AML and IFI

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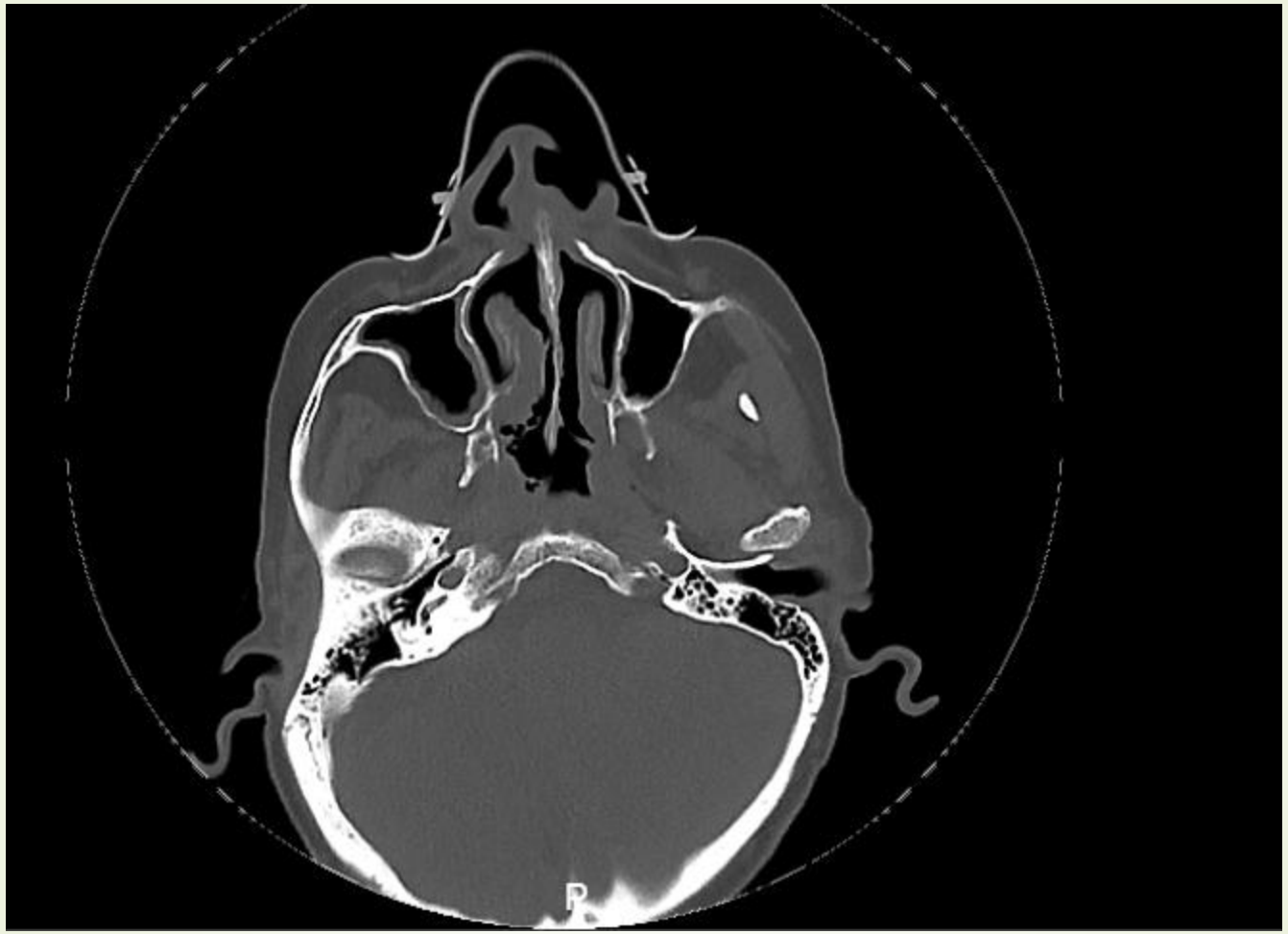
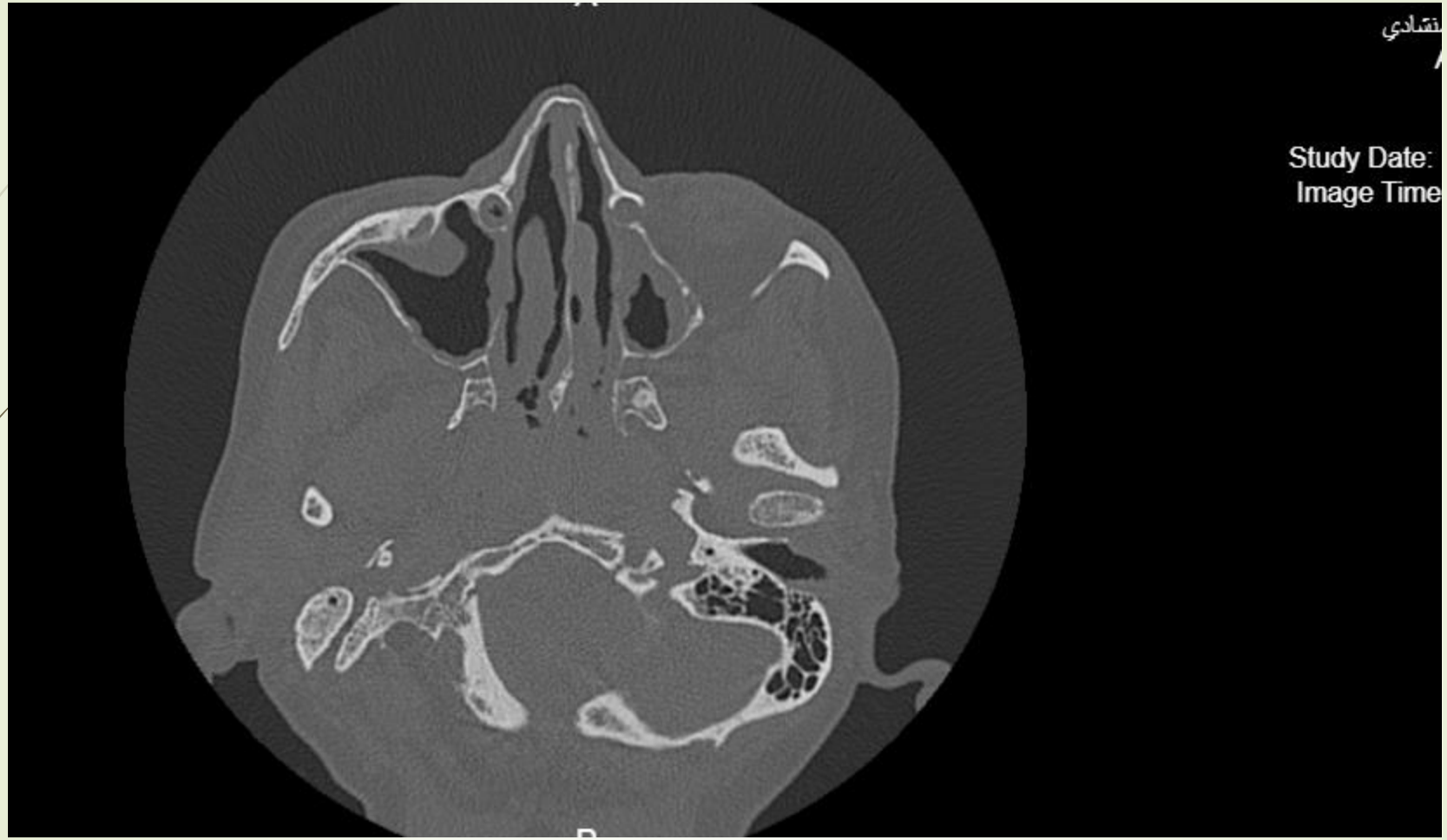
Case presentation:

