ASIA FUNGAL WORKING GROUP
an ISHAM working group

ISHAM
INTERNATIONAL SOCIETY FOR HUMAN AND ANIMAL MYCOLOGY

Co-organized with:

MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

Case Presentation:
Invasive Aspergillosis

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Patient Identity

Name	HW
Age	64 years
Date of birth	27 March 1961
Gender	Male
Admission date	4 May 2025

SUBJECTIVE

Chief Complaint

Fever and nasal pain since 12 days prior to hospital admission.

SUBJECTIVE

History of Present Illness

- The patient has a known history of very severe aplastic anemia since January 2025.
- Twelve days prior to hospital admission, the patient began experiencing intermittent fever with chills, nasal pain and headache radiating to the right jaw.
- The patient also reported numbness in the upper lip and right cheek area.
- There was a history of epistaxis one week prior, after which the patient felt nasal congestion.
- He was admitted to Hospital PJ on April 22, 2025, then was diagnosed with sinusitis.
- He was treated with antibiotic, without significant improvement. He was subsequently referred to referral hospital.

SUBJECTIVE

Past Medical History

- History of very severe aplastic anemia since January 2025

Family History

- No similar illnesses reported in the family.

SUBJECTIVE

Allergy History

- Suspected allergy to ibuprofen and paracetamol.

Medication History

- For the history of aplastic anemia, the patient has been taking **cyclosporin and eltrombopag.**
- At **Hospital PJ**, the patient received the following treatments:
  - Meropenem 1 g IV three times daily
  - Levofloxacin 750 mg IV once daily
  - Fluconazole 400 mg IV once daily
  - Eltrombopag 75 mg once daily
  - Methylprednisolone 31.75 mg IV once daily
  - Filgastrim 300 mcg SC once daily
  - Tranexamic acid 500 mg IV three times daily
  - Omeprazole 40 mg IV once daily
  - Ursodeoxycholic acid 500 mg three times daily
  - Hepatoprotector 1 tablet three times daily
  - Folic acid tablet once daily
  - History of PRC and TC transfusions.

OBJECTIVE

General Status

- General condition : moderately ill
- Level of consciousness: compos mentis

Vital Signs

- Blood pressure : 134/76 mmHg
- Heart rate : 92 bpm
- Respiratory rate : 18 breaths/min
- Temperature : 36.6 °C

