

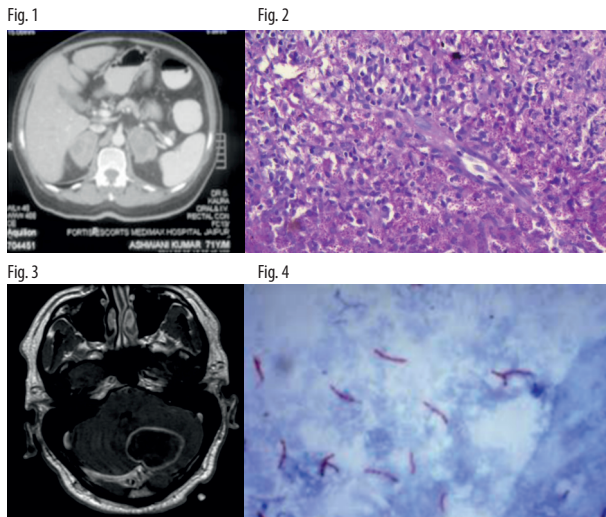


## A TALE OF TWO INFECTIONS

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A 70 year old male presented with history of fever, weight loss of 15 kg and headache of 1-2 months duration. He was admitted to a hospital where he was diagnosed as a diabetic with uncontrolled high sugars. He was HIV negative. A contrast CT of the chest and abdomen revealed necrotic mediastinal and pelvic nodes, enlarged adrenals with a central hypodense area and some endobronchial tree in bud lesions in the lungs (Figure 1). A CT guided biopsy of a pelvic node was done which showed only necrotic tissue on histopathology. A provisional diagnosis of tuberculosis was made and the patient was initiated on a regime of isoniazid, rifampicin, pyrazinamide and ethambutol. The dose of rifampicin was 450 mg against a body weight of 65 kg. Steroids were also started, reasons for which were not clear.

The patient continued to deteriorate even one month after starting treatment and at this time an adrenal biopsy was done which was suggestive of histoplasmosis (Figure 2). In view of persistent headache a contrast MRI brain was done which showed multiple enhancing lesions and an abscess in the cerebellum (Figure 3). A diagnosis of disseminated histoplasmosis was thus made and treatment with liposomal amphotericin B initiated. Anti TB treatment was stopped and steroids were tapered. The patient initially improved and then worsened with increasing headache. Repeat imaging showed increase in size of the brain abscess. He was taken up for urgent aspiration of the abscess. The pus was sent for smear microscopy and fungal culture. It showed plenty of acid fast bacilli on smear (Figure 4). With these reports of histoplasmosis in the adrenals and tuberculosis in the brain he was referred to our hospital.



At admission he was conscious but drowsy with no focal deficit. He was very malnourished and on nasogastric feeds. Vital parameters were stable. Routine investigations were unremarkable except for hyponatremia and hypokalemia. The slides of adrenal biopsy and the brain abscess were reviewed and the review confirmed acid fast bacilli in the brain abscess and yeast like organisms possibly histoplasmosis in the adrenals. A diagnosis of non CNS histoplasmosis and CNS tuberculosis was made. Liposomal amphotericin B was continued and patient was also started on itraconazole with a plan to stop liposomal amphotericin B once the itraconazole levels built up. He was also started on a non rifampicin based regime for tuberculosis including moxifloxacin, aminoglycoside, isoniazid, pyrazinamide, ethambutol and clofazimine. The patient did not improve significantly during hospital stay, was discharged on

### About FISF

The purpose of the Fungal Infections Study Forum is to conduct educational activities, undertake epidemiological and clinical studies and to promote research activities on invasive fungal infections. The results of such research would benefit the clinicians, mycologists and the general public. The trust was formed in view of emergence of Invasive fungal infections (IFIs) in India which is posing a serious challenge to the haematologists, critical care providers, ID specialists, pulmonologists, neurologists, medical mycologists and many other clinicians handling serious and immunocompromised patients. The trust is the independent working consisting of clinicians and mycologists and instituted on 3rd March 2012 at Mumbai, India.

