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Impact of lung function interpretation approach on pediatric bronchiolitis obliterans syndrome diagnosis after lung transplantation

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BACKGROUND: The diagnostic criteria for bronchiolitis obliterans syndrome (BOS) are predominantly adult-focused. The relationship between application and impact of reference equation choice on pediatric baseline lung function achieved and subsequent BOS diagnosis remains unclear.

METHODS: Lung function spirometry data (FEV_1, FVC and $FEF_{25–75}$) from pediatric subjects transplanted at the Great Ormond Street Hospital over a 10-year period were collated. Baseline values achieved after lung transplantation and BOS rates were examined. Raw values were compared with 2 different reference equations (the "Brompton" and modern collated "All-age" equations). The impact of $FEF_{25–75}$ baseline definition was investigated.

RESULTS: Fifty subjects were included, 17 males and 33 females, transplanted at a median (range) age of 14.0 years (3.2 to 17.3 years, 83% >10 years old), and followed for 1,028 (388 to 2,613) days post-transplantation. Raw values underestimated baseline lung function attainment for all indices. Magnitude of baseline lung function was affected by reference equation choice. Mean FEV_1 values were: Brompton 97.9% (SD 20.3%) and All-age 86.3% (SD 15.4%) of predicted ($p < 0.0001$). BOS 0p incidence was significantly higher for All-age predicted than for raw values (64% and 40%, respectively, $p = 0.027$). Modification of $FEF_{25–75}$ baseline (to either FEV_1 or FVC baseline) led to a reduction in BOS 0p detection ($p < 0.01$).

CONCLUSIONS: Modern collated reference equations should be used for lung function monitoring in pediatric subjects after lung transplantation. Standardization of $FEF_{25–75}$ baseline definition is urgently required. These data question the utility of the $FEF_{25–75}$ criterion as an early marker of BOS 0p in pediatric subjects.

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Bronchiolitis obliterans syndrome (BOS) is a leading cause of morbidity and mortality after lung transplantation.[1] This clinical surrogate for delayed allograft dysfunction was introduced due to the challenges of histologic diagnosis, and based on the relative decline in lung function (e.g., forced expiratory volume in 1 second [FEV_1]) from maximal values after lung transplantation (i.e., the subject's "baseline" lung function).[2,3] Originally, the earliest category of BOS (termed "BOS 1") was defined once FEV_1 had fallen by

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≥20% from the baseline value, and severity (Grades 1 to 3) was based on magnitude of FEV_1 decline. To facilitate earlier detection, an additional category, BOS 0p, was subsequently introduced, which was defined as an FEV_1 decline of ≥10% from baseline *and/or* the additional criterion of a ≥25% fall in mid-expiratory flows ($FEF_{25–75}$) from $FEF_{25–75}$ baseline value.[4] $FEF_{25–75}$ had been incorporated as this parameter was considered to be a better reflection of more peripheral airway changes, the primary site of the underlying pathophysiology.

Several aspects of the BOS definition require clarification, particularly for pediatric subjects. First, the definition of "true" $FEF_{25–75}$ baseline has been challenged, and a modification proposed to define at the point FEV_1 baseline is met, due to potential false early $FEF_{25–75}$ peaks in adult subjects.[5] Given the high lung-volume dependence of $FEF_{25–75}$ modification to forced vital capacity (FVC) at baseline may be more appropriate. Second, continuing somatic growth for pediatric subjects is not corrected for by absolute or "raw" lung function values. True lung function decline, relative to lung size, may also remain undetected. Pediatric-specific reference equations exist, generating percent-predicted values adjusted for factors such as age, height and gender. There are several different pediatric reference equations, each with their own inherent strengths and weaknesses. Centers often have to switch between reference equations as a subject ages, or use multiple reference equation combinations to cover all indices of interest, and this may have detrimental management implications.[6] To overcome these issues, reference data from several large historic cohorts were recently collated to develop "All-age" equations,[7] with smooth transition across a wide age range (4 to 80 years) and well-defined lower limits of normal for all ages. The impact of using these more accurate reference equations in this setting has not yet been evaluated.

