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## SELECTED MYCOLOGY PAPERS 2025

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### Pulmonary Coinfection of *Pneumocystis jirovecii* and Aspergillus Species

Stefan Hatzl et al. Open Forum Infectious Diseases, 2025 Jan 13;12(2): ofaf018.

This was a multicentre, retrospective observational study done in Austria from 2014 to 2024 which included 387 immunocompromised patients. In this cohort, 202 patients had IPA and 185 patients had PJP. In the cohort of the 202 patients with IPA, 4.5% also had *Pneumocystis jirovecii pneumonia* (PJP). Predictors of coinfection included elevated β-D-glucan and prolonged corticosteroid use. Coinfection correlated with reduced 30-day survival (22% vs 57%), suggesting that early identification and prophylaxis may improve outcomes.

#### Comments

This multicenter retrospective study highlights that IPA-PCP coinfection, though uncommon, does occur in patients on prolonged corticosteroids without prophylaxis and is associated with poorer outcomes. The authors suggest that very high BDG levels can predict co-infection, but since only nine co infected cases were identified, the analysis has its limitations and makes the proposed cutoff of 834 pg/ml unreliable. It is also possible that patients with higher BDG were more likely to be tested for PCP, which could explain the association. Prolonged corticosteroid exposure was the strongest and most consistent risk factor. This article highlights the clinical scenario that IPA patients on steroids without prophylaxis are at risk for PCP as well, and need high index of suspicion for early evaluation with imaging, BAL, and PCR.

### Rapid Differentiation of False Positives of Galactomannan Related to Contaminated Intravenous Fluids via a Pharmacokinetics Model and Innovative Web-Based Tool

Raeseok Lee et al. Open Forum Infectious Diseases, 2025 Apr 3;12(4):ofaf088.

Serum GM is an important criterion for diagnosis of IA in neutropenic patients. Unfortunately, there can be false positive results due to use of IV fluids which have been contaminated during production (similar to antibiotics such has piperacillin tazobactam). This study developed a pharmacokinetic and web-based tool to distinguish true GM positivity from false positivity caused by contaminated intravenous fluids. They enrolled a case group (9) which had false positive GM and compared them with controls (30 with proven / probable IPA) who had true positive GM. GM index in cases was measured at 0 (pretest), 24, and 48 hours after discontinuing contaminated fluids. The false-positive group had a higher initial GM index (median, 2.6) as compared with the true IA group (median, 1.6). Following the discontinuation of contaminated fluids, GM index levels rapidly decreased in the false-positive group but significantly increased in the true IA group ($P < .05$). The model predicted that in the false positive group, for an initial GM index of 3.0, levels would typically become negative (GM index <0.5) within a median of 2.3 days (95% CI, 1.51–3.8 days), with an estimated half-life of 23.6 hours (95% CI, 12.2–43.4 hours), indicating complete clearance within approximately 4.8 days. Simulations suggested that most false positives can be confirmed within 18 hours of stopping exposure, though lower initial GM indices require longer monitoring

#### Comments

Contaminated dextrose containing IV fluids adds to the long list of products that can lead to false positive GM including beta lactam antibiotics, blood products, total parenteral nutrition etc. This is an important issue in resource limited settings where poor quality control during the manufacturing process may lead to mold contamination. However, there are practical issues in using this tool to identify false positive GM including the cost of repeating GM and whether it will be possible to stop IV fluids in sick neutropenic patients, and whether the substituted fluid will be free from contamination. Additionally, physicians should be careful and use IV fluids from reputed manufacturers and avoid using dextrose containing fluids if possible.

### Management, Outcomes, and Predictors of Mortality of Cryptococcus Infection in Patients Without HIV: A Multicenter Study in 46 Hospitals in Australia and New Zealand

Julien Coussement et al. Clin Infect Dis.2025 Apr 30;80(4):817-825.

A retrospective study in 46 Australian and New Zealand hospitals was conducted to determine the outcomes of cryptococcosis in patients without HIV diagnosed between 2015 and 2019 and compared outcomes of *C. gattii* versus *C. neoformans* infections. Of 426 patients, 1-year all-cause mortality was 21%. *Cryptococcus gattii* infection was associated with a lower mortality than with

## Message from the Editor

Dear Friends,

A very warm welcome to the delegates of the 15th Annual Conference of the Clinical Infectious Diseases Society of India at Mumbai, India from the Fungal Infection Study Forum (FISF). FISF and CIDS are deeply interlinked societies and share many office bearers. In fact, you will be listening to many FISF board members during the conference.

Invasive fungal infections pose a formidable challenge in day to day clinical practice. The aim of FISF and this newsletter is to educate physicians about managing invasive fungal infections. We begin with a commentary on important mycology papers of 2025. This is followed by interesting cases of IFI. The first case is a case of intrabdominal sepsis due to *Saccharomyces cerevisiae* which highlights the dangers of unrestricted use of probiotics. This is followed by a case of mucormycosis and actinomycosis coinfection the only risk factor of which was COVID-19 and steroid use 4 years ago. Then there is a case of dual infection with Candida and Aspergillus where the problem of drug interactions of azoles is highlighted. This is followed by a case of invasive pulmonary aspergillosis in a severely neutropenic host when steroids had to be used. Finally, we finish with a case of advanced HIV infection where the need to screen for cryptococcal antigenemia is highlighted.

We encourage you to visit the FISF website **www.fisftrust.org** to access previous newsletters and other educational resources.

Wishing you an academically enriching time at the conference.