### MYCOCON 2016

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### Dear Friends

It has been some time since FISF has been mulling to publish its newsletter and it gives me great pleasure to present to you the first issue of this newsletter. This newsletter discusses an interesting case of coinfection with two organisms, the latest in published literature from the fungal world and also a pictorial quiz. Hope it adds to your fungal IQ. Feedback is welcome.

### Editor

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request with advice to continue medications at home. He died at home a couple of weeks later.

### Case discussion

The most unusual aspect of this case is existence of two infections in one patient with no other apparent immunodeficiency apart from diabetes. Disseminated histoplasmosis has been reported even in immunocompetent individuals. Similarly coinfection with tuberculosis and histoplasmosis is well described in patients with AIDS. A common clinical error is confusing histoplasmosis for tuberculosis in endemic areas since the clinical and radiologic manifestations of both are very similar. In fact many patients with histoplasmosis have received treatment for tuberculosis prior to diagnosis. Though the diagnosis of tuberculosis and histoplasmosis could not be established by culture, the smear microscopy findings were quite specific. When the adrenal biopsy was done, fungal cultures were not done since histoplasma was not suspected. When the brain abscess was aspirated, TB cultures were not sent since mycobacterial infection was not suspected.

The treatment of histoplasmosis depends on the severity of disease and whether CNS disease is present or not; it is well summarized in the IDSA guidelines. Since this patient's CNS disease was not due to histoplasmosis, 1-2 weeks of liposomal

amphotericin B followed by itraconazole for 12 months would be satisfactory. Itraconazole levels take up to 1 week to build up so overlapping amphotericin B and itraconazole is advisable. The capsule form of itraconazole has to be taken empty stomach and antacids should be strictly avoided. Since bioavailability of itraconazole is variable, drug level monitoring is also recommended. This patient also highlights the difficulty in treating histoplasmosis and tuberculosis together due to the significant interaction between rifampicin and itraconazole. The interaction is so significant that there is no choice other than using a non rifampicin based regime. A mention should also be made of the interaction between moxifloxacin and itraconazole in causing QT prolongation and hence the need for ECG monitoring.

It is unfortunate that the patient succumbed despite aggressive therapy. The case highlights the need to suspect histoplasmosis in an appropriate clinical setting so that early appropriate treatment can be instituted. It also illustrates the fact that though rare, two infections can coexist in the same patient and should be suspected when the clinical response is not as per expectations.

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## INVASIVE FUNGAL INFECTION: THE YEAR IN REVIEW

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**Piyush Chaudhari ID Fellow**  
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### 1) Understanding variability with voriconazole using a population pharmacokinetic approach: implications for optimal dosing

Michael J. Dolton

*J. Antimicrob. Chemother.* (2014) 69 (6): 1633-1641. doi: 10.1093/jac/dku031

In this study, non-linear mixed effects modelling (NONMEM) was undertaken of six voriconazole studies in healthy volunteers and patients. Dosing simulations to examine influential covariate effects and voriconazole target attainment (2–5 mg/L) stratified by CYP2C19 phenotype were performed. The  $V_{max}$  for voriconazole was found to be 41.2% lower in participants with one or more CYP2C19 loss-of-function (LoF) alleles compared with participants with no LoF alleles. Co-administration of phenytoin or rifampicin, St John's wort or glucocorticoids significantly increased voriconazole elimination. This study demonstrates that among patients without CYP2C19 LoF alleles, a majority are predicted to require higher dosing, of at least 300 mg twice daily, to achieve recommended trough voriconazole concentrations ( $\geq 2$  mg/L). Conversely, patients with CYP2C19 LoF alleles have substantially increased voriconazole exposure, with a significant proportion (29%–39%) at risk of potentially toxic voriconazole concentrations of  $\geq 5$  mg/L with 200 mg twice daily dosing.

#### COMMENTS

While voriconazole is the treatment of choice for IPA, better treatment is an unmet clinical need. Voriconazole exhibits highly variable, non-linear pharmacokinetics and is associated with a narrow therapeutic window. Simply pushing up the doses may result in a better response but at the cost of toxicity. Hence sophistication in the use of voriconazole is essential using therapeutic drug monitoring at multiple time points along with the information from CYP 2C19 polymorphism.

