REVIEW
ALLERGY AND RHINOLOGY
DOI: 10.5152/B-ENT.2023.231267

Retrobulbar Injection of Amphotericin B in the Management of Acute Invasive Fungal Sino-Orbital Infections

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Cite this article as: De Kezel M, Van Zele T, Ninclaus V, Coppens M. Retrobulbar injection of amphotericin B in the management of acute invasive fungal sino-orbital infections. B-ENT. 2023;19(4):258-266.

ABSTRACT

Objective: Treatment for acute invasive fungal rhinosinusitis consists of systemic antifungal therapy, early and aggressive surgical debridement, and reversal of immunosuppression. When the orbit is involved, the question is raised whether or not to perform orbital exenteration to gain local control. Alternatives have been proposed to spare the orbit such as retrobulbar injection of antifungal medication.

Methods: We present a series of 2 cases of invasive fungal sino-orbital infections treated in our institution. When local control could not be obtained with systemic therapy and surgery, both were successfully treated with additional retrobulbar injections of liposomal amphotericin B 3.5 mg/mL. We reviewed the literature for comparable cases and studies comparing retrobulbar injections to orbital exenteration.

Results: In our experience, a series of retrobulbar injection with liposomal amphotericin B 3.5 mg/mL was effective in 2 cases of orbital involvement, preventing an orbital exenteration. A review of the literature showed comparable cases in which local control was obtained with retrobulbar injections and 2 retrospective cohort studies which found similar mortality rates when comparing retrobulbar injections to orbital exenteration.

Conclusion: We therefore conclude that retrobulbar injections with liposomal amphotericin B are a safe and efficient treatment for invasive fungal sino-orbital infections to obtain local control. It is a minimally invasive procedure preventing orbital exenteration.

Keywords: Acute invasive fungal rhinosinusitis, acute invasive sino-orbital infection, amphotericin B, retrobulbar injection, sinus pathology

Introduction

Acute invasive fungal infection is a dreaded saprophytic infection in patients under severe immunosuppression such as chemotherapy, hematopoietic stem cell transplantation, solid organ transplantation, hematologic malignancies, or uncontrolled diabetes.[1-6] Infection occurs by penetration of the nasal mucosa after inhalation of fungal spores and invasion of neural and vascular structures. This causes ischemic vasculitis leading to infarction and necrosis of surrounding tissue and further spreading of the infection within hours.[7-12] The presenting symptoms are very unspecific including (neutropenic) fever, nasal congestion, facial pain, epistaxis, and facial swelling.[2,13]

Involvement of the periorbital space is seen due to the spreading of the fungus through the lamina papyracea from the sphenoid and anterior and posterior ethmoid.[9] This may lead to severe eye pain, orbital and facial edema, proptosis, ophthalmoplegia, irreversible vision changes, and eventually blindness.[10] An orbital infection can potentially progress to the central nervous system as a result of the direct communication between the orbit and the middle cranial fossa through the ophthalmic artery, the optic canal, or the superior orbital fissure.[6,13,14] Intracranial extension in turn may lead to cranial nerve deficits, lethargy, cavernous sinus thrombosis, and cerebrovascular accidents with a very high mortality rate.[1,3,13] In a large review published in 2013, orbital invasion was seen in up to 49.6% of patients, 21.2% had intracranial invasion, and 8.6% had cavernous sinus involvement.[15]

There is a high morbidity associated with the disease due to its extension to the palate, maxilla, orbit, and intracranial space.[3]

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Received: February 24, 2023 **Accepted:** July 31, 2023 **Publication Date:** October 26, 2023
Available online at www.b-ent.be

Historically, mortality rates were around 50%-80%.[2,9] An early diagnosis and treatment can decrease this to 10%-40%. Unfortunately, initial misdiagnosis is common, and treatment is often started for bacterial sinusitis, delaying the correct diagnosis.[3,4] Mortality rates are dependent on the causative pathogen, with Mucormycosis infection showing a higher rate of extension of the infection to the orbit and a higher mortality.[4,11] Other negative prognostic factors are orbital and intracranial involvement, irreversibility of immunosuppression, and advanced age.[10,16]

Diagnosis is made by nasal endoscopy including biopsy and microbiology samples to confirm a fungal infection with angioinvasion, accompanied by imaging to assess the extension of the infection. The most common fungal pathogens include *Aspergillus*, *Mucor*, and *Rhizopus*.[2,3,5,9] Imaging using high-resolution computed tomography (CT) scan shows areas of bony erosions while magnetic resonance imaging (MRI) shows loss of fat planes or soft tissue extension beyond the paranasal sinuses.[2,13,17] An increase in contrast enhancement implies an active infection, as a loss of contrast enhancement implies ischemia and necrosis.[18]

