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

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CLINICAL RESEARCH STUDY

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

Running head: Pneumocystosis in HIV-negative patients

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ABSTRACT

BACKGROUND*: Pneumocystis jiroveci* pneumonia in HIV-negative immunocompromised patients is associated with high mortality rates. Although trimethoprim-sulfamethoxazole (TMP-SMX) provides a very effective prophylaxis, pneumocystosis still occurs and may even be emerging, due to sub-optimal 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 (PMSI).

RESULTS: From 1990 to 2010, 293 cases of pneumocystosis were documented, of whom 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 three categories: i) 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; ii) intermediate risk (25-45 cases per 100,000 patient-year): Waldenström macroglobulinemia, multiple myeloma, and central nervous system cancer; and iii) 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.

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 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 cells 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 (ATS) advises 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, in order to better inform the targeted use of TMP-SMX prophylaxis in HIV-negative patients at higher risk.

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 which 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-Grunwald-Giemsa, Gomori-Grocott staining, or immunofluorescence) on bronchoalveolar lavage. Cases of pneumocystosis documented only by PCR were not included.[7] Only patients tested HIV-negative were included. Patients were identified through: i) the computerized database of the department of infectious diseases and intensive care unit (ICU); ii) the database of the parasitology-mycology laboratory, which serves as the reference center for pneumocystosis diagnosis in the area, and iii) 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 filled at discharge includes 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 in order to provide a description relevant for clinical practice, a hierarchization was applied to assign only one underlying condition per patient. If a patient had > 1 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, systemic inflammatory diseases, and ended with miscellaneous conditions. Following this hierarchy, a

case presenting, for instance, with 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 (i.e. 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 diagnosis 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 in 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).

Data analysis

An estimate of the incidence rates of pneumocystosis in each condition was derived by dividing the number of cases documented in this group by the number of patients followed-up for this condition in our institution over the study period, and then by the study duration (20.5 years). Underlying conditions were ranked according to the estimated incidence rates of pneumocystosis. For solid tumors, we only calculated incidence rates if there was > 1 case of pneumocystosis per cancer type. Categorical variables were expressed as proportion and

compared using Chi-square test or Fisher's exact test, as appropriate. A *P* value < .05 was considered statistically significant.

RESULTS

Pneumocystosis cases in non HIV-infected patients

From January 1990 to June 2010, 293 cases of pneumocystosis were documented. Among them, there were slightly more cases in non HIV-infected patients (n=154, 52.6%), than in HIV-infected patients (n=139, 47.4%). No significant trend in the incidence was observed in HIV-infected cases (46% of patients with pneumocystosis diagnosed during years 1990-1999 were HIV-infected, vs. 54% during years 2000-2010), and in non HIV-infected patients (46% during years 1990-1999, vs. 54% during years 2000-2010), figure 1. The proportion of pneumocystosis admitted in ICU was higher in HIV-negative patients than in non HIV-infected patients (51.9% vs. 28.1%, *P* = .006). Likewise, in-ICU mortality rates were higher in HIV-negative patients than in non HIV-infected patients (52.9% vs. 15.4%, *P* = .008). Underlying conditions of the 154 HIV-negative patients who developed pneumocystosis are detailed in table 1. Hematological malignancies represented the most frequent underlying condition (32.5%), followed by solid tumors (18.2%), inflammatory diseases (14.9%), solid organ transplants (12.3%), and vasculitis (9.7%). All patients with miscellaneous underlying conditions (12.3%) where on long term corticosteroid treatment when pneumocystosis occurred.

Prevalence of underlying conditions at risk in the area, and estimated incidence rates of pneumocystosis in these conditions

Among the nearly 120,000 hospitalizations coded each year in our institution during the study period, the repartition of patients per underlying condition is detailed in table 1. Data on some

conditions were not reliable, either because no specific code exist, because of overlap with other diseases, or because the code was created only recently. These include solid tumors (pharyngeal cancer or skin cancers, sarcomas), and inflammatory diseases/vasculitis (polyneuritis, autoimmune hepatitis, inflammatory bowel disease, Goodpasture syndrome, microscopic polyangiitis). Hence, the incidence rates of pneumocystosis could not be estimated for these conditions.

