Recognition, Diagnosis, and Treatment of *Cryptococcus gattii* Infections in The United States: A Survey of the Emerging Infections Network (EIN)

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Background

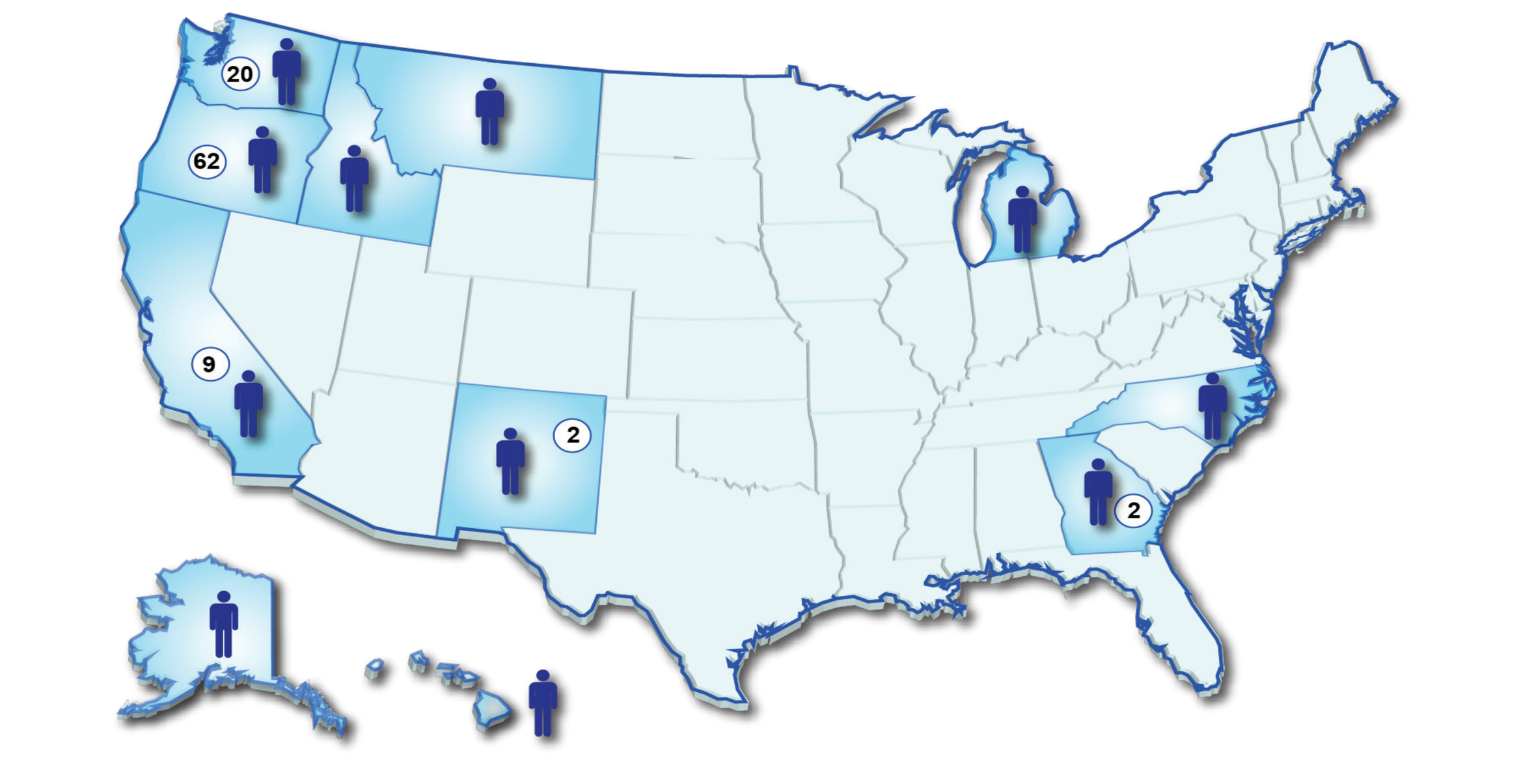
- Cryptococcal infections are caused primarily by two fungal species, *Cryptococcus neoformans* and *Cryptococcus gattii*
- *C. neoformans* usually causes meningitis in immunocompromised patients worldwide
- Until recently, *C. gattii* was thought to be mainly a pathogen of immunocompetent persons in tropical and subtropical regions