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*C. neoformans* (OR 0.47 (95% CI 0.23-0.95). Severe neurological symptoms at presentation was the strongest predictor of death (OR 8.46). Among patients with CNS cryptococcosis, *C. gattii* infection was associated with a higher risk of immune reconstitution inflammatory response (C-IRIS) than *C. neoformans* (21% versus 3%, P < .001). Serum cryptococcal antigen positivity and lung imaging abnormalities resolved slowly (resolution at 1 year in 25% and 34% of patients, respectively).

**Comments**

Severe neurological impairment as a poor prognostic marker of cryptococcal disease is well described in previous literature in HIV positive patients, hence similar correlation in HIV negative patients is understandable. There is limited Indian literature regarding *Cryptococcus gattii* infection hence occurrence of IRIS more prominently with *C. gattii vs C. neoformans* infection found in this study may be important to alert the clinicians to suspect cryptococcal IRIS and manage it appropriately.

**Sensitivity and Specificity of Plasma and Bronchoalveolar Lavage Fluid PCR for Diagnosing Pulmonary Mucormycosis in Subjects with Diabetes Mellitus**

Rana Sadaqat Nawaz et al. Mycoses, 2025 Apr;68(4):e70063

This study prospectively enrolled diabetic patients with suspected Invasive Mucor Disease (IMD) and assessed the performance of Mucor Genius PCR (index test) in plasma and BAL Fluid samples. The final diagnosis of IMD was based on microscopy, histopathology, cytology, and culture. A total of 103 patients were enrolled, of whom 43 (41.7%) were confirmed to have proven/probable pulmonary mucormycosis (PM). Plasma PCR showed a sensitivity of 18.6%, specificity of 90.7%, positive predictive value (PPV) of 66.7%, and negative predictive value (NPV) of 52.7%. With possible PM/IMD cases there was improved plasma PCR sensitivity to 30.0% and retained specificity at 90.7%. BAL Fluid PCR had better sensitivity (47.4%) but poorer specificity (69.6%), with a PPV of 56.3% and NPV of 61.5%. Plasma and BALF MucorGenius PCR had poor diagnostic performance for diagnosing PM among individuals with diabetes mellitus.

**Comments**

This prospective study assessing the utility of MucorGenius PCR in proven/probable mucormycosis patients demonstrates only 18.6% sensitivity in plasma and 47.4% in BAL fluid. These results differ from those of the systematic review which reported a sensitivity of 97.5 % in BAL and 81% in plasma (Brown L, Tschiderer L, Alanio A, et al. The diagnosis of mucormycosis by PCR in patients at risk: a systematic review and meta-analysis. *EClinicalMedicine*. 2025;81:103115). A higher sensitivity of plasma PCR would have been very useful to have a quick and non-invasive way to diagnose pulmonary mucormycosis a condition which is often missed. It is possible that the lack of immunocompromise leads to lower organism burden and lower tendency to invade the blood vessels and hence lower sensitivity. Other issues which need elucidation are need for repeat testing, performance of in-house versus commercial PCR platforms, false positives due to other infections like TB, IPA and false negatives if treatment has been started.

**Optimizing use of the (1-3)-β-D-glucan assay for the diagnosis of Pneumocystis jirovecii pneumonia**

Todd C. Lee et al. ScienceDirect, CMI Communications 2 (2025) 105061

The diagnosis of PCP is challenging, especially outside the HIV cohort, due to nonspecific clinical/radiological features, difficulty in performing invasive tests and limitations of current tests. Fungitell serum (1-3)-β-D-glucan (BDG) is a promising non-invasive tool but has moderate sensitivity and specificity, and needs to be interpreted correctly in individual clinical contexts. Lee at al propose combining their previously developed PCP clinical prediction score with BDG cutoffs (80pg/ml for ruling out PCP, >=400 pg/ml for ruling in) for guiding diagnosis. They also devised "Leaf plots" matching PCP scores with BDG post-test probabilities, which were stratified by HIV status. They found that in low-score patients, a negative BDG effectively excluded PCP, with NPV >=95%. This included HIV cohort score <=4 and Non-HIV cohort with PCP score <=3. In the high score patients (HIV+ with score >=5.5, and non-HIV score >=6.5) a BDG >=400 strongly supported diagnosis of PCP

In patients where the posttest probabilities are in the intermediate range (due to mid scores or intermediate ranges of BDG) further testing with bronchoscopy, PCP PCR would be needed for diagnosis.

**Comments**

The issues with the Lee model is that other risk factors apart from HIV and SOT which are increasingly encountered in clinical practice are not considered, there can be many other confounders that can influence scoring (radiology) and also BDG values. Besides, a large number of patients will actually fall in the gray zone where the predictive values obtained by the model will not be able to either rule in or rule out PCP.

Soman et al (Soman R, Singhal T, Rodrigues C, Joe G. Refining scores for non-invasive diagnosis of PCP. CMI Communications. 2025 Jun 19:105096.) illustrate this with the example of patient on methotrexate who had multiple radiology confounders: possible autoimmune lung disease, possible methotrexate toxicity, and abnormal labs (confounding LDH and BDG) generating a posttest probability of 20% with which PCP could not be reliably ruled out. They had to perform bronchoscopy with PCR to definitively exclude PCP for their patient.

## COMPLICATED INTRA-ABDOMINAL INFECTION DUE TO *SACCHAROMYCES CEREVISIAE*

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**Introduction**

Rare yeast infections are challenging to manage difficulties in owing in identification, absence of susceptibility breakpoints and treatment guidelines.

