MAJOR ARTICLE

Cryptococcus gattii in the United States: Clinical Aspects of Infection With an Emerging Pathogen

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Background. *Cryptococcus gattii* (*Cg*) has caused increasing infections in the US Pacific Northwest (PNW) since 2004. We describe this outbreak and compare clinical aspects of infection in the United States among patients infected with different *Cg* genotypes.

Methods. Beginning in 2005, PNW state health departments conducted retrospective and prospective passive surveillance for *Cg* infections, including patient interviews and chart reviews; clinical isolates were genotyped at the US Centers for Disease Control and Prevention (CDC). We examined symptom frequency and underlying conditions in US patients with *Cg* infection and modeled factors associated with death.

Results. From 1 December 2004 to July 2011, 96 *Cg* infections were reported to the CDC. Eighty-three were in patients in or travelers to the PNW, 78 of which were genotypes VGIIa, VGIIb, or VGIIc (outbreak strains). Eighteen patients in and outside the PNW had other molecular type *Cg* infections (nonoutbreak strains). Patients with outbreak strain infections were more likely than those with nonoutbreak-strain infections to have preexisting conditions (86% vs 31%, respectively; $P < .0001$) and respiratory symptoms (75% vs 36%, respectively; $P = .03$) and less likely to have central nervous system (CNS) symptoms (37% vs 90%, respectively; $P = .008$). Preexisting conditions were associated with increased pneumonia risk and decreased risk of meningitis and CNS symptoms. Nineteen (33%) of 57 patients died. Past-year oral steroid use increased odds of death in multivariate analysis ($P = .05$).

Conclusions. Clinical differences may exist between outbreak-strain (VGIIa, VGIIb, and VGIIc) and nonoutbreak-strain *Cg* infections in the United States. Clinicians should have a low threshold for testing for *Cg*, particularly among patients with recent travel to the PNW.

Since 2004, human *Cryptococcus gattii (Cg)* infections have been increasingly reported in the Pacific Northwest (PNW) region of the United States, with most cases being reported in human immunodeficiency virus (HIV)–uninfected patients from Washington and Oregon [1, 2]. These reports have followed the occurrence of an outbreak of *Cg* infection in British Columbia (BC), Canada, that has been ongoing since 1999 [3] and that is considered to be the likely source of the US outbreak [2, 4]. In North America, the outbreak of *Cg* infection has been associated with significant morbidity and high rates of mortality among those infected [1, 3]. Although many ideas have been postulated regarding the source of and reasons for the outbreak [5], to date, these remain unclear.

Cg is a genetically diverse organism that can be subdivided into at least 4 different molecular types: VGI, VGII, VGIII, and VGIV [6]. The outbreak of *Cg* infection in North America has largely comprised 3 clonal genetic subtypes of VGII, designated VGIIa, VGIIb, and VGIIc [7–9], first reported in association with the outbreak [1, 3, 7, 9]; to date, VGIIc has not been reported outside the United States. Infections with other,

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nonclonal VGII subtypes as well as VGI, VGIII, and VGIV have been reported previously from outside North America, frequently from otherwise healthy patients who develop severe central nervous system (CNS) disease as a result of their infection [10–17]. Rare reports of historic *Cg* infections in the United States also exist, primarily VGI- and VGIII-type infections from southern California [11, 18, 19, 20].

The Centers for Disease Control and Prevention (CDC), in conjunction with state and local health department partners, began coordinating *Cg* surveillance in the United States in 2009. We report the epidemiology and clinical characteristics of human *Cg* infections in the United States and discuss the possible influence of *Cg* molecular types and patient immune status on clinical presentation and disease course.

