



Case report

Cognitive biases and knowledge deficits leading to delayed recognition of cryptococcal meningitis



M. Deming^{a,b}, A. Mark^{d,1}, V. Nyemba^{a,b,2}, E.L. Heil^c, R.M. Palmeiro^b, S.A. Schmalzle^{a,b,d,*}

^a University of Maryland Medical Center, Department of Medicine, Division of Infectious Disease, 22 South Greene St, Baltimore, MD 21201, United States

^b Institute of Human Virology, University of Maryland School of Medicine, 725 W Lombard Street, Baltimore, MD 21201, United States

^c Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, 20 N Pine Street, Baltimore, MD 21201, United States

^d University of Maryland Medical Center Midtown Campus, Department of Medicine, 827 Linden Avenue, Baltimore, MD 21201, United States

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ABSTRACT

Cryptococcal meningitis is a potentially devastating infectious complication of immunosuppression best characterized in individuals with HIV. Early recognition of and appropriate antifungal therapy for cryptococcal meningitis has a profound effect on outcomes, but with more varied presentations in well-resourced countries recognition may be delayed. We present four cases of cryptococcal meningitis in immunosuppressed patients, each with significant delays in diagnosis. Pulling from recollections of providers and the documented chart assessments, we discuss and tabulate the cognitive biases and diagnostic errors that contributed to delay. We further explore the knowledge deficits regarding cryptococcal meningitis that appeared in these cases.

Once meningitis was considered, each of these cases of cryptococcal meningitis was rapidly diagnosed. Diagnostic delay was driven by knowledge deficits, followed by common biases such as availability heuristics and premature closing. These delays could be countered by maintaining broad differential diagnoses, re-evaluating the patient presentation after recognition of immunosuppression, and early consultation of specialists. Delay in diagnosis of cryptococcal meningitis is associated with high morbidity and mortality. By exploring the various case presentations and errors made, we hope to provide a counter to some of the knowledge deficits associated with cryptococcal meningitis, and to provide actionable advice for early consultation to infectious disease specialists in order to improve outcomes.

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Introduction

Cryptococcus neoformans is an opportunistic fungal pathogen with worldwide distribution, responsible for significant morbidity and mortality in high prevalence HIV settings. Clinicians in these settings often demonstrate familiarity with its recognition and management; clinicians in lower prevalence HIV settings may be less familiar with cryptococcosis and not consider this pathogen in other at risk populations including patients with malignancies, transplants, or those on immunosuppressive medication [1,2]. While *Cryptococcus* can infect any organ, it most commonly

presents as subacute cryptococcal meningitis (CM). These subacute symptoms can be non-specific and include lethargy, headache, malaise, and weakness, in addition to neurological complaints. Early mortality is reported at around 30% even with best available combination antifungal therapy [3–5], although this can be partially abrogated with therapeutic lumbar puncture [6]. Delays from symptom onset to diagnosis are associated with neurologic sequelae and mortality, and are particularly common where CM is rare [7–9].

The following cases highlight varied presentations of CM and the role of cognitive bias and diagnostic error that contributed to delayed diagnosis. Cognitive and diagnostic error is common - as high as 15% in fields with undifferentiated patients such as emergency and internal medicine [10]. Notably, diagnostic errors are associated with a proportionately higher morbidity and mortality than other types of medical errors, 29.1% vs 7.4% [11]. Diagnostic error falls into three conceptual categories: clinical reasoning (e.g., active metacognitive review), recruiting assistance (e.g., consulting specialists), and medical knowledge base

* Corresponding author at: 725 West Lombard Street, N147, Baltimore, MD 21201, United States.

E-mail address: sschmalzle@ihv.umaryland.edu (S.A. Schmalzle).

¹ Present address: Brown University, Alpert School of Medicine, Diagnostic Imaging Department, 593 Eddy St, Providence, RI 02903, United States.