- A 70 -year -old lady was admitted to hospital because of fever, malaise , oral cavity ulcer, dyspnea and epistaxis.
- The patient had received chemotherapy for the past 20 days due to AML.
- Physical exam: the appearance was ill, periorbital edema and necrotic ulcer in hard palate was remarkable.

Lab.data:

- CBC:
- WBC: 87.500 , seg=7%, lymph=8%, mono= 3%, blast: 82%
- Hb:6.3
- PLT:40 000, 15 000, 7 000
- ALT: 57
- AST:68
- CRP:61
- Cr: 0.8

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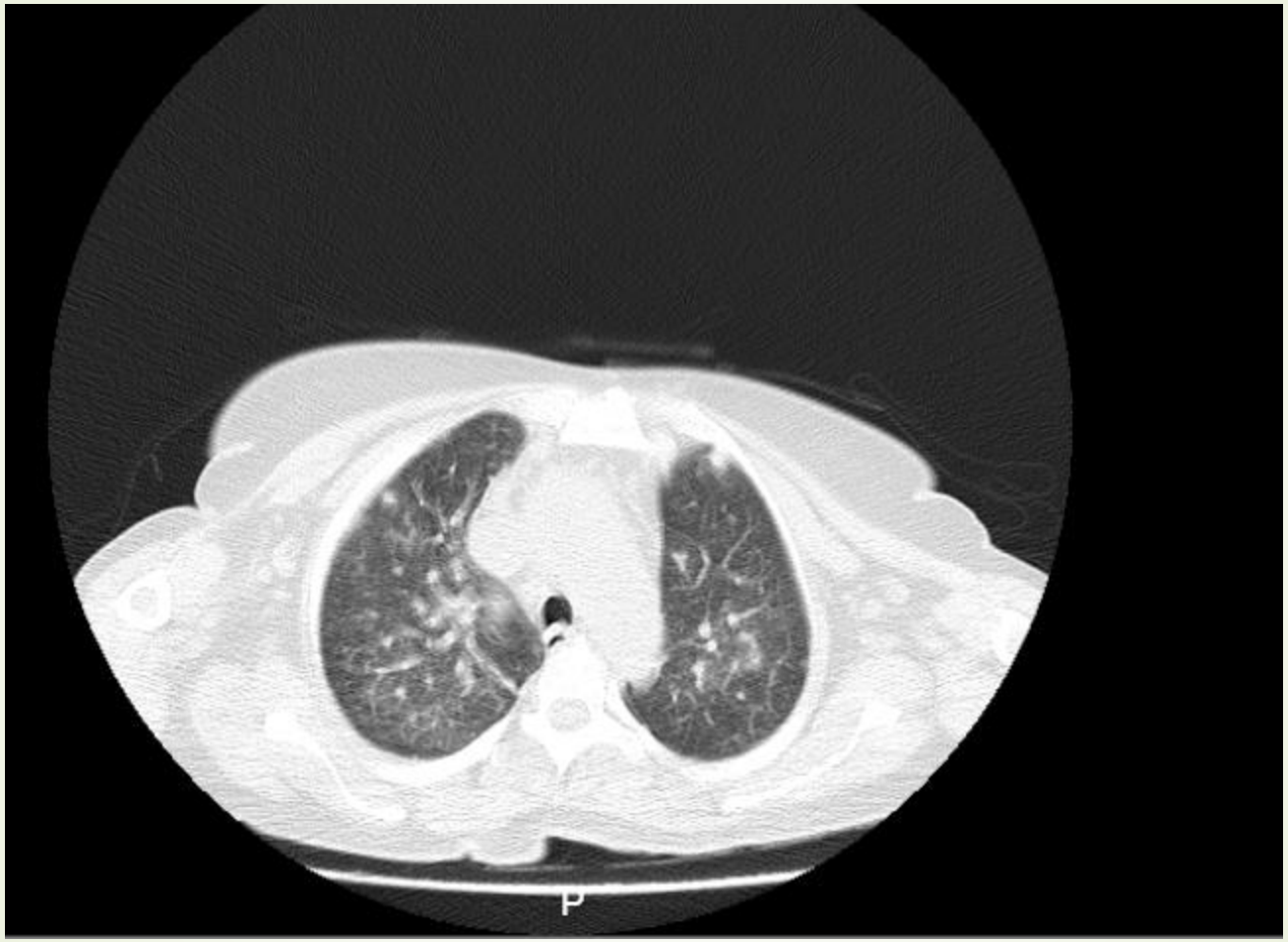
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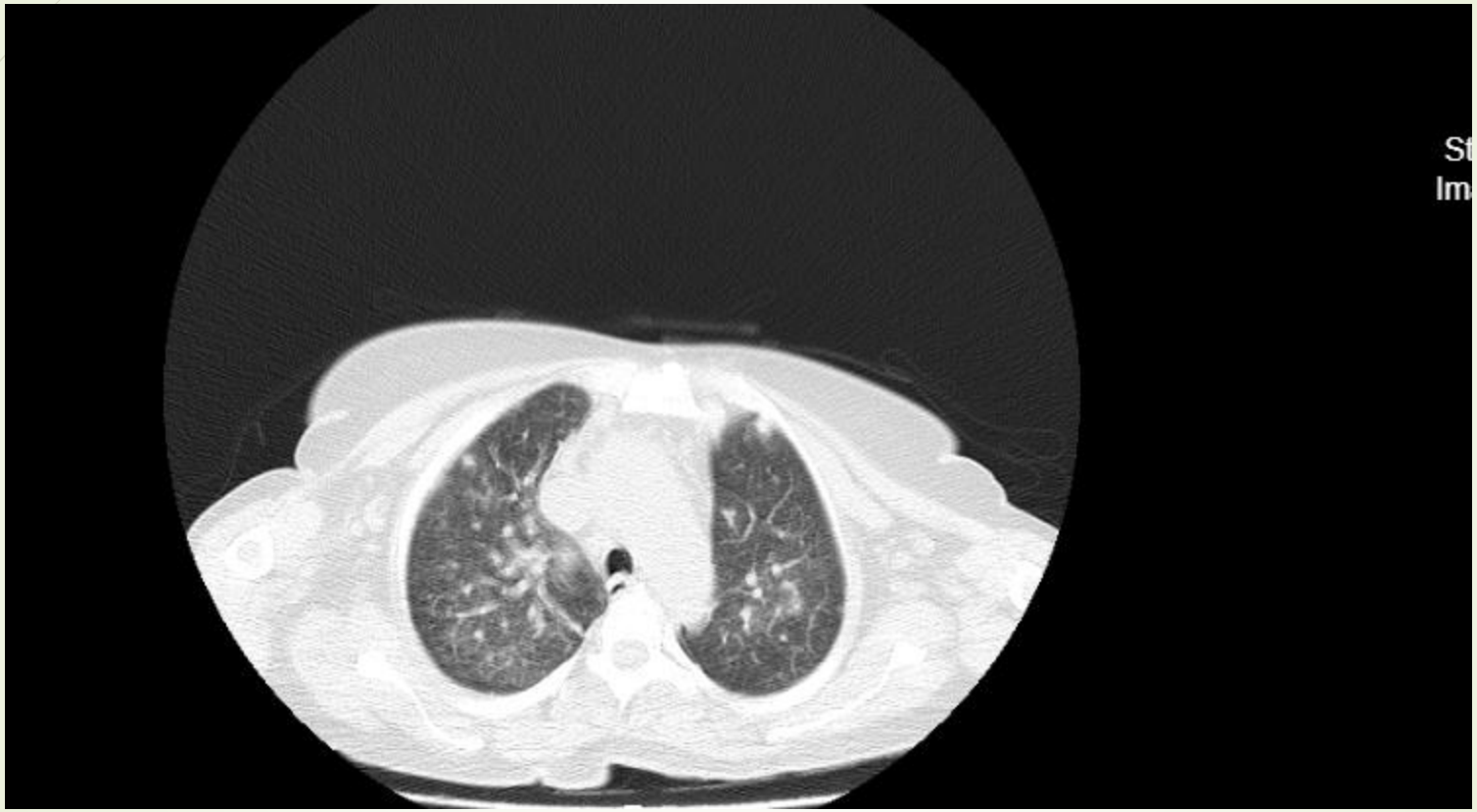