Lung transplantation centers may use a variety of approaches to interpret pediatric lung function data. Pediatric centers typically use percent-predicted values, but reference equation choice may vary as choice of equation has not been standardized. Adult centers transplanting adolescent subjects may use an adult approach that focuses on raw values. The aim of this study was to determine the impact of that variation in practice. Baseline lung function achieved and subsequent BOS diagnosis in children were investigated, based on longitudinal data collected at a single large pediatric transplant center. Current local pediatric practice (current reference equation values) was compared with both potential adult practice (raw values) and updated pediatric practice at the time of this analysis (All-age reference equation values).

Methods

A retrospective analysis of lung function data was performed from pediatric subjects undergoing lung or heart–lung transplantation at the Great Ormond Street Hospital (GOSH) over a 10-year period, from 2002 to 2011. Subjects were included if they had ≥1 year of lung function data available after lung transplantation. Medical records were reviewed in accordance with the guidelines of the research ethics committee of the Institute of Child Health and the GOSH for Children NHS Trust.

Spirometry was performed according to American Thoracic Society criteria for school-age children[8] and using pre-school age range-specific quality control in younger children.[9] Collated raw lung function variables were FEV_1, FVC, $FEF_{25–75}$ and FEV_1/FVC ratio. To investigate the effect of varying clinical practice, 3 different approaches were taken: the current clinical practice values were calculated using "Brompton" reference equations (termed "Brompton predicted" hereafter), which were the most commonly used equations in the UK at the time of this study[10]; absolute values were complied for the current adult approach (termed "raw" hereafter); and the updated approach was calculated using the recently collated "All-age" reference equations (termed "All-age predicted" hereafter).[7] This latter option was considered the optimal choice. As Brompton reference equations do not include $FEF_{25–75}$ reference data (only maximum expiratory flow at 50% and 25% of FVC), Brompton predicted $FEF_{25–75}$ values were not generated for this study. Incorporation of a separate $FEF_{25–75}$ reference equation was considered by the authors to be an overcomplication of the study design and did not reflect local management practice, which was one of the aims of the study.

Baseline was defined, as recommended in the BOS guidelines, as the average of the 2 highest post-transplantation values measured ≥3 weeks apart, regardless of how long the gap was between the 2 measurements. The time taken to reach baseline was defined at the time between the second value and the lung transplantation date. For $FEF_{25–75}$ baseline, 2 further types of baseline were calculated. The first was based on FEV_1-modified baseline as recommended by Rosen et al,[5] who noted an artificial early peak in $FEF_{25–75}$ values in some subjects in the initial post-transplantation period. This FEV_1-modified baseline for $FEF_{25–75}$ was calculated as the average of the 2 $FEF_{25–75}$ values at FEV_1 baseline. In addition, an FVC-modified baseline for $FEF_{25–75}$ was also calculated, defined as the average of the 2 $FEF_{25–75}$ values at FVC baseline.

The current BOS 0p criteria can be achieved by either a *persistent* decrease in FEV_1 of 10% from the post-transplantation baseline FEV_1 value or a *persistent* decrease in $FEF_{25–75}$ of 25% from the baseline $FEF_{25–75}$ value.[4] To assess the impact of the differing approaches, fulfillment of BOS 0p incidence was examined in 3 ways: by FEV_1 criteria alone; by $FEF_{25–75}$ criteria alone; or by both. BOS 1 was defined based on FEV_1 criteria alone, as outlined in recommendations (persistent decrease in FEV_1 of 20% of the post-transplantation baseline value).[4] For percent-predicted data, relative change in percent-predicted change, not actual change, was used (i.e., a 10% decrease, defined as 80% to 72%, not 80% to 70% predicted). Time to reach BOS was defined as time between baseline achieved and the first value fulfilling the BOS criteria specified. Clinical data for each subject contained within the hospital record was examined across the study period to ensure that other reasons for lung function decrease were not present (e.g., infection), as specified in the BOS recommendations.[4]

Statistical analysis was performed using SAS, version 9.2 (SAS Institute, Inc., Cary, NC). Proportions for categorical variables were compared using Fisher's exact test. Kaplan–Meier analyses were used to illustrate time to event occurrence (i.e., baseline achieved or time to BOS 0p or 1). Related-samples Wilcoxon's signed-rank test was used to compare differences in median values. Cox proportional hazards regression analysis was used to generate