**Case Report**

We present case of a 34-year-old male with overlap connective tissue disorder who was on follow-up with rheumatologist. His anti-nuclear antibodies (ANA) titre by immunofluorescence was positive (1:3200). ANA blot assay showed positivity for anti-SM, RNP and Ro-52. He was being managed with daily oral methyl prednisolone 4 mg, naproxen 250 mg, hydroxychloroquine 300 mg, methotrexate 10 mg twice per week. He had also received tofacitinib for 3 months earlier.

He presented with a week-long history of fever and severe abdominal pain limited to right iliac fossa. A computed tomography scan (CT) of abdomen revealed oedematous wall thickening of ileocecal region with a well-defined

peripherally enhancing collection with air foci along the medial aspect of ascending colon and loss of adjoining fat planes (Figure 1). Rectally administered contrast was seen to leak into the collection. Overall CT features were suggestive of contained perforation of ascending colon likely secondary to diverticulitis.

He underwent exploratory laparotomy and found to have perforated cecum, localised peritonitis, thickened mesentery with a loculated abscess in retrocecal region; which was drained and an aspirate from abscess was sent for culture. Right hemicolectomy was done and end-ileostomy was created. Medical part of his management included supportive care along with reduction of his immune suppression. The pus aspirate grew extended-spectrum- Beta-Lactamase (ESBL) producing *Escherichia coli* and non ESBL producing *Klebsiella pneumoniae*. His treatment with meropenem was continued for total 10 days and then patient was discharged.

He was readmitted three weeks later with fever of 3-4 days, fatigue and abdominal pain. A follow-up CT scan of abdomen showed no collection but fat stranding in the operated area. A fungal culture of previously sent pus aspirate culture was now available. *Saccharomyces cerevisiae* had grown on Sabouraud's dextrose agar and Potato dextrose agar after three weeks of incubation. The growth showed smooth creamy white colonies. Gram Stain showed budding yeast cells (Figure 2).

Species identification was done on Buker biotyper Sirius using MALDI-ToF MS (Matrix Assisted Laser Desorption/ionization Time-of-Flight Mass spectrometry) with a MALDI score of 1.72. Antifungal drug susceptibility was done using Sensititre YeastOne (ThermoFisher Scientific). The yeast showed low minimum inhibitory concentrations (MIC) against amphotericin B (0.25 µg/ml), all echinocandins, 5-flucytosine and most azoles (voriconazole 0.128µg/ml), except fluconazole for which, MIC was 8µg/ml (Figure 3). The interpretation of these MICs was mentioned as insufficient evidence (IE) in our lab report as no clinical breakpoints for susceptibility are available for *S. cerevisiae*.

Patient was asked about history of consumption of probiotics in recent months. He gave history of probiotic sachets (Sporit GG) taken for 6 days; which was prescribed to him by local gastroenterologist for abdominal pains 2 weeks before his surgery. The sachets contained *Saccharomyces boulardii* and *Lactobacillus rhamnosus* GG granules.

He was treated with liposomal amphotericin B at 5 mg/kg for one week followed by two weeks of intravenous voriconazole. The treatment was complicated by a brief period of subacute intestinal obstruction which was managed conservatively. Voriconazole administration led to transient neuropsychiatric adverse reaction with predominant depression, irritability and emotional lability which settled down after its discontinuation. Patient ultimately made a successful recovery from the complicated intra-abdominal infection caused by *Saccharomyces cerevisiae*.

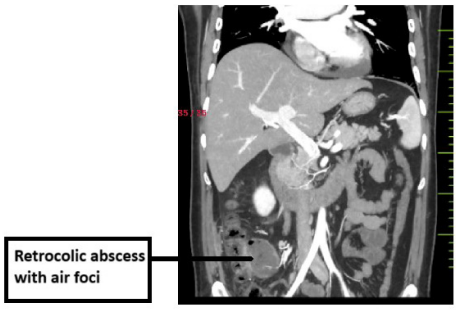


**Figure 1: CT scan findings**

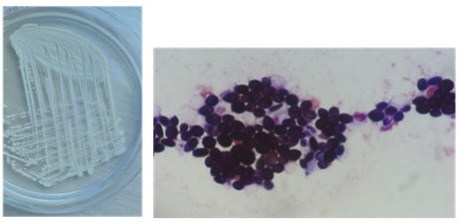

**Figure 2: Growth of *Saccharomyces cerevisiae* on Sabouraud's dextrose agar (SDA) and Gram stain showing oval budding yeast cells**

## Discussion

*Saccharomyces cerevisiae*, also known as the "Baker's cyst" or "Brewer's yeast", is an environmental fungus. It is commonly used in food industry for fermentation. The fungus is widely found in nature in fruits, soil, tree barks, wood etc. Its subtype *Saccharomyces cerevisiae var. boulardii* is often used as a probiotic because of its diarrhoea reducing properties. The organism is sturdy and is able to grow under aerobic and anaerobic conditions. It can survive high temperatures and acidic environments.

Human infections with *S. cerevisiae* were rare but now being increasingly recognised as cause of invasive fungal infections.[1] Most proven cases of invasive *S. cerevisiae* infection are diagnosed by growth in blood culture; only a minority of cases have conclusive evidence of end-organ involvement;1 such as an intra-abdominal abscess in our case. There have been several case reports of *Saccharomyces cerevisiae* fungemia with high mortality, which cite risk factors such as immune compromised status, admission in intensive care unit (ICU) and presence of central venous catheters (CVC).[2] The rise in incidence may be due to increasing demand and consumption of fermented beverages, food and probiotics. The yeast can occur as colonizer of skin, mucosa, gastrointestinal tract and vagina. It can lead to invasive disease in event of lowering of host immunity, placement of invasive devices or breach in epithelia/mucosal barrier, as happened in this case due to diverticular perforation.