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- Resection of sinuses was done after receiving platelet.
- The patient was admitted to the intensive care unit.
- Meropenem+vancomycin+ amphotericin liposomal was ordered.

Pathology:

- Nasal lesion resection: positive for fungal element, compatible with mucormycosis.
- Palate lesion: positive for fungal element compatible with mucormycosis.
- Nasal septum lesion resection: positive for fungal element compatible with mucormycosis.

Introduction:

- Due to indwelling venous catheters and toxicities of conditioning regimens, in particular, mucositis and gastrointestinal barrier impairment, both Gram-positive and Gram negative bacteria may cause fever and infection after high dose chemotherapy.

- Invasive fungal disease

- Review article : Prophylaxis, diagnosis and therapy of infections in patients undergoing high-dose chemotherapy and autologous haematopoietic stem cell transplantation. 2020 updateof the recommendations of the Infectious Diseases Working Party(AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). Annals of Hematology (2021) 100:321–336

Risk stratification:

- Patients with expected neutropenia < 500/µl for at least 8 days : high risk.
- Duration of neutropenia of up to 7 days: at standard risk for the development of an infection.
- Febrile neutropenia:
- Thorough physical examination of a febrile neutropenic patient is mandatory.
- Respiratory symptoms: spiral chest CT scan

Mucormycosis:

- Mucormycosis is an opportunistic fungal disease with high morbidity that primarily affects patients with decreased immunity.
- In the past two decades, it has become the third most prevalent invasive mold disease in patients with hematologic malignancies(HM), following candidiasis and aspergillosis.