Treatment consists of reversal of immunosuppression in addition to the start of adequate antifungal therapy. Systemic antifungal therapy alone will not be sufficient to obtain local control of the infection due to the local ischemia which limits the penetration of the systemic therapy into the infected area. Therefore, early and aggressive debridement of necrotic tissue is also an important pillar of the treatment.[12,19]

Patients with orbital invasion, loss of vision, and ophthalmoplegia are historically treated with orbital exenteration, an invasive and disfiguring surgical treatment. However, studies increasingly show that no clear additional survival benefit is seen after orbital exenteration.[8,15] Alternative treatments have been proposed in order to improve local disease control in the orbit and possibly avoid a mutilating exenteration, for instance, repetitive retrobulbar injection of liposomal amphotericin B 3.5 mg/mL, conservative debridement with irrigation of antifungal agents, or hyperbaric oxygen (HBO) therapy.[8-10,12,15,18,19-20-24]

We want to describe 2 cases successfully treated with repetitive retrobulbar injections with liposomal amphotericin B 3.5 mg/mL for an acute invasive sino-orbital fungal infection at the Ghent University hospital in the last year, and we performed an additional review of literature in search of similar cases.

Main Points

- We successfully treated 2 cases of acute invasive fungal rhinosinusitis with orbital involvement with retrobulbar injections of liposomal amphotericin B to obtain local control.
- We used 1 mL injections with 3.5 mg/mL liposomal amphotericin B on a weekly basis for 4 weeks, with the possibility of a second round.
- We found multiple similar cases in the literature in which local disease control was obtained with retrobulbar injections of liposomal amphotericin B.
- Two retrospective cohort studies comparing patients treated with and without retrobulbar injections of amphotericin B showed similar mortality and better visual acuity in the treated group.

Case Report Series

In the last year, 2 patients presented with an acute invasive fungal rhinosinusitis with orbital involvement and received an adjunctive treatment with repetitive retrobulbar injections of liposomal amphotericin B, followed by reversal of immunosuppression, systemic antifungal therapy, and surgical debridement. Written informed consent for publication of their clinical details and clinical images was obtained from the patients and approval was given by the Ghent University Ethics Committee. A copy of the consent form is available for review by the editor of this journal.

Case Report 1

The first patient was a 62-year-old man with a relevant history of type 2 diabetes, ethylic liver cirrhosis, chronic kidney failure, and atrial fibrillation. The patient received an orthotopic liver transplant in May 2019 and a second one in December 2020. He had immunosuppressive treatment consisting of mycophenolic acid 2 × 500 mg, tacrolimus 8 mg, and methylprednisolone 4 mg.

The patient presented in February 2021 with a sudden visual loss (vision 0.1) of the left eye, without any pain or rhinological symptoms. Blood glucose levels were 125 mg/dL at admission, and inflammatory parameters in the blood test were only mildly elevated (white blood cell count 4.8 × 10^3/µL and C-reactive protein (CRP) 38 mg/L). Ophthalmologic examination showed endogenous endophthalmitis, for which he received 2 urgent intravitreal injections with vancomycin and ceftazidime. An anterior chamber tap was taken for incubation which showed no arguments for bacterial invasion. Suddenly, on the left side, there was a deterioration to a painful acute blindness—light perception negative—half-sided facial numbness and arguments for an abducens nerve palsy. Nasal endoscopy showed a necrotic debris in the left upper nasal tract, which was acquired for culture and biopsy (Figure 1). An urgent CT scan was made, showing a sphenoidal, ethmoidal, and maxillary sinusitis with bony erosion of the posterior wall of the maxillary sinus, expansion to the pterygopalatine fossa and masticator space, erosion of the pterygoid process to the oval foramen, and expansion through erosion of the medial orbital wall and through the inferior orbital fissure to the orbital apex (Figure 2). An additional MRI confirmed orbital invasion with signs of endophthalmitis (Figures 3 and 4). Because the clinical picture was so suggestive, the diagnosis of an acute invasive fungal sino-orbital infection was made at this point, 3 days after the onset of visual loss.

Empirical intravenous liposomal amphotericin B treatment at 5 mg/kg was started, and urgent surgical debridement was performed with opening of all left-sided sinuses and pterygopalatine fossa. A fungus ball was found in the left posterior ethmoid, and an invasive fungal infection was seen in the pterygopalatine fossa. Samples were taken for histopathological and microbiological research, which both confirmed *Aspergillus fumigatus* as the causal pathogen. The systemic treatment was switched to voriconazole 6 mg/kg twice daily on day 1 and 4 mg/kg twice daily after. Immunosuppressive