² Present address: El Rio Community Health Center, 1230 S. Cherybell Stratavenue, Tucson, AZ 85713, United States.

(e.g., disease-specific education). In a structured review of 7926 patient records exploring diagnostic adverse events (DAE) across all medical specialties, human failure was identified as the main cause of diagnostic adverse events (96.3%), with a common theme of knowledge deficits responsible [11,12]. Individuals consistently and systematically stray from objective probability when making decisions, instead using personal experience comparing new events to recognized patterns [13]. These heuristics, or reasoning shortcuts, include, but are not limited to, availability heuristics (familiar diagnoses are considered more likely), anchoring (adhering to first impressions even as new information becomes available), and framing (whereby conclusions are influenced by the manner in which the information is presented). Consultations to specialists offer the opportunity to escape framing and availability heuristics as cases are reexamined from a new perspective. By exploring these four cases our goal is to raise awareness of preventable diagnostic errors, encourage early infectious disease consultation, and to help ameliorate the knowledge deficit surrounding CM presentations in lower prevalence HIV settings where CM is less common.

Case 1

A 33 year-old Honduran man presented to an emergency department (ED) with severe neck pain and stiffness accompanied by one week of right-sided sharp temporal headache. He reported fever, sensitivity to light and sound, nausea, and vomiting. He displayed photophobia but no neurologic deficits. Head CT without contrast showed no acute intracranial abnormality. The patient reported subjective improvement after treatment for 'migraine', and was discharged. Routine HIV screening was collected per protocol, but not resulted before discharge.

Four days later he presented to another ED for persistent symptoms; patient was notified of positive HIV result and admitted. History revealed unintentional weight loss of eight pounds that month and odynophagia. He had thrush on exam (not noted on the prior admission), and his CD4 count was 22 cells/ μ L. A CT head with contrast was benign. The ED noted a history of migraines (which patient denied). The admitting team noted that the pain first started at work (as a carpenter), and lack of documented fever. The patient had some subjective improvement after ondansetron, acetaminophen, and cyclobenzaprine. Headache and neck pain were attributed to muscle strain, and nausea to gastritis. He was discharged after 24 h with single strength trimethoprim-sulfamethoxazole prophylaxis, fluconazole for thrush, and a referral to the Infectious Disease (ID) clinic.

While registering the patient at the ID clinic, the intake social worker recognized his symptoms and referred him for direct admission for suspected CM. Diagnosis was confirmed with positive serum cryptococcal antigen, CSF cryptococcal antigen (CrAg) titer of 1:64, CSF culture growing *Cryptococcus neoformans* and elevated CSF opening pressure of 27 cm H₂O. He was started on liposomal amphotericin B and flucytosine induction therapy and symptoms abated after serial lumbar punctures (LP). With rapid improvement he was transitioned to high dose oral fluconazole, showed continued improvement on follow up with ID, and was subsequently started on antiretroviral therapy.

Case 2

A 42 year-old woman with systemic lupus erythematosus treated with chronic prednisone, fibromyalgia, chronic kidney disease, bipolar disorder, and anxiety disorder presented after leg weakness resulted in a fall. She had been admitted to the same hospital two weeks prior for dizziness and diagnosed with dehydration, and was recently discharged from a second hospital

two days prior with diagnosis of cystitis. MRI and MRA of the brain were unremarkable but erythrocyte sedimentation rate was elevated at 124 mm/h. She was again diagnosed with dehydration and encouraged to increase oral fluid intake.

