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Acute invasive fungal rhinosinusitis: our 2 year experience and outcome analysis

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Abstract

Purpose The incidence of Acute invasive fungal rhinosinusitis (AIFRS) is on the rise considering the multitude of comorbidities present in a single patient.The delay in suspecting the fungal etiology, presentation of the patient for an Otorhinolaryngology consult and lack of defined protocols affects outcome.This study looks in to the various aspects of treatment of AIFRS including sample collection, diagnosis and medicosurgical treatment. We propose a protocol for the management of these patients crafted from our outcome.

Methods Between September 2015–September 2017, 14 patients presented with AIFRS. Targeted samples were taken for Potassium hydroxide mount, histopathological studies and fungal culture. Management was initiated with antifungals and multi-approach surgical debridement.

Results Six of these patients had multiple comorbidities and most were uncontrolled diabetics. The average delay in presentation was 9 days. Potassium hydroxide mount was the screening test of choice. A minimum of two sittings of debridement was essential. In an average follow-up period of 15.12 months, all the patients are alive and disease free.

Conclusion A high index of suspicion, awareness among medical fraternity and precise sample collection aids a firm diagnosis. Simultaneous initiation of surgical debridement and anti-fungals is fundamental.

Keywords Invasive fungal rhinosinusitis · Mucormycosis · Diabetes mellitus · Liposomal amphotericin B · Outcome

Abbreviations

AIFRS	Acute invasive fungal rhinosinusitis
AmB	Amphotericin B
AE	Anterior ethmoidotomy
BA	Bronchial asthma
CKD	Chronic kidney disease
CT	Computerized tomography
DKA	Diabetic ketoacidosis
DNE	Diagnostic nasal endoscopy
FS	Frontal sinus
FESS	Functional endoscopic sinus surgery
HPE	Histopathological examination
HTN	Hypertension
IT	Inferior turbinate
IHD	Ischemic heart disease
LP	Lamina papyracea
Lip AmB	Liposomal amphotericin B
MS	Maxillary sinus
MMA	Middle meatal antrostomy
MT	Middle turbinate
MPGN	Membranoproliferative glomerulonephritis
NLD	Nasolacrimal duct
P_{in}	Posaconazole
PE	Posterior ethmoidotomy
KOH mount	Potassium hydroxide mount
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
ST	Superior turbinate
V	Voricanazole

Introduction

Acute invasive fungal rhinosinusitis (AIFRS) is a potentially lethal disease process whose timely diagnosis and management is crucial for the survival of the patient. This entity has many fungi as its causative factor. The commonly isolated

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fungi are [1, 3] Zygomycota—*Mucor, Rhizopus, Rhizomucor, Absidia* and other *Mucorales*, and Ascomycota-aspergillus species.

Patients with haematopoietic malignancies, those receiving bone marrow transplant, status post organ transplant, uncontrolled diabetes mellitus [4] or those on long term steroids are generally prone for this infection. Occasionally immunocompetent individuals are also affected.

Presentation is quite variable with symptoms like nasal obstruction, headache not responding to analgesics, nasal discharge, facial swelling, disturbances in vision, cranial nerve palsies and sepsis (Fig. 1). Mucormycosis [6] can involve rhino-cerebral, pulmonary, gastrointestinal, cutaneous, central nervous system and other miscellaneous sites like myocardium, bones, and kidney. However co-infection of fungi confuses the diagnosis.

These fungi are highly angioinvasive and causes tissue infarction, necrosis and thrombosis. This accounts for the blackish eschar and its florid spread. Neutrophils are the main line of defence against the fungi and the patients with neutropenia are particularly affected. Sakeena et al. [2] has proposed guiding treatment on absolute neutrophil counts; but none of our patients, neutropenia was detected at any stage. Instead uncontrolled diabetes mellitus or unmonitored steroid usage was the prime underlying factor. Adequate samples [7] for KOH mounts, fungal culture, biopsy and frozen section of the suspicious tissue guided our treatment. We advocate a combined approach of aggressive antifungal therapy and surgical debridement followed by antifungal nasal douche and serial endoscopic examinations. The treating team involves many physicians like otorhinolaryngologist, nephrologist and ophthalmologist. Considering the success of treatment in our series of patients, we propose a protocol for the treatment of AIFRS.