### 2) Initial Use of Echinocandins Does Not Negatively Influence Outcome in Candida parapsilosis Bloodstream Infection: A Propensity Score Analysis

Mario Fernández-Ruiz for the CANDIPOP Project, GEIH-GEMICOMED (SEIMC), and REIPIA

*Clin Infect Dis*. (2014) 58 (10): 1413-1421. doi: 10.1093/cid/ciu158

In the CANDIPOP study in 29 Spanish Hospitals, predictors for clinical failure (all-cause mortality between days 3 to 30, or persistent candidemia for  $\geq 72$  hours after initiation of therapy) in episodes of *C. parapsilosis* species complex BSI were assessed by logistic regression analysis. The impact of echinocandin-based regimen as the initial antifungal therapy (within the first 72 hours) was analysed by using a propensity score approach. Among 194 episodes of *Candida parapsilosis* BSI occurring in 190 patients clinical failure occurred in 58 of 177 (32.8%) of evaluable episodes. Orotracheal intubation and septic shock were found to be the risk factors for clinical failure, whereas early central venous catheter removal was protective. The initial use of an echinocandin-based regimen did not have any impact on the risk of clinical failure.

#### COMMENTS

Although treatment with Echinocandin may not be inferior, the real question is whether de-escalation to Fluconazole is in fact optimization of treatment. Should this be done expeditiously or only after the susceptibility is checked and patient has improved also remains an important question. This is particularly relevant in resource limited settings in view of the large cost difference between the Echinocandins & Fluconazole.

### 3) Serum Galactomannan Versus a Combination of Galactomannan and Polymerase Chain Reaction-Based Aspergillus DNA Detection for Early Therapy of Invasive Aspergillosis in High-Risk Hematological Patients: A Randomized Controlled Trial

José María Aguado

for the PCRAGA Study Group, the Spanish Stem Cell Transplantation Group, the Study Group of Medical Mycology of the Spanish Society of Clinical Microbiology and Infectious Diseases, and the Spanish Network for Research in Infectious Diseases

*Clin Infect Dis*. (2015) 60 (3): 405-414. doi: 10.1093/cid/ciu833

In an open-label, controlled, parallel-group randomized trial in 13 Spanish centers, adult patients with acute myeloid leukemia and myelodysplastic syndrome on induction therapy or allogeneic hematopoietic stem cell transplant recipients were randomized (1:1 ratio) to 1 of 2 arms: "GM-PCR group" (the results of serial serum GM and PCR assays were provided to treating physicians) and "GM group" (only the results of serum GM were informed). Positivity in either assay prompted thoracic computed tomography scan and initiation of antifungal therapy. No antimold prophylaxis was permitted. The cumulative incidence of "proven" or "probable" IA (primary study outcome) was lower in the GM-PCR group (4.2% vs 13.1%). By applying the combined strategy, there was reduction by 7 days in the median interval elapsed from the start of monitoring to the diagnosis of IA. (13 vs 20 days;  $P = .022$ ), as well as the use of empirical antifungal therapy (16.7% vs 29.0%;  $P = .038$ ). Patients in the GM-PCR group had higher proven or probable IA-free survival ( $P = .027$ ).

#### COMMENTS

This strategy seems to aid the early diagnosis of clinical IPA and may help resolve the suboptimal performance of serum galactomannan. The false positives due to generic piperacillin-tazobactam and false negative due to non-neutropenic status respectively could also be potentially corrected.