On the third presentation she was tachycardic, hypertensive, and was noted to have periods of confusion and disorientation. Her "nerves (were) acting up" and she was given IV lorazepam for anxiety. She also reported an intense headache and vomited after drinking oral contrast. Additional non-specific complaints included intermittent confusion, constipation, malaise, and pain in the head, neck, shoulder, back, stomach, and muscles. Physical exam was without focal neurologic deficit, although altered mental status was noted. Routine admission HIV screening was positive. CD4 cell count, HIV viral load, and serum CrAg were collected. The patient was reportedly difficult to interview because many family members were often at bedside and she occasionally declined to answer questions. On day two of hospitalization severe headache was noted. Ongoing tachycardia and hypertension were attributed to anxiety, and urinary retention to 'non-infectious cystitis' as she had a benign urinalysis. She was increasingly confused and sometimes mumbling unintelligibly. She reported to family that she was "having a panic attack" and then became acutely short of breath followed by cardiac arrest. She was resuscitated and transferred to the intensive care unit (ICU). Apical parenchymal infiltrates were noted on chest imaging and antibacterials initiated. Several hours later serum CrAg returned positive (titer 1:8192), ID was consulted, and liposomal amphotericin B and flucytosine were given. Initial LP opening pressure was 30 cm H₂O and CSF Gram stain showed yeast. The ICU team disagreed with strong recommendations by ID for serial LP based on CT imaging showing diffuse cerebral edema; LP was not pursued due to perceived "risk of herniation with no benefit". The following day, she lost all brainstem reflexes. On hospital day five family withdraw life-sustaining measures and declined autopsy after her death.

Case 3

A 61 year-old man with a history of follicular lymphoma complicated by myelodysplastic syndrome (MDS) presented to oncology clinic with subjective fever, malaise, and fatigue. He was receiving maintenance rituximab for MDS. Lung examination was clear but chest X-ray demonstrated new right middle lobe opacity and right pleural effusion. He was prescribed moxifloxacin for community acquired pneumonia and advised to follow up with pulmonology if symptoms persisted.

One week later he presented to the ED for worsening dyspnea and malaise, now with fever, tachycardia, and hypoxia with a P_aO₂ of 46 mmHg. Chest X-ray again revealed a right-sided consolidation, and he was admitted and started on broad spectrum antibacterials "because of immunocompromised state." The ID consultant recommended a chest CT and blood cultures. However, despite still requiring supplemental oxygen the patient reported improvement in symptoms and requested discharge prior to upcoming weekend. He was discharged on day 4 with oral azithromycin, cefpodoxime, and with a planned outpatient chest CT.

Two days later he was readmitted after blood cultures grew yeast. He had a further increased oxygen requirement and bilateral blurred vision. He was started on micafungin for fungemia, ophthalmologic exam and echocardiogram were requested, and ID consultants recommended an LP to evaluate for CM. He then had a minor fall with head impact, and soon thereafter had a seizure prompting transfer to the ICU, endotracheal intubation, and delay of the planned LP. The primary team started fluconazole for possible CM in addition to broad-spectrum antibacterials and acyclovir. LP opening pressure was 65 cm H₂O, with budding yeast

on the CSF Gram stain. ID consultants were notified and antifungals were appropriately changed to liposomal amphotericin B and flucytosine. A subsequent family meeting resulted in a de-escalation of care and he died 20 days after initial presentation to the oncology clinic. Serum cryptococcal antigen titer was 1:2048 and pleural fluid and cerebrospinal fluid (CSF) cultures subsequently grew *Cryptococcus neoformans*. Cause of death by autopsy was disseminated cryptococcosis.

Case 4

A 70 year-old man taking chronic prednisone and cyclophosphamide for IgA nephropathy was admitted for new-onset respiratory failure. He was diagnosed with non-ischemic cardiomyopathy (EF 45–50%) by echocardiogram, underwent cardiac catheterization and was diuresed. He developed new onset aphasia three days into this hospitalization. The MRI was notable only for a small acute infarct at the right splenium of the corpus callosum and “age related changes,” and his aphasia was attributed to “stroke.” Incidentally, a renal biopsy showed worsening of his nephropathy despite immunosuppression, so his cyclophosphamide was discontinued and prednisone tapered. He was discharged to a nursing home after a 10-day hospitalization.

