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EPIDEMIOLOGY AND DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS IN ICU

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Invasive fungal infections (IFI) in intensive care units (ICUs) are a leading cause of morbidity and mortality in critically ill patients. The majority of IFIs are caused by *Candida* spp., followed by *Aspergillus* spp. and mucoraceous fungi. Occasionally black mycelial fungi and rare moulds are also reported to cause infections. The magnitudes of the IFIs have been highlighted by multi-centres studies:

- In a point prevalence study at 1265 ICUs across 75 countries, candidiasis was reported at 17% patients and aspergillosis at 1.4% patients[1].
- In a study on ICU-acquired candidemia at 27 centres in India in 2011-2012, candidemia incidence was observed at 6.5 cases/1000 ICU admissions. The Indian epidemiology was found to be unique, as young people with lower morbidities acquired the infection early after ICU admission. In this study 31 yeasts were identified as causative agents with over 10% resistance to azoles. The study highlights the need for good diagnostic mycology laboratories across India with competence for accurate identification of fungal species and susceptibility testing[2].
- In another study at 11 centres at India, mould infection was found at an incidence rate of 10.1 cases/1000 ICU admissions. Though aspergillosis was reported in most (74.8%) of the patients, mucormycosis was reported in considerable number (23.9%) of patients. *Aspergillus flavus and A. fumigatus* were isolated in nearly equal frequency[3].
- Infections due to rare moulds and yeasts also create difficulty, as epidemiology of such infections are not known, identification is difficult, and susceptibility tests cannot be interpreted without breakpoints[4,5].
- At the same time delay in diagnosis and therapy of fungal infections increases mortality[6-8]. Intensivists prefer to prescribe empiric therapy in the ICU due to absence of diagnosis. However, during empiric therapy, in absence of local epidemiology it is not clear which fungi to target, and when to stop therapy.
- The current diagnostic attempts for IFIs start after clinical manifestations of infections. However, for better outcomes, diagnosis should be attempted at the time of entry of pathogen in the hosts which may be possible with evolving biomarker tests including lateral flow assay for aspergillosis, cryptococcosis, histoplasmosis etc.

Diagnosis of fungal sepsis

- Distinction between fungal and bacterial sepsis is difficult due to similar clinical presentation and frequent failure to isolate the causative agent. In autopsy proven invasive candidiasis, sensitivity of blood culture varies between 21-71%. The diagnosis of abdominal candidiasis is further difficult, as blood culture is positive in <15% of cases[9].
- Due to lack of accurate diagnosis, intensivists prescribe empirically both antibacterial and antifungal in patients with nosocomial sepsis. This is a challenge for antimicrobial stewardship. A provocative statement can be thus made – 'Delivering on antimicrobial resistance agenda not possible without improving fungal diagnostic capabilities'[10]. To implement antifungal

Message from the Editor

Dear Friends,

The Fungal Infection Study Forum extends a warm welcome to the delegates of the annual conference of Indian Society of Critical Care Medicine. This issue of our newsletter focusses on invasive fungal infections (IFI) in the intensive care unit. IFI's have become an increasing concern in ICU patients leading to an increased use of biomarkers and antifungals. The aim of this issue is to help intensivists avoid both under diagnosis and over diagnosis of IFI so that optimum outcomes are achieved without overuse of biomarkers and antifungals.

We begin with an essay on the epidemiology and diagnostic challenges of IFI in the ICU. Following this we have an overview of invasive mould infections in the ICU. Then we have a discussion related to the value of Beta D Glucan in diagnosis of invasive candidiasis (IC) taking into account the pretest prevalence of the disease. Finally we wind up with two cases, one of deep seated candidiasis and the other of a pseudo Mould infection.

The readers are urged to visit the FISF website www.fisftrust.org for more resources and contribute cases of invasive mould infections to the Indian Fungal Registry (details below)

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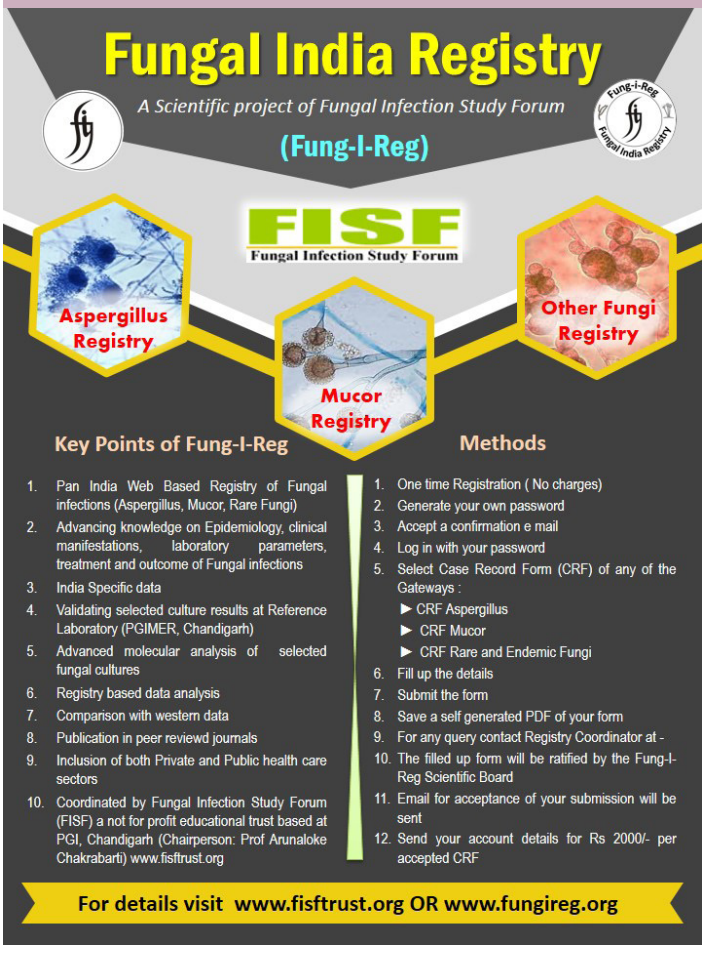