MATERIALS AND METHODS

Surveillance

Surveillance for *Cg* was passive and laboratory-based and began in PNW states during 2004–2005, when cases first began occurring. A case was defined as culture-confirmed *Cg* infection in a resident of the United States with illness onset on or after 1 January 2004. During 2004–2009, PNW cryptococcal isolates were sent to the BC Centre for Disease Control (BCCDC) for confirmation as *Cg*. Beginning in 2009, all isolates, including those previously identified at BCCDC, were submitted to the CDC. State and local health departments performed medical record reviews for patients with laboratory-confirmed *Cg* infection using standardized case report forms, which included questions about demographic characteristics, illness onset, signs and symptoms of infection, clinical findings, and patient outcome. Case report forms were forwarded to the CDC, which began coordinating national surveillance in October 2009; thus, chart reviews for cases occurring before October 2009 were done retrospectively.

As awareness of the outbreak expanded, cases were also reported and isolates were submitted to the CDC from other states, most commonly from a clinician aware of the PNW outbreak. In these states, both treating clinicians and state health departments assisted in completing and submitting patient case report forms. One isolate (from North Carolina) was kindly provided to the CDC by Dr Joseph Heitman (Duke University) several years after the patient's illness.

Complete demographic and clinical data were not available for all patients. Cases described in this report include all previously published infections associated with the US outbreak [1, 2, 21, 22].

Case-patient infections were defined as likely acquired in the PNW or BC if the patient resided in Washington or Oregon or resided in other states but reported a residential or travel history to Washington, Oregon, or BC during the year before illness onset. Infections in case patients residing outside the PNW who did not report residence in or travel to Washington or Oregon in the previous year were defined as not acquired in the PNW or BC.

A preexisting condition was defined as the use of oral corticosteroids during the year before illness onset; HIV infection; existing lung, renal, liver, or heart disease; blood cancers, diabetes, connective tissue disorders, or rheumatic conditions at the time of illness onset; a history of a solid organ or hematopoietic stem cell transplantation; or being a smoker at illness onset. Immunocompromising conditions were considered to be only solid organ or stem cell transplantations, connective tissue disorders, rheumatic conditions, past-year oral corticosteroid use, or HIV infection.

Laboratory Analysis

Isolates were sent to the CDC for species confirmation and genotyping. *Cg* was confirmed by culture using canavanine-glycine-bromothymol blue agar [23]; *Cg* genotype was identified by multilocus sequence typing of the genetic loci URA5, IGS1, LAC1, CAP59, GPD1, PLB1, and SOD1, as described elsewhere [24, 25].

Data Analysis

Case-patient demographic characteristics, travel history, clinical signs, symptoms, underlying conditions at presentation, and outcome were compared among patients with differing genotypes of infection. We compared genotype of *Cg* infection, clinical characteristics, and outcome between patients with and patients without any preexisting condition and between patients with immunocompromising conditions and all other patients. We also evaluated factors associated with death among patients with *Cg* infection by univariate and multivariate analysis.

Data were analyzed using SAS software, version 9.2 (SAS Institute). Relative risks and *P* values were calculated using the χ^2 or Fisher exact tests, when appropriate. The Wilcoxon rank-sum test was used to compare continuous variables. Logistic regression was used to calculate odds ratios in multivariate analysis. In the multivariate model selection process, models were explored using all variables that were significant in univariate analysis; variables that remained statistically significantly associated with death or had borderline statistical significance were included in the final model. The Hosmer–Lemeshow goodness-of-fit test was used to evaluate the fit of final model.

RESULTS

Cg Genotypes

By 1 July 2011, a total of 96 case patients had been reported to the CDC; 96 isolates (1 from each case patient) were received at the CDC for genotyping. Of these, 78 (81%) were genotypes VGIIa (n = 50), VGIIb (n = 6), or VGIIc (n = 22); these are hereafter referred to as outbreak-strain infections. Of 18 non-

VGIIa/b/c isolates (nonoutbreak-strain infections), 11 were VGI, 6 were VGIII, and 1 was of a subtype belonging to the VGII genotype, but not an outbreak strain (Table 1).