### 4) Determinants of Mortality in a Combined Cohort of 501 Patients With HIV-Associated Cryptococcal Meningitis: Implications for Improving Outcomes

Joseph N. Jarvis

*Clin Infect Dis*. (2014) 58 (5): 736-745. doi: 10.1093/cid/cit794

This is the largest study examining the factors determining the outcome in HIV-associated cryptococcal meningitis. 501 patients of HIV-associated cryptococcal meningitis from different geographical areas were prospectively followed for 10 weeks with patients from South Africa being further followed up to 1 year. The mortality was found to be 17% at 2 weeks and 34% at 10 weeks with majority of deaths beyond 2 weeks being due to other HIV-related causes. Altered mental status, high CSF fungal burden, older age, high peripheral WBC count, Fluconazole based induction treatment and slow clearance of CSF infection were independently associated with 2-week mortality. Low body weight, anemia and low CSF opening pressure were independent predictors of 10-week mortality in addition to the above factors. Large volume CSF drainage was found beneficial irrespective of opening CSF pressures. Mortality on 1 year follow up was 41%. Immune reconstitution inflammatory syndrome developing in 13% of the patients was found to be associated with 2-week CSF fungal burden and not with timing of initiation of ART which in this study was between 3-6 weeks after beginning antifungal therapy within which time neither the incidence of IRIS nor IRIS-related mortality increased.

#### COMMENTS

Cryptococcal meningitis is an important cause of morbidity and mortality in the HIV infected population. The problem is greater in certain parts of the world. The treatment choice is induction with Amphotericin B deoxycholate and 5-flucytosine which are frequently unavailable or difficult to use in many resource-limited settings. Alternative treatment with fluconazole based induction is clearly associated with slower fungicidal activity and increased mortality. Although raised

intracranial pressure has been associated with poor outcome in previous reports, this study showed that, if increased intracranial pressure is appropriately managed according to these guidelines, high CSF opening pressure was not associated with increased mortality.

### 5) FKS Mutant *Candida glabrata*: Risk Factors and Outcomes in Patients with Candidemia

Nicholas D. Beyda

Clin Infect Dis. (2014) 59(6): 819-825. doi: 10.1093/cid/ciu407

In this study done between 2009-2012, 72 patients were included and FKS1 and FKS2 genes were sequenced to identify mutations. FKS mutations were identified in 18 % (13 of 72 patients). Treatment failure occurred in 17 (30%) of 57 patients who received an echinocandin and was more common in patients with FKS mutants (6 of 10; 60%) compared with non-FKS mutants (11 of 47; 23%). Underlying gastrointestinal disorder and prior echinocandin exposure were independent predictors of echinocandin treatment failure. Treatment response and echinocandin minimum inhibitory concentrations varied among specific FKS mutations as all patients with prominent FKS mutations had higher MIC compared to only 1 of 5 with less prominent FKS mutation.

#### COMMENTS

The rise in azole resistance has prompted increasing use of echinocandins. However resistance to echinocandins is clearly emerging and may seriously compromise their use and increase the already high attributable mortality of *Candida* BSI.

### 6) T2 Magnetic Resonance Assay for the Rapid Diagnosis of Candidemia in Whole Blood: A Clinical Trial

Eleftherios Mylonakis

Clin Infect Dis. (2015) 60(6): 892-899. doi: 10.1093/cid/ciu959

In the first extensive multicenter clinical trial of a new nanodiagnostic approach, T2 magnetic resonance (T2MR), for diagnosis of candidemia demonstrated an overall specificity per assay of 98.9 to 99.9% for various *Candida* species. The overall sensitivity was found to be 91.1% with a mean time of  $4.4 \pm 1.0$  hours for detection and species identification. The limit of detection was 1 CFU/mL for *C. tropicalis* and *C. krusei*, 2 CFU/mL for *C. albicans* and *C. glabrata*, and 3 CFU/mL for *C. parapsilosis*. The negative predictive value was estimated to range from 99.5% to 99.0% in a study population with 5% and 10% prevalence of candidemia, respectively.

#### COMMENTS

Diagnosis of candidemia has always been difficult and is highly consequential to the patient. T2MR may herald a new paradigm in the molecular diagnosis of candidemia because it has: 1) high sensitivity; 2) short time to species identification; 3) lower limit of detection as low as 1 cfu/mL which is particularly useful for candidemia coming from the GI tract, in patients on antifungal agents and for *C. glabrata*. There is also the advantage of the test being done directly from a clinical sample & not requiring culture and sample purification.