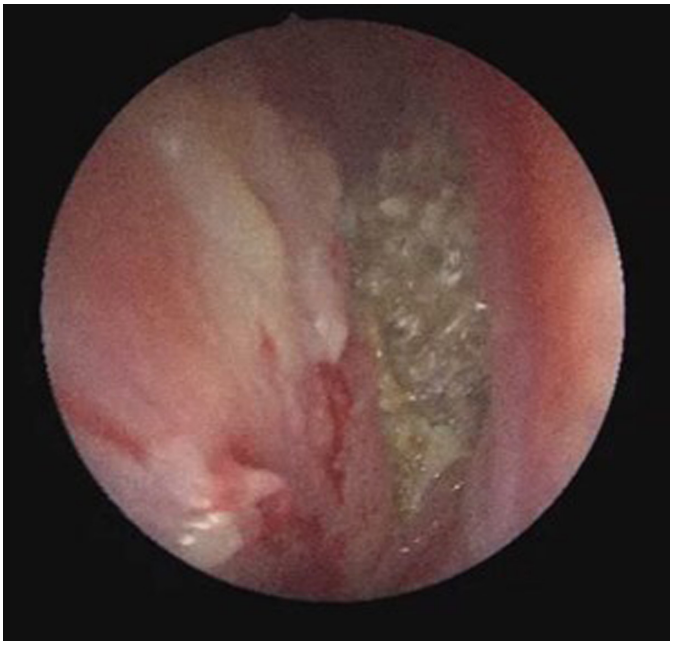

Figure 1. Nasal endoscopy showing a necrotic debris in the left upper nasal tract.

medication could not be discontinued due to the history of liver transplantation. A multidisciplinary follow-up with daily clinical evaluations by the Ear-Nose-Throat (ENT) specialist and the ophthalmologist, multidisciplinary case meetings, and MRI scans on a weekly basis were organized.

The MRI scan 1 week after surgery showed some increase in the orbital infection with proptosis (Figure 5). At this point, we decided that an additional therapy was needed to obtain local control of the orbit. An orbital exenteration was considered, but this procedure would require a long revalidation and would leave a mutilating result. Therefore, it was seen as an unfeasible physical and mental burden for the patient. As an alternative, weekly retrobulbar injections with 1 cc liposomal amphotericin B 3.5 mg/mL were administered after local anesthesia. After the first injection, we saw a slow but steady clinical improvement and a slow reduction of inflammation in the pterygopalatine fossa, and the injections were continued for 8

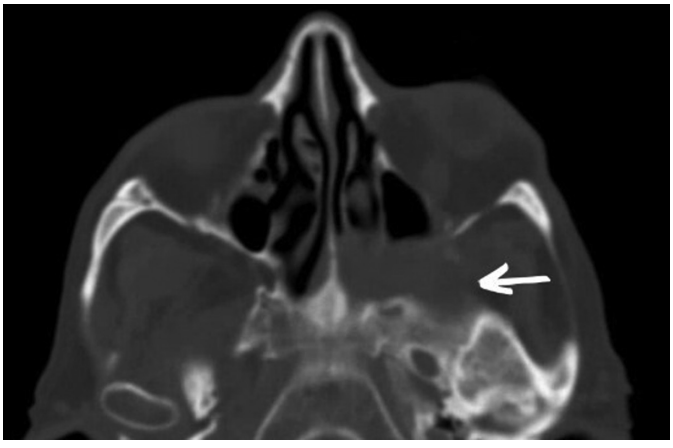

Figure 2. Contrast-enhanced computed tomography scan showing erosion of the posterior wall of the maxillary sinus with expansion to the pterygopalatine fossa.

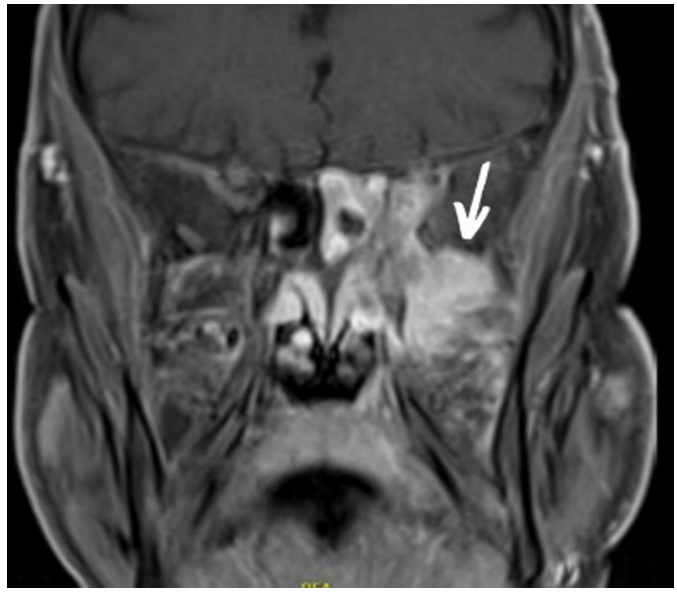

Figure 3. Contrast-enhanced T1-weighted magnetic resonance imaging showing fungal involvement of the pterygopalatine fossa.

weeks on a weekly basis (Figure 6). After 1 month of therapy with voriconazole, this was switched to isavuconazole 200 mg 3 times a day due to hepatotoxicity. The antifungal therapy was stopped after a total of 9 months, with continued control of the infection at this point. The eyesight on the left eye did not improve after the treatment, but orbital motility recovered completely.

