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Clinical risk factors for invasive aspergillosis in lung transplant recipients: Results of an international cohort study

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KEY WORDS:
invasive aspergillosis;
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anti-fungal prophylaxis;
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single-lung transplant

BACKGROUND: Invasive aspergillosis (IA) is a frequent complication in lung transplant recipients (LTRs). Clinical risk factors for IA have not been fully characterized, especially in the era of extensive anti-fungal prophylaxis. The primary objective of this study was to evaluate the clinical risk factors associated with IA in LTRs. The secondary objective was to assess the mortality in LTRs who had at least 1 episode of IA compared with LTRs who never had experienced IA.

METHODS: We conducted an international, multicenter, retrospective cohort study of 900 consecutive adults who received lung transplants between 2005 and 2008 with 4 years of follow-up. Risk factors associated with IA were identified using univariate and multiple regression Cox proportional hazards models.

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RESULTS: Anti-fungal prophylaxis was administered to 61.7% (555 of 900) of patients, and 79 patients developed 115 episodes of IA. The rate to development of the first episode was 29.6 per 1,000 person-years. *Aspergillus fumigatus* was the most common species isolated (63% [72 of 115 episodes]). Through multivariate analysis, significant risk factors identified for IA development were single lung transplant (hazard ratio, 1.84; 95% confidence interval, 1.09−3.10; $p = 0.02$,) and colonization with *Aspergillus* at 1 year post-transplantation (hazard ratio, 2.11; 95% confidence interval, 1.28−3.49; $p = 0.003$,). Cystic fibrosis, pre-transplant colonization with *Aspergillus* spp, and use of anti-fungal prophylaxis were not significantly associated with the development of IA. Time-dependent analysis showed IA was associated with higher mortality rates.

CONCLUSION: Incidence of IA remains high in LTRs. Single-lung transplant and airway colonization with *Aspergillus spp.* within 1 year post-transplant were significantly associated with IA.

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Patients who have undergone lung transplantation have a high risk of developing invasive aspergillosis (IA).[1,2] Decreased mucociliary clearance, impaired cough reflex, and continuous exposure of the lungs to the environment are among the factors that contribute to colonization with *Aspergillus* spp, which is found in 20% to 50% of patients.[3] However, the incidence of IA is lower, ranging from 3% to 15%, depending on series reported.[4−7]

IA is associated with high morbidity and mortality rates. Thus, prophylactic strategies targeting *Aspergillus* spp have been widely used by lung transplant centers. The anti-fungal drugs used for prophylaxis have changed over time. Voriconazole is currently the most widely used anti-fungal agent in lung transplant recipients (LTRs).[8] However, the efficacy of anti-fungal prophylaxis and the modalities of its use are debated.[9,10]

Some centers use universal prophylaxis for the first few months post-transplant in all LTRs, whereas others use targeted prophylaxis in patients with identified risk factors for IA.[3,11] Thus, proper identification of risk factors for IA is critical for the management of LTRs. Several studies, mostly single-center cohorts, have assessed risk factors for the development of IA in LTRs, but results are not always consistent. Given the number and the diversity of clinical parameters that need to be assessed, a multicenter study with a large number of patients is warranted. In addition, it is possible that the respective effect of individual risk factors has changed compared with earlier studies due to evolutions in the management of LTRs over time. The aim of our study was to assess the risk factors for the development of IA in a large, multicenter cohort of LTRs in the current era of widespread anti-fungal prophylaxis use.

Methods

Study design and patients

This multicenter, retrospective cohort study was conducted at 14 lung transplant centers across 9 countries in Europe, North America, and Australia. This cohort of patients was initially studied to assess a different outcome, the occurrence of squamous cell carcinoma in LTRs treated with voriconazole, and the study was powered accordingly.[12] We considered for inclusion all consecutive patients aged ≥ 18 years who underwent single-lung, double-lung, or heart-lung transplantation between January 1, 2005, and December 31, 2008. Patients with a simultaneous or sequential abdominal organ transplant were excluded. The study protocol was approved by Institutional Review Boards and/or Independent Ethics Committees at each site.

Data collection

Patient-level data were collected from complete or partial electronic medical records and collated into an electronic database developed and maintained by the coordinating center, the University Health Network, Toronto, Ontario, Canada.

Variables

Demographics and variables collected included recipient age at the time of transplant, sex, type of transplant (double-lung transplant, single-lung transplant, heart-lung transplant), repeat transplantation, underlying disease, dialysis, number of episodes of acute rejection, number of episodes of neutropenia (neutrophils $< 1.5 \times 10^9$/liter), diabetes, cytomegalovirus (CMV) infection (defined according to the American Society of Transplantation criteria[13]), immunosuppressive drugs, pre-transplant and post-transplant colonization with *Aspergillus* spp, and use of anti-mold prophylaxis.

We collected data on the following immunosuppressive medications for induction: monoclonal anti-body directed against interleukin-2 receptor, basiliximab, anti-thymocyte globulin (ATG) or monoclonal anti-body against CD-52, alemtuzumab. For maintenance immunosuppressive regimens, we collected data on tacrolimus, cyclosporine, mycophenolic acid or mycophenolate mofetil (MMF), azathioprine, and sirolimus, if the drug was used for at least 30 days during the follow-up period. For patients receiving calcineurin inhibitor (CNI) drugs, we also collected the number of episodes of supratherapeutic levels of CNI (elevated CNI levels were defined as cyclosporine trough >350 μg/liter or tacrolimus trough >20 μg/liter on at least 1 occasion).

We collected the use of anti-fungal prophylaxis (itraconazole, voriconazole, posaconazole, and amphotericin and its lipidic formulations, echinocandins). Prophylaxis strategies were variable, with some centers using universal prophylaxis and others using targeted prophylaxis in patients considered as high risk of IA. We collected data on