Eighty-one case patients (84%) resided in Washington or Oregon; of these, 33 reported travel history, 8 (24%) of whom reported travel at least once during the prior year to areas of BC or Vancouver Island where *Cg* infection is endemic. All 81 patients were considered likely to have acquired their infections in the PNW or BC. Of the 15 case patients residing outside Washington or Oregon, 2 (from Idaho and Alaska) reported extensive travel to both Washington and Oregon during the year before illness onset (Table 1); these infections were considered to have likely been acquired in the PNW. Of the 83 total case patients with likely *Cg* acquisition in the PNW or BC, 78 (94%) had outbreak-strain infections, compared with none (0%) of the 13 case patients with *Cg* acquisition outside the PNW or BC ($P < .0001$; Table 2).

Case Patients

Illness onset ranged from December 2004 through June 2011 (Figure 1). The number of cases reported from Washington and Oregon increased each year; increasing numbers of cases were also reported from outside these states in 2009, 2010, and early 2011.

Demographic data were available for 76 case patients (79%). The median age was 54 years (range, 2–95 years); 43 (54%) were male. Overall, the most common presenting symptoms were headache (61%), nausea (48%), cough (48%), weight loss (47%), and dyspnea (45%) (Table 3). Fifty-four percent of patients had documented pneumonia; 49% had meningitis. Fifty-two patients (76%) had a preexisting condition (Table 3).

Clinical presentation differed by the infecting genotype of *Cg*. Case patients with outbreak-strain infections were more likely than those with nonoutbreak-strain infections to present with symptoms consistent with respiratory disease, including cough ($P = .007$) or dyspnea ($P = .03$; Table 3). In contrast, certain clinical signs consistent with elevated intracranial pressure, including headache ($P = .04$), blurry vision ($P = .01$), or seizure ($P = .01$), were more frequent among case patients with nonoutbreak-strain infections. Overall, 75% of case patients with outbreak-strain infections had any documented respiratory symptom, compared with 36% of patients with nonoutbreak-strain infections ($P = .03$), whereas 90% of patients with nonoutbreak-strain infections had any documented CNS symptoms, compared with 37% of patients with outbreak-strain infections ($P = .008$; Table 3).

The presence of any preexisting condition was more frequent among case patients with outbreak-strain infections (86%) than among patients with nonoutbreak-strain infections (31%; $P < .0001$); immunocompromising conditions were also more frequent among case patients with outbreak-strain infections, although this difference was not statistically significant ($P = .06$;

Table 1. Infecting Genotypes, by State of Case-Patient Residence, Among US Human *Cryptococcus gattii* Infections, 2004–2011

Infecting subtype	Total, no. (%)	WA	OR	ID	AK	CA	NM	MT	MI	NC	GA	HI
VGI	11 (11)	1	3			2	1	1		1[a]	2	
VGII	1 (1)											1
VGIIa	50 (52)	16	33		1[b]							
VGIIb	6 (6)		6									
VGIIc	22 (23)	2	19	1[b]								
VGIII	6 (6)	1[a]				3	1		1[c]			
Total	96	20	61	1	1	5	2	1	1	1	2	1

Abbreviations: AK, Alaska; CA, California; GA, Georgia; HI, Hawaii; ID, Idaho; MI, Michigan; MT, Montana; NC, North Carolina; NM, New Mexico; OR, Oregon; WA, Washington.

[a] Patient reported travel to CA during year before illness onset.

[b] Patients reported extensive travel through WA and OR during year before illness onset.

[c] Patient reported travel to NM during year before illness onset.

Table 2. Comparison of *Cryptococcus gattii* Genotypes by Likely Location of Acquisition, US Infections, 2004–2010

Infecting subtype	Likely acquired in PNW/BC (n = 83)	Not acquired in PNW/BC (n = 13)	*P* value
VGI	4	7	
VGII (other)	0	1	
VGIIa	50	0	
VGIIb	6	0	
VGIIc	22	0	
VGIII	1	5	
Outbreak strain	78 (94)	0 (0)	<.0001
Nonoutbreak strain	5 (6)	13 (100)	

Abbreviations: BC, British Columbia; PNW, Pacific Northwest.