Case Report 2

The second patient is a 63-year-old man with an underlying myelodysplastic syndrome with a grade 3 neutropenia and a moderate anemia, diagnosed in May 2021. As the myelodysplastic syndrome was transitioning to acute myeloid leukemia,

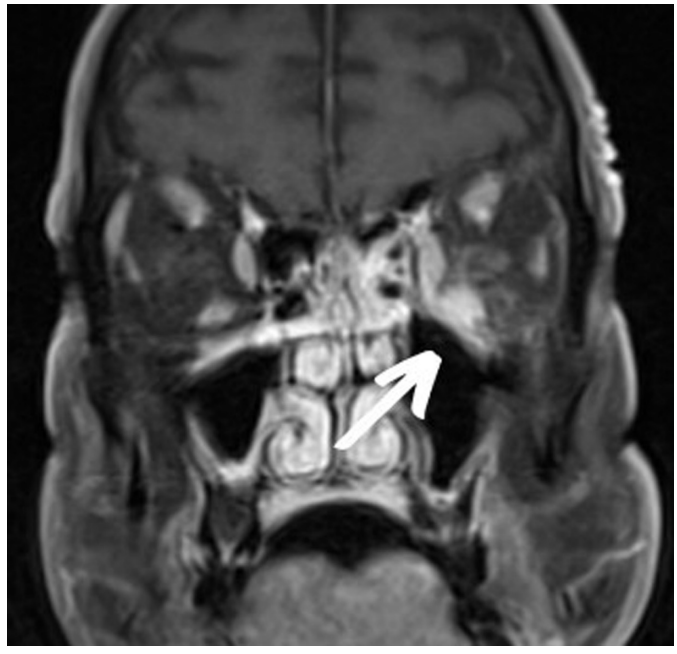

Figure 4. Contrast-enhanced T1-weighted magnetic resonance imaging showing expansion through erosion of the medial orbital wall and through the inferior orbital fissure.

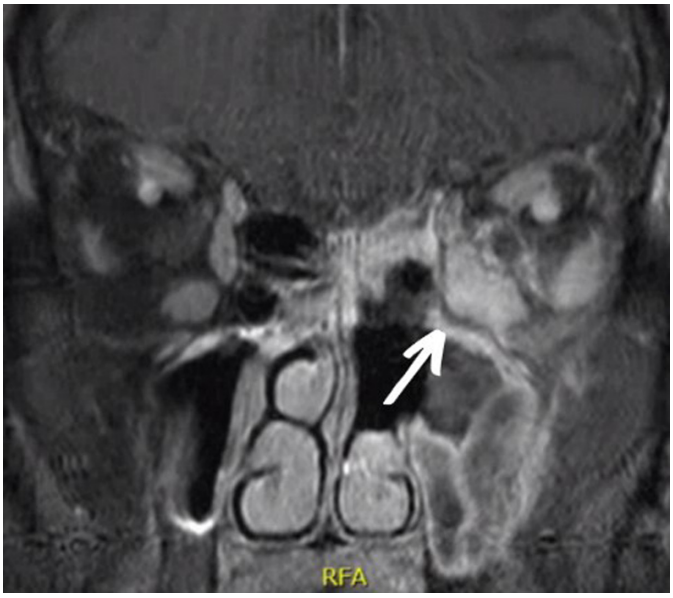

Figure 5. Contrast-enhanced T1-weighted magnetic resonance imaging showing an increased intraconal inflammation 7 days postoperatively.

the decision was made to start induction chemotherapy to conduct an allogeneic stem cell transplant.

One week after the first dose of induction chemotherapy, the patient developed neutropenic fever of unknown origin (white blood cell count 0.28 × 103/µL and CRP 134.4 mg/L), for which IV piperacillin/tazobactam was started daily. Three days later, he developed a right-sided headache, nasal congestion, clear rhinorrhea, and epiphora. Nasal endoscopy showed some secretions at the ostiomeatal complex on the right side, of which a swab was taken for culture. A CT scan of the sinuses showed limited rhinosinusitis of the right ethmoid sinuses, and treatment was switched to IV meropenem. When there was no clinical improvement after 2 days of treatment and blood CRP

Figure 6. Contrast-enhanced T1-weighted magnetic resonance imaging after 4 retrobulbar amphotericin B injections.