stewardship program in ICU, improvement of diagnosis of invasive candidiasis is essential.

- Two advanced techniques have improved turnaround time in diagnosis of invasive candidiasis. T2 magnetic resonance nano-particle-based technique has improved the turn-around time from 110 hours to 4 hours. However, high cost and possible targets of only five *Candida* species limit its use, and the test is not available in India[11]. MALDI-TOF has improved significantly the turnaround time for yeast identification[12]. The technique may be utilized for antifungal susceptibility testing in near future.
- Non-culture-based techniques including beta-D-glucan, *Candida* mannan and anti-mannan, *Candida albicans* germ tube antibody, multiplex *Candida* real time polymerase chain reaction have been developed to improve the sensitivity and turnaround time for diagnosis of invasive candidiasis. Among these techniques beta-D-glucan test is most popular and standardized in ICU. The tests are useful in high-risk group of patients with prevalence of invasive fungal infections at >15%, and more suited for 'ruling out' of fungal infections rather than 'ruling in'. In absence of direct demonstration of fungi, at least two consecutive biomarker tests should be positive to diagnose invasive candidiasis[13].
- The false-positivity of the biomarker tests should also be considered while interpreting the test. Serum beta-D-glucan test may be false positive in leaky gut, dialysis, during use of ampicillin-clavulanate or sulbactam therapy, immunoglobulin or albumin infusion, and bacterial septicaemia[14].
- The multi-drug resistant *Candida auris* is a major challenge in Indian ICUs due to its easy transmissibility, contamination of hospital environment, causing serious infection, and difficulty in identification. To prevent its entry in ICU, quicker identification of colonized referral patient from other hospital is essential. A PCR based technique, Auris ID (Olm Diagnostics) may be useful due to its capability to identify *C. auris* in clinical samples within 1-1.5 hours[15].

Diagnosis of invasive mould infection

- The diagnosis of invasive mould infections has multiple challenges: a) lack of awareness or belief of mould infections in ICU, b) non-specificity of clinical symptoms and signs, c) non-specificity of signs on imaging, d) difficulty to get invasive samples from thrombocytopenic critically ill patients.
- The characteristic imaging like halo, air-crescent signs are present in neutropenic patients, as the fungi can enter the blood vessels easily from alveoli and produce thrombosis and necrosis. However, in non-neutropenic critically ill patients, the fungi cannot enter the blood vessels easily due to presence of neutrophils. It produces non-specific signs like localized bronchiectasis, tree-in-bud, ground glass, nodule and consolidation. Therefore, any abnormality on imaging should not be ignored and consider during diagnosis of invasive fungal infections[16].
- The cultures of the respiratory tract secretions lack sensitivity, as moulds can grow from sputum in only 8-34% and from Broncho-alveolar lavage in 45-62% patients with IFIs. Further, *Aspergillus* spp. recovery from the respiratory tract usually represents colonization in immunocompetent patients. Thus, demonstration of fungi in tissue is essential for diagnosis, though collection of tissue samples is difficult in thrombocytopenic patients. After platelet infusion, an attempt for CT guided fine needle aspiration or open lung biopsy may improve diagnosis. The introduction of fiberoptic bronchoscopy and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in routine management has improved diagnosis. The identification of fungi may not be possible with the visualization of hyphae in tissue. In-situ hybridization and extraction of DNA from the tissue and molecular identification would help in fungal identification[17].
- The galactomannan (GM) antigen detection in serum and broncho-alveolar lavage fluid is the major biomarker test for diagnosis of invasive aspergillosis. Different formats are available for detection of GM like ELISA, lateral flow assay (LFA), single test format. The latter two tests are recent developments as point of care tests. Mannoprotein can also be detected by lateral flow method. The lateral flow tests, GM and mannoprotein detection help in early diagnosis of invasive aspergillosis provided the patient is not on antifungal prophylaxis. However, diagnosis by biomarker alone should be interpreted cautiously. Piperacillin-tazobactam and plasmalyte use, bacterial infections, yoghurt or pasta ingestion may cause false positive tests[18].
- Due to poor sensitivity and lack of standardization of conventional diagnostic protocol, EORTC-MSG developed a research definition of IFIs in neutropenic or immunosuppressed patients on the basis of host, clinical and mycological factors, which is recently updated[19]. However, non-neutropenic critically ill patients cannot be classified under these criteria due to absence of host factors. *Asp*ICU criteria have been proposed for such patients If *Aspergillus* spp. are isolated from respiratory tract sample or GM is positive with non-specific radiological signs, and when the patients have host factors like chronic obstructive pulmonary disease, decompensated cirrhosis, influenza. Though sensitivity of the *Asp*ICU criteria is good (92%), specificity is around 60%[20, 21].
- Influenza associated and COVID-19 associated pulmonary aspergillosis (CAPA) have emerged as new challenges, as infection rates have been reported around 10% in patients managed at ICUs. The diagnosis of influenza associated pulmonary aspergillosis may not be difficult, as tracheo-bronchitis has been reported in 55% of cases (biopsy tissue can be collected by bronchoscopy), and serum and BAL galactomannan are positive in 65% and 88% of cases respectively[22]. However, the diagnosis of CAPA remains controversial. Though international societies have proposed diagnostic algorithm for CAPA, the protocol requires standardization. Moreover, bronchoscopy and BAL galactomannan are required tests to diagnose CAPA.[23, 24]
- The diagnosis of non-*Aspergillus* invasive mould infection faces the difficulty of absence of standardized biomarker test. The awareness, serious attempt to collect invasive sample, and multi-disciplinary approach may improve the diagnosis of such patients.

