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MAJOR ARTICLE

Meningococcal Disease in Patients With Human Immunodeficiency Virus Infection: A Review of Cases Reported Through Active Surveillance in the United States, 2000–2008

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Background. Although human immunodeficiency virus (HIV) infection is an established risk factor for several bacterial infections, the association between HIV infection and meningococcal disease remains unclear.

Methods. Expanded chart reviews were completed on persons with meningococcal disease and HIV infection reported from 2000 through 2008 from 9 US sites participating in an active population-based surveillance system for meningococcal disease. The incidence of meningococcal disease among patients meeting Centers for Disease Control and Prevention acquired immune deficiency syndrome (AIDS) surveillance criteria was estimated using data from the National HIV Surveillance System for the participating sites.

Results. Thirty-three cases of meningococcal disease in individuals with HIV infection were reported from participating sites, representing 2.0% of all reported meningococcal disease cases. Most (75.8%) persons with HIV infection were adult males aged 25 to 64 years old. Among all meningococcal disease cases aged 25 to 64 years old, case fatality ratios were similar among HIV-infected and HIV-uninfected persons (13.3% vs 10.6%; $P = .6$). The cumulative, mean incidence of meningococcal disease among patients aged 25 to 64 years old with HIV infection ever classified as AIDS was 3.5 cases per 100 000 person years (95% confidence interval [CI], 2.1–5.6), compared with 0.3 cases per 100 000 person years (95% CI, 0.3–0.3) for persons of the same age group not reported to have AIDS (relative risk = 12.9; 95% CI, 7.9–20.9).

Conclusions. Individuals with HIV infection meeting the AIDS surveillance case definition have a higher incidence of meningococcal disease compared with the general adult population.

Keywords. disease surveillance; HIV; meningitis; meningococcal disease.

Although it is well established that individuals with human immunodeficiency virus (HIV) infection are at increased risk of several bacterial infections, including invasive pneumococcal disease [1], the association between *Neisseria meningitidis* infection and HIV infection is less clear. Like *Streptococcus pneumoniae* and *Haemophilus influenzae*, *N meningitidis* is an encapsulated bacterial pathogen that is normally an upper airway commensal, and systemic infections with these bacteria are associated with asplenia and complement deficiencies [2, 3]. Individuals with terminal complement deficiencies are at particularly elevated risk of invasive meningococcal infection [3].

Previous studies examining the association between HIV infection and meningococcal disease have produced conflicting results. Although some case series and studies from industrialized countries have suggested an increased risk of meningococcal infection in persons with HIV, early studies were limited by small numbers of patients [4–6]. In contrast, most reports from Africa have not shown an association [7–10]. Most recently, studies from South Africa [11], New York City [12], and England [13] with larger case numbers have reported elevated relative risks of meningococcal disease among HIV-infected individuals. Clinical data describing meningococcal disease in HIV-infected patients are also limited, although the South African study found HIV infection to be a risk factor for meningococcal bacteremia [11].

A better understanding of the association between HIV infection and meningococcal disease is important to inform prevention strategies. In this study, we reviewed cases of meningococcal disease in patients with diagnosed HIV infection

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reported through a population-based surveillance system for meningococcal disease [14, 15] and estimated the incidence of meningococcal disease in persons with HIV ever classified as stage 3, acquired immune deficiency syndrome (AIDS).

METHODS

Meningococcal Disease Surveillance

Surveillance of *N meningitidis* invasive infection was conducted through the Active Bacterial Core surveillance system (ABCs), part of the Centers for Disease Control and Prevention (CDC)'s Emerging Infections Program [14, 15]. The ABCs is an active, laboratory- and population-based surveillance system with sites in 10 states. The surveillance area included California (3 San Francisco Bay area counties), Colorado (5 Denver area counties), Connecticut, Georgia, Maryland, Minnesota, New Mexico (2004–2008), New York (15 Rochester and Albany area counties), Oregon, and Tennessee (11 Nashville, Chattanooga, and Knoxville counties). The population under surveillance was approximately 35 559 550 in 2008, representing 11.7% of the US population in 2008. A case of meningococcal disease was defined as the isolation of *N meningitidis* from a normally sterile site such as blood, cerebrospinal fluid, pleural fluid, or joint fluid in a resident of an ABCs catchment area. *Neisseria meningitidis* isolates were sent to state public health laboratories for serogroup determination and to the CDC Meningitis Laboratory for testing with serogroup-specific real-time polymerase chain reaction assays [16].