C. gattii Outbreak in North America

- An outbreak of *C. gattii* has been occurring since 1999 in British Columbia, Canada, and the United States Pacific Northwest
- *C. gattii* infections in these areas have been characterized by underlying (non-HIV) disease among most patients, and a high frequency of respiratory disease

C. gattii Outbreak in North America

Human *C. gattii* infections in the US, 2004 – August 2011



Rationale for Survey

- Underdiagnosis of *C. gattii* (or misdiagnosis as *C. neoformans*) may be occurring in the US
  1. *C. gattii* associated with the outbreak more often causes respiratory symptoms than meningitis and occurs in patients without HIV, which may result in low clinical suspicion
  2. Cryptococcal infection is commonly diagnosed with an antigen test which cannot distinguish *gattii* from *neoformans*; differentiation of cryptococcal species requires culture on a differential agar which might not be widely used
- We wanted to investigate the potential for outbreak-associated *C. gattii* infections outside of the US Pacific Northwest region

Materials and Methods

- We conducted a survey of infectious disease physicians in the Emerging Infections Network (EIN) to learn how infectious disease physicians in the US recognize, diagnose, and treat cryptococcal infections
  - The EIN is funded by the Centers for Disease Control and Prevention and sponsored by the Infectious Disease Society of America
- During February-March 2011, web-based surveys were distributed to the 1,342 infectious disease physician members
  - EIN staff at the coordinating center sent the initial invitation by email or fax with two reminders; questions are described in the table
  - 'Region' was defined by the four US census regions (Northeast, Midwest, South, and West) as depicted in figure 2
  - Responders not currently practicing in the US were excluded
- Results were analyzed with SAS version 9.2

Results

- Of the 1,342 physicians receiving the survey, 792 (59%) responded
- Two hundred and eighty six (36%) respondents reported treating any patients with cryptococcosis during the past year; the remaining respondents were excluded from further analysis