Our estimates of pneumocystosis incidence rates in the main groups at risk varied from 2.6 cases per 100,000 patient-year for lung cancer, to 93.2 per 100,000 patient-year for polyarteritis nodosa (figure 2). Among transplant recipients, estimates of incidence rates varied from 13.7 for heart transplant recipients, to 44.6 per 100,000 patient-year for kidney transplant recipients. In the hematological malignancies group, three diseases were characterized by high incidence rates (> 45 cases per 100,000 patient-year): non-Hodgkin lymphoma, chronic lymphocytic leukemia and acute leukemia, whereas patients with Waldenström macroglobulinemia and multiple myeloma had intermediate incidence rates (~30 cases per 100,000 patient-year). In the solid tumors group, estimates of incidence rates were in the lower range, except for central nervous system cancers with much higher incidence rates, estimated at 27.5 cases per 100,000 patient-year (p=0.002). In the inflammatory diseases group, pneumocystosis incidence rates were high in patients with polymyositis/dermatopolymyositis (53.6 cases par 100,000 patients/year), while other inflammatory diseases had incidence rates < 25 cases per 100,000 patient-year. In the vasculitis group, estimates of pneumocystosis incidence rates were strikingly high in patients with granulomatosis with polyangiitis (71.9 par 100,000 patients/year), despite broad recommendations for TMP-SMX use in this disease, and in patients with polyarteritis nodosa, the condition associated with the higher incidence rates (93.2 cases per 100,000 patient-year).

DISCUSSION

The main findings of this monocentric retrospective study on the incidence rates of, and the risk factors for pneumocystosis, are the followings: i) pneumocystosis remains a significant problem in both HIV-positive, and HIV-negative immunocompromised populations, with an annual number of cases unabated during the study period; ii) pneumocystosis is more severe in HIV-negative patients, as compared to HIV-positive patients, with much higher rates of ICU admission, and in-ICU mortality, as previously reported;[8] iii) hematological malignancies represent the main group at risk among non-HIV infected patients, as in other cohorts;[9] iv) the estimated incidence rates of pneumocystosis in non HIV-infected immunocompromised patients vary broadly, from 2 to > 90 cases per 100,000 patient-year.

To our knowledge, this is the first study to provide comparative estimates of the incidence rates of pneumocystosis across a wide range of groups at risk: Although previous studies estimated the incidence rates in patients with various inflammatory diseases,[10-12] transplant recipients,[6,13] and cancer,[14] their heterogeneous designs precluded any comparison of the incidence rates from one condition to another. By estimating incidence rates in a broad spectrum of groups at risk with the same methodology, this study allows a hierarchical classification of groups at risk: Briefly, three inflammatory diseases/vasculitis (polyarteritis nodosa, granulomatosis with polyangiitis, and polymyositis/dermatopolymyositis), and three hematological malignancies (acute leukemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma), are at high risk of pneumocystosis, with incidence rates > 45 cases per 100,000 patient-year. This suggests that more systematic use of TMP-SMX prophylaxis in these patients may be beneficial, especially given the high morbi-mortality associated with pneumocystosis in non HIV-infected patients, with ICU admission and in-ICU mortality rates at 51.9%, and 52.9%, respectively, in our series. Patients with Waldenström macroglobulinemia, multiple myeloma, and central nervous system cancer made up an

intermediate group at risk, with incidence rates ranging from 25 to 45 cases per 100,000 patient-year. In this group, we would recommend that the threshold to initiate pneumocystosis prophylaxis be low (i.e. any additional risk factor, such as prolonged use of corticosteroids, should prompt TMP-SMX initiation). Lastly, for most patients with solid tumors, inflammatory diseases, or Hodgkin lymphoma, estimates of incidence rates are < 25 cases per 100,000 patient-year, and pneumocystosis prophylaxis should not be routinely recommended. These estimates may be used as a guide to better target pneumocystosis prophylaxis.

The incidence rates of pneumocystosis in solid organ and hematopoietic stem cell transplant recipients are much lower in this study than previously reported: Indeed, in the absence of prophylaxis, incidence rates were as high as 41,000, 16,000, 14,000, and 11,000 per 100,000 patient-year, respectively, in heart, hematopoietic stem cell, kidney, and liver transplant recipients.[6] In our institution, TMP-SMX prophylaxis is routinely used during the first 6-12 months post-transplant, as recommended by the American Society of Transplantation,[15] the Kidney Disease Improving Global Outcomes Transplant Work Group,[16] and the Infectious Diseases Society of America/American Society of Blood and Marrow Transplantation guidelines for hematopoietic stem cell transplant recipients.[17] We only observed pneumocystosis in transplant recipients not receiving TMP-SMX, either because of severe intolerance, non-adherence, erroneous discontinuation, or in patients who were transplanted more than 6 months earlier (TMP-SMX not routinely indicated anymore). For similar reasons, our estimates of pneumocystosis incidence rates in patients with acute leukemia or lymphoma are lower than previous estimates dating back from times when TMP-SMX was not used in these populations (respectively 6,500 and 1,300 cases per 100,000 patient-year),[14] probably because patients most at risk (e.g. on fludarabine, R-CHOP, or corticosteroids > 20 mg/day), are routinely prescribed TMP-SMX.

