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A strategy for prevention of fungal infections in lung transplantation: Role of bronchoalveolar lavage fluid galactomannan and fungal culture

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BACKGROUND: The optimal strategy for prevention of invasive fungal infections in lung transplant recipients remains undetermined. We studied strategies based on bronchoalveolar lavage fungal culture and galactomannan for prevention of invasive aspergillosis in lung transplant recipients.

METHODS: Consecutive lung transplant recipients were evaluated during the period January 2010 to September 2014. Rates of invasive aspergillosis and all-cause mortality were recorded at 1 year. Criteria established by the International Society for Heart and Lung Transplantation were used to define invasive fungal infections. Multivariate Cox regression analyses were performed to assess the outcomes of mortality and invasive aspergillosis.

RESULTS: A total of 519 lung transplant recipients with 3,077 bronchoscopies were included in our study. The cumulative incidence of fungal infections was 14% (75 of 519).

Of these patients, 10.6% (54 of 519) developed *Aspergillus*-related clinical syndromes. Using multivariate analysis, pre-emptive therapy was associated with significantly lower rates of invasive aspergillosis at 1 year post-transplantation compared with no pre-emptive therapy (hazard ratio [HR] 0.23, 95% confidence interval [CI] 0.09 to 0.58). Pre-emptive therapy and invasive aspergillosis had similar mortality rates compared with no invasive aspergillosis, or negative culture and galactomannan at 1 year (HR 0.54, 95% CI 0.23 to 1.28; and HR 0.99, 95% CI 0.44 to 2.25, respectively). During follow-up, 50% (259 of 519) of patients were negative for galactomannan and *Aspergillus* culture in bronchoalveolar lavage, and did not receive anti-fungal treatment. Only 2 patients developed invasive aspergillosis in this cohort.

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CONCLUSIONS: Our study suggests that use of bronchoalveolar lavage culture and a galactomannan-directed pre-emptive approach significantly decreased the risk of invasive aspergillosis, allowing a 50% reduction in anti-fungal exposure compared with a universal prophylaxis approach, without affecting mortality at 1 year.
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Lung transplant recipients (LTRs) have the highest risk of contracting fungal infections among the solid-organ transplant population.[1] Among fungal infections, *Aspergillus* species predominate, constituting 60% of all fungal infections.[2] *Aspergillus* infections in LTRs are not only associated with increased morbidity, but may result in up to 29% mortality.[3] High rates of morbidity and mortality associated with *Aspergillus* infections have resulted in widespread use of universal anti-fungal prophylaxis in North America and Europe, a trend that continues to date.[4–6] However, the efficacy of universal anti-fungal prophylaxis has not been proven unequivocally. The 2 meta-analyses published to date showed differing results.[7,8] One meta-analysis of anti-fungal prophylaxis in LTRs showed that, irrespective of the anti-fungal agents used, there was no reduction in the rate of invasive aspergillosis (IA) among patients who received universal anti-fungal prophylaxis compared with no anti-fungal prophylaxis.[7] The other systemic review suggested that universal anti-fungal prophylaxis could reduce incidence of invasive *Aspergillus* infection. However, the studies included were limited by small sample size, single-center structure without randomization, mixed population (including heart/heart–lung transplant), and heterogeneity due to variations in immunosuppression, type, and duration of anti-fungal prophylaxis.[8] The American Society of Transplantation guidelines have presented universal prophylaxis as an option.[9]

Owing to the lack of proven efficacy and increased adverse events associated with universal anti-fungal prophylaxis, it seems reasonable to use a pre-emptive strategy.[10] We previously found that culture-directed pre-emptive therapy in LTRs missed half the cases of IA.[11] Galactomannan (GM) is a biomarker of IA and is reported to have higher sensitivity than traditional culture methods.[12,13] Our primary hypothesis was that a pre-emptive therapy strategy based on bronchoalveolar lavage (BAL) GM and fungal culture would be more sensitive in detecting cases of IA. We further explored whether the initiation of pre-emptive therapy based on the positivity of these tests would yield comparable survival results in LTRs without IA.

Methods

Patients

All consecutive LTRs ≥18 years of age and transplanted between January 2010 and September 2014 at the Toronto General Hospital/University of Toronto (TGH, Toronto, ON, Canada) were included in this study. Follow-up data were collected for up to 1 year post-transplant. The data collected included demographics, underlying lung disease, type of lung transplant, cytomegalovirus (CMV) donor/recipient status, immunosuppressive regimen, pre-transplant *Aspergillus* colonization, bronchoscopy findings, microbiology, pathology, radiology, anti-*Aspergillus* therapy, survival, and cause of death.

Patients underwent bronchoscopy with BAL as routinely scheduled, as well as at the discretion of their primary care physician for investigation of clinical symptoms suggestive of graft dysfunction, such as worsening of respiratory symptoms with fever and new or change in pulmonary infiltrate. All LTRs underwent bronchoscopy of the native lungs on the day of transplantation before native lung removal. Surveillance bronchoscopies were performed at 2 and 6 weeks, and at 3, 6, 9, and 12 months after transplantation.

Data were collected prospectively and ascertainment of clinical syndromes was done by 2 observers blinded to each other's evaluations. Random quality checks were done to ensure the caliber of data collection. The research ethics board of the University Health Network (15-9717-AE) approved the study.

Immunosuppression protocol

All patients included in the study were maintained on a regimen of cyclosporine/tacrolimus, prednisone, and azathioprine or mycophenolate; sensitized patients with donor-specific antibodies before or at the time of transplant received anti-thymocyte globulin if infection risks were judged to be acceptable by the attending physician, as reported in a previous study.[14]

Prophylaxis regimens

CMV. CMV-seronegative recipients with CMV-seropositive donors received 9 months of prophylaxis with valganciclovir 900 mg/day, adjusted for renal function, whereas CMV-seropositive recipients received 3 months of valganciclovir prophylaxis 900 mg/day.

Anti-fungal strategy

All LTRs with a history of pre-transplant *Aspergillus* colonization or history of IA within 6 months before transplantation received anti-fungal prophylaxis with voriconazole (200 mg, twice a day). Levels were not routinely measured. In case of intolerance or adverse events due to voriconazole, patients were started on inhaled amphotericin B (20 mg, twice a day) or an echinocandin anti-fungal at the discretion of the treating physician. The prophylaxis was discontinued if the Week 2 and Week 6 bronchoscopies were negative for BAL GM and fungal culture along with absence of new radiologic findings.