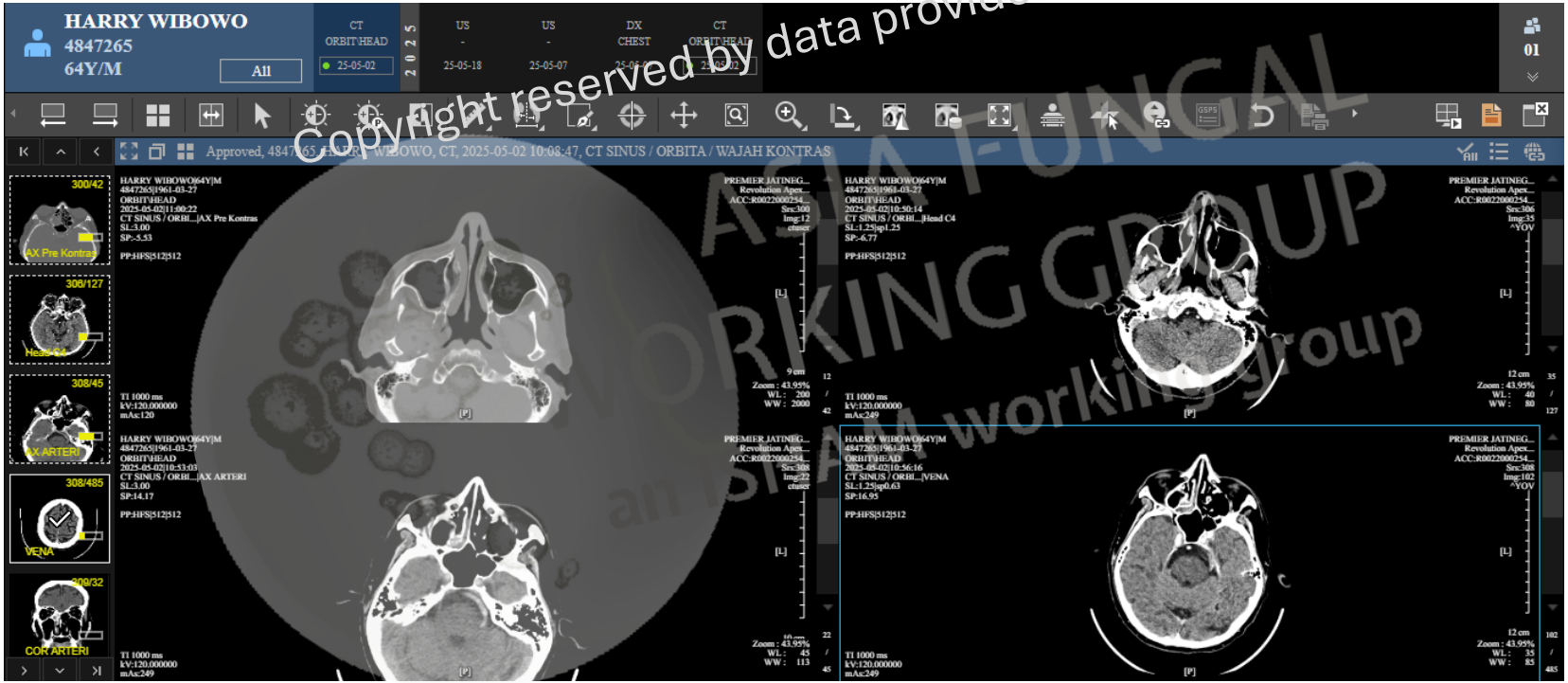
Sclera : icteric

No cranial nerve palsy

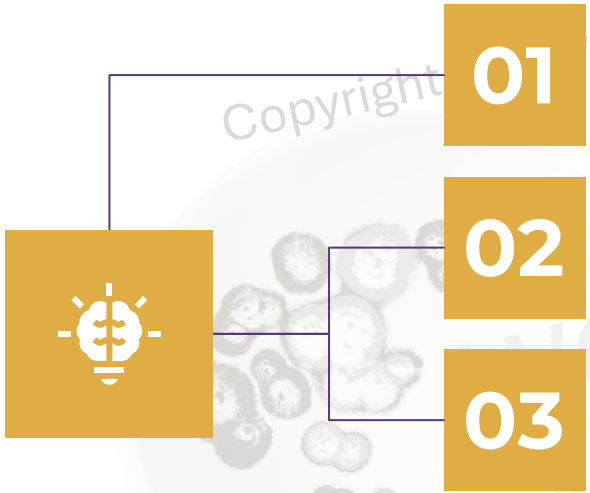
Abdominal USG : within normal limit

Nasoendoscopy (5 May 2025)

CT Scan – May 5, 2025



Assessment?



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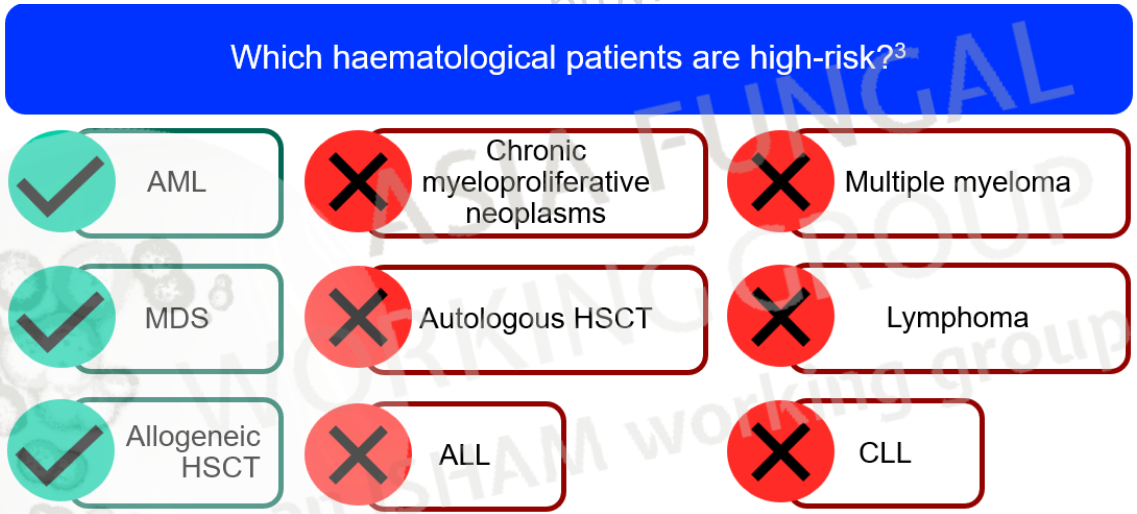
Population at risk of Invasive Mold Infection



ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplant; IFI, invasive fungal infection; MDS, myelodysplastic syndrome; SOT, solid organ transplant

1. Barton R. *Scientifica.* 2013;2013:459405;
2. Mercier T and Maertens J. *J Antimicrob Chemother.* 2017;72(Suppl. 1):i29–i38;
3. Maertens JA, *et al. J Antimicrob Chemother.* 2018;73:3221–30.

Clinical Presentation

Categories	Clinical presentation
Constitutional symptoms	fever (9-100%), headache (25-100%), altered mental status (11-27%)
Sinonasal signs and symptoms	nasal congestion (14-100%), nasal crusting/eschar (8-90%), rhinorrhea (21-66%), necrotic mucosa (21-100%), septal perforation/ulceration (9-38%)
Other otolaryngologic signs and symptoms	facial swelling (27-100%), facial/orbital/jaw pain (14- 86%), palate ulceration (5% to 25%), cough (up to 64%), trigeminal neuralgia (up to 25%)
Cranial nerve symptoms (25% to 49%)	
Ophthalmologic symptoms	

Int Forum Allergy Rhinol. 2023;13:1615–1714.

