CLINICAL RESEARCH STUDY

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Incidence of *Pneumocystis jiroveci* Pneumonia among Groups at Risk in HIV-negative Patients

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ABSTRACT

BACKGROUND: *Pneumocystis jiroveci* pneumonia in human immunodeficiency virus (HIV)-negative immunocompromised patients is associated with high mortality rates. Although trimethoprim-sulfamethoxazole provides a very effective prophylaxis, pneumocystosis still occurs and may even be emerging due to suboptimal characterization of patients most at risk, hence precluding targeted prophylaxis.
METHODS: We retrospectively analyzed all cases of documented pneumocystosis in HIV-negative patients admitted in our institution, a referral center in the area, from January 1990 to June 2010, and extracted data on their underlying condition(s). To estimate incidence rates within each condition, we estimated the number of patients followed-up in our area for each condition by measuring the number of patients admitted with the corresponding international classification diagnostic code, through the national hospital discharge database (Program of Medicalization of the Information System [PMSI]).
RESULTS: From 1990 to 2010, 293 cases of pneumocystosis were documented, of which 154 (52.6%) tested negative for HIV. The main underlying conditions were hematological malignancies (32.5%), solid tumors (18.2%), inflammatory diseases (14.9%), solid organ transplant (12.3%), and vasculitis (9.7%). Estimated incidence rates could be ranked in 3 categories: 1) high risk (incidence rates >45 cases per 100,000 patient-year): polyarteritis nodosa, granulomatosis with polyangiitis, polymyositis/dermatopolymyositis, acute leukemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma; 2) intermediate risk (25-45 cases per 100,000 patient-year): Waldenström macroglobulinemia, multiple myeloma, and central nervous system cancer; and 3) low risk (<25 cases per 100,000 patient-year): other solid tumors, inflammatory diseases, and Hodgkin lymphoma.
CONCLUSIONS: These estimates may be used as a guide to better target pneumocystosis prophylaxis in the groups most at risk.
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KEYWORDS: Hematological malignancy; HIV-negative; Inflammatory diseases; Organ transplant; *Pneumocystis jiroveci*; Vasculitis

Pneumocystis jiroveci pneumonia in human immunodeficiency virus (HIV)-negative patients has a poor prognosis, with in-hospital mortality rates of 50%, reaching 86% in patients with acute respiratory distress syndrome.[1,2] The high level of protection conferred by trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis suggests that extended use of this drug may decrease the burden of

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pneumocystosis in non-HIV-immunocompromised patients.[3] However, the wide spectrum of immunosuppressive conditions predisposing to pneumocystosis, and the limited data available on its incidence in non-HIV-infected patients, has precluded the establishment of evidence-based guidelines for pneumocystosis prophylaxis in these populations.

In HIV-infected patients, CD4 cell count in peripheral blood provides a simple and accurate method to determine the risk of pneumocystosis,[4] which led to the recommendations that TMP-SMX be initiated in any patient with CD4 counts <200 cells/μL, or 15%.[5] For HIV-negative patients, the accuracy of this biomarker is poorly characterized. The level of immunosuppression results from both the impairment in immunity related to the underlying disease itself, and from the immunosuppressive effect of drugs used to control these diseases, particularly corticosteroids. In this regard, the American Thoracic Society advises practitioners to consider prophylaxis when prednisone dose exceeds 20 mg/day for longer than 1 month, but acknowledges that this is not evidence based.[5] Of note, this statement does not take into account the heterogeneity of pneumocystosis risk across the wide spectrum of diseases in which corticosteroids are used. For example, the incidence of pneumocystosis among patients on corticosteroids is higher in granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) than in rheumatoid arthritis.[6] We aimed to provide original data on the spectrum of diseases associated with pneumocystosis in non-HIV-infected patients, and to estimate the incidence of pneumocystosis in these conditions to better inform the targeted use of TMP-SMX prophylaxis in HIV-negative patients at higher risk.

CLINICAL SIGNIFICANCE

- The risk of pneumocystosis in immunocompromised HIV-negative patients is particularly high (incidence >45 cases per 100,000 patient-year) in patients with polyarteritis nodosa, granulomatosis with polyangiitis, polymyositis/dermatopolymyositis, acute leukemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma.
- Other malignant and inflammatory diseases were at lower risk.
- These estimates may be used to better inform the targeted use of trimethoprim-sulfamethoxazole prophylaxis in HIV-negative patients.

MATERIALS AND METHODS

Pneumocystosis Case Definitions

We performed a retrospective analysis of all patients with pneumocystosis admitted from January 1990 to June 2010 to the Rennes University Hospital, a tertiary care teaching hospital that serves as the referral center for the area (catchment population estimated at one million inhabitants). A case was defined by a positive direct examination (May-Grünwald-Giemsa, Gomori-Grocott staining, or immunofluorescence) on bronchoalveolar lavage. Cases of pneumocystosis documented only by polymerase chain reaction were not included.[7] Only patients that tested HIV-negative were included. Patients were identified through: 1) the computerized database of the department of infectious diseases and intensive care unit (ICU); 2) the database of the parasitology-mycology laboratory, which serves as the reference center for pneumocystosis diagnosis in the area, and 3) the hospital discharge database from the Program of Medicalization of the Information System (PMSI), using the International Classification of diseases, 9th Revision, Clinical Modification (ICD-9-CM), code 136.3, and ICD-10-CM, code J17.3. We only analyzed the first hospitalization when pneumocystosis diagnosis was mentioned. Information provided at discharge included the major cause of admission and associated conditions. Underlying conditions were selected based on experts' discussions and literature knowledge. Considering the high diversity of conditions, and to provide a description relevant for clinical practice, a hierarchization was applied to assign only one underlying condition per patient. If a patient had more than one underlying condition, the case was assigned to the condition considered to be the most immunosuppressive. The selection started with hematological malignancies, solid organ transplant, solid tumors, vasculitis, and systemic inflammatory diseases, and ended with miscellaneous conditions. Following this hierarchy, a case presenting with, for instance, non-Hodgkin lymphoma and lupus, was recorded as non-Hodgkin lymphoma.

Incidence Rates of Pneumocystosis According to Underlying Conditions

To estimate the incidence rates in each condition, we had to estimate the denominator (ie, the number of patients followed in our geographic area for each condition over the study period). We performed a retrospective analysis of all patients hospitalized in our institution during the study period by searching discharge diagnoses for the corresponding ICD-9/10-CM codes: non-Hodgkin lymphoma (202.8, C85.9), chronic lymphocytic leukemia (204.1, C91.1), acute leukemia (205.0, C92.0), hematopoietic stem cell transplant (Z948.0, Z948.1), multiple myeloma (203.0, C90.0), Hodgkin lymphoma (201, C81), Waldenström macroglobulinemia (273.3, C88.0), central nervous system cancer (191, C71), breast cancer (174, C50), lung cancer (162, C34), rheumatoid arthritis (714.9, M05.8, M06.9), polymyalgia rheumatica (725.0, M35.3), Sjögren syndrome (710.2, M35.0), polymyositis (710.4, M33.2) and dermatomyositis (710.3, M33.9) merged into a single category, granulomatosis with polyangiitis (446.4, M31.3), polyarteritis nodosa (446.0, M30.0), giant cell arteritis (446.5, M31.6), and sarcoidosis (135.0, D86).

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