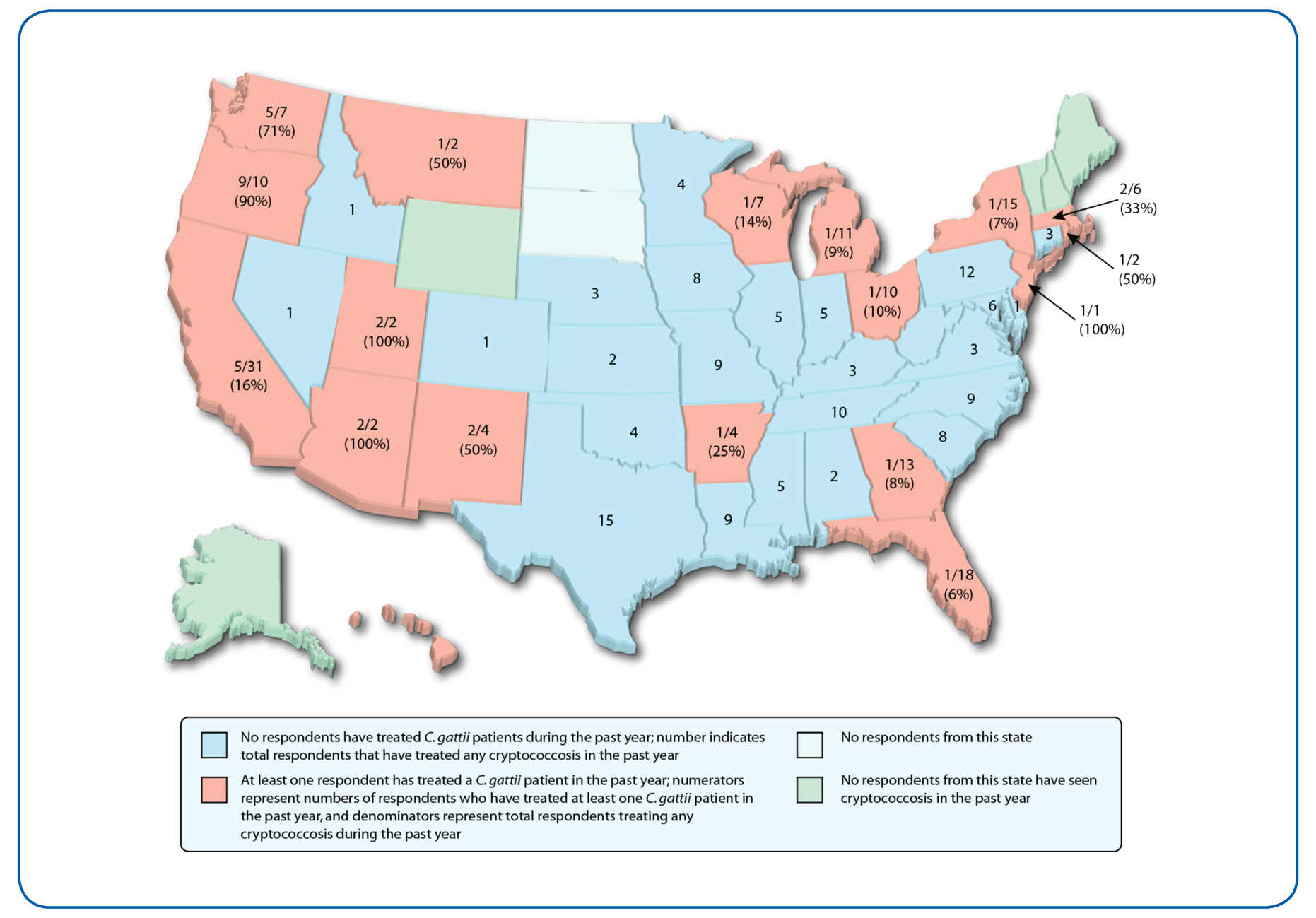


Figure 1: Distribution of respondents who have seen any cryptococcosis during the past year, and who have ever treated a patient with *C. gattii* infection, EIN survey, Feb-Mar 2011.