Chart Review

Chart reviews are routinely performed on all meningococcal disease cases to collect demographic and clinical data. Surveillance officers record HIV infection as a comorbid condition on the case report form if it is reported in the hospital record. For this study, meningococcal disease cases with onset dates from January 1, 2000 until December 31, 2008 in ABCs sites were included. Cases reported from the New York ABCs site were excluded due to local health information disclosure policies pertaining to HIV infection. Cases were also excluded from the Colorado site if reported from 2000 (due to incomplete data for that year since this site began participation in ABCs during 2000) and the Maryland site if reported from 2000 (because data on comorbid medical conditions were not reported by this site until after that year).

Expanded chart reviews were performed on persons with diagnosed HIV infection using a supplemental case report form, which included information on HIV disease-related data (eg, CD4 cell counts, AIDS-defining conditions, medications to treat HIV and for opportunistic infection chemoprophylaxis), meningococcal disease risk factors, comorbid conditions, meningococcal vaccination history, physical examination at presentation, hospital course, and complications. Data for the expanded chart reviews were abstracted from the inpatient hospital record for the episode of meningococcal disease; data from the patient's primary care clinic records also were included if available. Human immunodeficiency virus infection was classified as meeting the CDC AIDS surveillance case definition if data from the expanded chart review indicated a CD4 count ever less than 200 cells/μL and/or a history of an AIDS-defining condition [17]. A concurrent CD4 cell count was defined as a CD4 count dated within 3 months before the date of meningococcal disease presentation, performed during the hospitalization, or reported in the chart as current.

Analysis

Among meningococcal disease cases ages 25 to 64 years, clinical and microbiologic characteristics of those with diagnosed HIV infection were compared with those without HIV infection using the Fisher's exact test for categorical data and the Wilcoxon-Mann-Whitney test for continuous variables. Analyses of younger and older age groups were not possible due to the paucity of HIV-infected patients outside this age range.

Determination of meningococcal disease incidence among all HIV-infected individuals was not possible due to the absence of name-based HIV reporting in all states during the study years. Therefore, the cumulative, annual incidence of meningococcal disease among individuals aged 25 to 64 years with HIV infection that met the CDC AIDS surveillance case definition [17] was estimated. The number of persons with meningococcal disease and a history of a CD4 count less than 200 cells/μL or a history of an AIDS-defining condition was used as the numerator, and end-year AIDS case counts reported to CDC's National HIV Surveillance System for ABCs counties were used as the denominator. Because of increased levels of AIDS-defining condition ascertainment resulting from our chart review when compared with routine HIV surveillance (where most cases meet AIDS surveillance criteria with CD4 count criteria [17, 18]), a second incidence estimate was made including only HIV-infected meningococcal disease patients aged 25 to 64 years with a CD4 count ever <200 cells/μL in the numerator (excluding patients staged with only a history of an AIDS-defining condition). The cumulative annual incidence of meningococcal disease among patients aged 25 to 64 years that did not meet AIDS surveillance criteria was also estimated. For this calculation, the number of meningococcal disease cases with no HIV infection reported to ABCs or HIV infection reported but data from expanded chart review did not fulfill CDC AIDS surveillance criteria was used as the numerator. The denominator was the population of the study area that was not reported with AIDS, which was calculated by subtracting the number of end-year AIDS case counts reported to the CDC from the total population

for the ABCs counties based on US Census data. Confidence intervals (CIs) were calculated based on Jeffreys Prior method for incidence estimates and Mantel-Haenszel interval estimates for rate ratios.