The organism occurs as an oval budding yeast that forms smooth creamy colonies resembling candida. Its identification in the laboratory using conventional phenotypic and biochemical tests is difficult. MALDI-TOF Ms analyses unique ribosomal protein profiles giving rapid and correct identification of S cerevisiae and other non -candida yeasts. MALDI cannot identify Saccharomyces cerevisiae subspecies. We suspect that our patient has *Saccharomyces cerevisiae var. boulardii* infection based upon his history. For sub speciation, genomic sequencing is needed; which we have planned. For the *S. cerevisiae* species, there are no clinical breakpoints established by scientific societies. For amphotericin B and itraconazole, EUCAST (European Committee for Antimicrobial Susceptibility Testing) has set epidemiological cutoff values (ECOFFs) of 0.5 mg/L and 2 mg/L, respectively.[3,4]

Due to rarity of this infection, there is no standardized treatment leading to heterogeneity in management. Global guideline for the diagnosis and management of rare yeast infections recommends liposomal amphotericin B or amphotericin B deoxycholate as first-line therapy and fluconazole or an echinocandin as an alternative.[5] The management of fungemia due to S. cerevisiae draws parallel to management of *Candida* blood stream infection with ensuring removal of CVC, follow up blood cultures and ruling out metastatic foci of infection. Duration of treatment is variable and individualized

**Antifungal susceptibility by BMD Panel**

**Specimen:** Pus aspirate

**Organisms isolated:**
Sacchromyces cerevisiae

| Antifungal agent (MIC) | Interpretation |
|---|---|
| Anidulafungin (0.06 ug/ml) | IE |
| Micafungin (0.12 ug/ml) | IE |
| Caspofungin (0.12 ug/ml) | IE |
| Amophotericin B (0.25 ug/ml) | IE |
| 5-Flucytosine (<0.06 ug/ml) | IE |
| Posaconazole (0.5 ug/ml) | IE |
| Voriconazole (0.12 ug/ml) | IE |
| Itraconazole (0.5 ug/ml) | IE |
| Fluconazole (8 ug/ml) | IE |

**Note:**
*DST done by Broth Micro Dilution : Sensititre - Yeast One Thermo Fisher Scientific. *Clinical breakpoints not established due to Insufficient Evidence (IE)

**Figure 3: *Saccharomyces cerevisiae* susceptibility profile**

in most cases but is similar to duration of treatment of candidemia. The MIC obtained for voriconazole in our patient and other studies made voriconazole an effective alternative to amphotericin B.[2,6]

One avenue of prevention of *S. cerevisiae* infection is by avoiding use of probiotics in immune compromised patients or hospitalised elderly patients. In 2017, the European Medicines Agency reinforced a warning the *S. boulardii* containing probiotics should not be administered to critically ill or immune compromised persons.[2]

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## MUCOR INDUCTS A BYSTANDER INTO CRIME


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### Case Report

A 63-year-old male farmer with diabetes mellitus had COVID19 in 2020. He was admitted in ICU and was treated with steroids. He was alright till June 2025 when he noticed a non-healing ulcer over his hard palate (Figure 1). His diabetic control was good.

This was associated with nasal regurgitation of liquid during swallowing. He also complained of intermittent holocranial headache. CT PNS (Figures 2,3) showed an oro-nasal fistula with bony erosions in hard palate. There was an irregular soft tissue area along the floor of the left nasal cavity as well.

The patient underwent Functional endoscopic nasal sinus surgery (FESS) (Figure 4) which confirmed the radiological findings.

KOH and calcofluor stains as well as bacterial and fungal culture were negative. However, histopathology (Figure 5) of the tissue and bone from nasal floor and palate revealed bone invasion by pauci-septate, broad fungal hyphae. These showed right-angled branching and irregular, basophilic walls. PAS and GMS stains were positive on the same, suggesting mucormycosis. In addition, granule-like structures and basophilic colonies were observed. These stained positive with PAS and GMS, negative for 20% and 1% ZN stains, with branching, delicate filaments and a radiating architecture. Focal areas demonstrated the Splendore–Hoeppli phenomenon suggestive of actinomyces (Figure 6).

The patient was put on oral posaconazole and oral ampicillin with which he is doing well and has completed 3 months of follow up.

### Discussion

The clinical differential diagnosis in this case would have been infections like mucormycosis, aspergillosis, actinomycosis, leishmaniasis; inflammatory conditions like granulomatosis with polyangiitis; malignant conditions like NK cell lymphoma. Since this case was referred for infectious diseases opinion after the procedure & histopathology reports, the diagnosis had been made and confirmed. This patient had no other risk factors for mucormycosis apart from the COVID-19 infection 5 years ago. His diabetes was well controlled. While it seems odd that COVID-19 such a long time ago would predispose to mucormycosis, the author has seen other such cases at his institution where MM has presented years after COVID-19. Cases of mucormycosis and actinomycosis coinfection in the COVID-19 setting and otherwise have been previously reported.[1-4]

The likely scenario could be as follows: Mucorales likely initiated the breach in the mucosal barrier and actinomyces, a usual commensal of the oral cavity, gained entry into the tissue. Apart from this, it appears that one organism does not create a conducive metabolic environment favoring the other. Both infections are opportunistic and can affect individuals with weakened immune systems or underlying conditions like diabetes. The clinical behavior of both organisms shows transgression of tissue planes along with destruction and perforation. This overlap in clinical manifestations necessitates suspicion and adequate tests for both these organisms. Anaerobic cultures for actinomyces, avoiding grinding of tissue before culture for mucorales along with careful histopathology and special staining are necessary to diagnose these infections. Finding evidence of tissue invasion and of surrounding reaction as shown in