Clinical Presentation

Categories	Clinical presentation
Constitutional symptoms	
Sinonasal signs and symptoms	
Other otolaryngologic signs and symptoms	
Cranial nerve symptoms (25% to 49%)	facial anesthesia (8-55%), palatal anesthesia (up to 8%),15 and facial paralysis (25-44%)
Ophthalmologic symptoms	Loss of visual acuity (26-87%), proptosis (16-100%), ophthalmoplegia (17-60%), diplopia/extraocular muscle weakness (9-50%), ptosis (up to 100%)

Int Forum Allergy Rhinol. 2023;13:1615–1714.

ASSESSMENT

01 Rhinosinusitis, suspicion of Invasive Fungal Rhinosinusitis -- Mucormycosis dd/ Aspergillosis

02 Very severe anemia aplastic

03 Jaundice – suspicion of drug hepatotoxicity dd/ Invasive fungal infection

Diagnostic Plan?

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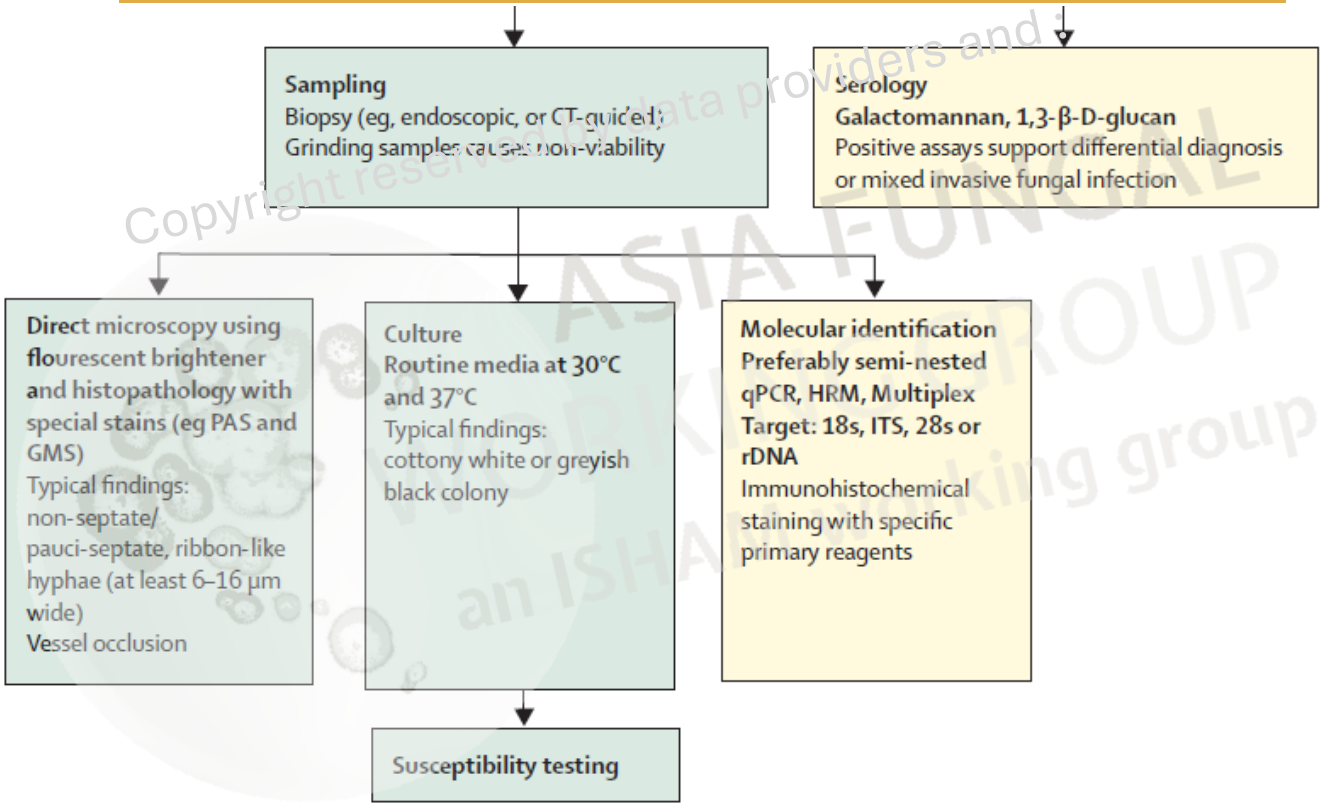
Invasive FRS:



Cornely OA, et al. Lancet Infect Dis 2019. doi.org/10.1016/S1473 3099(19)30312-3.