### 7) Epidemiology and Outcome of Fungemia in a Cancer Cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of Cancer (EORTC65031)

Oliver A. Cornely on behalf of the EORTC Infectious Diseases Group

Clin Infect Dis. (2015) doi: 10.1093/cid/civ293

In this prospective cohort study including 145 030 admissions of patients with cancer from 13 EORTC centers, incidence, clinical characteristics, and outcome of fungemia were analyzed. Fungemia including polymicrobial infection was due to: *Candida* spp. in 267 (90%), *C. albicans* in 128 (48%), and other *Candida* spp. in 145 (54%) patients. Favorable overall response was achieved in 113 (46.5%) patients by week 2. After 4 weeks, the survival rate was 64% (95% CI, 59%–70%) and was not significantly different between *Candida* spp. Multivariable logistic regression showed baseline septic shock and tachypnoea as poor prognostic factors whereas antifungal prophylaxis prior to fungemia and remission of underlying cancer were protective.

#### COMMENTS

This study puts Candidemia in hematopoietic stem cell transplantation in perspective and informs about the low incidence, although the consequence is significant. It underscores the importance of antifungal prophylaxis and remission of underlying cancer.

### 8) Application of the 2008 Definitions for Invasive Fungal Diseases to the Trial Comparing Voriconazole Versus Amphotericin B for Therapy of Invasive Aspergillosis: A Collaborative Study of the Mycoses Study Group (MSG 05) and the European Organization for Research and Treatment of Cancer Infectious Diseases Group

Raoul Herbrecht

Clin Infect Dis. (2015) 60(5): 713-720. doi: 10.1093/cid/ciu911

In this study 379 episodes of invasive aspergillosis (IA) as per GCAS were re categorized using the EORTC/MSG criteria. In addition baseline serum galactomannan levels were obtained from 249 (65.7%) of those episodes; from frozen sections. On following these patients the 12 weeks response rate was found to be higher with voriconazole (54.7%) compared with Amphotericin B (29.9%). The higher response rates with voriconazole were found to be comparable between possible IA and mycologically documented IA.

#### COMMENTS

This study shows that a reappraisal of older studies using modern methods also yields important information. Re categorization resulted in a demonstration of higher efficacy of voriconazole versus Amphotericin B deoxycholate. Voriconazole has been compared to a more toxic alternative which is no longer a favored preparation. Since liposomal Ampho B was not used, the uncertainty about the best drug for IA remains.

### 9) Incidence, characteristics and outcome of ICU-acquired candidemia in India

Arunaloke Chakrabarti

Intensive Care Med (2015) 41:285–295 DOI 10.1007/s00134-014-3603-2

In this prospective, multicentric, observational study at 27 medical and surgical ICUs across India, all consecutive patients who contracted ICU-acquired candidemia were enrolled. A total of 398 variables were recorded for every patient in standardized proforma. The overall incidence of candidemia was 6.51 cases per 1,000 ICU admissions, though the incidence varied significantly across the country. The adult candidemia patients were considerably younger (mean 49.7 years); contracted ICU-acquired candidemia significantly earlier (8 days) and had lower mean APACHE II scores (17.2) as compared to most other similar series. This study revealed high prevalence of *C. tropicalis* (41.6 %) while *C. albicans* and *C. parapsilosis* affected only 20.9 and 10.9 % of cases, respectively. We encountered *C. glabrata* candidemia in only 7.1 % of patients. Overall, 46.6 % of isolates were susceptible to all antifungals. Species-specific resistance rates against fluconazole ranged from 1.5 % in *C. glabrata* to 5.2% in *C. albicans*. 30-day crude mortality (44.7 %) is similar to the EPIC II international series (42.6 %).

#### COMMENTS

This is a landmark multicentric study combining data from all corners of a vast country like India. It highlights the wide spectrum of *Candida* species and the high rate of *C. tropicalis* infection. There were important differences among regions & also among public and private sector hospitals. In this study infections occurred rather early in the ICU stay and at relatively lower APACHE scores, thus highlighting the need for more stringent infection control measures. Azole and multidrug resistance are important issues which highlight the need for cultures and susceptibility tests and potentially impact the empiric choices of antifungal agents.