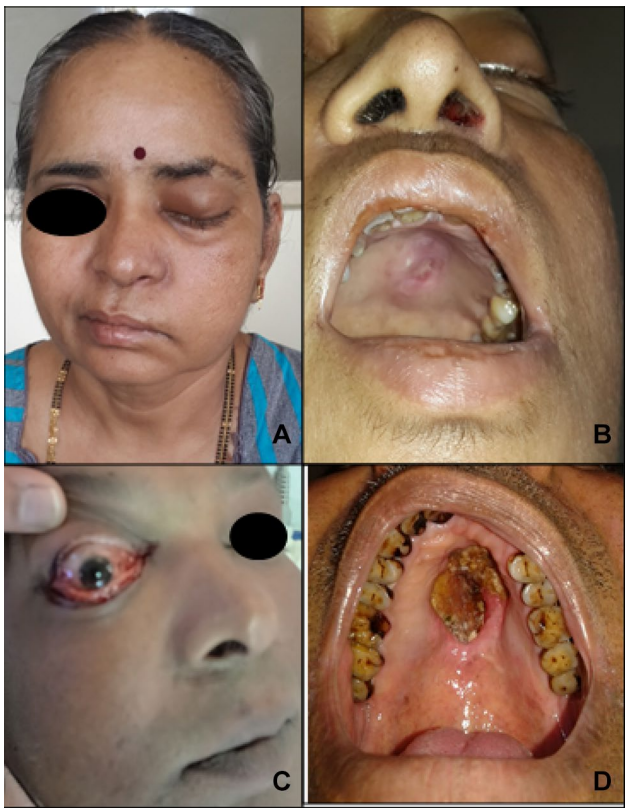


Fig. 1 Clinical presentation. **a** Uncontrolled T2DM patient with left facial palsy and nasal crusting. **b** Same patient in **a** with palatal ulcer. **c** CKD patient with orbital cellulitis. d Diabetic patient with non-healing palatal ulcer

Methods

In the time frame of September 2015–September 2017, we had a total of 14 patients of AIFRS. Of the total, 8 patients were treated as per proposed protocol (Table 1). Amongst the remaining 6 patients, 4 were excluded as they were lost to follow-up, 1 patient expired before the initiation of treatment and the other patient had a very atypical presentation. The unusual presentation being an isolated non healing zygomatic osteomyelitis which was later histopathologically diagnosed as mucormycosis and amphotericin B was initiated for the same.

The general mode of treatment was guided by KOH mount, fungal culture and histopathology (Table 2). Mucor is identified by the aseptae, ribbon like hyphae (10–20 µm) and Aspergillous by septate branching hyphae (3–6 µm) (Fig. 2).

The preoperative imaging studies of the Brain, paranasal sinus and orbit was undertaken depending on the involvement. Medical therapy with liposomal amphotericin B (Lip AmB) was started pre-operatively and all patients underwent endoscopic debridement to decrease the fungal load. With involvement of other sites like palate or zygoma, approaches were selected to debride the respective areas. In all the debridement including hard palate, the unhealthy nonviable tissue was debrided till healthy bleed was noted. Especially in cases of mucor the vascular territory affected was characteristically demarcated by the pale diseased tissue. The intraoral hard palate curettage done was left to heal by secondary intention and postoperative obturators was used in select cases. A minimum of two sittings of thorough debridement were done (Table 3). In case of contradictory results of KOH mount, fungal culture, pathology reports or insufficient response to Lip AmB, the case was considered as co-infection of fungi, and azole group of drugs were started. The non-availability of antifungal sensitivity testing limits evidence for the same. Conventional antifungal nasal douches were done in immediate postoperative period.