All statistical analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC). Two-sided *P* values less than 0.05 were considered significant. This study was determined to be nonhuman subjects research, exempt from human subjects regulations by the CDC Human Research Protection Office. The study was also determined exempt from human subjects regulations by the participating ABCs surveillance sites except for the Georgia Metropolitan Statistical Area (MSA) and Maryland sites. The study was approved by the investigational review boards of the Georgia MSA, Maryland Department of Health and Mental Hygiene, and Johns Hopkins School of Public Health.

RESULTS

During the study period, 1613 cases of meningococcal disease were reported. Thirty-three (2.0%) of these patients had a reported diagnosis of HIV infection. The median ages of HIV-infected patients and those without HIV infection were 41 years (range, 15–60) and 20.5 years (range, 0–98), respectively. Among patients aged 25 to 64 years, there were 491 meningococcal disease cases, 30 (6.1%) of whom had HIV infection reported (Table 1). In this age group, case fatality ratios were similar among HIV-infected and HIV-uninfected persons (13.3% vs 10.6%, $P = .6$). Other clinical characteristics, including meningococcal disease syndrome, and *N meningitidis* serogroups were similar among those with and without reported HIV infection, except a higher proportion of HIV-infected persons were male compared with persons without HIV infection (83.3% vs 51.4%, $P = .0007$).

Expanded chart reviews were completed for 32 of the 33 persons with HIV infection (97.0%). Comorbid conditions, physical examination findings, complications, and HIV-related clinical data are summarized in Table 2. Two patients had initially been suspected to have disseminated *Neisseria gonorrhoeae* infection based on clinical findings, including 1 with septic arthritis. Eighteen patients had infection that met the AIDS surveillance case definition, including 10 (55.6%) who had a history of a CD4 count <200 cells/μL found on chart review and 8 (44.4%) who met surveillance criteria based on a

Table 1. Clinical and Microbiologic Characteristics of Patients With and Without Reported HIV Infection, Aged 25–64, 2000–2008, in Active Bacterial Core Surveillance Sites[a]

Patient Characteristics	HIV-Infected (N = 30)	No HIV Infection Reported (N = 461)
Male, n (%)[b]	25 (83.3)	237 (51.4)
Median age (years)	44.5	44.0
Case fatality ratio (%)	13.3	10.6
Syndrome		
Meningitis, n (%)	11 (36.7)	238 (52.8)
Bacteremia, n (%)	11 (36.7)	140 (31.0)
Bacteremic pneumonia, n (%)	7 (23.3)	51 (11.3)
Other, n (%)	1 (3.3)[c]	22 (4.9)
Neisseria meningitidis serogroup		
B, n (%)	7 (25.0)	142 (33.3)
C, n (%)	11 (39.3)	134 (31.5)
Y, n (%)	8 (28.6)	139 (32.6)
W, n (%)	2 (7.1)	11 (2.6)

Abbreviations: HIV, human immunodeficiency virus.

[a]Denominators may vary due to missing data. *P* values for all comparisons >.05 unless otherwise noted.

[b]Fisher's exact $P = .0007$.

[c]Septic arthritis.

Table 2. Clinical Data of HIV-Infected Persons With Meningococcal Disease Reported by Active Bacterial Core Surveillance Sites, 2000–2008 (n = 32)[a]

