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Impact of gastroesophageal reflux and delayed gastric emptying on pediatric lung transplant outcomes

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BACKGROUND: Gastroesophageal reflux disease is thought to predispose to adverse lung allograft outcomes. However, little is known about the burden of gastroesophageal reflux (GER) and gastroparesis in pediatric patients. In this study we describe the burden of reflux and gastroparesis in children undergoing lung transplant, and evaluates their impact on allograft survival and rejection incidence.

METHODS: This study is a retrospective analysis of pediatric lung transplant recipients who had combined pH and multichannel intraluminal impedance testing (pH-MII) and gastric-emptying scans (GES). Hazard ratios with 95% confidence intervals (CIs) estimated from Cox proportional hazard models were used to examine the associations between reflux parameters and adverse allograft outcomes. Covariates considered in the multivariate analysis included abnormal pH-MII testing, abnormal GES and Nissen fundoplication status. Kaplan–Meier curves were created, with log-rank testing employed to assess differences between groups.

RESULTS: Thirty lung transplant recipients, aged 1 to 21 years, were identified. Eight of 30 patients (27%) had abnormal reflux by impedance, and 12 (40%) had abnormal pH-metry. Of 19 patients tested, 5 (26.3%) had evidence of gastric dysmotility; however, the severity of GER did not trend with delays in gastric emptying. Neither reflux burden by pH-MII testing nor fundoplication status impacted survival or rejection. However, delayed gastric emptying appeared significantly linked to the development of chronic lung allograft dysfunction, independent of GER.

CONCLUSIONS: In children, reflux burden and fundoplication status do not impact lung transplant outcomes, but gastric dysmotility may be linked to allograft dysfunction in children.

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Although pediatric lung transplant outcomes have improved over time, bronchiolitis obliterans syndrome (BOS), the most common form of chronic lung allograft dysfunction (CLAD), affects >50% of pediatric lung transplant recipients who survive 5 years post-transplant. BOS is also the foremost cause of death beyond 1 year after transplant.[1] Non-alloimmune risk factors—such as primary graft dysfunction, infection, ischemia–reperfusion injury and gastroesophageal reflux disease (GERD)—have been implicated in the development of BOS.[2–4]

Although GERD has been well-described in adult lung transplant recipients, and anti-reflux surgery appears to

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provide survival benefit in this population, there are no pediatric studies correlating reflux burden with survival post-transplant.[5–9] Furthermore, although a handful of adult studies have suggested that delays in gastric emptying are common and could have negatively impact survival, there have been no pediatric studies documenting the interrelationship between reflux, delays in gastric emptying and lung transplant survival and rejection.[10,11]

It is the goal of this study to characterize the burden of reflux and gastric dysmotility in pediatric lung transplant recipients and the resultant impact on survival and rejection incidence.

Methods

This is a retrospective study of children, ages 1 to 21 years, who underwent lung transplantation at Boston Children's Hospital between December 2004 and March 2015. All had combined pH and multichannel intraluminal impedance testing (pH-MII) within 12 months of transplant. A subgroup analysis was performed in patients who also underwent gastric-emptying scans. Approval was granted by the institutional review board at Boston Children's Hospital for the conduct of this study.

Post-transplant care

All patients underwent bilateral lung transplantation and followed a standardized immune suppression and surveillance bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies occurring at 1, 3, 6 and 12 months post-transplant and, in addition, when symptomatic or exhibiting declines in lung function.

Spirometry was also conducted according to established standards: weekly or biweekly in the first 2 months post-transplant; monthly until 6 months post-transplant; and every 3 to 6 months thereafter, as well as with any change in clinical status.[12,13]

Reflux detection

Before 2009, pH-MII was conducted based on the presence of symptoms. After 2009, pH-MII was universally performed after transplant regardless of symptoms, based on a reflux monitoring protocol. Catheter placement and monitoring followed published protocols and a minimum of 18 recorded hours was required for analysis.[14,15] pH-MII tracings were manually reviewed by either of 2 investigators (F.D. and R.R.) using BIOVIEW ANALYSIS version 5.3.4 dedicated software (Sandhill Scientific, Denver, CO).

Reflux definitions

A reflux episode was defined as a $>50\%$ drop from baseline impedance, measured in at least the distal 2 channels. Reflux episodes were classified as acid, non-acid or pH-only episodes, based on previously established definitions.[16] Full-column reflux was defined as reflux that reached the highest pair of sensors. The proportion of proximal and distal reflux was also calculated for each patient by measuring the sum of bolus clearance times in the proximal or distal esophagus divided by the study duration.

An impedance study was considered abnormal overall if there were >73 episodes of impedance during the study period.[17] The pH portion was defined as abnormal if pH <4 for $>6\%$ of the study period.[14] The respiratory symptom index (SI), defined as the proportion of respiratory symptoms temporally associated with reflux (occurring within 2 minutes of a reflux episode), was considered abnormal if SI was $>50\%$.[18]

Gastric-emptying studies

Before 2014, gastric-emptying scans (GES) were performed in patients with symptoms of postprandial fullness, heartburn, vomiting or abdominal pain. Since 2014, all patients undergoing lung transplantation had GES within 3 months after transplantation, once narcotics were weaned off. Patients underwent solid-phase GES when possible, but in cases where patients were unable to take solid food, liquid-phase GES were performed. Testing was performed using orally or gastrostomy tube–administered 0.52 mCi Technetium-99m sulfur colloid mixed with egg, milk or formula. Gastric emptying was considered delayed when $>60\%$ of the ingested food remained in the stomach after 1 hour of imaging.[19]

Diagnosis of acute rejection and CLAD

Transbronchial biopsy specimens were graded according to International Society for Heart and Lung Transplantation (ISHLT) standards, which assess the extent of perivascular and interstitial mononuclear cell infiltrates (A grades), as well as the degree of airway inflammation (B grades).[20] Acute cellular rejection was diagnosed when the sum of ISHLT Grades A and B totaled ≥ 2. In 2 patients, Grades A1B0 and A0B1 were treated as rejection when patients had significant declines in respiratory status or spirometry testing and were subsequently treated with empiric pulse steroid therapy.

CLAD in this study was defined as having either: (1) obliterative bronchiolitis (OB) on lung biopsy; or (2) persistent and irreversible decline in forced expiratory volume in 1 second (FEV_1) measurements (bronchiolitis obliterans syndrome, BOS) once other causes of lung function decline were ruled out. BOS was graded according to published guidelines.[2,21]

Survival

Lung allograft survival was defined as either the time elapsed between: (a) date of first lung transplantation and date of relisting in patients who received a second transplant; or (b) date of lung transplantation to the time of death.

Statistical methods

Continuous variables are presented as mean ($\pm$ standard error). Student's *t*-tests were used to compare means between 2 groups of study participants. Hazard ratios