Diagnosis, Prognosticators, and Management of Acute Invasive Fungal Rhinosinusitis: Multidisciplinary Consensus Statement and Evidence-Based Review with Recommendations

Aggregate Grade of Evidence	**C (Level 2: 2 studies; Level 3: 3 studies; Level 4: 9 studies)**
Benefit	Fungal cultures are important for speciation as different organisms have different antimicrobial susceptibility profiles and affect prognosis. When combined with histopathology, the sensitivity and rate of correct diagnosis is increased compared with either alone.
Harm	Tissue culture requires either a bedside procedure or general anesthesia in the operating room to acquire a sample, each carrying its own morbidity. Cultures can take up to 7 days to result and can yield no growth.
Cost	Delayed diagnosis.
Benefit–Harm Assessment	When used to supplement histopathology, fungal species identification carries a benefit for diagnosis and management of AIFS. Tissue samples for culture can be obtained during the procedure to obtain samples for histopathology with very little additional morbidity.
Value Judgment	Culture is important for fungal species identification and to supplement histopathology for improved diagnostic accuracy.
Policy Level	Recommendation: Recommend obtaining tissue cultures whenever possible.
Intervention	Obtain tissue samples for culture when working up a patient for AIFS.

Int Forum Allergy Rhinol. 2023;13:1615–1714.

Diagnosis, Prognosticators, and Management of Acute Invasive Fungal Rhinosinusitis: Multidisciplinary Consensus Statement and Evidence-Based Review with Recommendations

Aggregate Grade of Evidence	**C (Level 2: 1 study; Level 3: 1 study; Level 4: 2 studies)**
Benefit	Microscopic direct tissue examination can aid in the diagnosis of AIFS.
Harm	Sampling error can lead to a false negative diagnosis. Potassium hydroxide, Grocott–Gomori methanamine silver, and hematoxylin–eosin staining may not identify fungal elements and cannot provide fungal species information.
Cost	If fungal elements are not identified, there may be a delay in AIFS diagnosis and treatment.
Benefit–Harm Assessment	Direct examination of tissue for fungal elements can provide a rapid diagnosis of AIFS if fungal elements are seen. False-negative results are possible, but this can be worked around using direct examination as a complement to culture, PCR, and histopathology.
Value Judgment	Direct examination can be used to promptly identify fungal organisms in tissue during the workup of AIFS.
Policy Level	Recommendation: Recommend using direct examination of tissue during the workup of AIFS.
Intervention	During the workup of suspected AIFS, direct examination of tissue should be performed in conjunction with cultures, PCR, and histopathology.

Diagnosis, Prognosticators, and Management of Acute Invasive Fungal Rhinosinusitis: Multidisciplinary Consensus Statement and Evidence-Based Review with Recommendations

Aggregate Grade of Evidence	**C (Level 2: 1 study; Level 3: 3 studies; Level 4: 5 studies)**
Benefit	Serum GM can be used to aid in the diagnosis of AIFS.
Harm	Blood samples are required. It is more associated with invasive *Aspergillus* infections, which is one of many fungi that may cause AIFS. There is a non-negligible rate of false positivity that must be taken into consideration.
Cost	Missed diagnoses and false-positive results are a risk.
Benefit–Harm Assessment	When used as a part of the workup of AIFS, serum GM levels can be useful to raise suspicion and aid in diagnosis. Any harm from missed diagnoses/false positives can be tempered by using serum GM as a supplement and not as the only method.
Value Judgment	Use serum GM in addition to alternative methods to diagnose AIFS.
Policy Level	Option: Obtaining serum GM is an option in the workup of AIFS.
Intervention	Serum GM can be obtained as a supplement to other, more well-established means of diagnosis but should not be utilized as a stand-alone diagnostic test for AIFS due to significant limitations.

Int Forum Allergy Rhinol. 2023;13:1615–1714.

of hyphae on frozen section or cytologic analysis does not confirm invasive disease, and in patients without obvious mucosal changes on nasal endoscopy a biopsy may be "random" leading to a false negative. It could be argued that, when obvious mucosal changes exist (e.g., discoloration or necrosis), the patient should proceed directly to the operating room for both tissue sampling and debridement. Nonetheless, when feasible, either endoscopic tissue biopsy or FNAB may help support the decision to initiative appropriate treatment. Table 11 summarizes evidence surrounding use of bedside biopsy for AIFS diagnosis.