Conclusions

To improve the diagnosis of invasive fungal infections, following attempts should be made:

- Think of fungus in your patient and make serious attempts to prove the diagnosis.
- Distinction between bacterial and fungal sepsis is important for specific therapy and antimicrobial stewardship.
- Though T2Candida has improved candidemia diagnosis, the test is not available in India. Besides the test does not detect *C. auris* which is an important consideration in Indian ICU's.
- MALDI-TOF has improved fungal identification and may provide antifungal susceptibility data in near future
- *C. auris* screening at admission is important to prevent entry of the fungus in the ICU
- Beta-D-glucan test can help to screen out invasive candidiasis
- Galactomannan and lateral flow test would improve the diagnosis of invasive aspergillosis
- Other molecular methods for diagnosis of invasive fungal infections need further standardization. More research is required in this field to improve diagnosis and we need more competent diagnostic mycology laboratories in this country.

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INVASIVE ASPERGILLOSIS IN INTENSIVE CARE UNIT

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Introduction

Invasive aspergillosis (IA) in Intensive care unit (ICU) is usually seen in a setting of classic immunosuppressive states like hematological malignancy, post-transplant and post chemotherapy. IA has been increasingly reported in other non-classic immunosuppressed states in ICU like COPD on chronic steroid therapy, rheumatological or immunological conditions treated with immunomodulators, liver failure and post viral conditions like Influenza and SARS CoV-2 infections and finally critically ill patients with immunoparalysis during their latter part of ICU stay. This article will briefly describe the epidemiology, clinical presentation and management of IA.

Epidemiology

The burden of IA from ICU's in developing countries is not well reported. In an environmental study conducted in an Indian ICU, a high spore count of an average 82 cfu/mm^3 was found. In a study conducted by Fungal Infection Study Forum (FISF), epidemiology and management of invasive mould infection was studied in 11 ICUs across India in the year 2016/17. Of the 398 proven or probable cases in this study Aspergillus was commonest (82% followed by Mucor 14%). Aspergillus isolates were noted in 142 patients with Aspergillus flavus being the most common. Both classical and non-classical risk factors were noted in IA in this study. Invasive mould infection with both Aspergillus and Mucor were independent predictors of mortality with OR 1.78.

Diagnostic Criteria

Various diagnostic criteria have evolved over time to describe IA in various subset of ICU populations. These criteria usually included a combination of host factor (immunosuppression, COPD etc), Biomarkers (Galactomannan, Beta D Glucan), Mycological criteria (Fungal culture, PCR, histopathology) and Imaging criteria (Nodules) Based on these criteria, IA is usually described as Proven, Probable or Putative and possible. Proven is usually histopathology identification of IA or growth from non-sterile site. Probable is a host risk factor, positive biomarker and one or more mycological criteria. The following diagnostic criteria have been described

- Immunocompromised host : EORTC/MSGERC
- COPD : Bulpa
- ICU : AspICU Blot
- IAPA (Influenza associated invasive aspergillosis) : AspICU
- CAPA (Covid associated invasive aspergillosis) : ECMM/ISHAM

Difficulties in diagnosing IA in critically ill may be difficult due the following reasons

- Features of underlying disease may overlap with IA features
- Low sensitivity of serum galactomannan in non-neutropenic patients
- High incidence of false positive biomarkers : Galactomannan , Beta D glucan
- Absence of classical thoracic imaging features (Halo/Crescent)
- Difficulties in obtaining tissue samples in critically ill
- Frequent colonization with Aspergillus

Thus a high index of suspicion, prompt sampling of appropriate samples, if necessary early bronchoscopy and tissue diagnosis needs to be done to initiate an appropriate antibiotic.