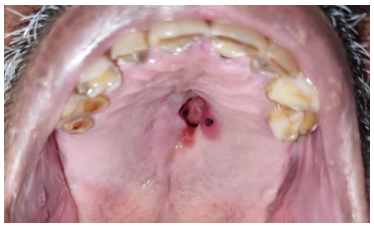
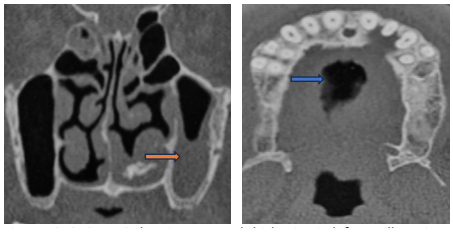


**Figure 1: Intra-oral view of hard palate with midline ulcer to the left of the midline.**



**Figures 2, 3: CT PNS showing mucosal thickening in left maxillary sinus (orange arrow) and oro-nasal fistula with bony erosions in hard palate (blue arrow).**

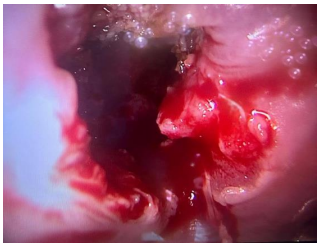


**Figure 4: FESS image of the oro-nasal fistula**

**Figure 5: Green arrow: broad, aseptate fungal hyphae of mucoralean mould**

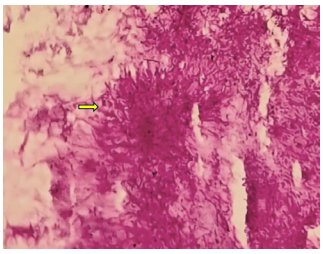


**Figure 6: Yellow arrow: Granule-like structure with branching, delicate filaments and radiating architecture of actinomyces**

Figures 5,6 has a special place in diagnosis and planning treatment. Appropriate treatment may include an azole such as posaconazole or isavuconazole for mucorales and amoxycillin or doxycycline for actinomyces.

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## MANAGEMENT OF DUAL INVASIVE FUNGAL INFECTION AND PLEURAL EFFUSION IN A PATIENT WITH RELAPSED B-ALL ON PONATINIB


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### Introduction

This case illustrates the problems of drug interactions while using azole antifungals.[1]

### Case Report

A 31-year-old male from Delhi NCR with a diagnosis of acute lymphoblastic leukemia (B-ALL), relapsed during maintenance therapy with dasatinib and was awaiting allogeneic hematopoietic stem cell transplantation (HSCT). Post-relapse chemotherapy involved mini Hyper-CVAD protocol (Course A), and the patient was initiated on ponatinib 45 mg OD due to high-risk Philadelphia chromosome-positive disease.

The patient was first admitted on May 20, 2021, with febrile neutropenia (TLC: 2270/µl, platelets 1,95,000/µl). Despite broad-spectrum antibiotics (meropenem, amikacin), fever persisted. Chest X-ray revealed a right-sided moderate pleural effusion (exudative, 3.5 cm). A course of empirical caspofungin was initiated for 14 days, leading to some improvement.

On June 14, 2021, the patient was readmitted with persistent fever and increased right-sided pleural effusion (Figure 1). A high-resolution CT scan on June 15, 2021 (Figure 2), demonstrated right side pleural effusion with lower lobe fibro-parenchymal changes with left upper lobe nodular infiltrates. Also present was left minimal pleural effusion with nodular pleural thickening. Serum galactomannan was 4.11 (grossly elevated). The pleural fluid analysis confirmed *Candida dubliniensis* susceptible to fluconazole, voriconazole, and amphotericin B. A diagnosis of candida empyema was made. In addition, probable invasive aspergillosis was considered due to elevated galactomannan levels. *Mycobacterium tuberculosis* was not detected in the pleural fluid. Despite therapy with liposomal amphotericin B (L-AMB), meropenem, and amikacin, fever persisted. Therefore, treatment was switched to voriconazole, with a simultaneous reduction of ponatinib from 45 mg to 30 mg daily to mitigate drug-drug interaction via CYP3A4 inhibition by voriconazole. The patient became afebrile and was discharged in stable condition.

Approximately 10 days' post-discharge, the patient returned with breathlessness, without fever. A chest X-ray demonstrated an increase in right-sided pleural effusion (Figure 4). At this time, the patient was on voriconazole. The question arose whether the effusion was related to candida empyema, aspergillus, or a side effect of ponatinib, particularly since pleural effusion is a known but less common side effect of ponatinib, occurring in 3-19% of cases. Laboratory findings included Hb 10 gm/dl, TLC 3330/µl, Platelet 231,000/µl, ESR 52 mm/hr, CRP 155 mg/l

### Discussion

The management of this patient raised significant concerns regarding drug-drug interactions, particularly between ponatinib and various antifungal agents:[2]

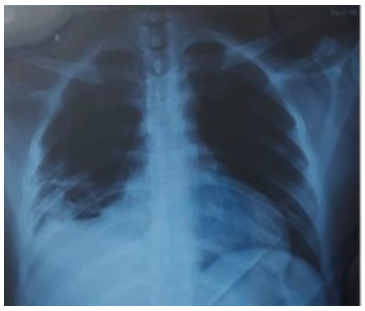

**Figure 1 : Right-side pleural effusion**

**Figure 2 : 15 June 2021 HRCT chest suggestive of right moderate pleural effusion with right lung lower lobe basal segment fibro parenchymal changes, left upper lobe nodular infiltrates, and left minimal pleural effusion with nodular pleural thickening.**