Twelve days later he was admitted from the nursing home to another hospital for altered mental status. History obtained by the admitting teams was that his new baseline was alert, oriented, following commands but with aphasia. He had become intermittently altered the previous week, no longer following commands. On initial evaluation he was nonverbal, not following commands, withdrawing but not localizing to pain. Pupils were equal and reactive but he did not consistently track. He had increased tone in the right upper extremity. Admission labs showed anemia and elevated BUN/creatinine; his HIV test was nonreactive. Chest X-ray showed interstitial edema versus diffuse airspace disease. Initial empiric antibacterials for hospital acquired pneumonia and acyclovir for possible herpes encephalitis were given.

Head CT showed diffusely prominent ventricles without sulcal widening, concerning for communicating hydrocephalus or a meningeal process. ID was consulted for possible sepsis, and requested a diagnostic LP and serum cryptococcal antigen given

immunosuppression and CT findings. MRI brain re-demonstrated ventriculomegaly, with subependymal flow suggesting recent onset. This finding was “not typical for normal pressure hydrocephalus,” and a meningeal process was again suggested. Serum CrAg resulted as positive on day three, and CSF CrAg titer was 1:4096. He was started on liposomal amphotericin B and flucytosine. The patient underwent weekly large volume LP until opening pressure normalized, completed a 6-week course of liposomal amphotericin B plus flucytosine induction and was discharged to a nursing home on fluconazole consolidation therapy. His neurologic status improved to intermittent tracking and occasional one-word answers, but he died out of hospital approximately one month after discharge.

Discussion

In these four cases, all suffered diagnostic error and delay in therapy of one to three weeks, with subsequent fatality in three patients. Notable commonalities are premature closure (Table 1) and knowledge deficits (Table 2) leading to delays in diagnosis. These knowledge deficits manifest as a failure to form a comprehensive differential and the associated lack of timely diagnostic work-up. Routine opt-out screening for HIV, recommended in all healthcare settings unless prevalence is <0.1%, identified the two individuals with HIV in these cases [14]. In patients with advanced HIV and altered mental status, meningitis should be at the forefront of a differential diagnosis. In medically developed countries, a more diverse population presents with CM, not just patients with advanced HIV, and this population often includes patients with iatrogenic immunosuppression. CM in non-HIV patients has a higher rate of morbidity and mortality in part due to the delays in diagnosis [4]. Two of these four cases were not HIV associated but related to iatrogenic immunosuppression, and these were fatal.

Recognition of meningitis is the first key element in appropriate diagnosis and treatment of CM, and often falls to primary and emergency care providers. CM may be a more esoteric diagnosis missed by intuitive processes, but it is readily tested once meningitis is considered. If not considered by the primary teams, it was considered by the ID consultants in each of these cases (or

Table 1
Heuristics contributing to delayed diagnoses of CM.

	Case #1 33 y.o. M	Case #2 42 y.o. F	Case #3 61 y.o. M	Case #4 70 y.o. M
Availability heuristic	Failure to recognize immunosuppression: Delayed HIV diagnosis	Failure to recognize immunosuppression: Delayed HIV diagnosis	Failure to treat as immunosuppressed: Rituximab, treated for community acquired then hospital acquired pneumonia	Failure to recognize immunosuppression: Cyclophosphamide was discontinued prior to second admission
Anchoring	Common diagnosis: Migraine, musculoskeletal strain, and gastritis. Search satisfying: History of manual labor noted and neck pain attributed to musculoskeletal injury.	Common diagnosis: Urinary tract infection	Common diagnosis: Pneumonia Search satisfying: Pneumonia diagnosed by imaging.	Common diagnosis: Pneumonia and stroke. Search satisfying: Altered mental status and stroke noted on MRI. Location inconsistent, but no further evaluation for aphasia
Framing	Premature closure: Subjective initial improvement in headache with migraine treatment, no additional workup or treatment. Inherited thinking: Prior diagnosis of migraine noted on admission, additional diagnoses added (gastritis, muscle strain) to migraine rather than re-evaluating.	Premature closure: New urinary retention & tachycardia considered to be due to “noninfectious cystitis” despite dizziness, fall, and elevated ESR. Fundamental attribution: Bipolar, reported her “nerves were acting up”, “difficult to interview”	Premature closure: Subjective improvement, but no improvement in hypoxia with pneumonia treatment Inherited thinking: Retained pneumonia diagnosis despite failure to improve on therapy, lack of cough, inconsistency of blurry vision.	Fundamental attribution: Admitted from nursing home with presumed poor baseline.