The sensitivity and specificity of the various tests were noted. The overall survival of patients at the end of

Table 1 Patient details and presentation

Patient	Age/sex	Comorbidities	Probable triggers	Day of onset of symptoms (prior to admission-D0)	Day of initiation of treatment (after admission)	symptoms
I	47/F	T2DM, HTN, Anemia, CKD	Acute on CKD anaemia	15 days headache	Day 8	Persistent headache despite treatment
II	64/M	HTN, IHD, healedpneumonia, BA exacerbation	Intravenous and inhalational steroids	19 days headache, preseptal cellulitis	Day 20	Headache persistent,frontal swelling-potts puffy, inadequate response to antibiotics
III	52/F	Anaemia	Anaemia	3 days headache, difficulty in opening left eye	Day 0	(L) ptosis, cavernous sinus thrombosis
IV	54/M	T2DM, HTN, IHD	Uncontrolled sugars	10 days nasal blockade, headache, right facial weakness, platal bulge	Day 3	Right facial palsy, palatal bulge
V	53/F	T2DM, HTN, hyothyroidism	Uncontrolled sugars	10 days facial swelling, 3 days facial weakness, periorbital swelling	Day 3	Left facial palsy, cavernous sinus thrombosis, hard palate ulcer
VI	46/M	T2DM	Uncontrolled sugars + DKA	3 days nasal blockade, headache, periorbital swelling	Day 5	Preseptalcellulitis, DKA
VII	56/F	T2DM, membranoproliferative glomerulonephritis, HTN	Intravenous steroids for MPGN	7 days left cheek swelling and pain, headache	Day 0	Palatal discoloration
VIII	27/F	T1DM, DKA	Uncontrolled sugars post-partum	5 days headache and frontal headache	Day 3	Orbital cellulitis, DKA

BA bronchial asthma, *CKD* chronic kidney disease, *DKA* diabetic ketoacidosis, *HTN* hypertension, *IHD* ischemic heart disease, *T1DM* type1 diabetes mellitus, *T2DM* type2 diabetes mellitus, *HTN* hypertension, *IHD* ischemic heart disease, *MPGN* membranoproliferative glomerulonephritis

Table 2 Diagnostic aids

Patient	KOH mount	Fungal culture	HPE
I	Positive/aseptate broad hyphae	Zygomycetes	Mucormycosis
II	Negative	No growth	Aspergillous
III	Negative	Aspergillous after 21 days incubation	Invasive aspergillous
IV	Positive /branching septate hyphae	No growth 6weeks	Mucormycosis
V	Positive/septate hyphae	Mucor	Mucormycosis
VI	Positive/broad aseptate hyphae	Mucor	Mucormycosis
VII	Positive/broad septate hyphae	No growth	Mucormycosis
VIII	Negative	Mucor species	Mucormycosis

The sensitivity of KOH test = 60% and specificity of KOH Test = 33.33% while the sensitivity of HPE = 100%, but specificity is 0

treatment at an average follow up period of 15 months was noted. Treatment directed outcome was calculated on the number of days of inpatient stay–early being ≤ 45 days and late > 45 days. Chi –square tests were used and $p < 0.05$ was considered significant.

Results

In the time frame of September2015-September 2017, 8 of the 14 patients who presented with AIFRS were treated as per protocol. The mean age of presentation of the patients was 49.8.

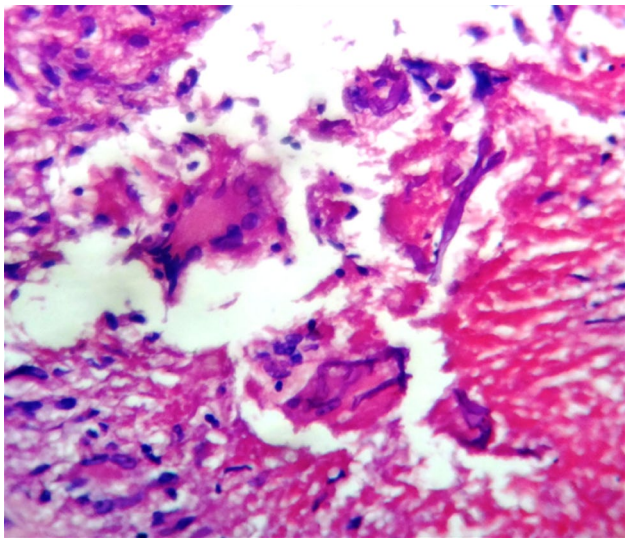


Fig. 2 Fungal hyphae noted with inflammatory changes

Almost 75% of the patients ($n=6$) had multiple comorbidities. About 75% ($n=6$) presented with diabetes, 25% ($n=2$) had chronic kidney disease, 25% ($n=2$) was on long term oral steroids, 25% ($n=2$) presented with diabetic ketoacidosis. The average delay in presentation to the hospital was 9 days and the average delay in initiation of treatment was 5.25 days. The varying presentation included persistent headache and facial heaviness, periorbital swelling, restricted movement of eye, palatal perforations, facial swelling, etc. (Table 1).

