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Adenovirus-Specific IgG Maturation as a Surrogate Marker in Acute Exacerbations of COPD

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BACKGROUND: B cells in airways and lung parenchyma may be involved in COPD evolution; however, whether their pathogenic role is beneficial or harmful remains controversial. The objective of this study was to investigate the maturation of adenovirus-specific immunoglobulins in patients with COPD with respect to clinical outcome.

METHODS: The presence of adenovirus-specific immunoglobulins during acute exacerbation of COPD (AECOPD) was analyzed at exacerbation and 2 to 3 weeks later. Patients with detectable adenovirus-specific IgM and low IgG avidity were grouped into fast and delayed IgG maturation. The clinical outcome of both groups was evaluated.

RESULTS: Of 208 patients, 43 (20.7%) had serologic evidence of recent adenovirus infection and were grouped by fast IgG maturation (26 patients) and delayed IgG maturation (17 patients). Baseline characteristics, AECOPD therapy, and duration of hospitalization were similar in both groups, but the AECOPD recurrence rate within 6 months was higher ($P = .003$), and there was a trend for earlier AECOPD-related rehospitalizations ($P = .061$) in the delayed IgG maturation group. The time to rehospitalization or death within 2 years was shorter in patients with delayed IgG maturation ($P = .003$). Adenovirus-specific IgG maturation was an independent predictor of the number of AECOPD recurrences within 6 months ($P = .001$) and the occurrence of hospitalization or death within 2 years ($P = .005$).

CONCLUSIONS: Delayed immunoglobulin avidity maturation following COPD exacerbation is associated with worse outcomes.

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ABBREVIATIONS: AECOPD = acute exacerbation of COPD

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COPD is characterized by chronic inflammation of the respiratory tract, which is further intensified during acute exacerbation.[1] The degree of inflammation increases with disease severity and persists long after smoking cessation.[2] Various immune cells orchestrate recruitment and activation of inflammatory cells that drive the pattern of structural changes in the lung tissue resulting from repeated tissue injury and repair. Alveolar macrophages, neutrophils, and subsets of T cells are considered key inflammatory cell types in COPD.[3-6] The involvement of B cells has gained attention, with increased numbers having been shown in large airways of patients with COPD.[7] B cells organized in lymphoid follicles have been recognized in small airways and lung parenchyma of patients with COPD, which further increases with COPD progression.[3,8] In these lymphoid follicles, antigen retention, immunoglobulin class switching, and affinity/avidity maturation occur.[9] The antigens responsible for this process are yet unknown. Antigens of microbial origin, cigarette smoke-derived antigens, and autoantigens have been suggested to activate B cells.[10,11] Thus, a protective as well as a harmful role of B-cell-generated antibodies seem plausible.[12] Hypothetically, different COPD phenotypes mount a distinct B-cell response relative to outcome.

The aim of this study was to investigate immunoglobulin avidity maturation in patients with COPD and its possible impact on clinical outcome. Preliminary data indicate serologic evidence of recent adenovirus infection in a considerable proportion of the population with acute exacerbation of COPD (AECOPD) studied. Thus, adenovirus-specific immunoglobulins during COPD exacerbation were investigated as a marker reflecting the individual B-cell response.

Materials and Methods

Study Population

From November 2003 to March 2005, patients hospitalized for AECOPDs at the University Hospital Basel were recruited. Patients were required to be aged > 40 years and to meet spirometric COPD criteria and the definition of AECOPD. Patients with immunosuppression, asthma, cystic fibrosis, or infiltrates as seen on chest radiographs were not included. AECOPD was defined as an acute, sustained worsening of the patient's condition beyond normal day-to-day variation.[13] Only patients hospitalized for AECOPD (severe AECOPD[14]) were included in the study.

Patients were monitored for recurrent moderate (requiring treatment with systemic corticosteroids, antibiotics, or both) and severe (requiring hospitalization or a visit to the ED) AECOPDs for 6 months. The trial was approved by the institutional review board and registered as the ProCOLD (Procalcitonin-Guided Antibiotic Therapy in AECOPD) study (Ethics Committee of Basel 232/03). Written informed consent was obtained from all patients. The primary study objective was to improve antibiotic prescription based on procalcitonin guidance as reported previously.[15] Herein, a post hoc analysis of the ProCOLD study was performed. A description of study assessments is provided in e-Appendix 1.

Serologic Assessment of Adenovirus Infection

Adenovirus-specific IgG and IgM were detected by enzyme immunoassay (Anibiotech Oy, Orgenium Laboratories Division) as described by the manufacturer. IgM-positive samples were retested after removal of IgG and rheumatoid factor. Serum samples were tested using a noncommercially available adenovirus IgG avidity enzyme-linked immunosorbent assay (Anibiotech Oy, Orgenium Laboratories Division). The adenovirus IgG avidity index was calculated from each specimen and expressed as percentage of IgG reactivity remaining in the urea-treated sample: $(OD_{urea}/OD_{reference}) \times 100$, where OD refers to optical density.[16-18] Criteria for low and high avidity were evaluated in an independent population. A detailed description is available in e-Appendix 1. Similar assays have been developed and established for other viral and nonviral infections.[16,17,19-21]

Serum samples at the start of hospitalization and after 2 to 3 weeks (14-21 days) were analyzed for adenovirus-specific immunoglobulin levels. Only patients with detectable adenovirus-specific IgM and low-avidity adenovirus-specific IgG on AECOPD hospitalization were analyzed further. These patients with serologic evidence of recent adenovirus infection were stratified into two groups determined by adenovirus-specific IgG avidity after 2 to 3 weeks: fast IgG maturation (high-avidity adenovirus-specific IgG) and delayed IgG maturation (low-avidity adenovirus-specific IgG).

Statistical Analyses

Discrete variables are expressed as counts (percentages) and continuous variables as mean ± SD or median (interquartile range). Comparability of groups was analyzed by the χ^2 test, Fisher exact test, Student *t* test, and Mann-Whitney *U* test, as appropriate. The Kolmogorov-Smirnov test was applied to assess normal distribution. Time to exacerbation, hospitalization, death, or a combined end point was described by Kaplan-Meier survival curves and compared by the log-rank test. Predictors of clinical outcome were investigated using linear and logistic regression models. All tests were two-tailed, and $P < .05$ was defined as significant. Data were analyzed using SPSS version 20 for Macintosh (IBM).

Results

Of 208 patients analyzed for adenovirus-specific immunoglobulins, 43 (20.7%) had detectable adenovirus-specific IgM and low-avidity adenovirus-specific IgG within 3 weeks of AECOPD. Twenty-six of these patients (60.5%) had high-avidity adenovirus-specific IgG after 2 to 3 weeks (fast IgG maturation), whereas the remaining 17 (39.5%) had low-avidity adenovirus-specific IgG after 2 to 3 weeks (delayed IgG maturation).

Age, sex, and COPD stage did not significantly differ between patients with fast and delayed adenovirus-specific IgG maturation ($P = .18$, .57, and .58, respectively). Likewise, other baseline characteristics were similar in both groups (Table 1).