Therapy

As ICU patients have limited physiological reserve and multiple comorbidities early empirical therapy of IA may need to be started in these patients based on possible or probable diagnostic criteria pending definitive results. Management challenges emerge due to comorbidities, organ dysfunction and multiple medications

Voriconazole is still recommended as a first line therapy for IA due to long term clinical experience. Therapeutic drug monitoring (TDM) is recommended not only for efficacy but to avoid toxic levels. This facility may not be available in many centres and the turnaround time is long. Posaconazole with TDM and Isavuconazole are alternatives and are better tolerated in clinical trials. Advantage of Isavuconazole is lesser need for TDM and less drug interactions. This is important as ICU patients are on multiple drugs and organ dysfunction which may interfere with voriconazole therapy. Liposomal Amphotericin B or Amphotericin deoxycholate is another option in patients who can not tolerate azoles or when diagnosis of a specific mold aspergillus vs mucor is in doubt. While echinocandins are fungistatic for aspergillus, they may be used when there is dilemma of Candida versus Aspergillus. Antifungal therapy duration needs to be individualized based on clinical and biomarker response and is usually prolonged for 4-6 weeks. Prophylaxis for IA is not advocated in critically ill patients.

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THE USE & VALUE OF BDG IN INVASIVE CANDIDIASIS: ISSUE OF DIAGNOSTIC STEWARDSHIP

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RD 40 M had gastro-intestinal stromal tumour (GIST) at the gastroesophageal junction & liver metastases. He was treated with Imatinib, but had no relief & so underwent GE junction excision, anastomosis & L lobe hepatic resection. 2 days later chest discomfort & dyspnea developed, desaturation occurred & was shifted to ICU. Right pleural effusion was found. The rapid development of an effusion producing a severe illness was most likely due to a gastroesophageal leak from anastomotic dehiscence. This was found on imaging & is shown with the arrow.

The patient had been taking Imatinib which has been associated with GI perforation, tumour necrosis & hemorrhage.

An endoscopic procedure was done to splint the anastomosis. Pleural fluid was tapped & cultured. While a polymicrobial infection of the pleural cavity was anticipated & the result was awaited, could performing serum BDG help in this situation to ascertain the presence of invasive candidiasis?

In the post operative period, stasis & anti-peristalsis is common. There can be retrograde colonization of the stomach & esophagus by bowel flora & leakage could have occurred thorough anastomotic dehisence. Candida is often a part of polymicrobial flora that comes from perforation of the GI tract, especially the upper GI tract.

It is generally agreed that anti-fungal treatment is justified at a threshold likelihood of invasive candidiasis (IC) of 15 to 30%. A non-culture based test like BDG assigns a certain probability of infection rather than being definitive. To be useful, it must change the likelihood beyond or below the pre-test likelihood. The test does not help greatly if this likelihood (prevalence) is very low & again when very high, but has the greatest clinical utility when it is intermediate as shown in the Table

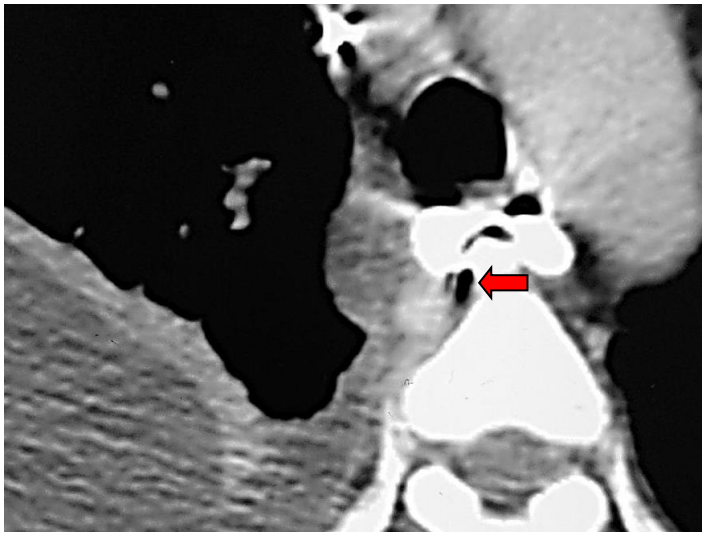

Table: Pre test prevalence, PPV, NPV and added value of BDG

Predisposing Factors	Invasive Candidiasis Prevalence %	BDG +ve PPV%	BDG-ve NPV%	Added value of the test
ICU admission	1	4	> 99.5	-
Sepsis shock, ICU > 4 d	3	11	99.2	-
Candida scores	10	31	97	+
Surgery for colonic perforation	10	22	95	+
Acute necrotizing pancreatitis Small bowel perforation	20	39	89.6	+
High risk biliary surgery, leak, gastro/ duodenal perforation	30	53	83	-

adapted from *Clancy CJ, Nguyen MH JCM 2018;56:e01909*. This analysis helps focus on the type of patient where the there is, or there is no incremental value of a non-culture based test, over pre-test likelihood & therefore on diagnostic stewardship.

