How to Suitablely Manage the Mucormycosis—Recommended Dose of Liposomal Amphotericin B and Other Management of Risk Factors?

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Abstract

Mucormycosis was an acute and invasive fungal infection with a high mortality rate. The treatment of mucormycosis was challenging. And the incidence of the mucormycosis seems to be increasing. The key to Mucormycosis therapy not only depend on anti-Mucor infection, but also included the management of some risk factors. Liposomal amphotericin B (L-AMB) was the first line drug to treat mucormycosis. The dosage regimen recommended by the guideline was often associated with higher nephrotoxicity and morbidity. A pharmacokinetic/pharmacodynamic (PKPD) model was conducted to evaluate suitable dosage regimens in Mucormycosis patients. 10mg/kg/day LAMB recommended in the guidelines might not be needed. 5mg/kg/day LAMB might be sufficient to achieve the target value of PKPD and indicated a good anti-Mucor effect. Successful management of mucormycosis was also based on suitable management of several risk factors which played a very important role in the progression of mucormycosis, such as iron factor, diabetes mellitus with acidosis and thrombosis. Application of deferasirox, statins and keep platelet level might be promising approaches in mucormycosis therapy.

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Running title:The Key to Mucormycosis Therapy

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Abstract

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Key Words

Mucormycosis, Liposomal amphotericin B, Iron Overload, Diabetes Mellitus with Acidosis , Thrombosis

Mucormycosis was a rare, emerging fungal infection, with high morbidity and mortality[1]. It was an opportunistic fungal infection of the zygomycete family that could cause various types of infections[2]. First described by Paulltaf in 1885[3], mucormycosis ranked third in prevalence among patients with hematological and allogeneic stem cell transplantation, following candidiasis and aspergillosis respectively[3-5]. Infections normally occurred through ingestion of contaminated food, inhalation of spores into the nares or lungs, or inoculation into disrupted skin or wounds. The most common sites of infection were sinuses (39%), lungs (24%), disseminated (23%), skin and soft tissue infection (19%)[6]. Despite advances in diagnosis and treatment, mortality from mucormycosis still remained high (from 32 to 70% according to organ involvement)[7]. The unspecific clinical manifestations of the disease, combined with rapid progression, made the diagnosis and treatment of mucormycosis very challenging[8]. In fact, the management to mucormysis is not only limited to suitable antifungal therapy, but also include the management of risk factors, which refer to iron factor, diabetes mellitus with acidosis and thrombosis.

Anti-Mucor infection Therapy

1.1 The dosage regimens for Mucor infection in the guideline

International guidelines[1, 9, 10] strongly recommended liposomal amphotericin B (L-AMB) therapy (10mg/kg/d) as the first-line treatment of choice in patients with mucormycosis. A few studies[11, 12] indicated that L-AMB 10mg/kg/d achieved good clinical efficacy and did not result in severe nephrotoxicity. Murine models indicated that L-AmB and AmB lipid complex (ABLC) efficacy was dose dependent and the best results were obtained with 10 mg/kg[13]. However, LAMB at high dosage was often associated with higher nephrotoxicity[14]. Krüger WH et al also showed that administration of LAMB (10mg/kg/d) were associated with a high morbidity (93.3%) and low cure rate (7.14%)[15]. The dosage regimens for mucormycosis is not clear.

1.2 The dosage regimens for Mucor infection by PKPD method

Monte Carlo simulations were conducted using pharmacokinetic (PK) parameters and pharmacodynamic (PD) data to determine the probability of target attainment (PTA) and cumulative fraction of response (CFR) in terms of maximum plasma concentration/minimum inhibition concentration (C_{max}/MIC) targets of LAMB. Four dosing regimens of LAMB were evaluated. The dosing regimens of the LAMB included 1mg/kg/day, 3mg/kg/day, 5mg/kg/day and 7.5mg/kg/day. All the PK parameters (C_{max}) were obtained from previously published studies and were shown in Table 1[16-18]. The percentage MIC distribution of LAMB for Mucor spp. was obtained from one previous study[19]. Cmax/MIC=10 and Cmax/MIC=14.4 were the PK/PD targets of LAMB in the treatment of Aspergillus infection[20]. Because there was currently no specfic target value for LAMB for Mucor infection, we used the above target value to conduct Monte Carlo simulation. As shown in Table 2, the CFR of 5mg/kg/day LAMB could provide good coverage against Mucor spp. regardless of whether C_{max}/MIC=10 or C_{max}/MIC=14.4 was applied as a parameter. Fig 1 showed that 5mg/kg/day LAMB could achieve similar effects to higher doses of LAMB.