Aggregate Grade of Evidence	C (Level 4: 4 studies; Level 5: 1 study)
Benefit	Detection of fungal elements at the bedside can better inform the need for surgical debridement.
Harm	There is limited tissue sampling that can be performed given patient discomfort and associated comorbid conditions, which limit safe removal of tissue.
Cost	Direct costs are attributable to frozen section analysis. Biopsies obtained at the bedside and waiting for histopathologic analysis may delay operative debridement.
Aggregate Grade of Evidence	C (Level 3: 1 study; Level 4: 6 studies)
Benefit–Harm Assessment	In cases where the diagnosis of AIFS is equivocal in an at-risk patient, bedside biopsies, particularly in abnormal tissue, may help gather more data in support of the decision to perform surgical debridement. This may be useful for diagnosis in patients who are unstable for surgery.
Value Judgments	Bedside biopsy may provide the most benefit when used to rule in AIFS, or when mucosal abnormalities can be sampled without significant bleeding risk or pain. FNAB serves as a minimally invasive alternative to endoscopic bedside biopsy, but may not yet be widely available.
Policy Level	Option: Bedside biopsy is an option in the workup of AIFS.
Intervention	Bedside biopsy may serve a role where mucosa can be sampled at the bedside with relative ease, but there is a risk of both false-negative and false-positive results. Care must be taken for patients at elevated risk for bleeding.

7 | IMAGING

Cross-sectional imaging with CT and MRI play vital roles as noninvasive diagnostic tests for the diagnosis

Diagnostic Plan

Laboratory Tests:

- Complete blood count, AST (SGOT), ALT (SGPT), electrolytes, total/direct/indirect bilirubin
- Galactomannan assay
- Fungal microscopy, culture
- Histopathology (pending for debridement)

Initial management plan?

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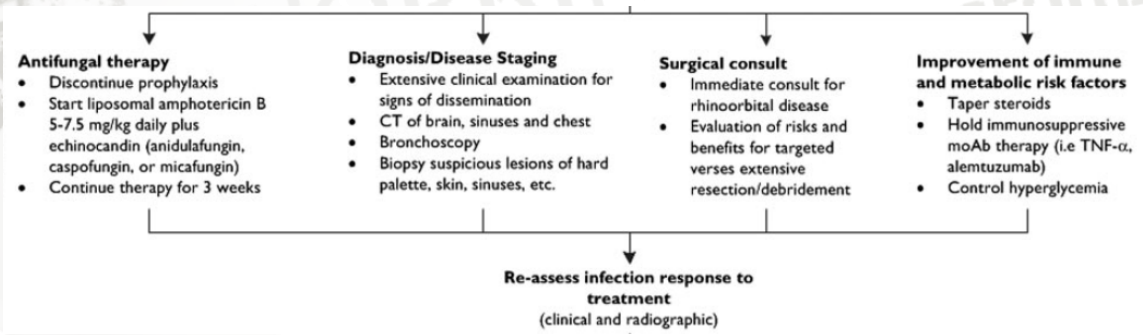
Key Steps of Successful Treatment

- Early diagnosis
- Reversal of underlying predisposing risk factors
- Surgical debridement
- Prompt antifungal therapy



Spellberg B, et al. Clin Microbiol Rev. 2005, 18:556–569.
Kontoyiannis DP, et al. Blood. 2011; DOI 10.1182/blood-2011-03-316430.

Management Plan

Medications & Fluids:

- IVFD NaCl 0.95% 50 mL every 12 hours
- Isavuconazole 200 mg tid 2 days, then 200 mg qd day 3 afterwards IV
- Filgastrim 300 mcg SC once daily
- Methylprednisolone : switch to 8 mg orally twice daily, discontinue IV administration
- Paracetamol 1 g IV

- Planned for debridement in the operating room but currently awaiting improvement in hemostasis.

	5 May 2025	6 May 2025	7 May 2025	8 May 2025	9 May 2025	12 May 2025
Hb (g/dL)	9.5	6.6	8.5	8.5	8.8	7.6
Ht (%)	26.3	18.3	24.2	24.1	24.5	22
WBC (x 10^3 uL)	0.94	0.42	0.47	0.59	0.99	0.93
Platelets (x 10^3 uL)	10	92	64	51	39	10
Bil T/D/I	6.3/3.8/2.5					
SGOT/PT	98/121					**Serum GM:** negative

- FFP 500 mL with premedication of diphenhydramine 10 mg IV
- 1 unit TC Apheresis with premedication of diphenhydramine 10 mg IV

- 500 mL leukodepleted PRC, with 1 ampoule IV diphenhydramine premedication

- 500 mL leukodepleted PRC, with 1 ampoule IV diphenhydramine premedication

- Pooled platelet concentrate/pheresis transfusion once daily for 2 consecutive days, premedicated with Diphenhydramine 1 amp IV + Dexamethasone 1 amp
- PRC LD (Packed Red Cells Leukodepleted) transfusion 300 cc

Susceptibility testing

Received: May 7, 2025 / Result: May 13, 2025

- **CLINICAL DATA** : Suspected invasive fungal rhinosinusitis, suspected Mucorales
- **SAMPLE TYPE** : Nasal tissue
- **EXAMINATION METHOD** : Susceptibility testing
- **RESULT** : **Susceptibility testing**
  Aspergillus fumigatus
  Amphotericin B : Sensitive
  Itrakonazol : Sensitive
  Ketokonazol : Sensitive
  Vorikonazol : Sensitive
- **CONCLUSION** : All antifungal agents listed above are sensitive to the live tissue sample.