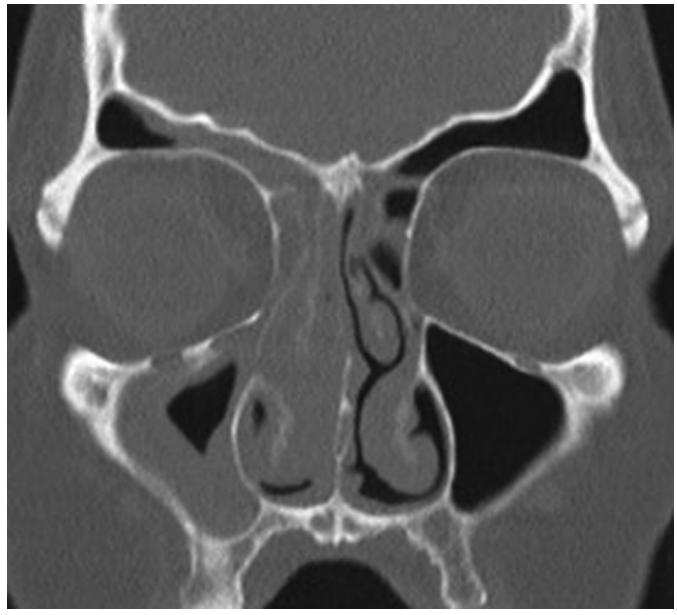

Figure 7. Computed tomography scan showing extensive mucosal swelling of the right nasal cavity without clear alignment of the middle and inferior turbinate and obliteration of the maxillary meatus.

had risen to 232 mg/L, a new CT scan was made, showing an increase in sinusitis with erosion of the bone surrounding the meatus of the maxillary sinus and enlargement of the sphenopalatine foramen on the right side (Figure 7). This raised the clinical suspicion of an acute invasive fungal rhinosinusitis.

Immediately, treatment was started with intravenous liposomal amphotericin B 5 mg/kg and isavuconazole 200 mg 3 times a day, at this point 8 days after the fever started. Urgent sinus surgery was performed after raising the platelet count to 100 000. During surgery, necrosis was seen in the middle turbinate, which was removed for histopathological and microbiological examination; further debridement was performed by opening the maxillary and ethmoid sinuses. Histopathological examination confirmed necrosis and fungal angioinvasion, and Polymerase Chain Reaction (PCR) testing confirmed the diagnosis of *mucormycosis*, despite the culture being unable to validate this.

Four days after surgery the patient developed a periorbital edema in the right eye with normal vision in both eyes (Figure 8). Urgent MRI scanning showed inflammation of the periorbital space and the eyelids with reactive myositis of the rectus medialis muscle but no clear signs of fungal orbital

Figure 8. Periorbital edema and ptosis.

Figure 9. Contrast-enhanced T1-weighted magnetic resonance imaging showing inflammation in the intraconal space.

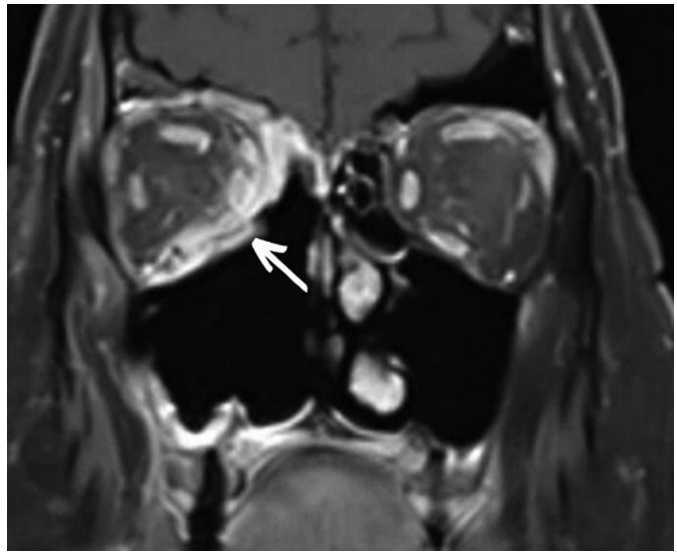

Figure 10. Contrast-enhanced T1-weighted magnetic resonance imaging after 3 retrobulbar amphotericin B injections.

invasion. As the scan still showed signs of fungal infection on the medial side of the maxillary sinus and in the right frontal sinus, a second surgical debridement was performed with a medial maxillectomy and a DRAFIIb. Local irrigation was performed with 50 mg/250 mL amphotericin B for 15 minutes.

After this second intervention, the inflammatory parameters started to decrease but the periorbital swelling and redness continued. Daily clinical evaluation was performed by both the ENT specialist and the ophthalmologist, and MRI scans were performed once a week. Two weeks after the last surgery, MRI showed that the fungal infection was spreading through the lamina papyracea (Figure 9). The decision was made to start weekly with retrobulbar injections of 1 cc liposomal amphotericin B 3.5 mg/mL, for a total of 4 injections. After the first injection, there was already some clinical improvement, with a decrease in periorbital swelling and redness. A week after the first injection, the patient's white blood cell counts normalized, and there was an obvious further clinical improvement (Figure 10). Eighteen months later, we still see complete control of the infection. The patient's vision and eye mobility remained unharmed, without any residual proptosis.