Monte carlo simulations illustrated that 5mg/kg/day LAMB might be sufficient to achieve the target value of PKPD and indicated a good anti-Mucor effect. Higher dose was not associated with improved efficacy. But it might lead to higher nephrotoxicity and mortality. As a result, the higher dose of 10mg/kg/day LAMB recommended in the guidelines might not be needed.

The reasons and management for the refractory Mucormycosis

To our knowledge, there was no definite treatment target value of L-AmB for Mucor infection. And in animal model, the area under the curve/minimum inhibition concentration (AUC/MIC) value of posaconazole for Mucor infection was lower than that for Aspergillus infection[20]. As a result, we speculated that the AUC/MIC value of amphotericin B for Mucor infection was also lower than that for Aspergillus infection. It illustrated anti-mucor infection might not be more difficult, compared with anti-Aspergillus. The key to the refractory of mucormycosis might depend on the management of risk factors. These risk factors were associated with the development of mucormycosis, including: iron factor, diabetes,especially with diabetic ketoacidosis and thrombus. These factors may also be important in treatment of Mucor infection.

2.1 Iron factor

2.1.1 The effect of iron overload in Mucormycosis

Iron had an essential role in the life cycle of Mucor and its utilization from the host was a critical pathogenetic mechanism of mucormycosis[21-25]. Patients with iron overload were predisposed to developing mucormycosis[23, 26]. Besides, another study[27] illustrated that iron restriction was the primary mechanism of inhibition of fungal growth in Mucor.

2.1.2 The different therapy drugs for iron overload have different influence on Mucormycosis

Deferoxamine (DFO) ,which chelated both iron and aluminum, used for iron overload therapy. It increased the risk of mucormycosis by enhancing growth and pathogenicity[28-31]. Previous clinical studies indicated the use of DFO for iron chelation therapy was associated with unique predisposition to mucormycosis. Patients receiving dialysis who are treated with the iron chelator DFO are also uniquely susceptible to a deadly form of mucormycosis[31-34]. The majority of patients with DFO-associated infection preaent with disseminated disease that was rapidly fatal, with a mortality rate that approaches 90 percent[31]. M de Locht et al illustrated that upon administration of DFO to iron overloaded or dialysis patients, the formed ferric-DFO complex was efficiently used as an iron source by Rhizopus, even in the presence of serum transferrin[30]. In summary, DFO therapy was a risk factor of mucormycosis.

In contrast with the iron chelator, DFO, other iron chelating agents, such as deferasirox and deferiprone, did not act as siderophores, and that meant, they did not increase the risk of mucormycosis. Studies in mice with mucormycosis found that these agents might improve survival and reduce the tissue fungal burden[35, 36]. Considering the role that iron played in pathogenesis, combined anti-Mucor therapy and compounds that inhibit iron accumulation were promising approaches to combat mucormycosis.

2.2 Diabetes mellitus and Acidosis factor

Diabetes mellitus is the leading underlying disease in patients with mucormycosis globally[37, 38]. Diabetes has been reported as a risk factor for mucormycosis in 75%[39] of cases in Iran, 73.5%[40] in India, and 72%[41] in Mexico. Diabetic patients often develop electrolyte perturbations such as diabetic ketoacidosis[42]. Meanwhile, the high glucose and acid environment may be in favor of growth of Mucor[6, 23]. Besides, the binding affinity of transferrin for iron was affected by pH. At pH values of 7.5-8.9, the binding affinity of transferrin for iron was very large. At acidotic conditions pH 4.5, the iron was released and the affinity was low. As a result, elevated serum concentrations of free iron were high in patients with diabetic ketoacidosis. It promoted the growth of Rhizopus oryzae and might enhance susceptibility to mucormycosis.