Table 2
Knowledge deficits associated with delayed diagnoses or improper treatment of CM.

Common Knowledge Deficit	Correct Approach
Cryptococcosis Diagnosis and Management Fear of adverse drug reactions leading to use of less effective therapies (Case 3)	Combination of AMB and 5-Flucytosine is associated with lower mortality rates than alternate therapies [3–5].
Reflexive use of empiric echinocandin when serious fungal infection is suspected (Case 3)	Echinocandins are appropriate for most Candidemia, but not recommended for treatment of Cryptococcosis due to intrinsic resistance [18]. Similar to antibacterials, antifungals have unique spectra of activity against different pathogenic fungi that must be taken into account when choosing empiric therapy.
Delayed initial LP (Case 1,2,3,4), and reluctance to perform repeat therapeutic LP due to perceived lack of necessity (Case 3)	Early and repeat therapeutic LP decreases morbidity and mortality in CM [6,7].
Reluctance to perform therapeutic LP due to concern for cerebral herniation (Case 3)	LP is recommended for management of increased ICP for CM in the absence of space occupying lesion on CNS imaging [18]. Although concern was noted for risk of herniation due to LP, a case series of 9 patients with extremely high ICP (>600 mm H2O) 7 patients survived with repeat LPs and appropriate antifungal therapy. Of the two mortalities, one was a very delayed presentation and the other had recurrent ICH despite initial improvement after LP [19]. For patients developing obstructive hydrocephalus other mechanical means of decreasing pressure can be pursued (eg. ventriculoperitoneal shunt, external ventricular drain) [18].
Failure to test for or consider undiagnosed HIV with OI in high prevalence settings (Case 1,2)	Routine opt-out testing is recommended over risk-based testing due to earlier and increased diagnosis of HIV [14,20]. High local prevalence rates may suggest need for more frequent screening.
Failure to consider other sites of Cryptococcal infection in immunocompromised hosts (Case 3, 4)	Cryptococcus species enter via inhalation (pulmonary) and can then disseminate (fungemia) to other body sites (cutaneous, skeletal, urogenital, ocular, hepatic, etc.) [1,18].
General Infectious Disease Diagnosis and Management Assumption that all PNA is typical bacteria (fungal, viral, or atypical bacteria often missed) (Case 3, 4), or assuming altered mental status is sepsis related rather than CNS process (Case 2,3).	Maintain broad differential diagnosis and test and treat as appropriate based on pretest probability of each. Obtain comprehensive samples for culture and microbiological analysis at initiation and escalation of therapy to direct treatment rather than relying on empiric therapy.
Consider atypical or opportunistic infections (OIs) in people living with HIV (Case 1,2) or other immunocompromised patients (Case 3, 4)	Consider broadening differential after recognition of immunosuppression, rather than limiting therapy to reflexive institution-specific 'broad spectrum' antibacterials for covering any infection
Failure to involve ID early in serious infections (Case 1, 2, 3, 4)	ID consults decrease mortality in certain infections [21–23]. Consultants can help advise on differential diagnosis, testing, and empiric therapy.

