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Immune status assessment in adult lung transplant candidates

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ABSTRACT

Background: Lung transplant recipients have an increased susceptibility to a variety of infections due to immunosuppressive therapy. Current guidelines recommend pneumococcal and other vaccinations, prior to lung transplantation to protect against post-transplant infections, but measurement of the antibody response to vaccination is not advised. Immune status investigation in lung transplant candidates, including the response to pneumococcal polysaccharide vaccination, has not been described.
Methods: Immune status investigation, including measurement of immunoglobulins, complement and the response to 23-valent pneumococcal polysaccharide vaccination (23vPPV) was performed in 81 adult lung transplant candidates.
Results: Eighteen patients had low IgG levels and 32 patients had low IgG1 and/or IgG2 levels. After vaccination with 23vPPV the median antibody concentration of all serotypes increased significantly. Fifty-two patients had protective IgG-post-vaccination antibody levels to at least 10 serotypes. Twenty-nine patients had an impaired response to 23vPPV.
Conclusions: In conclusion, a significant proportion of our cohort of lung transplant candidates had one or more abnormalities in the immune status. It is likely that these patients have an increased risk for infections after transplantation. Revaccination, including measurement of antibody response, and possibly antibody replacement therapy should be considered to minimize infection risk.

1. Introduction

Solid organ transplant recipients have an increased susceptibility to infections caused by a broad spectrum of pathogens [1]. Pre-transplant screening and management are designed to minimize infection risk after transplantation. After transplantation, all patients receive immunosuppressive medication and can be considered immunodeficient. For optimal infection prevention it is advised to update vaccinations in transplant candidates prior to transplantation. Recommended vaccinations include 23-valent pneumococcal polysaccharide vaccination (23vPPV), 13-valent pneumococcal conjugate vaccine (13cPCV) and other (childhood) vaccinations [2,3].

Pneumococcal polysaccharide vaccination can be used to prevent pneumococcal disease but can also be used to measure the status of the humoral immune system and therefore is part of the immune investigation protocol in patients with suspected immunodeficiency [4]. In current guidelines immune status investigation, including the response to pneumococcal polysaccharide vaccination, prior to lung transplantation is not included in the standard screening protocol. Humoral immunodeficiency is not a contraindication to lung transplantation [5], but some reports suggest that immunodeficient patients have a complicated post-transplant course [6].

Lung transplant candidates suffer from end-stage lung disease. Chronic immunosuppressive therapy might influence immune status and vaccination responses in this population. It is of clinical importance to know whether these patients have an impaired immune status as this can increase infection risk after transplantation. As far as we are aware, this has not been studied before.

Therefore, we performed immune status investigation including evaluation of the polysaccharide antibody response in a group of lung transplant candidates.

Abbreviations: ICD-10, International Classification of Diseases 10; MBL, Mannose-binding lectin; 23vPPV, 23-valent pneumococcal polysaccharide vaccination; 13vPCV, 13-valent pneumococcal conjugate vaccination.

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2. Objective

The objective of this study is to assess the immune status of lung transplant candidates, including the responsiveness to pneumococcal vaccination. It therefore can provide the rational arguments for the existing vaccination guidelines.

3. Materials and methods

The St. Antonius Hospital, Nieuwegein, the Netherlands, is a tertiary referral hospital for lung transplantation in collaboration with the University Medical Center in Utrecht. Patients are seen at the St. Antonius Hospital with all indications for lung transplantation except cystic fibrosis. This study reports on all patients who underwent screening for lung transplantation in the St. Antonius Hospital in the period 2009–2012 and were placed on the waiting list.

Clinical characteristics, use of medication, immune status assessment at time of screening for lung transplantation and follow-up data were collected from patient records. All diagnoses were categorized according to the International Classification of Diseases 10 (ICD-10) used by Eurotransplant. Recurrent respiratory infections were defined as having three or more infectious periods per year. Infectious episodes were categorized as sinusitis, bronchitis or pneumonia. Medication use was reviewed and patients were considered to be on immunosuppressive therapy if this medication was used as maintenance therapy and had well-known immunosuppressive (side) effects [7].

Standard immune investigation according to the protocol of the European Society of Immune Deficiencies (ESID) [4] included immunoglobulins, IgG subclasses, isohaemaglutinins, and antibodies to protein antigens. Serum immunoglobulin and IgG subclass concentration were measured by nephelometry on an Immage 800 (Beckman-Coulter, Brea, CA, USA) and Siemens BN Prospec (Siemens Healthineers, Erlangen, Germany), respectively. Lower limits of normal for serum immunoglobulins and IgG subclasses were as follows: IgM 0.4 g/L, IgG 7.0 g/L, IgA 0.7 g/L, IgG1 4.9 g/L, IgG2 1.5 g/L, IgG3 0.2 g/L, IgG40.08 g/L [8]. Isohaemagglutinins were determined on (BG-0) test cells (Ortho-Diagnostics, Turnhout, Belgium) in a 2-fold dilution series.

