Incidence of pneumocystosis among patients exposed to immunosuppression

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Background: The decision to administer prophylaxis to patients receiving immunosuppression against pneumocystosis remains a dilemma.

Objective: To determine overall and age-specific 5-year pneumocystosis incidence within a population exposed to immunosuppressants.

Methods: Retrospective cohort analysis identifying incident pneumocystosis cases among adults without HIV, AIDS, or cancer exposed to immunosuppressant, corticosteroid therapy, or both.

Results: We identified 406 new cases among patients prescribed an immunosuppressant, corticosteroid, or both. Overall incidence of pneumocystosis was 0.012% (406/3,366,086). Incidence was highest in those exposed to immunosuppressant and corticosteroid medications (0.199%), followed by those exposed to immunosuppressant alone (0.012%), corticosteroid alone (0.008%), and neither medication (0.001%) ($P < .001$). The greatest risk differences were noted between groups exposed to immunosuppressant and corticosteroid compared with neither (0.198%, 95% confidence interval [CI] 0.166%-0.230%) or immunosuppressant alone (0.188%, 95% CI 0.155%-0.221%). The greatest relative risks (RRs) were noted among those receiving immunosuppressant and corticosteroid compared with those exposed to neither (RR 122.5, 95% CI 100.9-148.8) or immunosuppressant alone (RR 16.5, 95% CI 7.3-37.4).

Limitations: We could not confirm dose and duration of exposures.

Conclusion: Incidence of pneumocystosis among patients exposed to immunosuppressants is very low. Prophylaxis for patients receiving combination immunosuppressant and corticosteroid therapy, the group at highest risk, might be warranted. (J Am Acad Dermatol 2019;80:1602-7.)

Key words: corticosteroid; Explorys; immunosuppression; *Pneumocystis jirovecii* pneumonia; pneumocystosis; prophylaxis; Steven-Johnson syndrome; sulfamethoxazole; toxic epidermal necrolysis; trimethoprim.

Outside of the context of HIV infection or AIDS, the opportunistic infection *Pneumocystis jirovecii* pneumonia (PJP) is most frequently observed in the setting of iatrogenic immunosuppression. PJP-related mortality in this subgroup is estimated to be as high as 40%.[1,2] Incidence of PJP is reduced by as much as 85% in patients receiving prophylaxis with trimethoprim/sulfamethoxazole (TSX), with a resulting decrease in mortality.[1,3] However, TSX is also known to cause a number of serious adverse events, such as hyperkalemia, hypoglycemia, thrombocytopenia, hemolytic anemia, aplastic anemia, agranulocytosis, fulminant hepatotoxicity, anaphylaxis, interstitial nephritis, immune thrombocytopenia, aplastic anemia, drug reaction with eosinophilia, and systemic

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symptoms, as well as Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[1,4]

There is limited evidence to guide dermatologists on the risk-to-benefit ratio of administering prophylaxis with TSX to patients with inflammatory and autoimmune skin diseases. The purpose of this study was to investigate incidence of PJP in a population-based sample of patients receiving immunosuppression with or without corticosteroids.

CAPSULE SUMMARY

- This population analysis contributes to the limited amount of data guiding dermatologists on the need to administer prophylaxis against pneumocystosis with trimethoprim/sulfamethoxazole.
- Benefit of prophylaxis with trimethoprim/sulfamethoxazole appears to outweigh risk for severe drug reaction for patients receiving combination corticosteroid and immunosuppressant therapy.

MATERIALS AND METHODS

This was a retrospective cohort analysis using a multihealth system data analytics and research platform (Explorys) developed by IBM Watson Health (Cambridge, MA).[5] Clinical information from electronic medical records, laboratories, practice management systems, and claims systems is matched by using a single set of unified medical language system ontologies to create longitudinal records for unique patients. The data are standardized and curated according to common controlled vocabularies and classifications systems including International Classification of Diseases, Systemized Nomenclature of Medicine—Clinical Terms (SNOMED-CT), Logical Observation Identifiers Names and Codes, and RxNorm.[6-10] At present, the database encompasses 27 participating integrated health care organizations. Over 55 million unique lives representing ~15% of the population across all 4 census regions of the United States are captured. Patients with all types of insurance as well as those who are self-pay are represented. Population counts are reported by the database to the nearest 10 to prevent patient identification. Counts reported as <10 were recorded as equal to 2. This investigation was approved by the institutional review board of the Feinstein Institute for Medical Research at Northwell Health.

