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Pulmonary Function Monitoring for Bronchiolitis Obliterans Syndrome in Pediatric Allogeneic Stem Cell Transplant Recipients

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ADMINISTRATIVE INFORMATION

Support - American Thoracic Society.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 May 2024 and was last updated on 15 May 2024.

INTRODUCTION

Review question / Objective #1. Patients: Children and young adults (<25 years of age) scheduled to undergo allo-Human Stem Cell Transplant (aHSCT). Intervention: Pre-transplant pulmonary function testing (PFT) using spirometry, measurement of static lung volumes, or diffusion capacity for carbon monoxide (DLCO). Comparator: No PFT. Outcomes: Diagnostic yield (abnormal PFT), BOS diagnosis post-transplant, BOS severity at diagnosis, post-transplant mortality.
#2. Patients: Children and young adults (<25 years of age) who underwent aHSCT. Intervention: Post-transplant surveillance PFT (at least two tests in the first 12 months after aHSCT) using spirometry, measurement of static lung volumes, or DLCO. Comparator: No surveillance PFT. Outcomes: Diagnostic yield (abnormal PFT), timing of BOS diagnosis, BOS severity at diagnosis, mortality, supplemental oxygen use.

Rationale Bronchiolitis obliterans (BOS), in which immune-mediated injury to the small- and medium-sized airways results in worsening fixed obstruction with air trapping, is the primary pulmonary manifestation of chronic graft versus host disease (cGVHD) in this population. Monitoring allo-human stem cell transplant (aHSCT) recipients with serial PFT allows for objective longitudinal assessment, with the goal of identifying pre-symptomatic BOS. Rate and/or severity of decline in lung function has been associated with worse outcomes in cohort studies including mostly adult HSCT recipients. The two questions addressed in this review relate to the timing of PFT and specific tests to be performed prior to and after aHSCT. These questions aim to find the best strategy of performing PFT that leads to early identification of post aHSCT BOS in children.

Condition being studied Bronchiolitis Obliterans (BOS) developing after allo-Human Stem Cell transplant in children. BOS in children is often an

indolent condition but is associated with high morbidity and mortality. There are few treatment options for established BOS and a sub-set of patients with BOS develop rapid decline in lung function, sometimes resulting in death. There is a possibility that early identification of BOS will result in early institution of appropriate treatments, resulting in less morbidity and mortality.

METHODS

Search strategy Electronic literature searches of Medline were conducted by a medical librarian. Standard methodology for conducting systematic reviews as per guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions were followed.

Participant or population Children and young adults (<25 years of age) who underwent allo-Human Stem Cell Transplant (aHSCT).

Intervention 1. Pre-transplant pulmonary function testing (PFT) using spirometry, measurement of static lung volumes, or diffusion capacity for carbon monoxide (DLCO).
2. Post-transplant surveillance PFT (at least two tests in the first 12 months after aHSCT) using spirometry, measurement of static lung volumes, or DLCO.

Comparator No surveillance pulmonary function tests.

Study designs to be included All type of studies will be considered for inclusion. These include systematic reviews, randomized controlled trials, observational studies with at least the intervention group included. Where randomized control trials are available, only these will be considered for the outcomes included in these trials and observational studies data will only be included for outcomes not reported in the randomized trials.

Eligibility criteria We included observational studies that reported results of pulmonary function test (PFT) among patients <25 years age, before or after the transplantation of any follow-up duration. We only included studies reported as full text. Conference abstracts were not included in this review.

Information sources Medline.

Main outcome(s) Diagnostic yield (abnormal pulmonary function test), timing of bronchiolitis obliterans (BOS) diagnosis, BOS severity at diagnosis, mortality, supplemental oxygen use.

Additional outcome(s) Length of hospital stay, length of intensive care unit stay.

Data management Title/abstract screening was conducted by two screeners using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Full-text screening was conducted by two independent reviewers. Discrepancies between reviewers were identified and resolved by an independent third reviewer. Data from relevant studies were extracted using a specifically developed standardized data extraction form in Microsoft Excel.

Quality assessment / Risk of bias analysis The risk of bias assessment will be performed by a trained methodologist. Risk of bias for randomized trials will be assessed using the revised Cochrane risk-of-bias tool for randomized trials. Risk of bias (study quality) of observational studies was assessed using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies. Certainty of evidence will be assessed across outcomes using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) format available on the website (https://gradepro.org/).

Strategy of data synthesis We will combine data among like study designs i.e. data from randomized studies will be pooled only with data from other randomized studies. We will not pool data from experimental studies with those of observational studies. Metanalysis will be performed for randomized and quasi-randomized (such as before-after studies) studies. Metanalysis will be performed if at least two studies are available to be pooled. We will use 'Fixed-effect model' if studies have similar patients, interventions and outcomes and the concept of one 'true effect size' among studies can be assumed. We will use 'random-effects model' where there are slight differences among studies and different effect sizes can be expected in different studies. Relative risk and mean difference will be reported for categorical and continuous variables respectively. Statistical heterogeneity will be reported as I^2. Substantial heterogeneity will be defined as I^2 50%, as suggested by the Cochrane Handbook. Heterogeneity will be investigated by considering differences in study quality, interventions and sub-populations. Funnel plots will be used to describe publication bias when 10 studies are available for the metanalysis. Data from observation studies will be described in a narrative fashion without statistical pooling.

Subgroup analysis Pre-defined subgroups: Young children (<5 years age) who are unable to perform PFT, Children receiving whole body radiation prior to transplant.

Sensitivity analysis Pre-defined analysis: If enough studies exist with pre-transplant radiation then a sensitivity analysis will be done for studies without pre-transplant radiation therapy.

Language restriction None.

Country(ies) involved United States of America, Australia.

Other relevant information In 2022-23, an American Thoracic Society (ATS) working group prepared clinical practice guidelines on the detection of bronchiolitis obliterans in pediatric aHSCT patients. This systematic review was part of that effort. ATS's confidentiality rules prevented us from registering the protocol before the completion of the project.

Keywords bronchiolitis obliterans, allo-human stem cell transplant, pulmonary function tests.

Dissemination plans Results will be published in a peer-review journal.

Contributions of each author

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