IgG antibodies to protein antigens of CMV, EBV, and Toxoplasma were determined on an automated immunoassay analyser (Liaison XL, DiaSorin, Saluggia, Italy). Complement activity was determined by measuring AP (alternative pathway), CP (classical pathway) and MP (lectin pathway), using a commercially available enzyme immunoassay (Wielisa®; Wieslab, Lund, Sweden) [9]. When complement MP activity was <10%, genotyping was performed to confirm MBL deficiency. Genotypes 0/0 and XA/0 were considered to be MBL deficient.

Patients were vaccinated intramuscularly with one dose of 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23; Merck, Rahway, NJ, USA) containing 25 μg purified type-specific capsular polysaccharides of 23 pneumococcal serotypes. Blood samples were drawn before and 3–6 weeks after vaccination to evaluate the response to vaccination. Serum samples were stored at −80 °C until use. IgG antibodies against 14 different pneumococcal polysaccharides were measured on a Luminex platform (Luminex Corporation, Austin, TX, USA), using a quantitative multiplex immunoassay: the XMAP pneumococcal immunity panel. This assay allows measurement of serotype-specific anticapsular polysaccharide IgG antibodies to the following serotypes: 1, 3, 4, 8, 9N, 12F, 14, 19F, 23F, 6B, 7F, 18C, 19A, and 9V (Danish nomenclature), corresponding to serotypes 1, 3, 4, 8, 9, 12, 14, 19, 23, 26, 51, 56, 57, and 68 according to the American nomenclature, respectively.

For categorization of the antibody response to pneumococcal polysaccharide vaccination, the 2015 AAAAI/ACAAI classification schedule was used [10]. Protective antibody levels against an individual given pneumococcal serotype are defined as an antibody concentration >1.3 μg/mL. A positive immune response to a given serotype is defined as having a post-vaccination antibody concentration >1.3 μg/mL and a ≥ 2-fold antibody concentration increase between the pre- and post-vaccination serum samples. A patient is considered to be a responder if at least 70% of the antibody responses to the serotypes tested (i.e. 10 of the 14 serotypes tested) were positive. According to this classification responses are categorized as [1] normal, [2] mildly impaired (antibody levels >1.3 μg/mL for ≥70% of serotypes, but ≥2-fold increase between pre- and post-vaccination antibody titers for <70% of serotypes), [3] moderately impaired (antibody levels >1.3 μg/mL for <70% of serotypes) or [4] severely impaired (antibody levels >1.3 μg/mL for ≤2 serotypes).

For statistical analyses the Fisher's exact test, Mann-Whitney *U* test were used where appropriate. For data management and statistical analyses Microsoft Excel 2010 and IBM SPSS Statistics for Windows (version 22.0) were used. Graphs were made with GraphPad Prism version 2.0. Differences were considered to be significant at the p value <0.05.

The local medical ethics committee approved the study. All patients gave formal written informed consent.

4. Results

Eighty-one patients on the waiting list for lung transplantation were included in this study (Table 1). 46 patients were female. The median age was 52 years. The majority of patients was diagnosed with emphysema or lung fibrosis. At time of screening for lung transplantation, 29 patients suffered from recurrent respiratory tract infections, 26 patients used ≥5 mg prednisone daily as their only immunosuppressant medication, 11 patients were on immunosuppressive therapy other than prednisone and 6 patients used a combination of immunosuppressive therapy including prednisone.

Immune status investigation showed 5 patients with a decreased serum IgM level, 4 patients with a decreased IgA and 18 patients with a decreased IgG (Table 2). Twenty-six patients had a decreased IgG1 and 17 patients had a decreased IgG2. In 11 of these patients, both IgG1 and IgG2 were decreased. Six patients had a genotypically confirmed MBL deficiency, 3 had XA/0 and 3 patients 0/0 genotype. No abnormalities in the classical and alternative complement pathway were found.

Eighty patients (99%) had IgG specific antibodies to at least one protein antigen (i.e. CMV, EBV or Toxoplasma), 56 (69%) patients to at least two protein antigens and 19 (23%) to all three protein antigens.

Response to 23-valent pneumococcal polysaccharide vaccination was measured when patients were placed on lung transplantation

Table 1
Clinical characteristics of 81 lung transplantation candidates.

Patient characteristics	
Total	81
Female	46
Median age (years)	52
Age range (years)	18–64
Eurotransplant diagnosis category	
COPD/emphysema	43
Alpha-1 antitrypsin deficiency	8
Idiopathic pulmonary fibrosis	9
Other pulmonary fibrosis	11
Hypersensitivity pneumonitis	2
Sarcoidosis	4
Lymphangiomyomatosis	1
Primary pulmonary hypertension	3
Infections	
Recurrent respiratory tract infections (>3/year)	29
Immunosuppressive medication	
Use of maintenance corticosteroids ≥5 mg/day only	26
Use of maintenance corticosteroids and other immunosuppressive therapy	11
Use of non-corticosteroid immunosuppressive medication only	6