**Table 1: Azole interactions with CYP enzymes**

| Azole | CYP2C19 Metabolism | CYP2C9 Metabolism | CYP3A4 Metabolism | CYP2C19 Inhibition | CYP2C9 Inhibition | CYP3A4 Inhibition |
|---|---|---|---|---|---|---|
| Voriconazole | +++ | +++ | + | ++ | ++ | +++ |
| Posaconazole | - | - | - | - | - | +++ |
| Isavuconazole | - | - | ++ | - | - | ++ |

Test Name :BACTEC CULTURE-C/443 Specimen : PLEURAL FLUID

Clinical Interpretation if any : NO GROWTH AFTER 48 HOURS OF AEROBIC INCUBATION

Organisms Isolated : 1 . Candida dubliniensis

Clinical Interpretation if any : NO GROWTH AFTER 48 HOURS OF AEROBIC INCUBATION 2nd subculture

ANTIBIOTIC SENSITIVITY REPORT

| Antibiotic | Organism1 | |
|---|---|---|
| AMPHOTERICIN B | S | <=0.25 |
| FLUCONAZOLE | S | 1.0 |
| FLUCYTOSINE | S | <=1 |
| VORICONAZOLE | S | <=0.12 |

R - Resistant S - Sentitive MS - Moderate Sensitive

**Figure 3: Pleural fluid analysis confirmed *candida dubliniensis* with pleural fluid being sent in blood culture bottles (17 Jun 2021)**

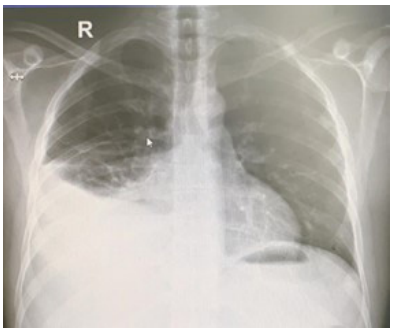


**Figure 4 : Chest X-ray demonstrated an increase in right-sided pleural effusion on voriconazole**

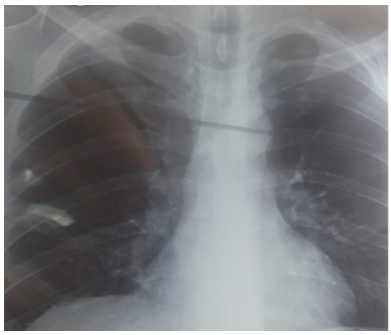

**Figure 5: Chest X-ray from August 10, 2021, 15 days after switching from voriconazole to isavuconazole.**

1. Voriconazole + Ponatinib: Voriconazole inhibits CYP3A4, increasing Ponatinib levels, thereby necessitating a dose reduction. However, pleural effusion could be a Ponatinib-related adverse effect, compounded by Voriconazole's impact on drug metabolism.
2. Posaconazole + Ponatinib: Similar to Voriconazole, Posaconazole also inhibits CYP3A4, increasing Ponatinib levels, leading to recommendations to reduce Ponatinib dose to 30 mg daily.
3. Alternative Antifungal Therapy: Consideration of other antifungal agents, such as Isavuconazole (a moderate CYP3A4 inhibitor with less interaction) and Echinocandins (minimal drug interactions), may offer safer alternatives for long-term management. The patient's candidiasis and probable aspergillosis justify the use of an azole, but close monitoring is required.

Voriconazole, Posaconazole, and Isavuconazole exhibit different interactions with CYP enzymes (Table1), affecting their metabolism and inhibitory potential. Voriconazole has strong involvement in both CYP2C19 and CYP2C9 metabolism and moderately with CYP3A4 (hence genetic polymorphisms affect metabolism of voriconazole and thus levels), while strongly inhibiting all three enzymes. Posaconazole does not rely on CYP2C19 or CYP2C9 for metabolism but strongly inhibits CYP3A4. In contrast, isavuconazole moderately interacts with CYP3A4 for metabolism and inhibition, without affecting CYP2C19 **or** CYP2C9 (Table 1).

After transitioning from voriconazole to isavuconazole on August 10, 2021, a follow-up chest X-ray (Figure 5) demonstrated complete resolution of the right-sided pleural effusion. Hence we can conclude that the increase in pleural effusion was due to high levels of ponatinib due to its interaction with voriconazole. The change to isavuconazole succeeded in bringing down ponatinib levels and thus the pleural effusion cleared.

### Conclusion

This case highlights the complexity of managing invasive fungal infections in immunocompromised patients receiving targeted therapies like ponatinib. Careful attention to drug interactions is essential, particularly involving CYP3A4 inhibitors like voriconazole and posaconazole. Pleural effusion, a known but uncommon side effect of ponatinib, further complicates the clinical picture. Ongoing monitoring and potentially switching to less interactive antifungals, such as isavuconazole or echinocandins, may be critical in managing this patient. Isavuconazole was chosen as it was superior to echinocandins for managing the aspergillosis. A multidisciplinary approach, including infectious disease and hematology-oncology teams, is paramount for successful outcome.