	14 May 2025	15 May 2025	16 May 2025	16 May 2025	18 May 2025	18 May 2025
Hb (g/dL)	6.5	8.2	7.3	6.8	7.5	7.9
Ht (%)	18.3	23.4	20.7	19.3	21.9	23.2
WBC (x 10^3 uL)	0.31	0.22	0.28	0.15	0.12	0.08
Platelets (x 10^3 uL)	40	34	37	44	1	5

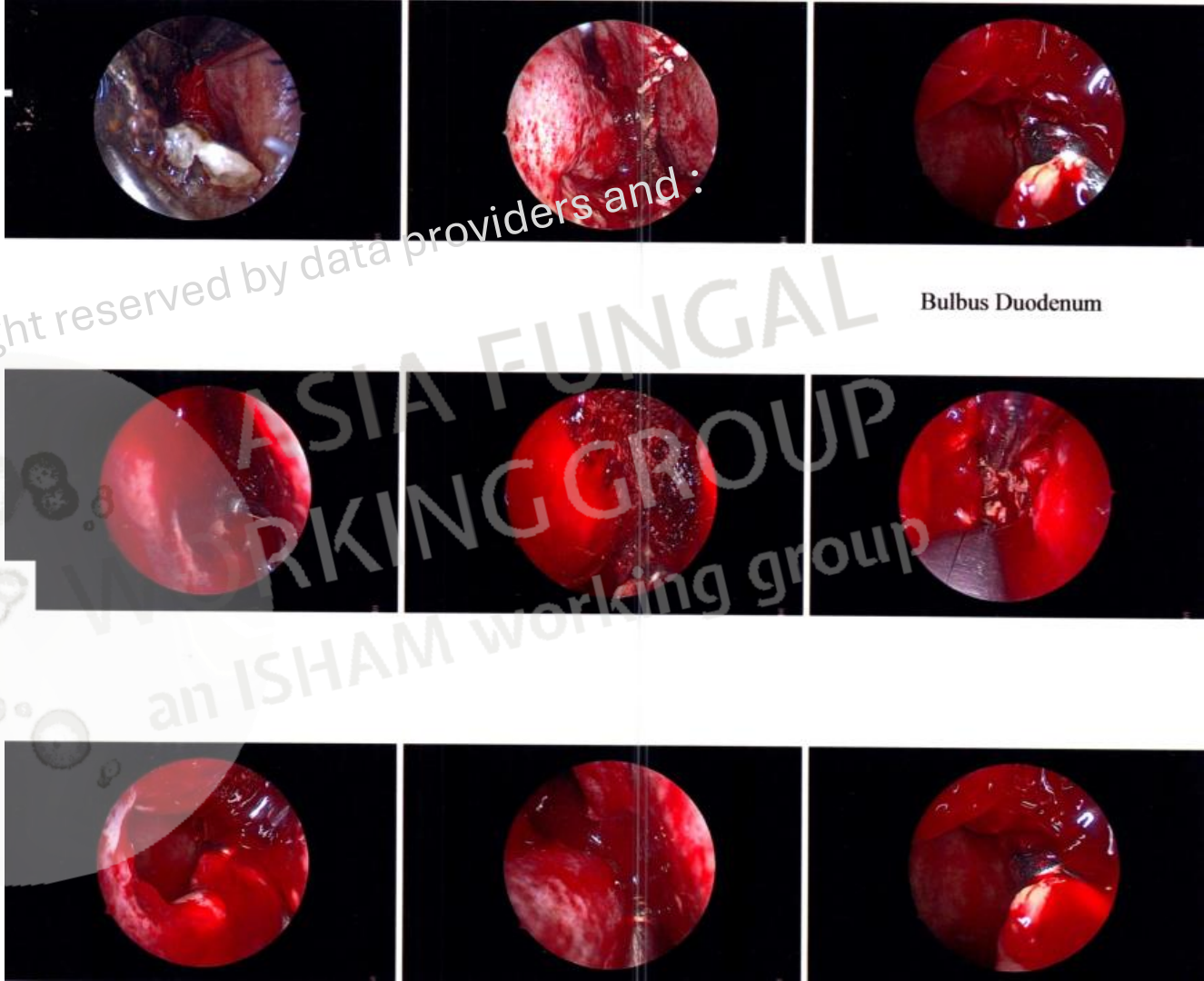
- Transfusion apheresis platelet concentrate (1 unit) + Leukodepleted packed red cells (PRC LD) 500 cc

- **DEBRIDEMENT**
- Apheresis platelet transfusion 1 unit before procedure (at 16:00)
- PRC LD 300 cc and tranexamic acid 3 x 500 mg IV post-procedure

- PRC LD (Leukodepleted Packed Red Cells) transfusion 300 mL (available blood)
- PRC LD 300 cc and tranexamic acid 3 × 500 mg IV post-procedure

- PRC LD (Leukodepleted Packed Red Cells) transfusion 300 mL (available blood)
- PRC LD 300 cc and tranexamic acid 3 × 500 mg IV post-procedure

FESS + debridement (15 May 2025)



Follow Up – 18 May 2025

Hemodynamically unstable, with a tendency toward low BP at 84/44 mmHg supported by NE at 0.3 mcg/kgBW/min, HR 135 bpm, on NRM at 15 L/min, RR 30–40 breaths per minute.