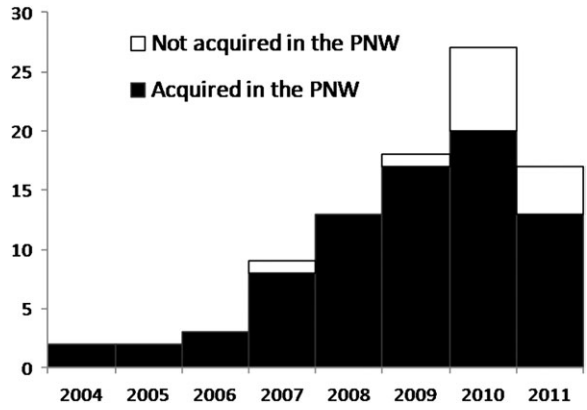

Figure 1. Human infections with *Cryptococcus gattii*, by date of illness onset and likely acquisition location, United States, January 2004–June 2011, by illness onset year (n = 91). Data from 5 patients for both initial report year and onset year were missing. Abbreviation: PNW, Pacific Northwest.

Table 3. Characteristics of *Cryptococcus gattii* Patients and Infections, by Genotype of Infection, US *C. gattii* Outbreak, 2004–2010

Characteristics	Overall (N = 76)	Genotype		*P* value
		Outbreak strain (n = 64)	Nonoutbreak strain (n = 12)	
Age	52, 54 (2–95)	53, 56 (2–95)	41, 45 (18–56)	.007
Mean, median (range), years				
<20	3 (4)	2 (3)	1 (8)	
20–29	3 (4)	2 (3)	1 (8)	
30–49	29 (38)	21 (33)	8 (67)	
50–69	32 (42)	30 (47)	2 (17)	
≥70	9 (12)	9 (14)	0 (0)	
≥50 years	41 (54)	39 (61)	2 (17)	.009
Male sex	43/79 (54)	33/64 (52)	10/15 (67)	.29
Presenting signs/symptoms				
Headache	37/61 (61)	27/50 (54)	10/11 (91)	.04
Nausea	27/56 (48)	21/45 (47)	6/11 (55)	.64
Cough	31/65 (48)	30/54 (56)	1/11 (9)	.007
Weight loss	27/58 (47)	21/49 (43)	6/9 (67)	.28
Dyspnea	25/56 (45)	24/46 (52)	1/10 (10)	.03
Fatigue	20/45 (44)	17/37 (46)	3/8 (38)	.72
Vomiting	23/55 (42)	17/44 (39)	6/11 (55)	.34
Fever	25/65 (39)	23/65 (43)	2/11 (18)	.18
Anorexia	16/52 (31)	13/42 (31)	3/10 (30)	1.00
Muscle pain	18/58 (31)	15/48 (31)	3/10 (30)	1.00
Chills	18/59 (31)	14/49 (29)	4/10 (40)	.48
Chest pain	15/60 (25)	11/49 (22)	4/11 (36)	.44
Night sweats	13/56 (23)	11/46 (24)	2/10 (20)	1.00
Neck stiffness	12/53 (23)	9/43 (21)	3/10 (30)	.68
Blurry vision	9/49 (18)	4/39 (10)	5/10 (50)	.01
Photophobia	5/53 (9)	4/44 (9)	1/9 (11)	1.00
Seizure	4/49 (8)	1/41 (2)	3/8 (38)	.01
Papilledema	3/49 (6)	1/40 (3)	2/9 (22)	.08
Any respiratory symptom	42/62 (68)	38/51 (75)	4/11 (36)	.03
Any CNS symptom	23/50 (46)	15/41 (37)	9/10 (90)	.008
Clinical findings				
Pneumonia	31/57 (54)	26/44 (59)	5/12 (42)	.32
Meningitis	29/59 (49)	21/47 (45)	9/13 (69)	.21
Cryptococcoma: lung	20/61 (33)	14/48 (29)	5/12 (42)	.51
Cryptococcoma: brain	6/24 (25)	3/16 (19)	4/9 (44)	.21
Preexisting conditions				
Any preexisting condition[a]	52/68 (76)	47/55 (86)	4/13 (31)	<.0001
Immunocompromised	34/68 (50)	30/55 (55)	3/13 (23)	.06
Oral steroid use	29/62 (47)	25/49 (51)	3/13 (23)	.11
Lung disease[b]	17/59 (29)	14/47 (30)	2/12 (17)	.48
Kidney disease[b]	14/59 (24)	11/46 (24)	2/13 (15)	.71
History of cancer	14/61 (23)	13/49 (27)	0/12 (0)	.05
Diabetes	12/61 (20)	11/50 (22)	1/11 (9)	.44
Heart disease[b]	12/59 (20)	9/46 (20)	2/13 (15)	1.00
Solid organ transplant	12/60 (20)	9/47 (19)	2/13 (15)	1.00
Current smoker	10/65 (15)	8/54 (15)	2/11 (18)	.67
Rheumatic condition	6/56 (11)	5/45 (11)	1/11 (9)	1.00
Liver disease[b]	5/56 (9)	5/44 (11)	0/12 (0)	.57
Connective tissue disorder	5/59 (8)	3/47 (6)	1/12 (8)	1.00
HIV infection	4/59 (5)	3/47 (6)	0/12 (0)	1.00