Discussion

We discussed 2 cases of an acute invasive fungal sino-orbital infection, where a local administration of liposomal amphotericin B was administered in the retrobulbar space as an additional therapy because local control of the infection could not be obtained with systemic therapy and surgical debridement of necrotic tissue. Both cases were treated successfully, and patients survived without the need for orbital exenteration. A literary review was performed to compare our method and results with other cases published in the last 10 years.

Administration Method

The point of insertion of the needle for a retrobulbar injection is chosen as the junction of the 2/3 medial and 1/3 lateral along the inferior orbital rim. The retrobulbar needle is inserted perpendicular to the skin and advanced parallel to the orbital floor. A first pop could be felt on penetrating the orbital septum. Once the tip of the needle crosses the equator of the ocular globe, the needle is further advanced to the superior and medial direction until a second pop is felt crossing the muscle cone reaching the retrobulbar space. First local anesthetic using 2.5 cc of lidocaine 2% and 2.5 cc of levobupivacaine is injected. Then, the patient is asked to close the eyes while waiting for the local anesthetic to work, and then the antimycotic drug is injected.

In the literature, the concentration of amphotericin B ranged from 1 to 3.5 mg/mL, and the volume for injection ranged from 1 to 1.5 mL. The frequency of administration ranged from a daily to a weekly basis. The timing of injection varies in previous cases and depends on the clinical and radiological findings.[24]

Case Reports

Previous case reports are listed in Table 1. Mainville and Jordan[14] had good results with retrobulbar amphotericin B injections on top of a systemic treatment with amphotericin B and a surgical debridement of the maxillary sinus in a 61-year-old patient who had an invasive *Aspergillus* infection originating from the right maxillary sinus and expanding to the inferior orbit after a heart transplant. They gave 1 mL of 3.5 mg of amphotericin B every 2-3 days for a total of 3 weeks. They saw a complete resolution of the orbital inflammation by 8 weeks; unfortunately the patient did die due to multi-organ failure 12 weeks after initiating therapy.[14]

Colon-acevedo et al[11] treated a 36-year-old woman with T-cell lymphocytic leukemia who developed a left-sided invasive sino-orbital infection with *Aspergillus flavimatus*. The patient received systemic liposomal amphotericin B, 2 staged surgical debridement, and a retrobulbar injection of 1 mL of amphotericin B 3.5 mg/mL. When the infection was not controlled, the injections were increased with 4 additional injections every 2-3 days, and they tried 20 daily HBO sessions. After 5 days, clinical improvement was seen, and the patient fully recovered when her blood count started to recover another 8 days later.[11]

Table 1. Overview of Case Reports of Invasive Fungal Sino-Orbital Infections Treated with Retrobulbar Injections of Amphotericin B

Mortality	Died of Multiple Organ Failure	Survived	Survived	Survived	Survived	Died of ARDS
Local effect	Infection control, vision 20/200, partially restricted up gaze	Infection control, vision 20/20, abduction deficit	Infection control, vision 20/20, normal eye movement	Infection control, orbital compartment syndrome, vision 20/25, limitation in depression	Infection control, vision 20/40, abduction deficit	–
Administration mode	3.5 mg/1 mL, every 2-3 days 5 injections + 6 irrigations	3.5 mg/1-1.5 mL, every 2-3 days 6 injections	3.5 mg/1 mL, 3 daily injections, repeat after 2-day break	3.5 mg/1 mL, every 2-3 days 5 injections	1 mL of 3.5 mg/mL, 2 injections with 3-day interval	3.5 mg/dL, 3 daily injections
Systemic treatment	IV amphotericin B	IV antibiotics, amphotericin B, oseltamivir and acyclovir, IV voriconazole	IV amphotericin B and caspofungin; oral posaconazole	IV voriconazole and caspofungin	IV amphotericin B and micafungin; oral posaconazole	IV amphotericin B, vancomycin, cefepime, caspofungin, IV dexamethasone
Vision	20/200	20/20	20/30, worsened to 20/200	20/20, worsened to 20/200	20/20, worsened to 20/200	Not assessed
Causative pathogen	*Aspergillus*	*Aspergillus fumigatus*	Mucormycosis	*Aspergillus*	Mucormycosis	Mucormycosis
Underlying illness	Cardiac transplant	T-cell lymphocytic leukemia	Bilateral lung transplant	Renal transplant	Poorly controlled type II DM	Poorly controlled type I DM, COVID-19 ARDS
Age, Sex	61, Male	36, Female	68, Male	27, Male	55, Male	60, Male
Author	Mainville and Jordan[14]	Colon-Acevedo et al[11]	Hirabayashi et al[21]	Brodie et al[25]	Safi et al[26]	Mekonnen et al[2]

COVID-19, coronavirus disease 2019. ARDS, acute respiratory distress syndrome. DM, Diabetes Mellitus

Another case was published in 2016 by Hirabayashi et al,[21] where a 68-year-old man with a lung transplant received 1 mL retrobulbar injection of amphotericin B 3.5 mg/mL on 3 consecutive days, next to endoscopic debridement and systemic antifungal therapy for an invasive sino-orbital *Mucormycosis* infection. After 72 hours, his vision, orbital edema, and eye movement normalized. However, 2 days later his vision deteriorated again, without any visible disease progression on MRI. Three new retrobulbar injections were administered without any other therapeutic adjustments, and the patient's vision was restored again.[21] As no other changes were made to the administered therapy apart from the second round of retrobulbar injections, we could say that the efficacy of the retrobulbar injections in this case is clear.