In this case of an upper GI perforation as in the bottom row, the pre-test likelihood was already high & use of BDG to further increase the likelihood of invasive candidiasis is not very clear. Performing tests entails cost, laboratory overload, error in over- interpretation which may lead to unnecessary, expensive, toxic therapy.

Hence treatment with Meropenem, Tigecycline to cover GNB, anaerobes & GPC was started along with Micafungin which penetrates well into the pleural space. Pleural fluid culture was done which showed Enterobacter cloacae, Enterococcus faecalis & Candida tropicalis. These pathogens had been anticipated and were already being treated. Pleural space drainage was done, Micafungin was transitioned to Fluconazole as Candida tropicalis was found to be susceptible. Antimicrobials were continued for 3 weeks & the patient made an uneventful recovery.

APPROACH TO A DIAGNOSIS OF DEEP-SEATED CANDIDIASIS

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Invasive candidiasis (IC) is a fatal condition with a mortality rate of 40-60% in ICU patients.[1] IC encompasses candidemia without deep-seated and solid organ involvement, deep-seated and solid organ candidiasis without candidemia, and patients who have both candidemia and deep-seated and solid organ candidiasis.[2] Diagnosis of IC is challenging, because blood culture has a sensitivity of 50-70% for diagnosis and is frequently sterile (>85%) in patients with only deep-seated candidiasis.[3]

Diagnosis requires direct sample (collected either during surgery or CT or Ultrasound guided percutaneous aspiration) from the infected site. Abdominal drain fluid kept for >24 hours is not useful. In patients with deep-seated or parenchymal involvement, tissue biopsy for routine staining, culture, and histopathologic evaluation frequently leads to a definitive diagnosis. Serum beta D glucan (BDG), a fungal biomarker, is useful in diagnosis of IC with 81% sensitivity and 60% specificity.[4] Two sequential BDG (separated by 3-4 days) has 100% sensitivity and 75% specificity.[5]

Clinicians may encounter difficulties in BDG interpretation due to false-positive results with a variety of medical conditions or pharmacological interventions such as bacteraemia, receiving beta-lactamase inhibitor containing antimicrobials, cellulose filter haemodialysis, cotton gauze packing into abdominal cavity, plasma, albumin and intravenous gamma globulin therapy. Interpretation of BDG is tricky and should be guided by clinical and microbiological data. A negative BDG has a high negative predictive value. In the appropriate clinical circumstances, the BDG can be useful for detection of deep-seated invasive candidiasis (eg intra-abdominal candidiasis) when blood cultures are negative. The disadvantage of fungal biomarkers and histopathology is that they do not provide additional information on candida species and drug susceptibility.

Case

A 55-year-old diabetic male presented to the emergency department with complaints of abdominal pain, distension, and vomiting three to five times a day for last three days. He had non-bloody diarrhoea two days back. He denied any symptoms of fever, hematemesis, or melena. A month ago, the patient had been treated for acute pancreatitis caused by primary hyperparathyroidism. With acute pancreatitis, he was also diagnosed with diabetes for the first time. He was then managed conservatively for pancreatitis and parathyroidectomy was done. He was non-smoker and denied alcohol consumption.

Physical examination at ER revealed toxic look, with tachycardia, and abdominal distention with diffuse tenderness. The results of the laboratory workup were as follows: CBC: 8.8 gm/dL, WBC: 29,500/cmm, DLC: 91% polymorphs Platelet count: 3,24,000/cmm, RBS: 476mg/dL. SGPT: 79 IU/L, Bilirubin: 0.67 mg/dL, Alkaline phosphatase: 263, S. Acetone: 5 mmol/L, S. Creatinine: 1.08 mg/dL, Na: 126, K: 4.72, S. Lipase: 601 (23-300), Amylase: 60 (30-110), CRP: 10.1 (<1 mg/dL), S. Ca: 13.28 mg/dL, Mg: 1.3 (1.6-2.3mg/dL). HIV and HBsAg were non-reactive. X-Ray Chest showed elevated left dome of diaphragm, X-Ray Abdomen revealed free gas under diaphragm. Computerized tomography with rectal contrast showed pancreatic body and tail replaced by necrotic material, with multiple internal air foci, moderate pneumoperitoneum, no obvious leak of rectal contrast. (Fig 1)