Table 3 continued.

Characteristics	Overall (N = 76)	Genotype: Outbreak strain (n = 64)	Genotype: Nonoutbreak strain (n = 12)	*P* value
Outcomes				
Hospitalized	64/70 (91)	52/58 (90)	12/12 (100)	.58
Died of or with infection	19/57 (33)	17/47 (36)	2/10 (20)	.47

Specific preexisting conditions are shown as proportion of all patients with information on that condition. Any respiratory symptom includes cough, dyspnea, and/or chest pain; any CNS symptom includes neck stiffness, blurry vision, papilledema, photophobia, and/or seizure.

Abbreviation: HIV, human immunodeficiency virus.

[a] Some patients had >1 preexisting condition.

[b] Not transplant.

Table 3). No single preexisting condition, except a history of cancer ($P = .05$), differed in frequency by *Cg* genotype. Current smoking was the only reported preexisting condition for 5 patients; 4 had outbreak-strain infections. The presence of any preexisting condition was positively associated with pneumonia, dyspnea, or any respiratory symptom at presentation and negatively associated with male sex, meningitis, and CNS symptoms at presentation (Table 4). All other presentation symptoms, frequency of hospitalization or death, and the presence of cryptococcomas were not different between patients with and those without without a preexisting condition (data not shown).

When comparing characteristics of case patients with VGIIa, VGIIb, and VGIIc infections, case patients with VGIIb infection were more likely than those with VGIIa infection to be male (5 of 5 vs 19 of 42; $P = .05$), and case patients with VGIIa infection were more likely than those with VGIIb infection to present with nausea (16 of 27 vs 0 of 5; $P = .04$). Other patient and clinical characteristics, including patient outcome, did not differ among case patients with VGIIa, VGIIb, or VGIIc infections (data not shown).

Patient Outcomes

Ninety-one percent of patients were hospitalized, and 19 patients (33%) died of *Cg* infection, a median of 59 days after illness onset. In univariate analyses, age ≥50 years, diabetes, liver disease, and a history of oral steroid use increased the risk of death (all $P \leq .01$; Table 4). The presence of any CNS symptom at presentation was associated in univariate analyses with a decreased risk of death ($P = .003$). Risk of death was not different between patients with and without pneumonia, meningitis, any (all) preexisting conditions, or any (all) immunocompromising conditions (Table 4).

In a multivariate model that included the presence of any CNS symptom at presentation, age ≥50 years, and past-year oral steroid use, oral steroid use remained positively associated with death ($P = .048$) and CNS symptoms remained negatively associated with death ($P = .035$). The final model provided an adequate fit for the data (goodness-of-fit test, $P = .85$; Table 4).