Cases of PJP were identified using the Systemized Nomenclature of Medicine—Clinical Term "pneumocystosis," which has a 1:1 correspondence with International Classification of Diseases, Ninth Revision, code 136.3, to identify the outcome. Using the RxNorm ontology for generic and branded drugs, we identified the following 4 exposure cohorts: 1) ≥1 immunosuppressant prescription and no corticosteroid prescription; 2) ≥1 corticosteroid prescription and no immunosuppressant prescription; 3) ≥1 prescription for both immunosuppressant and a corticosteroid; and 4) no prescription for either immunosuppressant or corticosteroid. We included the following medications in our definition of immunosuppressant: azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, rituximab, and tacrolimus. The following medications were included in our definition of corticosteroid: prednisone, prednisolone, methylprednisolone, and dexamethasone.

Statistical analysis

The study population included adult patients with an active status in the database during December 2012-December 2017; who did not have a diagnosis of HIV, AIDS, or cancer; and who had information on age. Age in years was recorded as a categorical variable; we stratified patients into 3 age groups: 18-44 years, 45-64 years, ≥65 years. The primary outcome of interest was new diagnosis of PJP. So that the exposure of interest occurred before the outcome, patients having PJP diagnoses before the study start date were excluded, as were patients having the medication exposures of interest after their date of PJP diagnosis.

We obtained population-level counts of patients with first-ever diagnoses of PJP and those with no diagnosis of PJP during the study period for each age group and exposure group. Overall and age-specific 5-year PJP incidence was calculated for each exposure type. Incidence stratified by age was compared across treatment groups by using the Cochran-Mantel-Haenszel method. In large data sets, such as the one analyzed herein, hypothesis testing will produce statistically significant P values even in the absence of clinically significant treatment effects. As such, hypothesis tests were not performed. Crude and age-adjusted relative risks (RRs) and risk differences were estimated with 95% confidence intervals (CIs). All analyses were performed by using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Patients exposed to immunosuppressants, corticosteroids, or both are described in Fig 1. We identified 406 new cases of PJP among patients with any exposure to immunosuppressant, corticosteroid, or both. Among patients with any exposure, 44.8% of those who developed PJP were

Abbreviations used:

CI:	confidence interval
PJP:	*Pneumocystis jirovecii* pneumonia
RR:	relative risk
SJS:	Steven-Johnson syndrome
TEN:	toxic epidermal necrolysis
TSX:	trimethoprim/sulfamethoxazole

aged 65 years or older. In comparison, only 23.3% of those who did not develop PJP after any exposure were aged 65 years or older.

During the 5-year study period, overall incidence was highest in the group exposed to combination immunosuppressant and corticosteroid therapy (0.199%), followed by the groups exposed to only immunosuppressants (0.012%), only corticosteroids (0.008%), and neither immunosuppressants or corticosteroids (0.001%). The incidence among those receiving combination immunosuppressant and corticosteroid therapy was 0.187%-0.234%, immunosuppressants alone was 0.01%-0.017%, corticosteroids alone was 0.002%-0.018%, and neither therapy was 0.0004%-0.003%. The highest incidence (0.234%) occurred among patients aged 18-44 years who were exposed to combination immunosuppressant and corticosteroid therapy (Fig 2).

Age-adjusted risk differences and their associated 95% CIs for selected group comparisons are reported in Fig 3. The smallest risk differences were noted between patients exposed to immunosuppressant alone (0.011, 95% CI 0.001-0.02) or corticosteroid alone (0.006, 95% CI 0.005-0.007) compared with neither medication. The greatest risk differences were noted between patients exposed to combination immunosuppressant and corticosteroid therapy compared with neither medication type (0.198, 95% CI 0.166-0.23) and immunosuppressants alone (0.188, 95% CI 0.155-0.221). Similarly, the greatest RRs were noted among patients receiving combination immunosuppressant and corticosteroid therapy compared with patients receiving neither medication type (RR 122.5, 95% CI 100.9-148.8) or only immunosuppressants (RR 16.5, 95% CI 7.3-37.4).

DISCUSSION

In this study, we have observed a low overall incidence of PJP among patients exposed to immunosuppressants, corticosteroids, or a combination of these medications. The incidence of and RR for PJP are greatest among patients exposed to combination immunosuppressant and corticosteroid therapy.

Reported incidences of PJP among patients with autoimmune and inflammatory skin disease have ranged 0%-4.3%.[4,11-15] On the basis of these studies, incidence of PCP in the dermatologic immunosuppressed population was estimated to be 1.3%.[16] However, most of these studies were based on small and highly selected cohorts (size range 138-801), within which were exceedingly low event rates (range 0-7). As a result, reported incidences are highly variable, rendering interpretation of risk and guidance on prophylaxis uncertain. Moreover, none of these previous studies provided subgroup (ie, age or exposure group) analyses to identify those at highest risk, also likely because of limited cohort sizes and low event rates.