Exploratory laparotomy was performed after intravenous fluid resuscitation and hyperglycemia was controlled with insulin infusion. Empiric antibiotic injection meropenem 1g q8h was started after sending blood cultures. No bowel perforation was identified during surgery and pancreatic necrosectomy was performed. Intraoperative material was sent for microbiological work up and histopathological examination. Both blood (two bottles out of two) and necrosed pancreatic material grew E. coli which was sensitive to BL-BLIs, carbapenems, aminoglycosides, and quinolones. Histopathological examination showed totally necrotic material with complete loss of structural details. Viable pancreatic tissue was absent. Section showed presence of many pseudomycelial GMS positive forms of Candida species with thin septae. (Fig 2). Patients serum Beta D glucan was 349 pg/ml (positive > 80pg/ml). Injection Caspofungin was started for intraabdominal candidiasis. Post operatively patient was vitally stable. Caspofungin and meropenem were given

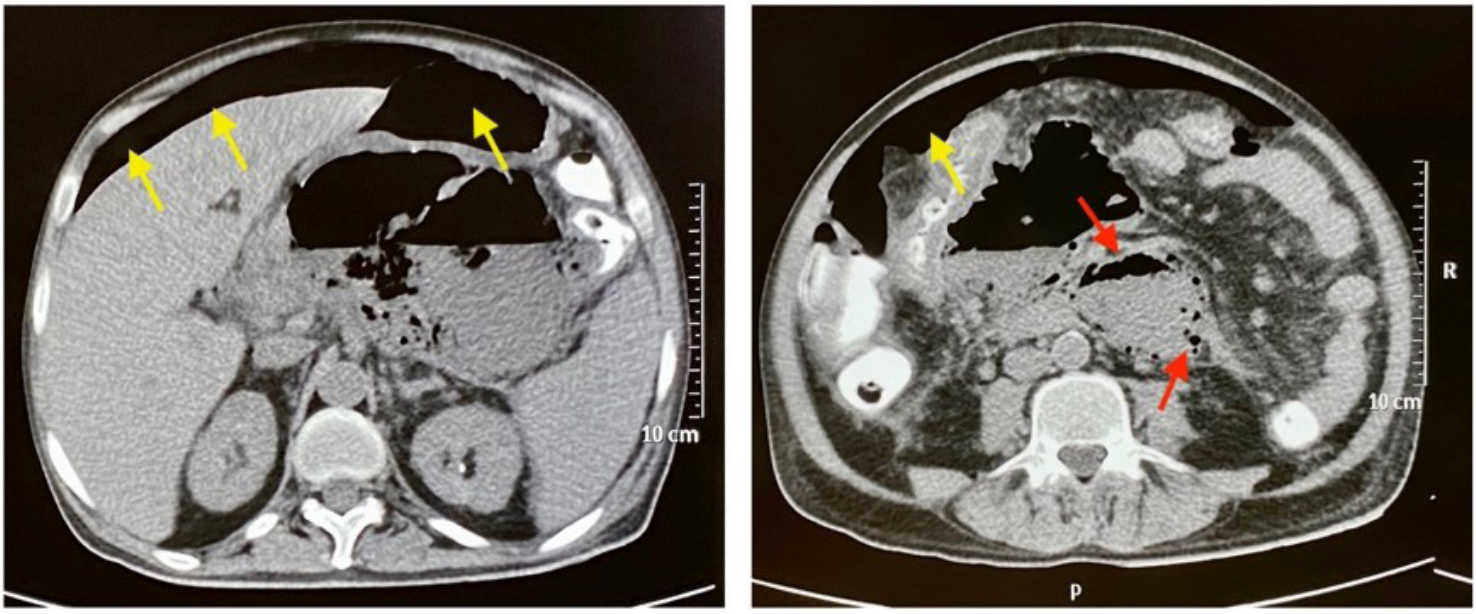

Figure 1: CT scan Abdomen showing necrotic material with internal air foci in the pancreatic region and free gas under diaphragm