At 10:00 PM, arterial blood gas (ABG) was checked: PaO_2 = 96.3 mmHg, $PaCO_2$ = 32.5 mmHg. HFNC was initiated.

At 10:00 PM, blood glucose 75 mg/dL. Administered 2 vials of 40% Dextrose. Rechecked at 12:30 AM — BG was low, given 4 more vials of D40%, followed by continuous infusion at 15 mL/hour. Rechecked at 1:30 AM — BG was 106 mg/dL. Lactate level was 10.2 mmol/L — given a loading of Asering (Total 500 mL). History of hypokalemia with potassium level of 3.2 mmol/L in the ward — corrected with 50 mEq KCl over 8 hours.

At 10:15 PM, critical lab values: platelet count 5,000/µL, Hb 7.9 g/dL. Transfused 1 unit of TC apheresis and 300 mL of leukocyte-depleted PRC

At 1:00 AM, blood pressure remained low; NE was increased up to 0.5 mcg/kgBW/min.

At 3:10 AM, HR began to decrease to 89 bpm. The on-call doctor was notified. The family was informed and requested full resuscitation efforts, including CPR and intubation.

At 03:20, the patient was intubated using an ETT size 7.5, positioned at 20 cm depth.
At 03:28, HR dropped to 50 bpm and progressed to asystole. CPR was performed for 44 minutes, with a total of 5 ampoules of epinephrine administered.
At 04:06, the patient was declared deceased.

Parasitology Examination

Date Received: May 16, 2025 / Date Collected: May 23, 2025

- **CLINICAL DATA** : Suspected invasive fungal infection, fungus in the nasal cavity
- **SAMPLE TYPE** : Septal tissue
- **EXAMINATION METHOD** : Direct smear, culture, and susceptibility testing
- **Result** : Direct smear: **Presence of true septate hyphae (+)**
  Culture: Fungal colony growth of ***Aspergillus fumigatus***
  Susceptibility testing:
  Aspergillus fumigatus
  Amphotericin B : ***Susceptible dose-dependent (SDD)***
  Itrakonazol : Sensitive
  Ketokonazol : Sensitive
  Vorikonazol : Sensitive
- **KESIMPULAN** : ***Aspergillus fumigatus*** colony growth was found in the septal tissue sample. The presence of this fungus in the septal tissue may indicate colonization or be the causative pathogen.

Pathological Anatomy Report

- **Date Received** : May 16, 2025 / Date Reported: June 2, 2025
- **CLINICAL DIAGNOSIS** : Invasive fungal rhinosinusitis
- **CLINICAL NOTES** : Ethmoid cell mucosa

Macroscopic	Start of Surgery: 19:30 Time Tissue Removed from Body: – Time Fixation Began: 20:00 Number of Tissue Samples Sent: – Fixative Volume: 10x the volume of the tissue Date of Sectioning: May 16, 2025, at 12:30 Received 1 bottle labeled with the name HW, without additional information, containing irregular tissue fragments measuring 0.4 × 0.3 × 0.3 cm, brown, firm consistency. All fragments were processed and embedded in 1 cassette.
Microscopic	Surgical specimen from the ethmoid sinus shows fragments of tissue, some of which are lined by pseudostratified ciliated columnar epithelium. The stroma appears edematous with mild to moderate infiltration of inflammatory cells, including lymphocytes, plasma cells, and a few polymorphonuclear (PMN) cells. Fungal hyphae are observed among the tissue. Areas with fibrotic stroma, seromucinous glands, and non-neoplastic cartilage are also noted. Grocott methenamine silver (GMS) staining yields a positive result for fungal hyphae and spores. Topography code: C31.1 (Ethmoid sinus) Morphology code: H473.2 (Invasive fungal sinusitis)
Conclusion	The histological findings are consistent with chronic sinusitis with fungal colonies, **suggestive of invasive fungal rhinosinusitis.**

Points of Discussion

- Clue of early suspicion of invasive fungal rhinosinusitis
- Role of biomarker
- Debridement – perfect time
- Antifungal of choice
- Prophylaxis: when and how?
- Suggestion to improve patient outcome

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THANK YOU

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Infections Table of Contents
Discussion