Our estimates of pneumocystosis incidence rates were much higher in patients with central nervous system cancer, than in patients with lung or breast cancer ($P = 0.002$), as previously reported.[18] This association is usually ascribed to the high doses of corticosteroids used for the control of brain tumors-related edema,[19] and led some experts to recommend systematic prophylaxis in patients with malignancies who receive > 20 mg/day of prednisone or equivalent, for > 1 month.[18] Although ATS recommends pneumocystosis prophylaxis in all patients with malignancies receiving cytotoxic chemotherapies,[5] the German Society of Hematology and Oncology proposes two levels of recommendations: i) strong evidence (A-I) in patients with acute lymphoblastic leukemia, CD4 cells < 200/µL, or chronic use of steroids; ii) risk status not entirely conclusive (C-III) in patients with chronic neutropenia, acute myeloid leukemia, and patients treated with R-CHOP, or high-dose cytarabine.[20] Although fludarabine was not mentioned in these guidelines, this was the only drug associated with increased risk of pneumocystosis in patients with lymphoproliferative disorders in a recent case-control study.[21] However, estimates of the risk associated with specific immunosuppressive agents are crippled by interactions with the risk associated with the underlying conditions, and their regular use in combinations with other immunosuppressive agents. Immunosuppressive drugs other than corticosteroids have been associated with increased risk of pneumocystosis, including cyclophosphamide,[22] and prolonged, high-doses methotrexate.[23] Transplant recipients receiving azathioprine or ciclosporine were found at lower risk than those on tacrolimus, while limited data are available about the risk associated with mycophenolate mofetil or sirolimus use.[24] Lastly, cases of pneumocystosis have been reported in patients treated with rituximab,[25,26] or tumor necrosis factor alpha inhibitors.[23,27]

In a prospective observational study, Mansharamani et al. found that a cut-off at 300 CD4 cells/µL would capture 91% of cases of pneumocystosis in HIV-negative patients,[28] but this cut-off would also capture 39.1% of patients on corticosteroids, most of whom would be

unaffected by pneumocystosis. Administering prophylaxis to such large numbers of patients would unnecessarily expose patients to drug-related adverse events. Indeed, among all patients administered TMP-SMX prophylaxis in a meta-analysis,[29] the rate of discontinuation due to adverse event was 15.2%, with a 3.1% rate of severe adverse events. A risk-benefit analysis suggested that only patients with estimated risk of pneumocystosis > 3.5% should be initiated on TMP-SMX prophylaxis.[29]

Study Limitations

This study has limitations: Firstly, its monocentric design implies that findings may not be replicable in other settings, given the heterogeneity of practices regarding pneumocystosis prophylaxis in non-HIV patients, and the variability of pneumocystosis epidemiology. Second, given its retrospective design, and the strict inclusion criteria (pneumocystosis had to be documented, and recorded), we probably underestimated the actual number of cases. However, this underestimation probably affected all conditions at risk, and is thus unlikely to have affected their rankings. Lastly, the main limitation resides in the methods used to estimate the denominator for the calculation of incidence rates: we assumed that all patients affected by at risk conditions would be hospitalized at least once during the study period in our referral hospital, and then captured through the hospitalization coding system. This assumption is at risk of various biases, including underestimation of the denominator (e.g. patients only followed as outpatients, or admitted elsewhere; coding errors), or overestimation (e.g. patients who died or moved to another area remained in the denominator, although no more at risk of being admitted for pneumocystosis in our institution).

CONCLUSIONS

Despite these limitations, this study is the first to provide comparative estimates of pneumocystosis incidence rates across a broad spectrum of conditions at risk in non-HIV infected patients. Our findings may be used to better target pneumocystosis prophylaxis according to the level of risk: low for most solid tumors and inflammatory diseases, and for Hodgkin lymphoma; intermediate for Waldenström's macroglobulinemia, multiple myeloma, and patients on corticosteroids for brain tumors; and high for polyarteritis nodosa, polymyositis/dermatopolymyositis, granulomatosis with polyangiitis, acute leukemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma. This approach should decrease the burden of pneumocystosis in HIV-negative patients.

