Diagnosis and Treatment of Patients with Autoimmune Bullous Disorders in Germany

Enno Schmidt, MD, PhD[a,b,*], Detlef Zillikens, MD[a]

KEYWORDS

• Autoantibody • Bullous • Pemphigus • Pemphigoid
• Therapy

In Germany, 5250 fully trained dermatologists were registered at the end of 2009, including 900 working in hospitals and 4000 in outpatient clinics and private practices (statistics of the German Medical Association; www.bundesaerztekammer.de). Almost all patients with autoimmune bullous disease are initially referred to dermatology departments at university or nonuniversity hospitals for diagnosis and treatment decisions. Most patients are initially treated as inpatients and then allocated to specialized outpatient departments of the hospital or private practices according to the patients' preferences.

At the University of Lübeck and the University of Kiel, specialized interdisciplinary outpatient departments for the treatment of patients with immunobullous diseases have been established in Comprehensive Centers for Inflammation Medicine. In these centers, patients with inflammatory diseases are managed in interdisciplinary teams, including interdisciplinary outpatient clinics and weekly case conferences. This approach facilitates clinical studies, data collection, and biobanking.

Health insurance is compulsory in Germany. It covers all costs for treatment regimens that have been licensed for a particular disease. In addition, for life-threatening diseases, off-label treatments that have been shown to be beneficial are covered.

EPIDEMIOLOGY

The incidence of pemphigus was calculated to be 2.3 new cases per million per year in Germany.[1] With a population of 82.14 million, including 15.57 million inhabitants with a migration background at the end of 2008 (Federal Institute of Statistics, www.destatis.de), about 200 newly diagnosed patients with pemphigus per year are expected in Germany. The age-adjusted incidence of pemphigus vulgaris was 9-fold higher in patients with a migration background compared with native Germans.[1] The incidence of bullous pemphigoid (BP), by far the most frequent autoimmune blistering disease, has been determined to be 13.4 per million per year in a recent prospective study in 2001 and 2002 in Lower Franconia, a well-defined region in

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[a] Department of Dermatology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany
[b] Comprehensive Center for Inflammation Medicine, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany
* Corresponding author. Department of Dermatology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany.
E-mail address: enno.schmidt@uk-sh.de

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southern Germany, followed by pemphigoid gestationis (2.0 per million per year) and mucous membrane pemphigoid (2.0 per million per year).[2] Based on these data, in 2002, a total of 1830 new patients with immunobullous disorders were estimated. The incidence of BP in Germany has doubled within the last 10 years,[2,3] an observation that may be related to the increasing age of the general population and advances in the diagnostic tools. Because the incidence of BP dramatically increases with age resulting in an incidence of 150 to 190 per million per year for patients who are 80 years and older,[2,4] in 2010, at least 3450 new patients with autoimmune blistering diseases can be expected to be diagnosed in Germany.

SURVEY AMONG SECONDARY AND TERTIARY REFERRAL CENTERS FOR AUTOIMMUNE BULLOUS DISEASES

A standardized questionnaire was sent to all 34 university departments and 38 nonuniversity hospitals with inpatient dermatology departments. The questionnaire consisted of 4 questions about the diagnostic procedures for immunobullous disorders performed in the departments: (1) direct immunofluorescence (IF) microscopy; (2) indirect IF microscopy on monkey esophagus, guinea pig esophagus, human salt-split skin, monkey bladder, rat bladder, and complement binding test on human salt-split skin; (3) commercially available enzyme-linked immunosorbent assay (ELISA) systems, including BP180 NC16A, BP230, desmoglein 1, desmoglein 3, and envoplakin; and (4) in-house ELISA systems and immunoblotting analyses for the detection of autoantibodies against BP180, BP230, laminin 332, type VII collagen, p200 protein, α6 integrin, β4 integrin, desmoplakin I/II, periplakin, and envoplakin. For each test system, the answer yes or no could be marked.

In the treatment section of the questionnaire, first-line therapies for pemphigus vulgaris/foliaceus and BP were requested. In addition to the most frequent therapeutic regimens that could be marked with a cross, other options could be added as free text.

All 34 university departments and 30 of 38 (79%) nonuniversity hospitals with inpatient care for patients with dermatologic problems completed the questionnaire, resulting in a total response rate of 89%.

DIAGNOSIS

All university and 93% nonuniversity departments performed direct IF microscopy. Indirect IF microscopy on monkey/guinea pig esophagus and human salt-split skin was done in 76% and 68% of university departments and 50% and 23% nonuniversity departments, respectively. Commercial ELISA systems for antidesmoglein and anti-BP180 antibodies were applied in 65% and 76% of university departments and 30% and 37% of nonuniversity departments, respectively. Noncommercial assays for the detection of autoantibodies in immunobullous diseases were used in 19% of dermatology departments, including 21% of university departments and 17% of nonuniversity departments. In addition, in 27% of departments, sera were sent for evaluation to external laboratories, including both university departments of dermatology and private laboratories.

This is the first survey on the diagnostic methods for immunobullous diseases in Germany. This survey reveals that direct IF microscopy is within the standard diagnostic repertoire in almost all dermatologic departments. Detection of serum antibodies by indirect IF microscopy and commercial ELISA systems is also widespread, whereas more sophisticated noncommercial systems are only used in a few specialized departments. A more detailed analysis of the diagnostic standard for immunobullous disorders in Germany is in preparation.

The diagnostic pathway for immunobullous dermatoses at the Department of Dermatology in Lübeck is summarized in **Fig. 1** along with recent reviews.[5,6] Diagnostic criteria used in the authors' department are detailed in **Table 1**.[2]

All diagnostic procedures on both outpatients and inpatients, including the serial determination of circulating autoantibodies during the follow-up period, are covered by the health insurances.

TREATMENT

High-quality controlled prospective clinical trials for the treatment of autoimmune blistering diseases are rare, therefore treatment decisions are mainly guided by published reviews in this field[7–11] or personal experiences. In contrast to the United Kingdom,[12,13] in Germany, no recommendations of the National Society of Dermatology for the treatment of immunobullous disease are available. For mucous membrane pemphigoid, guidelines for both diagnosis and treatment have been published following an international consensus conference.[14] Corticosteroids, dapsone, and cyclophosphamide (for severe cases) are the only drugs licensed for treatment of autoimmune bullous diseases in Germany.

Bullous Pemphigoid

In the present survey, topical clobetasol propionate 0.05% ointment was used as first-line treatment of BP in 68% of university hospitals and 67%