Lactic acidosis is also occasionally seen in patients with leukemia, lymphoma, and solid malignancies[43-46]. Lactic acidosis is one of the metabolic complications of leukemia. Patients develop lactic acidosis at both first onset and relapse[43, 47, 48]. This may be one of the reasons that immunocompromised people are

susceptible to mucormycosis. In these patients, correction of ketoacidosis is important to reduce the risk of Mucor infection.

2.3 Statins

Statins, a class of drug used for the treatment of hyperlipidemia, may also be a protective factor. Hyperlipidemia increases the risk of diabetes. On the other hand, diabetes could result in hyperlipidemia[49]. Many diabetic patients take statins for hyperlipidemia therapy. Diabetic patients increased rapidly in the western world. But the number of reported cases of zygomycosis in patients with diabetes mellitus has decreased since the 1990s[50]. That may be due to the widespread use of statins in patients with diabetes. Present study reported that the widespread use of statins in patients with diabetes mellitus may be a protective factor against mucormycosis[51, 52]. Firstly, exposure of R. oryzae to statins decreased germling formation[51, 52]. Statins are competitive inhibitors of HMG-CoA[53]. HMG-CoA reductase is a key enzyme to synthesized ergosterol via the acetate-mevalonate pathway. Ergosterol is a critical component of the fungal cell wall[54]. Statins may inhibit germling formation through inhibiting the formation of the fungal cell wall. Secondly, statins can decrease the level of melanin in Mucor[52]. Melanin, a type of pigment, is thought to play an important role in virulence and pathogenicity of melanized fungi. Melanin is thought to contribute to the evasion of host immune responses [64]. Loss of melanin not only attenuated virulence in both fly and mouse models of mucormycosis but also increased the susceptibility to the oxidative agent peroxide[52]. Besides, it has been suggested that statins decrease the ability of R. oryzae to damage endothelial cells[52]. Statins are known to improve vascular endothelial health[55], reduce inflammation, and eliminate prothrombotic[56, 57]. Mucormycosis has an affinity for invading blood vessels and cause thrombosis and tissue necrosis[6]. Thus, statins may possibly be a novel therapeutic drug for Mucormycosis.

2.4 Thrombosis factors

Thrombosis is a main characteristic of mucormycosis[58]. It has been suggested that platelets play a important role in fighting Mucor infection[59]. In vitro studies show that platelets adhere to both Mucorales spores and hyphae to suppress spore germination as well as cause hyphal damage. Platelet interaction can significantly inhibits fungal germination and reduces Rhizopus, Mucor, Lichtheimia and Rhizomucor hyphal growth[60]. Hematopoietic stem cell transplantation (HSCT) and chemotherapy patients often have lower platelet levels[61, 62]. This may be one of the reasons that these people are prone to Mucor infection. Excessive thrombosis also leads to thrombocytopenia[63, 64]. Despite this, antithrombotic therapy is not universally mentioned in International treatment guidelines[1, 9, 10]. This might be due to the fact that mucormycosis also has the risk of bleeding. Zafer Koc et al[65] reported a case of rhino-orbital-cerebral mucormycosis with diffuse subarachnoid hemorrhage. And the patient's clinical status deteriorated rapidly and he died at last. There was also a case[66] that presented with aplastic anemia and subsequently complicated by systemic mucormycosis. And then he developed intracranial infarction and hemorrhage. Another study[67] also illustrated that mucormycosis might caused massive lower gastrointestinal bleeding. More research is needed to explore whether antithrombotic therapy can improve the prognosis of mucormycosis and how to balance between thrombosis and risk of bleeding. Keep appropriate platelet level may also be another promising approach in Mucormycosis treatment.

Conclusion

Mucormycosis was known as an emerging opportunistic, angioinvasive, and devastating fungi infection with high mortality. Though several relative guidelines was developed, evidence regarding optimal therapy for mucormycosis were limited because of its rarity, differences in comorbidities and infection sites. The dose of 10mg/kg/day LAMB recommended in the some international guidelines for anti-mucor infection might not be needed because of high nephrotoxicity and morbidity. 5mg/kg/day LAMB might achieve anti-mucor efficacy. In addition to the anti-mucor treatment, management of risk factors was also important, such as iron factor, diabetes mellitus with acidosis and thrombosis. Combined deferasirox and statins might be promising approaches in mucormycosis therapy. Besides, keep platelet level might also be another promising approach in Mucormycosis and need futher study to explore.

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