### 10) Evaluation of an early step-down strategy from intravenous anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial

Jose Vazquez

BMC Infectious Diseases 2014, 14:97

This open-label, non-comparative study evaluated an intravenous (IV) to oral step-down strategy. Patients with Candidemia/Invasive candidiasis(C/IC) were treated with IV anidulafungin and after 5 days of IV therapy had the option to step-down to oral azole therapy (fluconazole or voriconazole) if they met prespecified criteria. In total, 282 patients were enrolled, of whom 250 were included in the MITT population. Sixty percent (60%) of patients enrolled in this study underwent early step-down (by Day 7) to either fluconazole or voriconazole. In general, patients in the early switch subpopulation had global response rates that were higher than the modified-intention-to-treat population at all time points. Median time to negative blood culture for all patients was two days (with Day 1 being the first dose of study drug), and approximately 90% of patients achieved a negative blood culture by Day 5.

#### COMMENTS

Critically ill patients with candidemia are conventionally treated with an echinocandin and transitioned down later to fluconazole. Advice about the precise time point when this IV to oral switch should be done varies. IDSA recommends as early as possible once the patient is stable and blood cultures have become negative. ESCMID recommends the switch after 10 days if the patient is stable and tolerates oral therapy. The oral switch is less likely possible after recent GI surgery where there is concern about per oral absorption. In this study blood culture clearance occurred after 2 days and IV to oral switch was carried out at 5 days. The global response rates were similar in the early switch population as compared to late switch with the advantage of convenience, shorter length of ICU stay and potential cost saving.



## 11) Evaluation of Fingerstick Cryptococcal Antigen Lateral Flow Assay in HIV-Infected Persons: A Diagnostic Accuracy Study

Darlisha A. Williams

Clin Infect Dis. (2015) doi: 10.1093/cid/civ263

In this study done in HIV infected adults with suspected meningitis in Uganda, CRAG LFA (IMMY, Norman, Oklahoma) tests were performed on fingerstick whole blood, plasma/serum, and CSF. Venous blood was also collected and centrifuged to obtain serum and/or plasma. CSF was tested after lumbar puncture. Of 207 participants, 149 (72%) had fingerstick CRAG-positive results. The positive results from fingerstick whole blood were in concordance with serum/plasma CRAG in all patients and 138 (93%) with a positive CSF CRAG. No persons with cryptococcal meningitis had negative fingersticks.

### COMMENTS

This test has the potential to greatly simplify the diagnosis of cryptococcal meningitis and prompt the clinician to take appropriate diagnostic and therapeutic measures.

## 12) A Breath Fungal Secondary Metabolite Signature to Diagnose Invasive Aspergillosis

Sophia Koo

Clin Infect Dis. (2014) 59(12): 1733-1740. doi: 10.1093/cid/ciu725

Using thermal desorption-gas chromatography/mass spectrometry, the in vitro volatile metabolite profile of *Aspergillus fumigatus*, the most common cause of IA, and other pathogenic aspergilli were characterized by prospectively collecting breath samples from patients with suspected invasive fungal pneumonia from 2011 to 2013, and assessing whether patients with proven or probable IA could be differentiated from patients without aspergillosis. The monoterpenes camphene,  $\alpha$ - and  $\beta$ -pinene, and limonene, and the sesquiterpene compounds  $\alpha$ - and  $\beta$ -trans-bergamotene were distinctive volatile metabolites of *A. fumigatus* in vitro, distinguishing it from other pathogenic aspergilli. Detection of  $\alpha$ -trans-bergamotene,  $\beta$ -trans-bergamotene, a  $\beta$ -vatirenene-like sesquiterpene, or trans-geranylacetone identified IA patients with 94% sensitivity and 93% specificity.

