Association [CHA], Kansas City, Kansas) containing inpatient billing data from 43 not-for-profit tertiary children's hospitals.[12] Contributing hospitals are located in 17 major metropolitan areas and account for 85% of admissions to freestanding children's hospitals in the United States. The PHIS database includes patient demographics, diagnoses, discharge disposition, hospitalization costs, and Clinical Transaction Classification codes for procedures and clinical services for each day of a hospital stay. Data quality and reliability are ensured through a joint effort between the CHA and the participating hospitals. Every participating hospital performs coding audits monthly, and the CHA performs data quality checks to ensure that classified errors occur in <2% of a hospital's data.[13-15] Before distribution to end-users, CHA deletes all patient identifiers. The research was reviewed by the institutional review board at The University of Colorado and was deemed exempt and classified as non-human subjects research.

All patients <18 years of age who underwent liver transplantation at a PHIS center between January 1, 2004, and December 31, 2012, were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) procedure codes for liver transplantation (50.51 and 50.59). Multivisceral transplants were included in the study cohort as were patients requiring retransplantation.

We identified hospitalizations for RSV and 11 VPIs (influenza, pneumococcus, meningococcus, *Haemophilus influenzae*, human papillomavirus, varicella, pertussis, rotavirus, measles, mumps and hepatitis A) during the first 2 years post-transplant using ICD-9-CM diagnosis codes (**Table I**; available at www.jpeds.com). We chose not to include the code 466.19 (bronchiolitis, other) to identify patients with RSV because these children could have any infectious cause of bronchiolitis, not just RSV. Although this may underestimate the number of RSV cases, we believe the validity of cases identified was improved. Additional information about these hospitalizations gathered from the PHIS data set included duration of hospital stay, need for ICU management ("ICU Flag" coded by PHIS), need for mechanical ventilation (Clinical Transaction Classification codes 521160, 521161, 5261162, 521164, 521165, 521166, 521167, 521169, and the "Ventilation Flag" coded by PHIS), allograft rejection (ICD-9-CM codes 996.80, 996.82, 996.84), retransplantation (ICD-9-CM codes 50.51 and 50.59), death, and median adjusted hospitalization costs.

Statistical Analyses

Descriptive statistics were used to characterize the subjects by age, sex, ethnicity, race, and reason for initial liver transplantation. Because immunosuppression is greatest in the first year post-transplantation, rates of hospitalization and case fatality ratios were calculated for each infection in the first year post-transplantation. Comparisons, using independent *t* tests and Wilcoxon tests as appropriate, were made between the group of patients who never had a hospitalization for R/VPI and those who did. Because influenza and RSV are 2 of the most common infectious causes of hospitalization in the general pediatric population, we performed multivariate logistic regression to understand demographic and predictive health factors for a hospitalization owing to RSV or influenza during the first 2 years after pediatric liver transplant. Factors significant at $P < .25$ in bivariate analyses were tested in multivariate models by using a backward elimination procedure in which the least significant predictor in the model was eliminated sequentially. At each step, estimates were checked to make sure other variables were not largely affected by dropping the least significant variable. This strategy resulted in the retention of only those factors that were significant at $P < .05$ in the final model. We chose not to include race/ethnicity in the final model because there was a significant amount of missing data. We adjusted both the RSV and influenza models for year of transplant. All statistical analyses were performed by using SAS software (SAS 9.4, SAS Institute, Cary, North Carolina).

Results

Between January 1, 2004, and December 31, 2012, 2554 patients who underwent liver transplant at a PHIS center were identified. Four hundred fifteen of these patients (16.3%) had a total of 544 cases of R/VPIs in the first 2 years post-transplantation. Of these 415 patients, 92 (22.2%) had R/VPI during their initial transplant hospitalization. Patients with R/VPI were significantly younger ($P < .001$) and more likely to be Hispanic ($P < .001$) than those children who did not have a hospitalization for R/VPI (**Table II**). Multivisceral transplant recipients were more likely to have been hospitalized for R/VPI than liver transplant only recipients ($P < .001$). Patients with and without R/VPI were similar with respect to sex and race (**Table II**). There was no difference in the rate of hospitalization for R/VPI between patients transplanted for biliary atresia, the most common indication for pediatric liver transplantation, versus other causes of liver disease (**Table II**). Of the 544 cases of R/VPI, 478 (87.9%) had a primary hospitalization diagnostic code consistent with R/VPI.

Hospitalizations for R/VPIs

RSV, rotavirus, and influenza were the most common potentially preventable illnesses for which pediatric recipients of a