Preoperative diagnostic battery of tests included KOH mount, fungal culture and histopathological examination. KOH acted as screening test for fungal aetiology; however it was the combination of clinical presentation and KOH results which aided decision to start antifungals. KOH tests were positive for 62% patients, culture were positive in 62% cases and pathologic analysis detected fungi in 100% cases. In 62% cases both KOH and HPE detected fungi (Table 2).

Simultaneous initiation of debridement and medical therapy is crucial. Surgical debridement was done via endonasal,

Table 3 Surgical management

Patient	Surgical finding—FESS	Additional approach 1	Additional approach2	Additional approach3	No of sittings	Duration of inpatient stay
I	MT necrosed-amputated, MMA, AE, PE, sphenoidotomy, ST, IT removed	NIL	NIL	NIL	1	29
II	LP-dehiscent-periorbita exposed, FS filled with necrotic material	External frontal approach-drain kept—AMB douche	NIL	NIL	1	44
III	Right MT amputated,left sphenoid posterolateral wall, clivus dehiscent, dural exposure	Nasal AMB douche	NIL	NIL	1	40
IV	MMA-roof of MS eroded, posterolateral wall dehiscent with osteomyelitis	Hard palate osteomyelitis-intraoral curettage	Transzygomatic ostomyelitic bone curettage	Nasal AMB douche	2	65
V	UP necrosed, middle meatus filled with fungal debris with erosion of posterolateral walls	Hard palate—intraoral curettage	NIL	NIL	2	47
VI	UP necrosed, MS-anterior,posterior walls erosion, sphenoidotomy	Intraoral hard palate bone curettage	Nasal AMB douche	NIL	2	57
VII	Endoscopic medial maxillectomy, NLD eroded	Sublabial incision − 3 cm of anterior wall maxillary sinus eroded—disease removal upto zygoma and floor of orbit	Nasal AMB douche	NIL	2	45
VIII	MT Necrosed, MMA, FS filled with debris frontal trephination and AmB wash	Supraperiosteal frontal incision and debridement of necrotic frontal bone	Osteoplastic bicoronal flap—anterior table drilled	Nasal AmB douche	3	52

AmB amphotericin B, *AE* anterior ethmoidotomy, *FS* frontal sinus, *FESS* functional endoscopic sinus surgery, *LP* lamina papyracea, *MS* maxillary sinus, *MMA* middle meatal antrostomy, *MT* middle turbinate, *NLD* nasolacrimal duct, *PE* posterior ethmoidotomy, *ST* superior turbinate

tranzygomatic or transpalatal approach (depending on the site of affliction). Endonasal debridement was done for 25% of the patients while 25% required more than two approaches. Atleast 50% of the patients required two sittings of debridement while 37.5% required only one sitting and 12.5% ($n=1$) required three sittings (Table 3). All the patients were trained to do nasal douche with antifungals post operatively for a week. The number of patients with an early duration of inpatient stay (≤ 45 days) was 50% while the other 50% had a delayed stay (>45 days). Diabetic patients had a significant delay in inpatient stay ($p=0.03$) while the presence of hypertension had no relation ($p=0.84$).

The patients were managed on liposomal amphotericin B which was started preoperatively or simultaneously in the operation theatre. An average dose of 2.65 gm of Lip AmB was given during the average in patient stay of 47 days. Serial diagnostic endoscopic examination guided the need for second debridement and the total dose of drug. In case of clinical suspicion of co-infection, azole group of drugs were started with considerable clinical improvement. In patient V, isolates from palatal perforation showed aspergillous and nasal mucosa demonstrated mucor and hence the introduction of two classes of drugs significantly helped this patient. Sharana Mahomed et al. [9] also reports successful usage of amphotericin B and azole group of drugs. Co-infection is often a neglected aspect in treatment and limited data are available regarding the same. Patients were regularly monitored for nephrotoxicity and were managed with the help of a nephrologist. Active daily correction of electrolytes and renal parameters prevented the need for dialysis. Anti-fungal nasal douche was done in the immediate post-operative period and its effectiveness is yet to be established in randomised control study. In an average follow-up period of 15.12 months, all of the patients are alive and disease-free (Table 4).