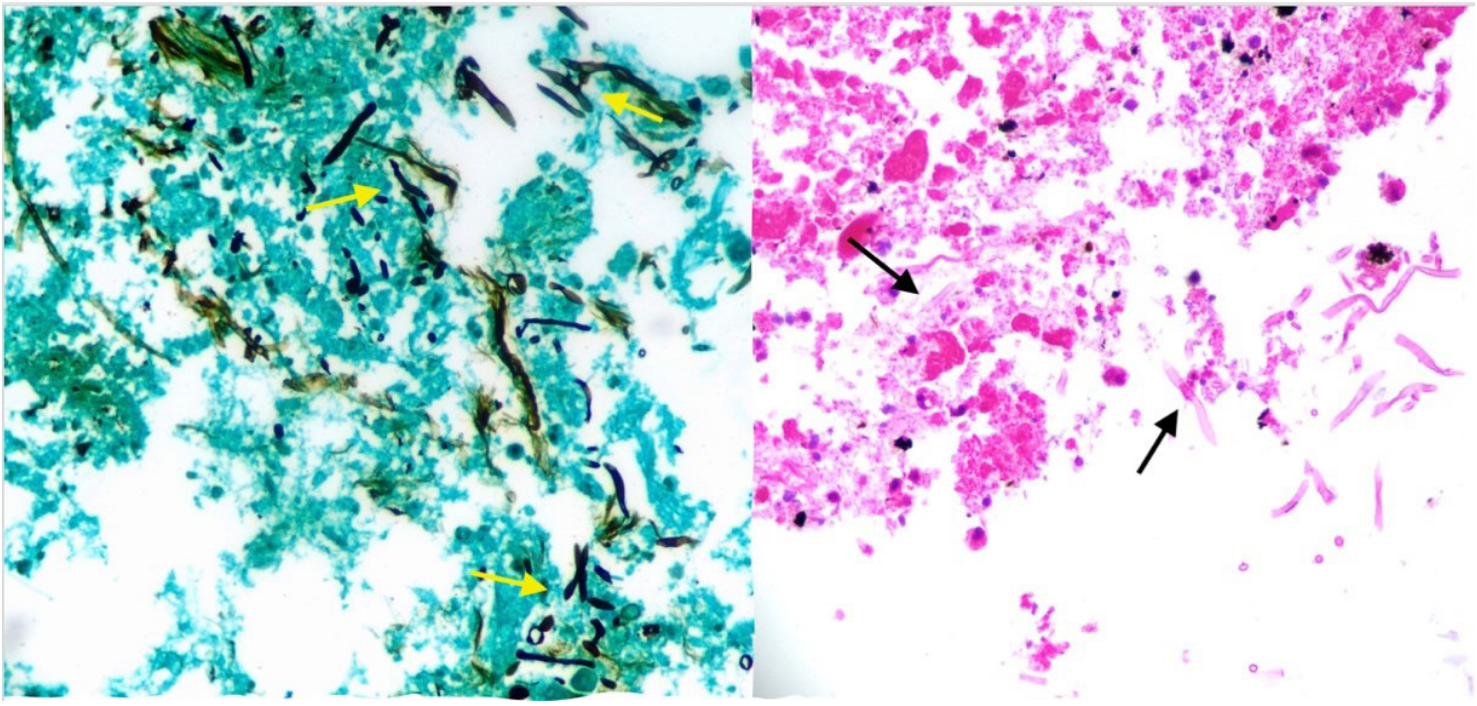

Figure 2: Histopathologic examination of necrotic material with GMS and PAS stain showing pseudomycelial structure of candida species (Black and Yellow arrows)

for two weeks and ten days respectively. Patient was discharged on fifteenth hospitalization day in a stable condition. He was asymptomatic on follow up after one week.

Learning pearls

Timely and appropriate diagnostic work up for the infectious agent in patient is critical for better outcome. Spending money on diagnostics is both cost effective and promotes rational antimicrobial treatment. Diagnostic stewardship is one of the important component of antimicrobial stewardship program. This patient received an optimal diagnostic work up to identify organisms. Blood culture sent on arrival to ER yielded E.coli (Patient didn't had fever on presentation), surgeon wisely sent tissue for microbiological and histopathological work up, which grew E.coli and histopathology showed candida. S. BDG supported the diagnosis of invasive candidiasis. Mixed bacterial & fungal infection are seen in the two-third of the cases.[6] A key component, in addition to the choice of antifungal medication, for the successful treatment of intraabdominal candidiasis was early source control by pancreatic necrosectomy.[4,7]

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DO NOT BE ENTICED TO TREAT BY MICROSCOPY ALONE

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Case

A 45 year old male patient was admitted with a dengue-like illness. He had severe thrombocytopenia and therefore was given platelet transfusion, after which he developed transfusion associated lung injury (TRALI) as shown in Figure 1. He received two doses of steroids, developed mounting azotemia and volume overload, for which he received diuresis. During the course of this illness a sputum test was done.

Sputum smear was positive for a clump of thin, septate, acute angle branching mould as shown in Figure 2.

Hence ID consultation was sought. A diligent search of additional fields of the smear was asked for which was negative. Several more sputum samples also did not reveal the same finding. The serum galactomannan was found to be negative as well. (Figure 3).

Therefore, it was advised that no specific treatment for the mould may be used. The Chest Xray improved with diuretics (Figure 4). The patient improved clinically and was discharged.

Discussion

The diagnosis of invasive pulmonary aspergillosis, according to the criteria as defined by the European Organisation for the Research and Treatment of Cancer/