- Nasal and cutaneous mucormycosis. Frontiers in Cellular and Infection Microbiology 01 frontiersin.16 September 2022.

Risk factors:

- diabetes mellitus, ketoacidosis
- HM, other cancers(poor prognosis)
- hematopoietic stem cell transplantation,
- neutropenia,
- corticosteroids,
- trauma, normal people
- iron overload,
- IDU
- Neonatal prematurity,
- and malnutrition

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- Pulmonary, rhino-orbital-cerebral, cutaneous, and disseminated are the most common clinical manifestations of mucormycosis.
- Invasive mucormycosis is difficult to diagnose owing to nonspecific clinical manifestations and imaging.
- Owing to the rapid progression of mucormycosis, timely diagnosis and the administration of antifungal therapy are crucial to improve patient prognosis.(more than 6 days of treatment delay doubled the mortality rate).

Clinical manifestations:

- fever
- Pulmonary mucormycosis The triad of "cough, dyspnea, chest pain", hemoptysis.

- Chest X.ray&spiral chest CT scan: cavity, ground-glass lesion, consolidation, pleural effusion, atelectasis, halo sign, reverse halo sign, air-crescent sign.

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- Rhino-orbital mucormycosis :
- Facial edema, pain, nasal congestion, rhinorrhea, eye pain, chemosis, proptosis,epiphora, and palatal ulcer destruction.

- Imaging:
- Thickened oedematous mucosa, opacification or obliteration of paranasal sinuses and bony destruction in CT.

Diagnosis:

- Early diagnosis and timely effective treatment are keys to improving the survival probability of IM in patients with HMs.
- The accurate diagnosis of IM relies on a series of a high index of suspicion, assessment of presenting signs and symptoms, radiographical studies, cultures and direct examinations of clinical specimens, and histopathology.

- Notably, there are no commercially available biomarkers to identify this disease.
- β-D-glucan and galactomannan assays do not detect antige components of Mucorales cell wall.

Diagnosis:

- Generally, histopathology and culture are gold standards for IM diagnosis.

- **Probable IM diagnosis** is based on corresponding host factors (such as neutropenia, allo-HSCT, HMs…), imaging features (including "reverse halo" sign, multiple (≥10) nodules on pulmonary CT scan, vessel occlusion on CT pulmonary angiography or sinusitis, bony destruction on cranial CT or MRI) and culture or microscopical detection from sputum, BAL, bronchial brush, or aspirate.

Therapy:

- Treating underlying diseases, reducing or stopping corticosteroids and other immunosuppressive treatments.

- **First-Line Treatment:**
- Radical surgical debridement with margins clear of infection for the treatment of IM if conditions permit.
- Two or more debridement operations.

- Global guideline for the diagnosis and management of mucormycosis: An initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect. Dis. 2019

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- Patients with HMs often cannot tolerate surgery due to serious underlying diseases, coagulation dysfunction and disseminated mucormycosis; so, the role of surgery is limited.

Liposomal Amphotericin B (L-AmB)

- L-AmB has a strong anti-Mucorales activity whose minimum inhibitory concentration against most strains of Mucorales in vitro is less than 1 μg/mL.
- First choice for treatment of IM.
- Nephrotoxicity
- L-AmB combined with surgery is strongly recommended as the first-line treatment of IM by ECMM guidelines.
- 5–10 mg/kg

Isavuconazole:

- Is a new generation of broad-spectrum triazoles with good pharmacokinetic characteristics.
- Isavuconazole IS approved as one of the first-line antifungals of IM in the United States, while it IS approved to treat patients with IM who are not suitable for AmB in Europe.
- CNS Infection?
- Compared with other azole drugs, isavuconazole not only has a broad antifungal spectrum, but also has higher safety.

Clinical use:

- lacks an FDA indication for invasive candidiasis.
- Isavuconazole is currently FDA approved for the treatment of invasive aspergillosis based on a global, multicenter, randomized double-blind trial.
- The second of the current FDA-approved indications for isavuconazole is the treatment of invasive mucormycosis in adults
- New Perspectives on Antimicrobial Agents: Isavuconazole. Antimicrob Agents Chemother 2022 .