CM = cryptococcal meningitis; AMB = liposomal amphotericin B; LP = lumbar puncture; ICP = intracranial pressure; PNA = pneumonia; OI = opportunistic infection.

the ID social worker in case 1) – a finding consistent with the improved outcomes associated with ID consults [15]. Overall sensitivity of cryptococcal antigen testing is high: 94% for CSF and 93% for serum. Among HIV-negative immunocompromised hosts serum antigen is less sensitive (89%), but CSF antigen sensitivity approaches 97% [16]. The diagnostic failure common to each of these cases appears to be failing to consider an atypical presentation of a common disease (meningitis) rather than failing to send specialized tests, as each diagnosis was made by rapid antigen testing or gram stain rather than culture. Thus, serum CrAg testing could be considered in immunocompromised patients presenting with mild neurological or non-specific symptoms.

CM is an infectious complication of immunosuppression with severe consequences for missed and delayed diagnoses. Knowledge deficits can be partially compensated for by appropriate consultation to specialists – as seen when ID consultants recommended appropriate antifungal therapy or early and repeated LPs, both of which are associated with improved outcomes [17]. However, that first essential recognition of meningitis falls to primary providers. While availability heuristics are often useful, they led to delayed diagnoses in these cases. Opportunities to rectify these mistakes could have come with adherence to guidelines (eg. routine HIV testing and follow-up) or recognition of the incongruity of results that were ignored because they did not fit the initial diagnosis (premature closure). Recognition of the cognitive biases and countering them by active metacognition, recruiting assistance by consulting specialists, or increasing a knowledge base is essential to reducing diagnostic error and improving outcomes.

Informed consent

Written informed consent was obtained from the living patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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M. Deming: Writing - original draft, Writing - review & editing, Data curation. **A. Mark:** Writing - original draft, Data curation. **V. Nyemba:** Writing - original draft, Data curation. **E.L. Heil:** Writing - review & editing. **R.M. Palmeiro:** Writing - review & editing. **S.A. Schmalzle:** Supervision, Writing - original draft, Writing - review & editing, Data curation.

References

- [1] Schmalzle SA, Buchwald UK, Gilliam BL, Riedel DJ. Cryptococcus neoformans infection in malignancy. *Mycoses* 2016;59:542–52. doi:<http://dx.doi.org/10.1111/myc.12496>.