DISCUSSION

We describe an outbreak caused by the emerging pathogen *Cryptococcus gattii*, with most cases occurring in Washington and Oregon. With the exception of a single *Cg* isolate reported during the early 1970s from Seattle [26], infections associated with this outbreak [2, 21, 22, 24, 27, 28] are the only published human *Cg* infections from these states. We found that *Cg*-infected patients detected in our surveillance were most frequently aged 30–69 years; were infected with *Cg* genotypes VGIIa, VGIIb, or VGIIc; and had underlying preexisting conditions that might have predisposed them to infection. However, we also found that infections caused by other genotypes of *Cg* are occurring, probably less frequently, in states outside Washington and Oregon. *Cg* infections in the United States are associated with a high mortality rate, regardless of *Cg* genotype or the presence of a preexisting condition in the patient.

Of importance, we found that different genotypes of *Cg* are associated with different clinical profiles during infection. Patients with outbreak-strain infections, most of whom resided in Washington or Oregon, more commonly presented with respiratory than CNS symptoms; in fact, 63% of patients with outbreak-strain infections had no symptoms specific to CNS infection. In contrast, all but 1 patient with nonoutbreak-strain infections, most of whom resided outside Washington or Oregon, had CNS symptoms, whereas only a minority had respiratory symptoms. The more frequent respiratory findings among patients with outbreak-strain infections are important: *Cg* infection should be considered in patients with serious respiratory illness and recent exposure to the PNW.

In contrast to the relative infrequency of preexisting conditions among patients with nonoutbreak- strain infections, we found that the vast majority of patients with outbreak-strain infections had preexisting conditions. In addition, patients with outbreak-strain infections were significantly older than patients with nonoutbreak-strain infections, which may also reflect comparatively more immunosuppression among patients with outbreak-strain infections. Thus, the clinical profile of patients

Table 4. Associations Between Patient Characteristics and Outcomes, *Cryptococcus gattii* Outbreak, United States, 2004–2011

		Univariate analysis		Multivariate analysis	
Variable 1	Variable 2	RR (95% CI)	*P* value	OR (95% CI)	*P* value
Any preexisting condition versus none	Male sex	0.54 (.39–.76)	.004		
	Pneumonia	3.6 (1.3–10.1)	.002		
	Dyspnea	2.5 (.86–7.0)	.06		
	Any respiratory symptom	1.6 (.89–2.8)	.06		
	Meningitis	0.59 (.37–.95)	.04		
	Headache	0.53 (.37–.74)	.004		
	Seizure	0.09 (.01–.76)	.02		
	Blurry vision	0.22 (.06–.83)	.03		
	Photophobia	0.12 (.01–1.0)	.05		
	Any CNS symptom	0.46 (.26–.80)	.03		
Death from or with *Cg*	Age category				
	<20	2.4 (.36–16.6)	.42		
	20–29	0.86 (.73–1.1)	1.00		
	30–49	Ref	NA		
	50–69	1.6 (1.0–2.4)	.05		
	≥70	3.0 (.93–9.9)	.008		
	≥50 versus <50 years	2.1 (1.3–3.5)	.005	5.5 (.78–38.5)	.087
	Pneumonia	1.3 (.76–2.1)	.39		
	Meningitis	1.3 (.74–2.4)	.36		
	Any preexisting condition	1.2 (.91–1.6)	.33		
	Immunocompromising condition	1.5 (.90–2.5	.13		
	Liver disease[a]	3.4 (2.1–5.3)	.01	NI	NI
	Diabetes	4.8 (1.4–16.3)	.009	NI	NI
	Use of oral steroids	2.2 (1.2–4.1)	.01	7.1 (1.01–49.3)	.048
	Any CNS symptom	0.14 (.02–.92)	.003	0.03 (.001–.78)	.035

Abbreviations: *Cg, Cryptococcus gattii*; CI, confidence interval; CNS, central nervous system; NI, not included; OR, odds ratio; Ref, reference group; RR,relative risk.

[a] Not transplant.

with nonoutbreak-strain infections in the United States—CNS disease primarily in otherwise healthy patients—appears to be similar to that reported for many patients with nonoutbreak-strain *Cg* infections outside North America [10, 12, 14, 29–31].