Clinical Characteristics		N (%)
Past Medical History, Physical Exam on Admission, and Complications		
History	Previous meningococcal vaccination	0
	Tobacco use	11 (35.5)
	Asplenia	1 (3.1)
	Complement deficiency	0
	Diabetes mellitus	3 (9.7)
	Liver disease	5 (16.1)
	Chronic renal disease	3 (9.7)
Exam	Cachexia, malnourishment, or wasting	5 (18.5)
	Fever ≥100.5°F (38°C)	25 (80.6)
	Rash	13 (41.9)
	Altered mental status or comatose	9 (31.0)
Complications	ICU admission	16 (55.2)
	Respiratory failure requiring intubation	8 (25.0)
	Purpura fulminans	1 (3.1)
	Waterhouse-Friederichsen syndrome	1 (3.1)
	Death	4 (12.1)
HIV-related clinical data[b]		
CDC AIDS surveillance case definition met		18 (56.3)
	History of AIDS-defining condition only	8 (44.4)
	History of CD4 ever <200 cells/μL only	6 (33.3)
	Both AIDS-defining condition and CD4 criteria met	4 (22.2)
Concurrent CD4 count available		22 (68.8)
	≥500 cells/μL	7 (31.8)
	200–499 cells/μL	9 (40.9)
	<200 cells/μL	6 (27.3)
History of HAART use ascertainable		25 (78.1)
	Currently taking at time of presentation	16 (64.0)
	Previous use	7 (28.0)
	Never used	2 (8.0)
Currently taking opportunistic infection prophylaxis at time of presentation[c]		7 (22.6)

Abbreviations: AIDS, acquired immune deficiency syndrome; CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; ICU, intensive care unit.

[a]Denominators may vary due to missing data.

[b]Reported data on CD4 percentages and HIV viral load testing was limited and are not shown.

[c]Defined as taking trimethoprim-sulfamethoxazole, azithromycin, dapsone, or other medication specifically for prophylaxis against *Pneumocystis* pneumonia or *Mycobacteriam avium* complex infection.

reported AIDS-defining condition alone. Twenty-two persons with HIV had a concurrent CD4 count available, with 6 persons (27.3%) having a CD4 count less than 200 cells/μL. Data on HIV viral loads, CD4 percentages, and CD4 count nadir history were limited (data not shown). The case fatality ratios were similar among HIV-infected patients who met the CDC AIDS surveillance criteria and those who did not (11.1% vs 14.3%, $P = .8$).

A total of 491 cases of meningococcal disease among persons aged 25 to 64 were reported to ABCs from study sites, 17 of whom had HIV infection that met the CDC AIDS surveillance case definition. The mean number of persons living with HIV infection ever classified as AIDS in this age group each year during 2000 to 2008 in the included ABCs sites was 53 212, resulting in a cumulative, mean incidence of 3.5 cases per 100 000 person years (95% CI, 2.1–5.6) for meningococcal disease among persons reported with AIDS. The incidence of meningococcal disease among the population not reported with AIDS (ie, patients with meningococcal disease without HIV reported or patients with HIV infection that did not meet the AIDS surveillance case definition based on chart review) was 0.3 cases per 100 000 person years (95% CI, .3–.3), resulting in a rate ratio of 12.9 (95% CI, 7.9–20.9) of meningococcal disease among persons with infection meeting the AIDS surveillance case definition. The rate ratio among men (11.8; 95% CI, 6.7–20.6) was not significantly different from that among women (15.1; 95%, CI 5.6–40.6; $P > .05$ for the comparison). The rate ratio among persons aged 25–44 years (12.5; 95% CI, 6.8–25.6) was similar to that among those aged 45–64 (13.2; 95% CI, 6.2–25.2).

Ten of the seventeen meningococcal disease patients aged 25 to 64 with HIV infection meeting the AIDS surveillance case definition had a report of a CD4 count <200 cells/μL. When including only these patients as cases of meningococcal disease among persons reported to have AIDS (and considering the excluded 7 cases as cases of meningococcal disease among those not reported with AIDS), the mean incidence of meningococcal disease among persons reported with AIDS was 2.1 cases per 100 000 person years (95% CI, 1.1–3.7), resulting in a rate ratio of 7.5 (95% CI, 4.0–14.0) when compared with the incidence of meningococcal disease among the population aged 25 to 64 years that were not reported with AIDS.