CLINICAL USE: PROPHYLAXIS

- The use of mold-active prophylaxis, specifically posaconazole, is recommended in patients at high risk for invasive fungal infections (IFIs):
- prolonged neutropenia due to chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS),
- and hematopoietic cell transplant (HCT) recipients requiring augmented immunosuppression for graft-versus-host disease (GVHD)

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- Isavuconazole represents an attractive alternative to posaconazole for primary prophylaxis due to its similar spectrum of anti-fungal activity and proven efficacy in treating invasive aspergillosis and mucormycosis in similar patient populations. ???

- In addition, the tolerability, reliability of absorption with oral administration, favorable drug–drug interaction profile, and lack of QTc interval prolongation make the compound appealing in this setting.

Isavuconazole:

- loading dose 372 mg of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) three times daily for 2 days, orally or intravenously, and then changed to a maintenance dose 372 mg of isavuconazonium sulfate once daily.

- therapeutic drug monitoring is not routinely required for isavuconazole.

Posaconazole Iv Formulation/Delayed Release Tablet

- It can be seen that posaconazole new formulations had good efficacy and safety as the **first-line treatment or salvage treatment** of IM in patients with HMs, but due to the limited sample size of the study, the exact efficacy of the drug needs to be further verified.
- The recommended dose of posaconazole intravenous formulation and delayed release tablet was 300 mg twice a day on the first day, followed by 300 mg once a day, regardless of diet.
- Study: the author suggested that the trough level of posaconazole should be monitored on the fourth day of posaconazole delayed release tablet treatment.

Antifungals Combination Therapy:

- IM of patients with HMs is usually difficult to control and dose-dependent nephrotoxicity often makes patients unable to tolerate high doses of AmB; thus, these patients always have poor prognosis.
- **Study**: The result showed that compared with AmB monotherapy, initial treatment with AmB plus posaconazole new formulations or isavuconazole was associated with a trend toward lower treatment failure (43% vs. 64%, p = 0.136), although the difference was not statistically significant.

- Mucormycosis in Hematopoietic Cell Transplant Recipients and in Patients With Hematological Malignancies in the Era of New Antifungal Agents. Open Forum Infect. Dis. 2021.

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- **To sum up**, the combination of antifungals showed good therapeutic effect.

- Patients who have refractory IM, or who do not respond to monotherapy or who cannot tolerate the toxicities associated with high-dose L-AmB monotherapy, can choose antifungals combination therapy.

Salvage therapy:

- Patients who are with recurrent/refractory IM or intolerant to initial treatment of L-AmB need to turn to second-line treatment schemes.

- The ECMM guideline strongly recommended that isavuconazole, posaconazole intravenous formulations or tablets could be used as salvage treatment for patients with IM.

- Posaconazole is effective as salvage therapy in zygomycosis: A retrospective summary of 91 cases. Clin. Infect. Dis. **2006**,

BT-MCR:

- Breakthrough mucormycosis (BT-MCR) usually occurs in patients who are treated with antifungals without anti-Mucorales activity, mainly voriconazole and echinocandins.
- **STUDY**:Between 2000 and 2020, 103 patients experienced BT-MCR in a single center, among whom 16 patients developed BT-MCR while on Mucorales-active antifungals (nine cases of isavuconazole, six cases of posaconazole, one case of AmB) and the other 87 patients developed BT-MCR while on antifungals without anti-Mucorales activity such as voriconazole, echinocandins, and itraconazole.
- Clinical Features and Treatment Progress of Invasive Mucormycosis in Patients with Hematological Malignancies. J of Fungi 2023. Review

In conclusion:

- for patients who can tolerate surgical treatment, early debridement and removal of involved lesions can significantly improve the survival rate. However, surgery is not applicable to all patients.

- Patients with critical underlying diseases, coagulation disorders, and disseminated mucormycosis often cannot tolerate radical surgery.

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- L-AmB is still the drug of choice for treatment of IM, but the intravenous formulations and tablets of both isavuconazole and posaconazole are also effective antifungals of IM.
- Patients who are refractory to monotherapy or cannot tolerate toxicities associated with high doses of L-AmB can try combination therapy of antifungals.
- Patients who are refractory or intolerant to L-AmB initial therapy can turn to salvage treatment with isavuconazole or posaconazole.