Our analysis included patients with all types of diseases who were iatragenically exposed. Patients with HIV or those who receive chemotherapy for cancer are known to have a high risk of developing PJP. However, risk in patients with inflammatory or autoimmune disease is less clear due to the limited literature in these subgroups. Amber et al advocated for disease-specific analysis of PJP incidence,[4] citing evidence that patients with granulomatosis with polyangiitis, for example, have a significantly higher risk (6% incidence) for pneumocystis.[17] However, this concept is based on a single analysis at a specialized clinic that included only 180 granulomatosis patients with polyangiitis, 11 of whom developed PJP after being exposed to a combination immunosuppressant and corticosteroid therapy.[17] Although baseline disease status and immunologic aberrancy is likely to contribute to risk for PJP, exposure to iatrogenic immunosuppression, especially in combination, might be a stronger driver of PJP risk. As such, our approach of evaluating PJP risk among those exposed to iatrogenic immunosuppression might offer additional insight into this important clinical dilemma.

A dermatologist's decision to provide prophylaxis against PJP for patients receiving immunosuppressant and/or corticosteroid therapy must be guided by an assessment of the benefit-to-risk ratio. Although the benefit of prophylaxis in this context is high, the potential risks associated with TSX exposure are also not trivial. Up to 13.8% of patients without HIV discontinue TSX for any adverse event,[1,18] and 3.1% discontinue TSX due to a severe adverse event.[3] While it is estimated that <0.003% of patients exposed to TSX develop SJS or TEN,[19] mortality might be as high as 30%.[20] Taking into context this historical data, the incidence of PJP observed in our analysis is generally 66 times greater than the estimated historical incidence of developing SJS or TEN with TSX exposure. Although we cannot directly compare risk for PJP in our analysis to risk for SJS or TEN with TSX exposure because our population might have important differences from

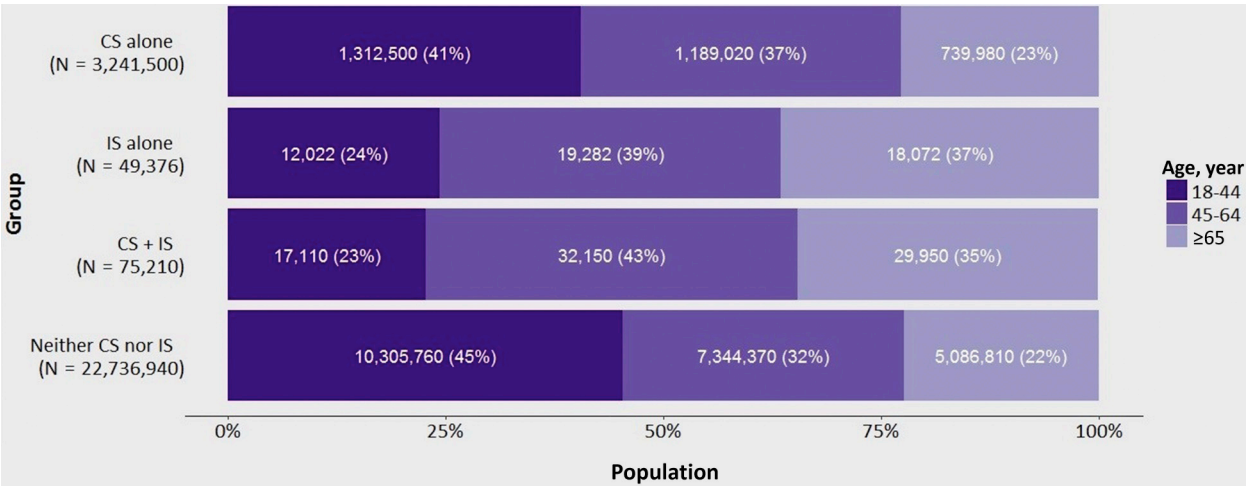

Fig 1. Patient age distribution according to medication group. Number and percentage of patients in each of 3 age groups (18-44, 45-64, ≥65 years) are shown for each exposure category. *CS*, Corticosteroid; *IS*, immunosuppresant.