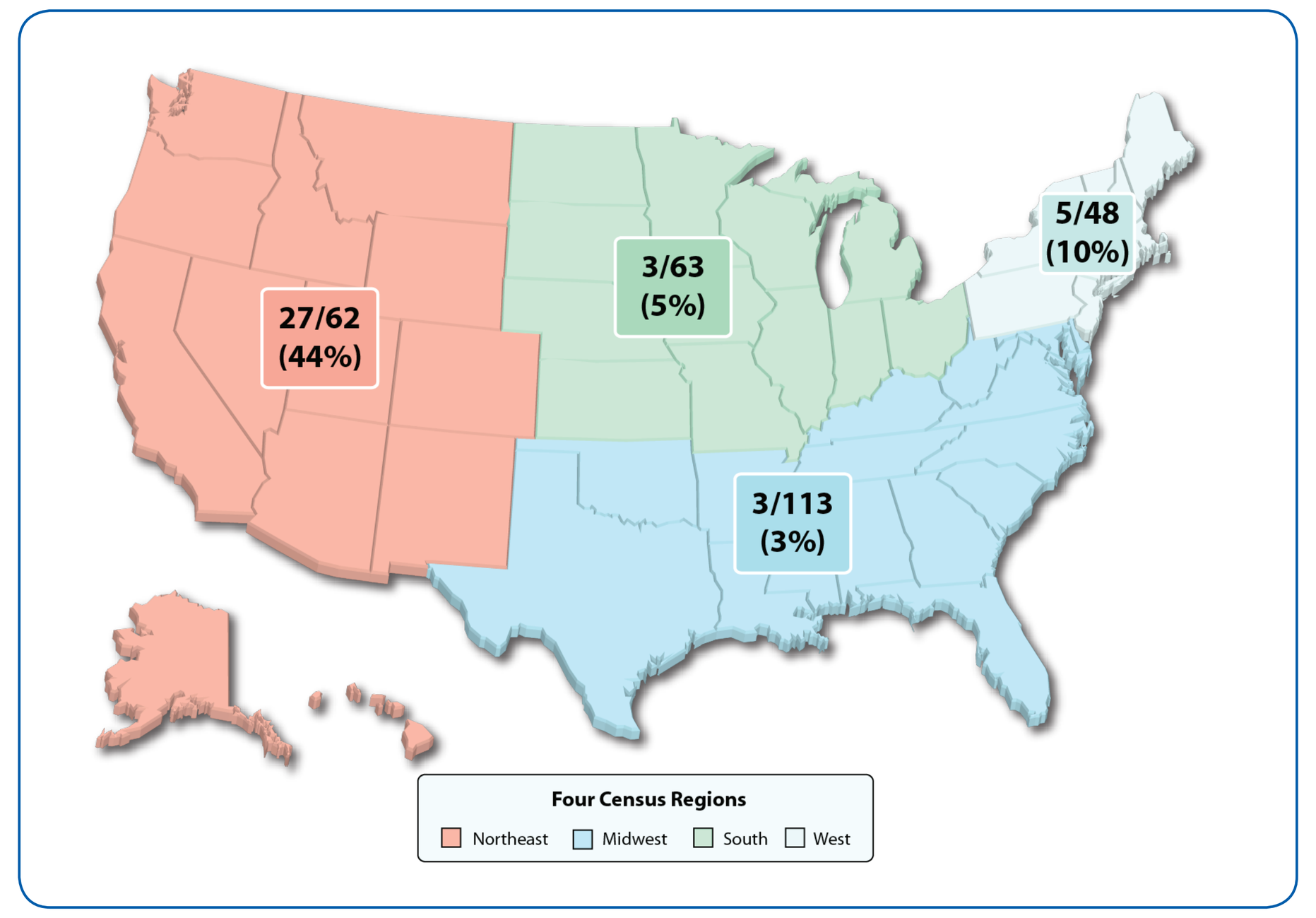


Figure 2: Proportion of survey respondents who reported treating a patient with *C. gattii*, among those who saw a patient with cryptococcosis in the past year, by region, EIN survey, Feb-Mar 2011.

Table. Physician responses to EIN survey, Feb-Mar 2011.