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## WHEN WE HAD TO USE STEROIDS IN A PATIENT WITH INVASIVE PULMONARY ASPERGILLOSIS


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### Introduction

The use of immunosuppression including steroids is contraindicated/ discouraged in patients with invasive aspergillosis as it is reported to be associated with higher mortality. It is however sometimes unavoidable as the case below illustrates

### Case Report

This 72-year-old female presented with cough for 2 weeks with mucopurulent expectoration and fever for 5-6 days. There was prior history of diabetes mellitus, dyslipidemia, bilateral knee replacement. Her CBC done outside showed Hb 10.4, TLC 1100, Neutrophils 0, platelets 242,000, CRP 23 mg/dl. Hence she was referred to our hospital. At admission she was febrile with RR

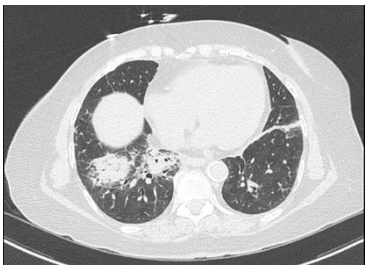

**Figure 1: Axial CT showing consolidation with surrounding halo**

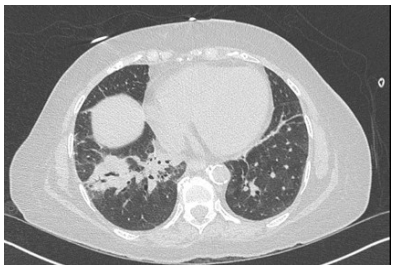

**Figure 2: Follow up CT showing cavitation in the nodule**

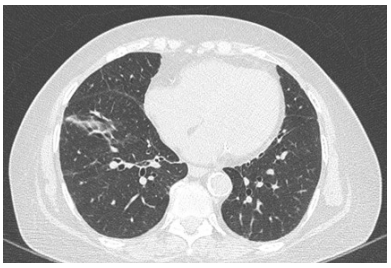

**Figure 3: Follow up CT after completion of therapy showing complete resolution**

18/ min and distress. Saturation was 95% and there were bilateral crepts. A diagnosis of severe neutropenia with pneumonia was made and she was admitted to the intensive care unit.

The CT showed consolidation in the right lower lobe with surrounding halo (Figure 1). Blood cultures and serum GM sent. Treatment with IV meropenem and IV posaconazole was initiated. Bone marrow aspiration and biopsy showed no myeloid cells. GM CSF 300 mcg SC was started. Buffy coat transfusion was given daily. Blood cultures were negative. Serum GM was 0.15. One week later the fever continued. ANC continued to remain 0. Repeat CT showed no change in the nodular consolidation. Bronchoscopic lavage was done. Aerobic cultures grew carbapenem resistant *Klebsiella Pneumoniae*. BAL GM was 0.45. Fungal cultures were negative.

Possibility of autoimmune neutropenia was considered. ANA was negative. Hence after much debate and with the background of a possible invasive fungal infection IV methylprednisolone @80 mg daily was initiated. GM CSF and daily granulocyte transfusions were continued. Three days after initiating steroids and 10 days after admission the TLC was 1800 and ANC 540 and 7 days after starting steroids the TLC was 54,800 and ANC 34,000. At this point the growth factors were stopped and steroids were tapered. The patient got fever again. Blood cultures grew CRKP and hence treatment with ceftazidime avibactam and aztreonam was initiated. Fever continued and repeat CT showed cavitation of the lesion (Figure 2). CT guided biopsy was done. The aerobic culture grew CRKP and the histopathology showed septate acute angle branching hyphae consistent with aspergillus. The fungal cultures were negative. The serum posaconazole level was 0.5. The dose was increased to 400 mg/ day and patient discharged. The repeat level was 2. The patient was given 6 weeks of posaconazole after reaching the therapeutic level. Repeat CT showed clearing of the lesion (Figure 3). The patient remains well on follow up.

### Discussion

The cause of the neutropenia in the patient remains unknown but probably had an immune mechanism as patient responded to steroids. She never had recurrence of neutropenia in the 3 years follow up. The other point of discussion is negative serum and BAL GM in the setting of severe neutropenia where a sensitivity of at least 80%is expected.[1-3] The diagnostic yield would have been higher with a CT guided biopsy instead of a BAL which should have been the preferred investigation on day 1. Then there is the issue of use of steroids in this patient with possible IPA (because at the time the steroids were given the patient only met host and radiologic criteria). A recent systematic review reported the risk of mortality to be 2.5 times higher in IA if steroids were coadministered.[4] In this patient fortunately, the use of steroids facilitated the recovery of neutrophil count and helped recovery from the IPA.

Finally, there is the issue of choice of antifungal for IPA. All the three azoles, voriconazole, posaconazole and isavuconazole are equally efficacious.[5,6] However, the latter two have fewer adverse effects and are preferred unless there is CNS involvement.

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## THE UTILITY OF SERUM CRYPTOCOCCAL ANTIGEN SCREENING IN THE MANAGEMENT OF PATIENTS WITH ADVANCED HIV INFECTION. A CASE-BASED DISCUSSION


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### Background

Cryptococci are ubiquitous, found in decomposing organic matter in soil, certain trees (notably on Vancouver Island, Pacific Northwest USA), and bird droppings. A dense gelatinous capsule improves the survival of cryptococcus in the environment. Infection occurs through the inhalation of yeast cells, triggering the innate immune system. Alveolar macrophages eradicate cryptococci via phagocytosis and granuloma formation. Like mycobacteria, cryptococci can survive intracellularly following phagocytosis and can evade effective immune responses, establishing latent infection in immunocompetent hosts.[2] Cryptococcal antigenemia under immunosuppression is most likely caused by reactivation of a latent infection.[3] The WHO recommends screening for serum cryptococcal antigen (CrAg) in adults and adolescents with CD4 counts <200 cells/µL.[1] This recommendation can help in early diagnosis and treatment of

HIV patients with cryptococcal infection. Early diagnosis with appropriate treatment can reduce morbidity and mortality in HIV-associated cryptococcal diseases, especially in high-burden countries like Africa. Lumbar puncture (LP) is advised to exclude subclinical CM in all CrAg-positive asymptomatic patients.[1] Three tests – the latex agglutination (LA), the enzyme-linked immunosorbent assay (ELISA), and the lateral flow assay (LFA) – are available to detect CrAg in the serum, body fluids or urine.