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Figure legends

Figure 1 Cases of *Pneumocystis jiroveci* pneumonia diagnosed from January 1990 to June 2010

Figure 2 Estimated incidence of *Pneumocystis jiroveci* pneumonia among groups at risk

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Table 1 Main underlying conditions in 154 consecutive cases of *Pneumocystis jiroveci* pneumonia in non HIV-infected patients, and number of patients hospitalised with this condition (1990-2010)

Underlying condition	Number of pneumocystosis cases n (% of total cases in non-HIV patients)	Total number of patients with the underlying condition
Haematological malignancies	50 (32.5%)	6 035
- Non-Hodgkin lymphoma	19	2 006
- Chronic lymphocytic leukemia	11	1 030
- Acute leukemia	8	730
- Haematopoietic stem cell transplant	5	638
- Multiple myeloma	3	480
- Hodgkin lymphoma	2	812
- Waldenström macroglobulinemia	2	339
Solid tumours	28 (18.2%)	
- Central nervous system cancer	7	1 242
- Breast cancer	6	3 600
- Lung cancer	3	4 879
- Pharyngeal cancer	3	
- Skin cancer	2	
- Sarcoma	2	
- Esophagus, kidney, thymus, adrenal gland, cholangiocarcinoma	One patient each	
Inflammatory diseases	23 (14.9%)	
- Rheumatoid arthritis	8	1 574
- Goodpasture syndrome	3	
- Polymyalgia rheumatica	3	1 235
- Polymyositis/dermatopolymyositis	2	182
- Polyneuritis	2	
- Sjögren syndrome	2	488
- Sarcoïdosis		1 269
- Inflammatory bowel disease	One patient each	
- Auto-immune hepatitis		
Solid organ transplant	19 (12.3%)	
- Kidney	11	1203
- Liver	6	1329
- Heart		357
- Lung	One patient each	25
Vasculitis	15 (9.7%)	
- Granulomatosis with polyangiitis	5	339
- Microscopic polyangiitis	4	
- Polyarteritis nodosa	3	157
- Giant cell arteritis	3	1 277
Miscellaneous	19 (12.3%)	
- Glomerulonephritis	5	
- Interstitial lung disease	2	
- Acute alcoholic hepatitis	2	
- Cirrhosis	2	
- Congenital immunodeficiency	2	
- Hydatiform mole, post-radiation myelitis, cryptogenic organizing pneumonia, acute cophosis	One patient each	
- Other causes with long term corticotherapy	2	

HIV = human immunodeficiency virus

Table 2 Logistic regression analysis of pneumocystosis incidence taking as a reference the group of patients with breast or lung cancer (n = 3600 + 4879 patients)

Risk of pneumocystosis	**Odds Ratio [CI95%]**	***P***
High risk		
- Polyarteritis nodosa	18.3 [4.9-63.4]	<0.0001
- Granulomatosis with polyangeitis	14.1 [1.7-42.3]	<0.0001
- Polymyositis/dermatomyositis	10.5 [2.2-48.7]	0.0028
- Non-Hodgkin lymphoma	9.0 [4.1-19.2]	<0.0001
- Chronic lymphocytic leukemia	10.2 [4.2-24.6]	<0.0001
- Acute leukemia	10.4 [4.0-24.6]	<0.0001
Intermediate risk		
- Waldenström macroglobulinemia	5.6 [1.2-25.9]	0.0282
- Multiple myeloma	5.9 [1.6-21.9]	0.0078
- Central nervous system cancer	5.3 [2.0-14.8]	0.0009
Low risk		
- Rheumatoid arthritis	4.8 [1.85-12.5]	0.0012
- Polymyalgia rheumatica	2.3 [0.6-8.5]	0.2140
- Horton granulomatosis	2.2 [0.6-8.2]	0.2331
- Hodgkin lymphoma	2.3 [0.5-10.8]	0.2813
- Sjögren syndrome	1.9 [0.2-15.3]	0.5324
- Sarcoïdosis	0.7 [0.1-5.8]	0.7773

CI95% = confidence interval 95%

Figure 1 Cases of *Pneumocystis jiroveci* pneumonia diagnosed from January 1990 to June 2010