Although we identified few *Cg*-infected case patients infected with HIV, the proportion of HIV infection among all *Cg* cases was substantially above the population average (0.6%) [32], suggesting that, although it is uncommon as a risk factor, HIV infection may increase the risk of developing clinical *Cg* infection in the United States. These findings are similar to previous reports from BC [3] and contradict the common perception that *Cg* infection is exclusively a disease of otherwise healthy individuals.

Case patients had high morbidity and mortality related to *Cg* infection, with 91% of patients requiring hospitalization and a case-fatality rate of 33%. In addition, we found that a history of oral steroid use was associated with increased odds of death in all patients. Of interest, having a CNS symptom at presentation was strongly associated with decreased risk of death. This might be attributable to the lower frequency of preexisting conditions among patients exhibiting CNS symptoms, compared with patients without CNS symptoms. Alternately, earlier recognition of disease may be occurring among patients with CNS symptoms, resulting in earlier and improved treatment. However, our sample size was small, and future studies addressing factors associated with patient death will be critical to providing data to support optimal patient care.

Infections with nonoutbreak-strain *Cg* have never been reported to occur in a clonally expanding, outbreak pattern. Similarly, nonoutbreak-strain *Cg* in the United States does not appear to be clonally expanding, and these sporadic infections should be considered independently—although not with less concern—from the ongoing outbreak in the PNW. Of note, *Cg* has been reported previously in the United States, mostly from southern California [11, 18, 33]; a recent study of 30 human *Cg* isolates collected from southern and central California during the early 1990s showed that 28 were VGIII, 3 were VGI, and 1 was VGII [20], similar to the genotypic profile of *Cg* isolates that we found in states outside the PNW. These data suggest that VGI and VGIII *Cg* infections now being observed in California

may be representative of long-standing *Cg* endemicity in the state. In addition, sporadic *Cg* infections have, rarely, occurred in patients from states outside the PNW in the past [11, 19, 33]. It is unclear whether the infections now being reported from other states are attributable to enhanced awareness and surveillance or whether they represent an unrecognized public health problem in these regions. Continued awareness and surveillance of these infections is important to determine the burden of nonoutbreak-strain infections, particularly outside the PNW.

In contrast, the clonal expansion of outbreak strains of *Cg* represents a novel health concern in North America. With existing data, it is challenging to predict the extent of the future geographic or human spread for these outbreak strains. Improved and continued surveillance and collection of clinical data on these infections will be critical to understanding the precise nature of the differences between these and the nonoutbreak-strain infections in the United States.

Our data have several limitations. First, we had limited numbers of nonoutbreak-strain infections, and thus, some epidemiologic associations might be obscured or, conversely, overrepresented. Second, as noted above, our data are based on the early functioning of a new surveillance system and probably overrepresent severe infections, whereas less severe infections may be going unnoticed or unreported. In addition, because not all clinical laboratories determine *Cryptococcus* identity to the species level (and many infections are diagnosed using antigen testing alone), species *gattii* infections are likely presumed to be due to *Cryptococcus neoformans* at least some of the time and are therefore not identified by surveillance. Third, multivariate analysis was limited because of small sample size and collinearity among some of the variables examined. Fourth, our data on treatment were incomplete and did not permit analysis of patient outcomes by treatment type. Finally, because of differential levels of clinician awareness of and reporting practices for *Cg* between the PNW and other states, reporting of *Cg* infections from states outside the PNW is not comparable to reporting in the PNW, and thus, the conclusions that can be made from comparisons among infections of different *Cg* genotypes might be limited.

In summary, we describe an ongoing outbreak of *Cg* infection in the United States with substantial associated morbidity and mortality. Because of this high mortality, consideration of *Cg* infection in patients with respiratory symptoms with or without coexisting meningitis, particularly among persons with exposure to the PNW, is warranted. Clinicians in all areas of the United States should be aware of this newly emerging pathogen and the diversity of clinical signs and symptoms that can occur with *Cg* infection.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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