DISCUSSION

We found a substantially increased risk of meningococcal disease among adults with HIV infection that met AIDS surveillance criteria, compared with all other individuals not reported with AIDS. The clinical presentations and outcomes of meningococcal disease in these patients were generally similar to those in patients without HIV infection, and patients presented with a wide range of CD4 counts. Because the incidence of meningococcal disease in the United States has decreased significantly over the past decade [19], and the prevalence of HIV infection in the United States in recent years is estimated to be less than 500 per 100 000 persons [20], the total number of meningococcal disease cases among persons living with HIV is likely low. Because not all ABCs sites had name-based HIV case reporting during the period considered for this evaluation and not all persons with HIV have been diagnosed and reported, we were not able to estimate an incidence of meningococcal disease among all persons with HIV infection. For our calculation of incidence, we included those living with HIV infection ever classified as AIDS, which includes persons with immune reconstitution; therefore, it is important to emphasize that our incidence estimate applies to a patient population with variable levels of immunocompetence. Although this population is not necessarily representative of the larger population of persons living with HIV infection, the increased relative risk we observed for meningococcal disease is similar to those observed for HIV-infected individuals in New York City, South Africa, and England [11–13].

In this study, almost half of the patients with meningococcal disease and HIV infection that met AIDS surveillance criteria did not have a CD4 cell count history available and were staged only with a history of an AIDS-defining condition. Because the majority of persons included in the US HIV surveillance system are staged with immunologic (CD4 count) criteria rather than an AIDS-defining condition history [18], we considered the possibility that our meningococcal disease incidence calculation might be inflated by the incongruous patterns of criteria used in staging. To address this possibility, we calculated the incidence of meningococcal disease among those reported with AIDS including only patients with HIV infection and a history of a CD4 cell count <200 cells/μL in the numerator. Although the incidence calculated was lower, the rate ratio was still elevated (7.5) when compared with the incidence of meningococcal disease in the population not reported with AIDS.

Our study is subject to other limitations. A patient's HIV status may not have been known to the treating physician. Among the patients with HIV infection reported in ABCs, many inpatient medical records had incomplete CD4 count histories (ie, current counts or nadir count), and the history of previous opportunistic infections is likely also incomplete. Therefore, our ascertainment of patients with HIV infection meeting CDC AIDS surveillance criteria is presumably incomplete. It should also be noted that the AIDS surveillance case definition used by the CDC during the period of this study included a subset of cases without laboratory-confirmed HIV infection [21]. The above factors would bias our estimates towards an underestimate of meningococcal disease risk in persons with HIV meeting AIDS surveillance criteria. On the other hand, any incomplete ascertainment of persons with HIV infection meeting the AIDS surveillance criteria in the general population would bias our estimates of meningococcal disease risk in this population towards an overestimate.

We were unable to control for possible confounding due to smoking, which is an established risk factor for meningococcal disease, due to limited tobacco use history reported in the ABCs surveillance system during the study period. Smoking prevalence among HIV-infected individuals has been described to be as much as 3 times the prevalence in the general population [22]. The risk of meningococcal disease among smokers is 2–3 times the risk among nonsmokers [23]. Further study may help elucidate the portion of the increased risk for meningococcal disease among HIV-infected persons that might be attributable to smoking or other risk factors associated with meningococcal disease.

This study is limited to patients reported during 2000 through 2008; therefore, our findings do not reflect any changes in disease epidemiology since 2008. It is noteworthy to mention that since 2012, there have been multiple reports of meningococcal disease clusters among men who have sex with men (MSM) [24, 25]. Among cases in MSM where HIV status was known, as many as 59% of patients were HIV-infected [24]. In our study, data on MSM status were not collected in our expanded chart review or the standard ABCs case report form.

CONCLUSIONS

In summary, we observed an increased incidence of meningococcal disease among patients with HIV ever classified as AIDS in the United States. Our findings are consistent with those of other population-based studies that have shown an increased incidence of meningococcal disease among HIV-infected persons [11–13]. Considering these studies, in June 2016 the US Advisory Committee on Immunization Practices approved a recommendation for routine vaccination of HIV-infected persons aged ≥2 months [26].

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