Question, response	Overall (n=286)	Northeast (n=48)	Midwest (n=63)	South (n=113)	West (n=62)
	No. (%) (among providers who have seen any patients with cryptococcosis during the past year)				
No. patients with cryptococcosis seen during the past year					
1-4	218 (76)	41 (85)	55 (87)	71 (63)	51 (82)
5-8	49 (17)	6 (13)	7 (11)	29 (26)	7 (11)
9-12	12 (4)	1 (2)	1 (2)	8 (7)	3 (5)
>12	7 (2)	0 (0)	0 (0)	5 (4)	1 (2)
Proportion of those patients with cryptococcal pneumonia (with or without meningitis)					
0-25%	213 (75)	39 (81)	49 (78)	89 (79)	36 (59)
26-50%	33 (12)	1 (2)	6 (10)	13 (12)	13 (21)
51-75%	8 (3)	1 (2)	1 (2)	4 (4)	2 (3)
76-100%	31 (11)	7 (15)	7 (11)	7 (7)	10 (16)
Common methods of obtaining a diagnosis of cryptococcosis (all that apply)					
Cryptococcal antigen test	272 (94)	48 (100)	58 (92)	110 (97)	56 (90)
Microscopy	95 (33)	16 (33)	13 (21)	42 (37)	24 (39)
Culture	210 (73)	33 (69)	50 (79)	82 (73)	45 (73)
Histopathology	75 (26)	10 (21)	10 (16)	31 (27)	24 (39)
(Any combination of tests that does not include culture)	76 (26)	15 (31)	13 (21)	31 (27)	17 (27)
Clinical lab routinely or on request can differentiate *C. neoformans* from *C. gattii*‡	131 (66)	20 (67)	28 (68)	48 (64)	35 (66)
Proportion of cryptococcal infections in HIV-uninfected patients					
0-25%	154 (54)	32 (68)	26 (41)	70 (62)	26 (42)
26-50%	48 (17)	5 (11)	15 (24)	16 (14)	12 (19)
51-75%	32 (11)	3 (6)	9 (14)	11 (10)	9 (15)
76-100%	51 (18)	7 (15)	13 (21)	16 (14)	12 (24)
Seen cryptococcal infections in HIV-uninfected patients with no known risk factors during past 5 years	78 (27)	6 (13)	13 (21)	26 (23)	33 (53)
Considers species of *Cryptococcus* as a factor of interest in diagnosis or when treating a patient	179 (63)	22 (46)	36 (57)	71 (63)	50 (81)
Considered *C. gattii* as a differential diagnosis for pneumonia in a person from the Pacific Northwest	153 (54)	19 (40)	29 (48)	63 (57)	42 (68)
Ever treated/consulted on a patient known to have *C. gattii*	38 (13)	5 (10)	3 (5)	3 (3)	27 (44)

NOTE. Not all respondents answered all question.

*Region is defined by the four census regions: Northeast (Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont), Midwest (Indiana, Illinois, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin), South (Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia), West (Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, New Mexico, Nevada, Oregon, Washington, Wyoming)