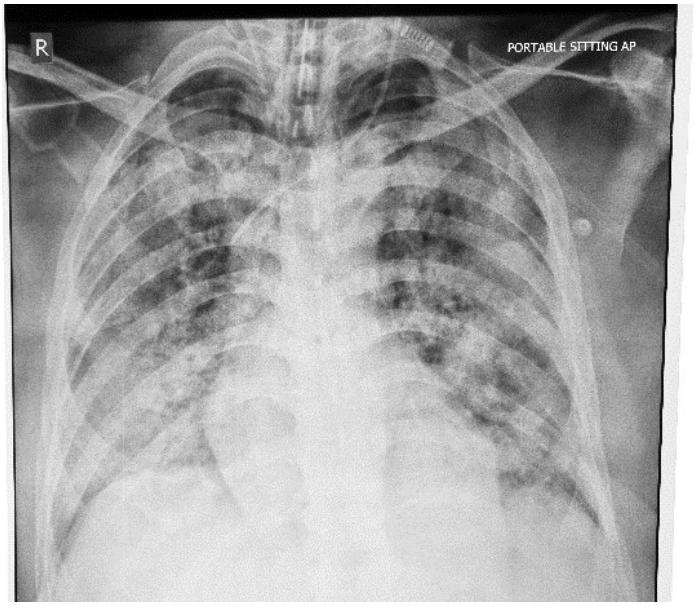

Figure 1: Bilateral basal pulmonary infiltrates, suggestive of TRALI

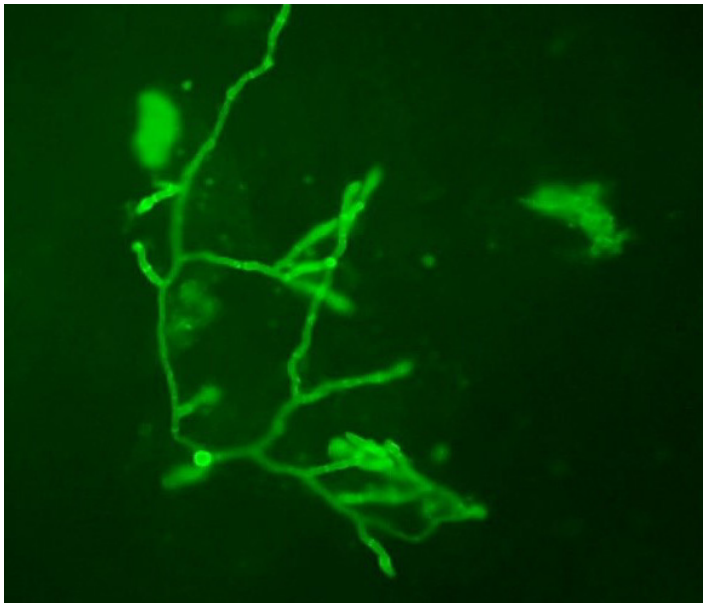

Figure 2: Acute angle, branching, septate fungal elements

Result No. : LB-2022-021

Bed No. : ICU311 Ward No. : ICU 03 :

Investigations	Methods	Result	Unit	Biologi
TEST				
GALACTOMANNAN				
SPECIMEN		SERUM		-
PATIENTS VALUE		0.2445	INDEX VAL	-
PATIENTS RESULT		NEGATIVE		-

Aspergillus Galactomannan

Figure 3: Serum Galactomannan: Negative

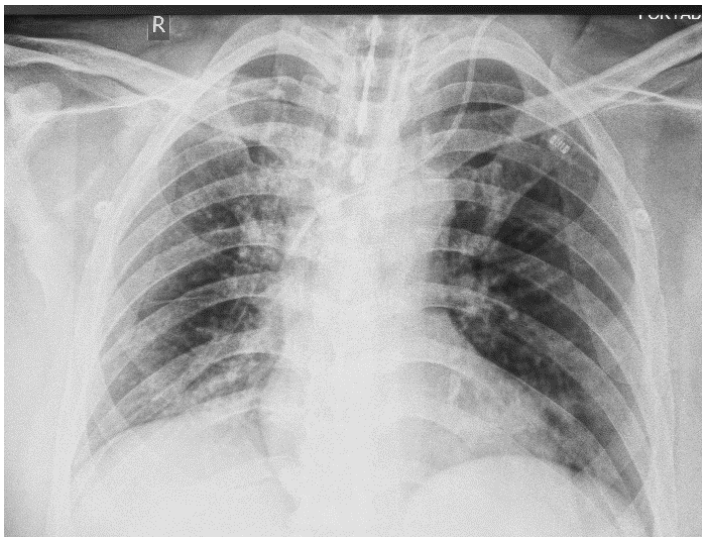

Figure 4: Resolution of pulmonary infiltrates

Mycoses Study Group (EORTC/MSG), is based on host factors, clinical/radiologic syndrome & mycological tests. This conceptual framework can be applied to other groups of patients who have different host factors such as ICU patients , COPD, influenza, COVID-19. [1,2,3,4] The clinical/radiologic features & the sampling methods & thresholds for biomarkers have also been modified to suit the particular circumstances of these patients.

A diagnosis of probable IPA is based on the presence of a combination of host factors, clinical features, and positive mycology. However, in this patient there was a dengue-like (non-respiratory) illness which is not considered as a host factor. Although he had received steroids the exposure was very brief. Chest radiography did not show the typically described findings like nodules, halos & cavitation. Except one clump of mould seen in one of the smears, the biomarker (Galactomannan) in serum was negative, although it is recognized that the sensitivity of serum galactomannan in non-neutropenic patients is low.

This led to a very low probability of invasive Aspergillosis & the patient was not treated in the interest of anti-fungal stewardship.

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