- [2] Pappas PG, Perfect JR, Cloud GA, Pankey GA, Lancaster DJ, et al. Cryptococcosis in human immunodeficiency virus–negative patients in the era of effective azole therapy. *Clin Infect Dis* 2001;33:690–9, doi:http://dx.doi.org/10.1086/322597.
- [3] Lightowler JVJ, Cooke GS, Mutevedzi P, et al. Treatment of cryptococcal meningitis in KwaZulu-Natal, South Africa. *PLoS One* 2010;5:e8630, doi:http://dx.doi.org/10.1371/journal.pone.0008630.
- [4] Bratton EW, El Husseini N, Chastain CA, et al. Comparison and temporal trends of three groups with cryptococcosis: HIV-infected, solid organ transplant, and HIV-negative/non-transplant. *PLoS One* 2012;7:, doi:http://dx.doi.org/10.1371/journal.pone.0043582.
- [5] Day J, Chau T, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med* 2013;368:1291–302, doi:http://dx.doi.org/10.1136/pgmj.52.607.305.
- [6] Rolfes MA, Hullsiek KH, Rhein J, Taseera K, Schutz C, et al. The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. *Clin Infect Dis* 2014;59:1607–14, doi:http://dx.doi.org/10.1093/cid/ciu596.
- [7] Aye C, Henderson A, Yu H, Norton R. Cryptococcosis—the impact of delay to diagnosis. *Clin Microbiol Infect* 2016;22:632–5, doi:http://dx.doi.org/10.1016/j.cmi.2016.04.022.
- [8] Wu J, Xu B, Ou X, Zhu L, Weng X. Factors associated with mortality in cryptococcal meningitis. *Zhonghua Yi Xue Za Zhi* 2010;90:.
- [9] Katchanov J, von Kleist M, Arasteh K, Stocker H. 'Time-to-amphotericin B' in cryptococcal meningitis in a European low-prevalence setting: analysis of diagnostic delays. *QJM* 2014;107:799–803, doi:http://dx.doi.org/10.1093/qjmed/hcu077.
- [10] Berner ES, Graber ML. Overconfidence as a cause of diagnostic error in medicine. *Am J Med* 2008;121:. doi:http://dx.doi.org/10.1016/j.amjmed.2008.01.001.
- [11] Zwaan L, De Bruijne M, Wagner C, Thijs A, Smits M, van der Wal G, et al. Patient record review of the incidence, consequences, and causes of diagnostic adverse events. *Arch Intern Med* 2010;170:1015–21, doi:http://dx.doi.org/10.1001/archinternmed.2010.146.
- [12] Graber ML, Kissam S, Payne VL, Meyer AN, Sorensen A, Lenfestey N, et al. Cognitive interventions to reduce diagnostic error: a narrative review. *BMJ Qual Saf* 2012;21:535–57, doi:http://dx.doi.org/10.1136/bmjqs-2011-000149.
- [13] Kahneman D, Tversky A, Khaneman D, Tversky A. Subjective probability: a judgment of representativeness. *Cogn Psychol* 1972;3:430–54, doi:http://dx.doi.org/10.1016/0010-0285(72)90016-3.
- [14] Branson BM, Handsfield H, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR* 2006;55:.
- [15] Spec A, Olsen MA, Raval K, Powderly WG. Impact of infectious diseases consultation on mortality of cryptococcal infection in patients without HIV. *Clin Infect Dis* 2017;64:558–64, doi:http://dx.doi.org/10.1093/cid/ciw786.
- [16] Antinori S, Magni C, Fasan M, Parravicini C, Ag CSF. The role of cryptococcal antigen assay in diagnosis and monitoring of cryptococcal meningitis. *J Clin Microbiol* 2005;43:5828–9, doi:http://dx.doi.org/10.1128/JCM.43.11.5828.
- [17] Shoham S, Cover C, Donegan N, Fulnecky E, Kumar P. Cryptococcus neoformans meningitis at 2 hospitals in Washington, D.C.: adherence of health care providers to published practice guidelines for the management of cryptococcal disease. *Clin Infect Dis* 2005;40:477–9, doi:http://dx.doi.org/10.1086/427213.
- [18] Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2010;50:291–322, doi:http://dx.doi.org/10.1086/649858.Clinical.
- [19] Sun H-Y, Hung C-C, Chang S-C. Management of cryptococcal meningitis with extremely high intracranial pressure in HIV-infected patients. *Clin Infect Dis* 2004;38:1790–2.
- [20] Duffus W, Kettinger L, Stephens T, Gibson J. Missed opportunities for earlier diagnosis of HIV infection—South Carolina, 1997–2005. *MMWR* 2006;55:1269–72, doi:http://dx.doi.org/10.1001/jama.297.2.149.
- [21] Lee RA, Zurko JC, Camins BC, Griffin RL, Rodriguez JM, McCarty TP, et al. Impact of infectious disease consultation on clinical management and mortality in patients with candidemia. *Clin Infect Dis* 2018;60–2, doi:http://dx.doi.org/10.1093/cid/ciy849.
- [22] Lahey T, Shah R, Gittzus J, Schwartzman J, Kirkland K. Infectious diseases consultation lowers mortality from *Staphylococcus aureus* bacteremia. *Medicine (Baltimore)* 2009;88:263–7, doi:http://dx.doi.org/10.1097/MD.0b013e3181b8fccb.Infectious.
- [23] Burnham JP, Olsen MA, Stwalley D, Kwon JH, Babcock HM, Kollef MH. Infectious diseases consultation reduces 30-day and 1-year all-cause mortality for multidrug-resistant organism infections. *Open Forum Infect Dis* 2018;5:1–5, doi:http://dx.doi.org/10.1093/ofid/ofy026.