OVERALL INFECTION RISK IN PATIENTS WITH CANCER[a]	DISEASE/THERAPY EXAMPLES	FEVER & NEUTROPENIA RISK (See FEV-2)	ANTIMICROBIAL PROPHYLAXIS [d,e,f,g,h,i]
Low	• Standard chemotherapy regimens for most solid tumors • Anticipated neutropenia less than 7 d	Incidence low	• Bacterial - None • Fungal - None • Viral - None unless prior HSV episode
Intermediate	• Autologous HCT • Lymphoma[c] • Multiple myeloma[c] • CLL[c] • Purine analog therapy (ie, fludarabine, clofarabine, nelarabine, cladribine) • Anticipated neutropenia 7–10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - Consider prophylaxis during neutropenia and for anticipated mucositis (See INF-2); consider PCP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)
High[b]	• Allogeneic HCT including cord blood • Acute leukemia ▸ Induction ▸ Consolidation • Alemtuzumab therapy • GVHD treated with high-dose steroids (>20 mg daily) • Anticipated neutropenia greater than 10 d	Incidence usually high, significant variability may exist	• Bacterial - Consider fluoroquinolone prophylaxis • Fungal - Consider prophylaxis during neutropenia (See INF-2); consider PCP prophylaxis (See INF-6) • Viral - During neutropenia and longer depending on risk (See INF-3, INF-4, INF-5)

KEY: CLL = chronic lymphocytic leukemia, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant, HSV = herpes simplex virus, PCP = *p*neumo*c*ystis *p*neumonia

[a]Categories of risk are based on several factors, including underlying malignancy, whether disease is in remission, duration of neutropenia, prior exposure to chemotherapy, and intensity of immunosuppressive therapy.

[b]In high-risk patients, additional prophylaxis may be necessary; for example, consider penicillin and TMP/SMX for allogeneic HCT recipients with GVHD.

[c]This is a heterogenous disease. Therefore, treatment modalities and the type of malignancy affect risk level.

Table 26
Primary prophylaxis

Population	Intention	Intervention	SoR	QoE	Comment
Haematological malignancies, e.g. AML with prolonged and profound neutropenia	Lower incidence of IA	Posaconazole 200 mg tid suspension or 300 mg tablet qd	A	I	AML/MDS induction only. TDM especially with oral suspension. Tablets more bioavailable, bridging with posaconazole IV formulation possible
		L-AmB 12.5 mg 2 ×/weekly, nebulized, with undetermined dose of fluconazole	B	I	AML
		ABLC 3 mg/kg 3 ×/weekly	C	II_h	No difference to L-AmB regimen
		Micafungin 50 mg qd	C	II_t	
		L-AmB 10 mg/kg q7d	C	II_u	
		L-AmB 50 mg abs q2d	C	II_u	
		L-AmB 15 mg/kg q14 d	C	II_u	
		Voriconazole	C	II_t	Not better than fluconazole
		Itraconazole 400 mg/day, oral solution	D	II	No difference to fluconazole ($n = 195$) and more toxicity
Acute lymphoblastic leukaemia, remission induction chemotherapy	Lower incidence of IA	L-AmB 5 mg/kg biw	D	I	L-AmB more toxic than placebo, no significant reduction in IA rate
Autologous HSCT or treatment of haematological malignancies besides acute leukaemia	Lower incidence of IA	Any mould active agent	D	III	
Allogeneic HSCT (until neutrophil recovery)	Lower incidence of IA	Posaconazole 200 mg tid suspension or 300 mg tablet qd	B	II_t	Neutropenia duration approximately identical, TDM
		L-AmB 12.5 mg biw, nebulized, with fluconazole	B	II_t	
		Voriconazole 200 mg bid	C	I	Not better than fluconazole, TDM
		Micafungin 50 mg/day	C	I	But no difference in subgroup analysis for aspergillosis
		Itraconazole 400 mg/day oral solution	D	I	Toxicity issues; TDM
Allogeneic HSCT (after neutrophil recovery and no GvHD)		Any antifungal agent	D	III	No study demonstrated outcome advantage
Allogeneic HSCT (with moderate to severe GvHD and/or intensified immuno-suppression)		Posaconazole 200 mg tid suspension or 300 mg tablet qd	A	I	TDM
		Voriconazole 200 mg bid	C	II	Not better than fluconazole; TDM
		itraconazole 400 mg/day, oral solution	C	II	Toxicity issues; TDM
		Micafungin 50 mg/day	C	III	Only few patients with GVHD
Allogeneic HSCT (until neutrophil recovery)	To reduce IA attributable mortality	Posaconazole 200 mg tid suspension or 300 mg tablet qd	B	II_t	Neutropenia duration approximately identical; TDM
Allogeneic HSCT (after neutrophil recovery, without GvHD)		Any other antifungal	D	III	No study demonstrated outcome advantage
Allogeneic HSCT (with moderate to severe GvHD and/or intensified immuno-suppression)		Posaconazole 200 mg tid suspension or 300 mg tablet qd	A	II	Mainly IFD-attributable mortality, TDM