**Case history**

Mr. DJP, 59-year-old male businessman residing in Ahmedabad, Gujarat, presented in June 2025 with diarrhoea, a 5 kg weight loss, occasional twitching of the right angle of the mouth and three episodes of dizziness in the last two weeks. He was diagnosed with HIV in Feb 2020, and he stopped antiretroviral treatment in August 2021 after taking it for 18 months. He denies tobacco or alcohol consumption. Examination showed oral thrush.

His workup revealed a CD4 cell count of 53 (5%) $mm^3$ and an HIV-1 plasma viral load of 34,50,000 copies/ml. Hb: 9.3, TC 7780, DC 86/8/2/3, creatinine 0.68 mg/dL, and SGPT 37 IU/L. MRI was unremarkable except T2WI showed periventricular hyperintensities and cortical atrophy – both features are common in patients with chronic HIV infection. USG abdomen showed few subcentimeter lymph nodes.

Serum CrAg, performed as his CD4 count was < 200/$mm^3$, was positive.

**What should be the next appropriate step?**

1. Should we start him on treatment for asymptomatic cryptococcal antigenemia with fluconazole?
2. Should we perform a lumbar puncture to rule out cryptococcal meningitis?
3. Should we start ART with fluconazole for asymptomatic cryptococcal antigenemia?

CrAg is detectable in blood prior to the onset of symptoms. Cryptococcal antigenemia can be found in asymptomatic infection (CSF CrAg-negative), subclinical infection (CSF CrAg-positive, India ink microscopy, or culture positive for Cryptococcus spp. but without overt meningism), or clinical symptomatic infection (cryptococcal meningitis). HIV patients with cryptococcal antigenemia were associated with a 2- to 3-fold higher risk of death within 6 months compared with patients without cryptococcal antigenemia with similar CD4 counts.[4] CrAg titers can be performed from serum, but it can't accurately predict the presence of meningitis. Patients with a serum CrAg titer of >1:80–1:160 are associated with a higher risk of meningitis. Lumbar puncture is advised to exclude subclinical infections in all the patients with S. CrAg positive irrespective of symptoms.[1]

CSF examination was performed in our case, as he has some symptoms referable to CNS involvement. CSF opening pressure was 110 mm of CSF (normal), total white cells 4 (all lymphocytes), glucose 28 mg/dL with random blood sugar 112 mg/dL, and protein 30 mg/dL. India Ink examination was negative; CSF CrAg titre was 1:640 and CSF culture grew *Cryptococcus neoformans*.

Our patient is likely to have a subclinical infection, as he has no major clinical and radiological (MRI) symptoms favouring intracranial infection with CSF positive for cryptococcal infection. An odd point in this case was a low CSF glucose. Around one-third of individuals with asymptomatic cryptococcal antigenemia have subclinical CM.[5]

**Treatment:**

Asymptomatic cryptococcal antigenemia: Fluconazole monotherapy is recommended for the treatment of asymptomatic cryptococcal antigenemia. Fluconazole 800 mg/day for 2 weeks followed by 400 mg/day for 8 weeks followed by 200 mg/day for 1 year or until a rise in CD4 counts, preferably more than 350/$mm^3$. Higher fluconazole dosages up to 1200 mg/day are also recommended by South African guidelines.[6] South African treatment guidelines suggest starting antiretroviral treatment after 2 weeks of fluconazole treatment.[6]

Treatment of subclinical meningitis: Fluconazole monotherapy is suboptimal for the treatment of subclinical meningitis. This should be treated as full-fledged meningitis with amphotericin B and flucytosine

We used standard treatment with liposomal amphotericin B (3 mg/kg/day), plus 5 flucytosine 4500 mg per day in divided doses for two weeks, along with TMP-SMX prophylaxis. A repeat CSF examination at 2 weeks showed an opening pressure of 90 mm of CSF: a total of 2 white cells, glucose of 30 mg/dL (RBS of 102), protein of 30 mg/dL, and a CSF CrAg titer of 1:320 with a sterile CSF culture. The patient was then started on antiretroviral treatment (TAF/FTC/DTG) with fluconazole (400 mg/day) consolidation, completed 8 weeks of follow-up and had no clinical features of IRIS.

**Conclusions**

All the newly diagnosed patients with CD4 < 200 $mm^3$ should be screened with serum cryptococcal antigen testing. LFA from serum is point-of-care testing recommended by WHO. Lumbar puncture is advised for all with positive serum CrAg irrespective of symptoms. Combination antifungal treatment of L-AmB with 5-flucytosine is recommended for the treatment of cryptococcal meningitis and subclinical infection.

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**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 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 haematologists, critical care providers, ID specialists, pulmonologists, neurologists, medical mycologists and many other clinicians handling serious and immunocompromised patients.The trust consists of clinicians and mycologists and was instituted on 3rd March 2012 at Mumbai, India