### COMMENTS

Current diagnostic methods for IPA viz. radiological and galactomannan fall short due to less specificity and sensitivity. Invasive methods such as biopsy are difficult due to the hematological & physiological condition of the patient. Hence a simple non-invasive test is welcome. The host-*Aspergillus* interaction appears to activate secondary metabolites clusters which are not required for primary growth and require substantial diversion of resources. These metabolites have a role in intra-species communication, deterring competing microorganisms and contributing to the survival of the organism. The findings in the study provide proof of concept but additional work is needed to identify secondary metabolite signatures of other *Aspergillus* species, Mucorales, & additionally quantify the fungal burden and assess response to treatment.

## PICTORIAL QUIZ

**Dr Arunaloke Chakrabarti**

**Head, Department of Medical Microbiology**

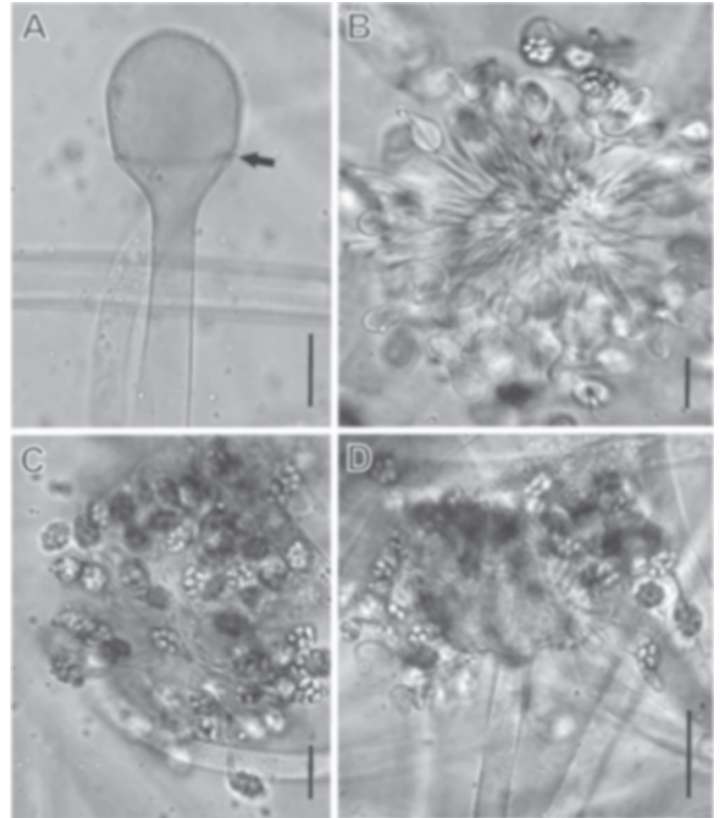
Post Graduate Institute of Medical Education and Research  
Chandigarh

A 57-year-old woman presented with a week's history of swelling and loss of vision in the right eye and right-sided nasal obstruction. She had a history of fever, vomiting, and itching in the right eye, with intermittent episodes of altered sensorium. She had poorly controlled diabetes mellitus for the previous 8 years and hypertension for 5 years. A contrast-enhanced computed tomographic (CT) scan of her brain and orbit showed bilateral polypoidal opacification of the maxillary, sphenoid, and ethmoid sinuses together with involvement of the cavernous sinus.

**Mycology findings:** Direct examination of a portion of the nasal crust in a KOH mount showed hyaline, coenocytic hyphae 4.0 to 7.0  $\mu$ m in diameter. Culture on SDA with and without chloramphenicol at 25°C, 37°C, and 40°C in the dark, after 48 h of incubation grew white, cottony mycelia which turned olive brown over the next 2 to 3 days.

**Outcome:** She was started on an intravenous infusion of conventional amphotericin B deoxycholate at 50mg/day. Although surgical debridement and biopsy for histopathological study was planned, it could not be undertaken in view of the rapidly deteriorating condition of the patient. On the 10th day of hospitalization, the patient died due to cardiac arrest following multiorgan failure.

Microscopic appearance of the fungus isolated is given in the photograph. Identify the fungi.



Immaculata Xess et al. J Clin Microbiol. 2012;50:1491-4.

Answer:

*Thamnostyllum lucknowense*