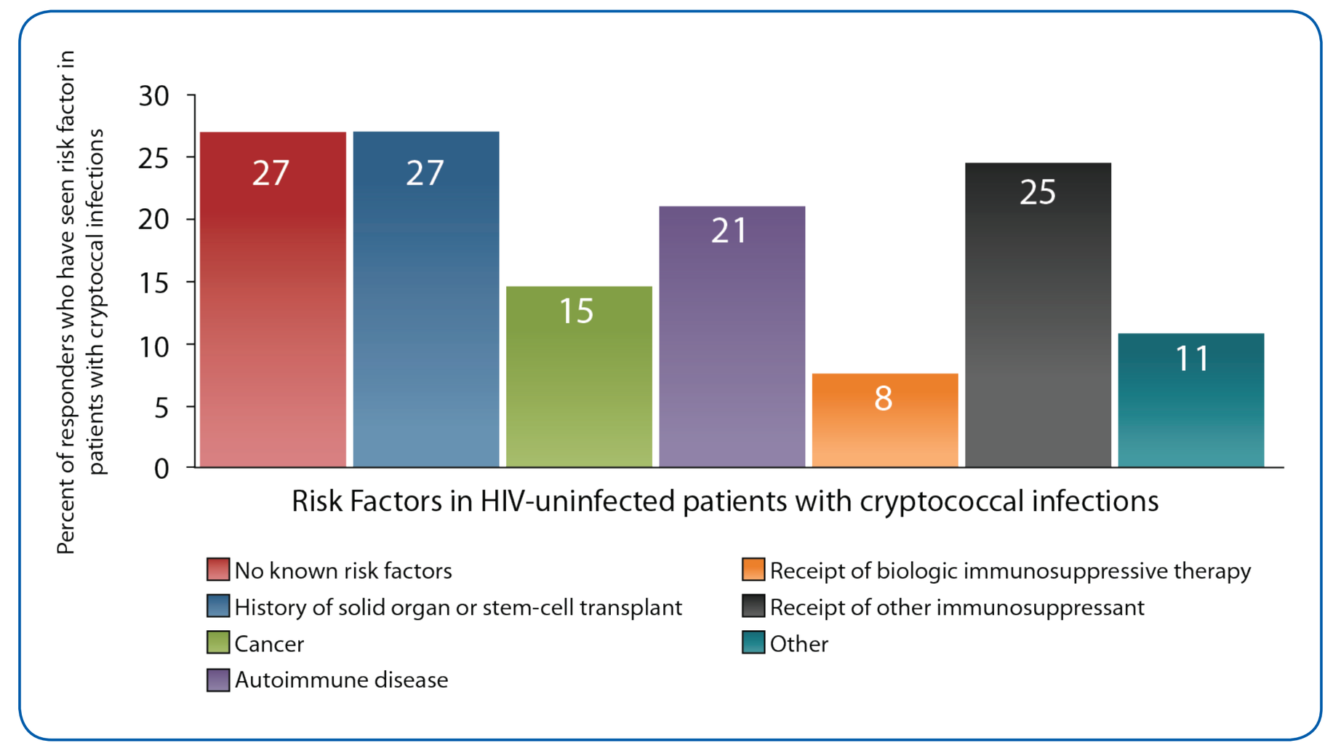
‡ Excludes 'Don't know' response

Higher proportions of respondents from the West reported that >25% of their cryptococcosis patients had cryptococcal pneumonia

Nearly all respondents reported using a cryptococcal antigen test for diagnosis; 73% obtain a culture

Risk factors seen in HIV-uninfected patients (Figure 3)

Table: Physicians responses to EIN survey, Feb–Mar 2011



Percent of responders who have seen risk factor in patients with cryptococcal infections
30
25
20
15
10
5
0
27
27
15
21
8
25
11
Risk Factors in HIV-uninfected patients with cryptococcal infections
No known risk factors
History of solid organ or stem-cell transplant
Cancer
Autoimmune disease
Receipt of biologic immunosuppressive therapy
Receipt of other immunosuppressant
Other

Figure 3: Risk factors seen in HIV-uninfected patients with cryptococcal infections, EIN survey, Feb–Mar 2011

Key Points

- Nearly all respondents were aware of the *C. gattii* outbreak
  - Many already considered *Cryptococcus* species a factor of interest in patient diagnosis or treatment, but this was more frequent among physicians in the West compared with other areas of the US
- Higher proportions of respondents from the West, compared with the South, the Midwest, or the Northeast, reported that >25% of their cryptococcosis patients had pneumonia

Key Points continued

- Nearly all respondents used cryptococcal antigen test (CrAg) for diagnosis
  - 73% commonly obtained a culture (with or without CrAg)
  - 26% used a combination of tests (CrAg, microscopy, histopathology) that did not include culture
- Approximately 1/3 of labs cannot distinguish *C. neoformans* from *C. gattii*, but this is similar across the US census regions
- The proportion of respondents treating cryptococcosis patients who lacked known risk factors for infection during the past five years was much higher in the West, compared with other areas of the US

Conclusions

- Cryptococcal infections with characteristics similar to outbreak-associated *C. gattii* (respiratory symptoms, in patients with underlying disease) may be occurring outside of the Western US, but they are likely relatively infrequent
- Geographically nonspecific underdiagnosis of *C. gattii* may be occurring in the US due to laboratory limitations
- To better understand the burden of *C. gattii* in the US, clinicians and labs should be made aware of the need to obtain cultures and methods of distinguishing cryptococcal species

Limitations

- Results are limited to infectious disease physicians who are members of the EIN and responded to this survey, and are therefore likely not generalizable to all US health practitioners

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