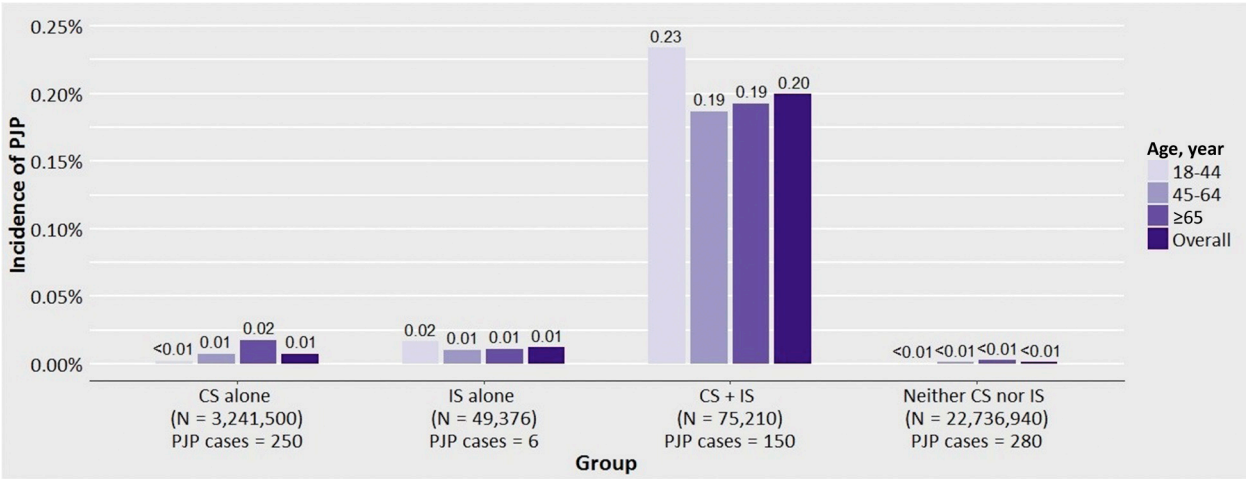

Fig 2. Incidence of PJP according to medication group and age. Numbers above bars indicate the incidence of PJP within each subgroup rounded to the nearest hundredth of a percent. *CS*, Corticosteroid; *IS*, immunosuppressant; *PJP*, *Pneumocystis jirovecii* pneumonia.

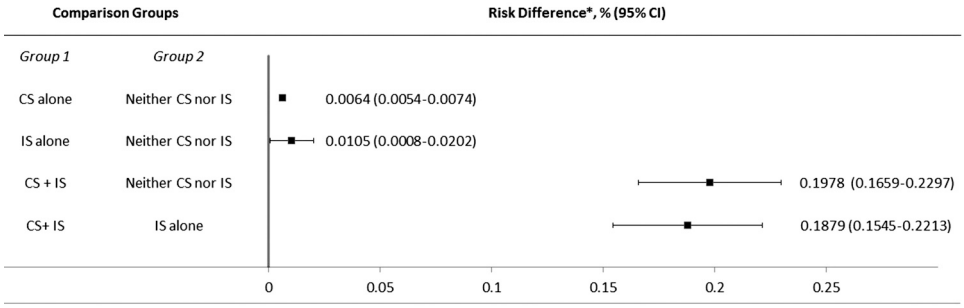

Fig 3. Absolute risk difference for *Pneumocystis jirovecii* pneumonia (PJP) across selected exposure comparisons. *CI*, confidence interval; *CS*, corticosteroid; *IS*, immunosuppresant; *PJP*, *Pneumocystis jirovecii* pneumonia. *Risk difference is defined as the incidence of PJP infection in group 1 minus the incidence of PJP infection in group 2. Risk differences were age adjusted by using the Cochran-Mantel-Haenszel method.

historical cohorts, the comparison suggests that prophylaxis might be warranted for patients exposed to combination immunosuppressant and corticosteroid therapies.

Our analysis on PJP incidence includes the largest and most heterogeneous cohort of patients exposed to immunosuppressants, corticosteroids, or both sampled from various academic and community health care settings across all US census regions. For these reasons, we believe these results might be better generalized than previous analyses on the subject matter.

This retrospective analysis also has important limitations which warrant consideration. We could not capture patients with PJP who went undiagnosed, and as such, the incidence reported herein might be underestimated. We were also unable to confirm dose and duration of exposures, both of which likely influence risk for PJP. While we identified prescription of corticosteroids and immunosuppressants, the nature of codified data does not allow us to confirm that patients filled the prescription or took the medication(s) as prescribed. Although we excluded patients with HIV, AIDS, or cancer, we might not have accounted for all of the comorbidities that might increase risk for PJP. While some immunosuppressants might be associated with differential risk for PJP, the low number of events associated with some medications did not allow for a stratified analysis. There are also some immunosuppressants that are rarely prescribed by dermatologists, such as sirolimus and rapamycin, which were excluded from the analysis. This has the potential to result in misclassification bias, as patients with exposure to an immunosuppressant not defined in our analysis might be classified as having no exposure.

In conclusion, we observed a low overall risk for PJP among patients without HIV, AIDS, or cancer who are exposed to iatrogenic immunosuppression. Incidence of PJP was highest among patients on combination immunosuppressant and corticosteroid therapy. The results of this analysis should be validated through prospective study. On the basis of our results and the literature on this topic, PJP prophylaxis for patients receiving combination immunosuppressant and corticosteroid therapy is warranted. Clinicians should continue to assess the benefit-to-risk ratio for TSX prophylaxis for all patients receiving immunosuppressant therapy on the basis of the patient's individual comorbidities and related contextual factors.

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