Brodie et al[25] treated a 27-year-old man with a history of renal transplantation for an invasive fungal rhinosinusitis caused by *Aspergillus*. Immunosuppression was immediately stopped and intravenous antifungal therapy was started in addition to an aggressive surgical debridement. Postoperatively, there was a progressive ptosis and an afferent pupillary defect when repeated MRI scans showed disease progression at the orbital apex. Because they did not want to perform an orbital exenteration in a patient with preserved eyesight, an endoscopic orbital decompression and retrobulbar injections with 1 mL amphotericin B 3 mg/mL were started every 2-3 days for a total of 5 injections. The treatment was complicated with an orbital compartment syndrome after the fifth injection requiring a canthotomy and cantholysis. The fungal infection was controlled completely under this treatment, and the patient did not lose his eyesight.[25]

A case report by Safi et al[26] is about a 55-year-old male with poorly controlled type II diabetes mellitus and a left-sided sino-orbital *Mucormycosis* infection with proptosis, facial pains, and diplopia. The patient had urgent surgery and intravenous treatment with amphotericin B, micafungin, and oral posaconazole. On postoperative day 3, a repeat CT revealed multiple orbital abscesses, but despite a second debridement, the situation deteriorated further with vision deterioration and MRI now showing a left-sided temporal lobe cerebritis. One milliliter retrobulbar injections of 3.5 mg/mL amphotericin B were given on day 6 and day 9, after which the ophthalmological symptoms started to decrease and the vision improved to 20/40 after the second injection. After strict blood sugar control and further intravenous

treatment, a steady clinical improvement was seen with a complete resolution of the cerebritis and stable vision. Eye movement was restored except for a deficit in abduction which persisted.[26]

Mekonnen et al[27] recently published a case of a 60-year-old diabetic patient who was intubated in the intensive care unit following a coronavirus disease 2019-associated acute respiratory distress syndrome when he showed a proptosis of the right eye. The CT scan showed a right-sided sinusitis with erosion of the lamina papyracea and orbital involvement and tissue culture and biopsy identified *Rhizopus* species. Intravenous amphotericin B was started together with a strict insulin treatment because of a hemoglobin A1c of 14% at admission, but the patient also received dexamethasone to improve his respiratory status, which caused a difficult-to-manage hyperglycemia. Three daily retrobulbar injections of 3.5 mg/mL were administered to the right eye and the patient could only undergo a surgical debridement on day 10 because of his precarious respiratory status requiring prone ventilation. Acute kidney failure forced the team to switch the amphotericin B to posaconazole. The patients' health status declined further during the hospital stay and unfortunately he died of ARDS after 31 days of intensive treatment. It is unclear to what extent the fungal infection was still present at this point.[27]

Retrospective Cohort Studies

We found 2 retrospective cohort studies evaluating the use of retrobulbar injections of amphotericin B (Table 2). Ashraf et al[22] compared 2 groups of patients with invasive sino-orbital rhinosinusitis before and after the start of complementary treatment with retrobulbar infections of amphotericin B in 2015. The injections were administered at 3.5 mg/mL, and 1 mL was given for 3 consecutive days in most cases. They found that both patient groups had similar mortality (40.0% pre-2015 vs. 36.7% post-2015), but the patient group receiving retrobulbar injections had a significantly lower risk of exenteration (26.5% pre-2015 vs. 9.1% post-2015) and had less eyes that lost vision (50.0% pre-2015 vs. 12.5% post-2015).[22]

Another study evaluated 12 invasive fungal rhinosinusitis patients who received retrobulbar injections of amphotericin B with 24 patients who did not. Patients received 1 mL injections of amphotericin B in a 1 mg/mL solution every other day for 2 weeks, then every week for 2 months. They found an insignificant difference in mortality (9.3% in the treated group vs. 29.2% in the control group) and exenteration (23.1% in the treated group vs. 47.8% in the control group), but they found significantly better visual acuity change at 3 months follow-up (76.9% stable or improved in the treated group vs. 39.1% in the control group).[23]

When looking at our and these previous cases, retrobulbar injections of amphotericin B seem like a safe and effective alternative to orbital exenteration. The cases in which a concentration of 3.5 mg/mL was given seem to have superior results over the cases treated with 1 mg/mL.