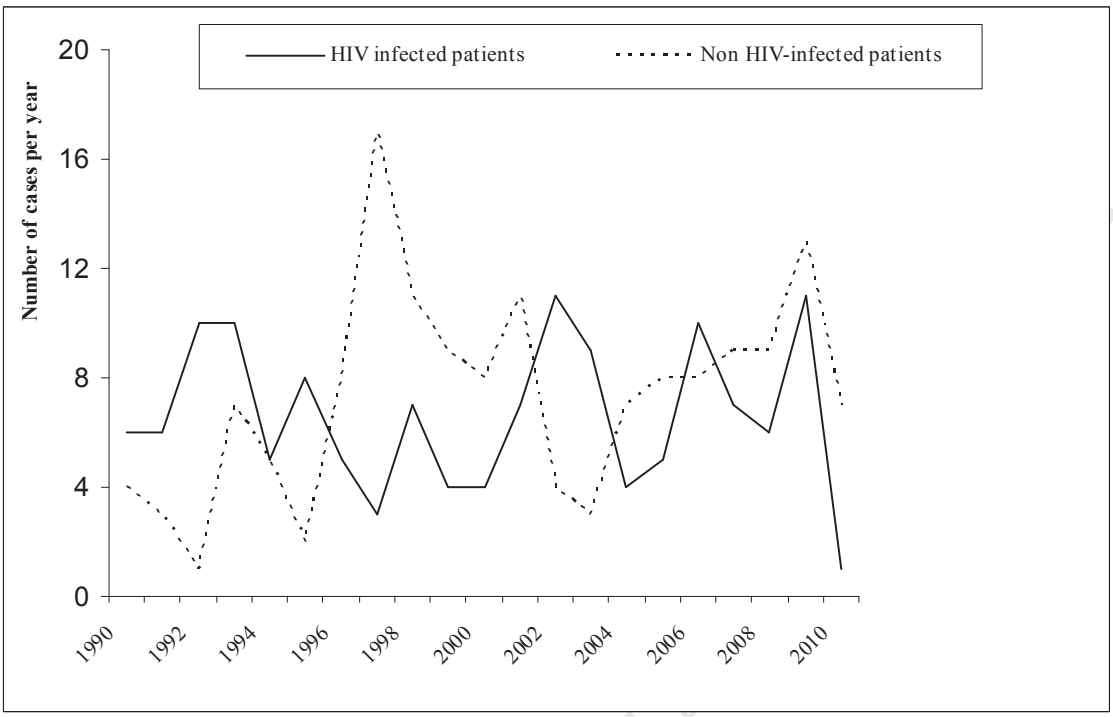
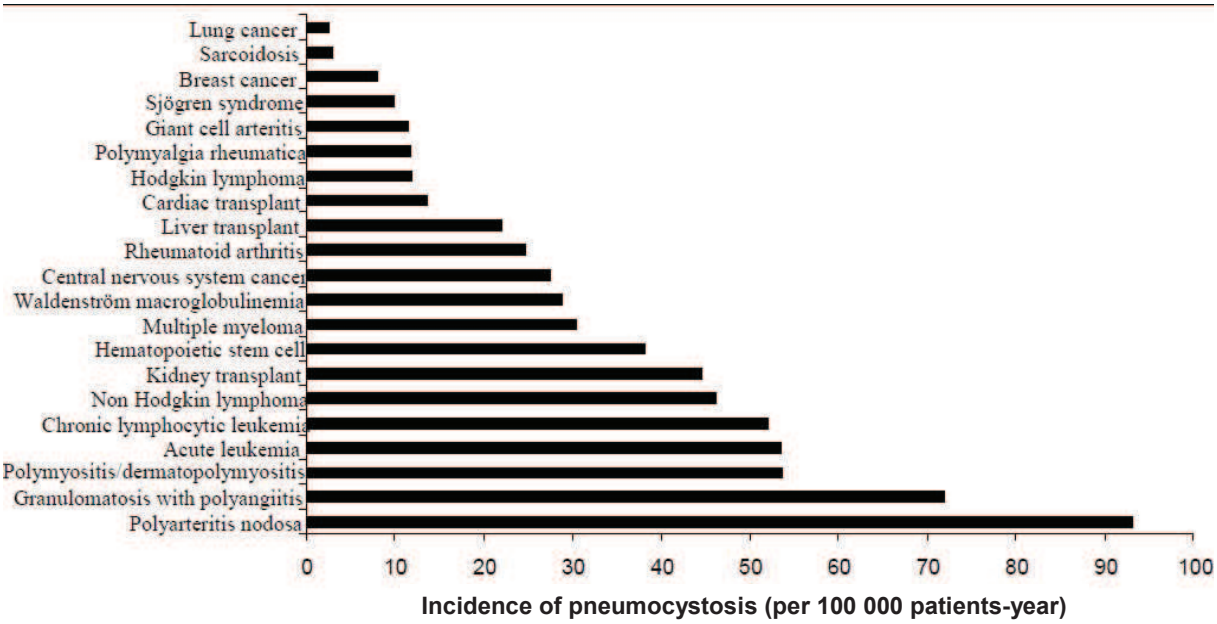


Figure 2 Estimated incidence of *Pneumocystis jiroveci* pneumonia among groups at risk



CLINICAL SIGNIFICANCE

- This observational study found that 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 trimethoprime-sulfamethoxazole prophylaxis in HIV-negative patients.