Side Effects

Systemic side effects of amphotericin B, such as fever, bone marrow suppression, and renal toxicity are well known, but amphotericin B can exhibit local toxicity. When looking at the possible side effects of retrobulbar injections we see that they can cause a transient inflammation and soft-tissue edema, which can make it harder to assess the response to the treatment, but which can also lead to an orbital compartment syndrome requiring a canthotomy and cantholysis in a certain degree in order to avoid necrosis.[25] By using a liposomal formula, inflammation is kept to a minimum. Another possible side effect is neurotoxicity, which has been documented as the possible etiology in a small number of cases of visual loss after intrathecal amphotericin B for meningitis but has not yet been reported for retrobulbar injections.[21,22,24] Also, general complications of retrobulbar injections such as hemorrhage, ocular globe injury, optic nerve damage, extraocular muscle injury, and spread of medication to the brain can occur. A previous study showed a complication rate of 4.3%, with most complications being self-limiting.[17,24] Thus, patients will need to be monitored closely after administering these injections.

Orbital Exenteration

Indications to consider orbital exenteration in literature are ophthalmoplegia, complete vision loss, and intracranial involvement. We must consider the fact that orbital exenteration is an extensive surgery requiring long general anesthesia and revalidation after surgery, while these patients generally already have a complex medical history and an inferior general medical state. Some say exenteration could increase survival in the presence of rapid progression and intracranial spread, but others report orbital exenteration to be a risk factor for poor overall survival. A possible explanation being that orbital exenteration is typically performed for patients in the end-stage disease.[19,24]

Table 2 Overview of Retrospective Cohort Studies of Invasive Fungal Sino-Orbital Infections Treated with Retrobulbar Injections of Amphotericin B

Authors	Administration Mode	Treatment Group	Control Group	Results
Ashraf et al[22]	3.5 mg/1 mL, 3 consecutive days (most cases)	Post-2015: retrobulbar injections AMB (30 patients)	Pre-2015: No retrobulbar injections (20 patients)	Similar mortality (36.7% vs. 40%); lower risk of exenteration (9.1% vs. 26.5%); less eyes that lost vision (12.5% vs. 50%)
Arreenich et al[23]	1 mg/1 mL, every 2 days for 2 weeks, then every week for 2 months	Retrobulbar injections AMB (12 patients)	No retrobulbar injections (24 patients)	Similar mortality (8.3% vs. 29.2%); similar risk of exenteration (23.1% vs. 47.8%); better visual acuity (76.9% vs. 39.1%)

Hargrove et al[8] did a literature review of 292 cases of mucormycosis infections of the sinus and/or orbit ranging from 1943 to 2004. They found that the only patients who had a survival benefit from orbital exenteration were those with fever. In this retrospective study, some clinically relevant indicators, such as ophthalmoplegia, loss of vision, and time of onset that were not assessed as the clinical details were inadequate. Also, retro-orbital injections were not evaluated in this study.

Orbital exenteration should therefore only be considered in clearly necrotic or nonfunctional orbital tissue, after the administration of retro-orbital injections did not improve the clinical situation. This decision should only be made after discussion with the patient that there may not be a survival benefit.[15,19] Orbit retention is also possible in patients whose underlying medical condition is rapidly controlled, for example, diabetics.[10] The key to a successful treatment remains high suspicion and early diagnosis.

Conclusion

Acute invasive fungal rhinosinusitis is a serious saprophytic infection in immunosuppressed patients associated with a high mortality rate. Fungal invasion of the orbit can quickly lead to intracranial extension of the infection due to the direct communication between the orbit and the middle cranial fossa; therefore, orbital invasion is often treated by orbital exenteration, a complex and disfiguring surgery requiring general anesthesia and long recovery in patients with complex pathology and extended medical history. However, in recent years, less invasive alternatives were developed such as retrobulbar injections of amphotericin B. At Ghent University Hospital, we have successfully treated 2 cases with retrobulbar injections in the past year. While the literature does not show clear advantages in terms of mortality rates when comparing retrobulbar injections with amphotericin B to orbital exenteration, retrobulbar injections appear to result in stable or improved visual acuity and a lower exenteration rate. Therefore, we believe that retrobulbar injections of amphotericin B are a safe and accessible treatment option. We prefer to do the least invasive procedure, knowing that more invasive options are available if the situation were to deteriorate.

Ethics Committee Approval: This study was approved by Ethics Committee of Ghent University Hospital (Approval No: EC/062-2022/sds, Date: 14/09/2022).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.D.K., T.V.Z., V.N., M.C.; Design – M.D.K., T.V.Z., V.N., M.C.; Supervision – T.V.Z., V.N., M.C.; Materials – T.V.Z., V.N.; Data Collection and/or Processing – M.D.K.; Analysis and/or Interpretation – M.D.K.; Literature Search – M.D.K.; Writing – M.D.K., M.C.; Critical Review – T.V.Z., V.N.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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