The orbital complications of the patients are as shown in pie chart (Fig. 2). About 50% of patients had preseptal cellulitis, 37% had orbital cellulitis, 25% presented with cavernous sinus thrombosis while 37% had no orbital involvement per se. The orbital complications were managed in consultation with an ophthalmologist conservatively with intravenous antibiotics and topical preparations. Daily visual assessment was done and none of patients required decompression or exenteration for the same.

Discussion

The lack of established protocols for the treatment of invasive fungal sinusitis often leaves question marks when it comes to accurate decision making. The number of cases detected in our institute is on the rise which necessitates the need for a protocol. A sudden hike in cases is noted during the monsoon season. The causative organisms are often present in the upper airways [3] and a predisposing environment triggers the infectious spread. Systematic probing into the probable trigger factors and corrective measures initiated along with medico-surgical treatment is the key.

In our study uncontrolled diabetes mellitus was the most common trigger factor and adequate control of blood sugar is vital [7]. Ketoacidosis is associated with early angioinvasion as the low serum pH decreases the phagocytic activity of neutrophils and other macrophages. Neutrophils are the major line of defence against these fungi. The reported survival rates is quite varied in literature with Kasapoglu et al. [3] reporting 76.5%, Marcus et al. [4] 21%, Justin et al. [5] 46% and Kiran Bala et al. [7] 70.6%.

The presentation varies from patient to patient. The characteristic blackish eschar is a hallmark sign but is present only in 40–50% of cases [6] and one should not wait for the same. The delay in presentation for an Otorhinolaryngology consult and the delay in initiation of treatment (average number of days = 5) can contribute to valuable time lost. The delay was later attributed to the inefficiencies in sample collection and reporting. Educating other departments

Table 4 Medical management

Patient	Diabetic status	Total drug dosage	Complications	Post discharge	outcome
I	Yes	2 gm(AmB) + V	Hypokalaemia	NIL	Alive disease free, 18 months
II	No	2 gm(AmB) + V	Hypokalaemia, acute kidney injury-renal tubular dysfunction, hypocalcaemia	1 month V	Alive disease free, 8 months
III	No	2 gm(AmB)	Hypokalaemia	NIL	Alive disease free, 12 months
IV	Yes	2.9 gm(AmB) + V	Hypokalaemia, acute kidney injury	NIL	Alive disease free, 19 months
V	Yes	2.3 gm(AmB) + V	Hypokalaemia, acute kidney injury, hospital acquired diarrhoea	6 months V	Alive disease free, 25 months
VI	Yes	2.5 gm(AmB)	Hypokalaemia, chills, anaemia	NIL	Alive disease free, 18 months
VII	Yes	2 gm(AmB)	Hypokalaemia, chills	NIL	Alive disease free, 17 months
VIII	Yes	5.5 gm(AmB) + P	Anaemia, hypokalaemia, acute kidney injury	2 weeks P	Alive disease free, 4 months

AmB liposomal amphotericin B, *P* posaconazole, *V* voricanazole

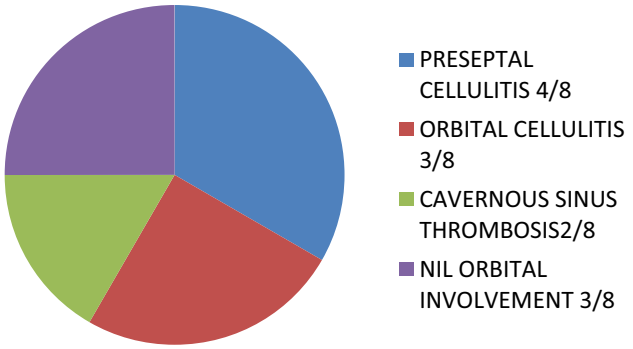


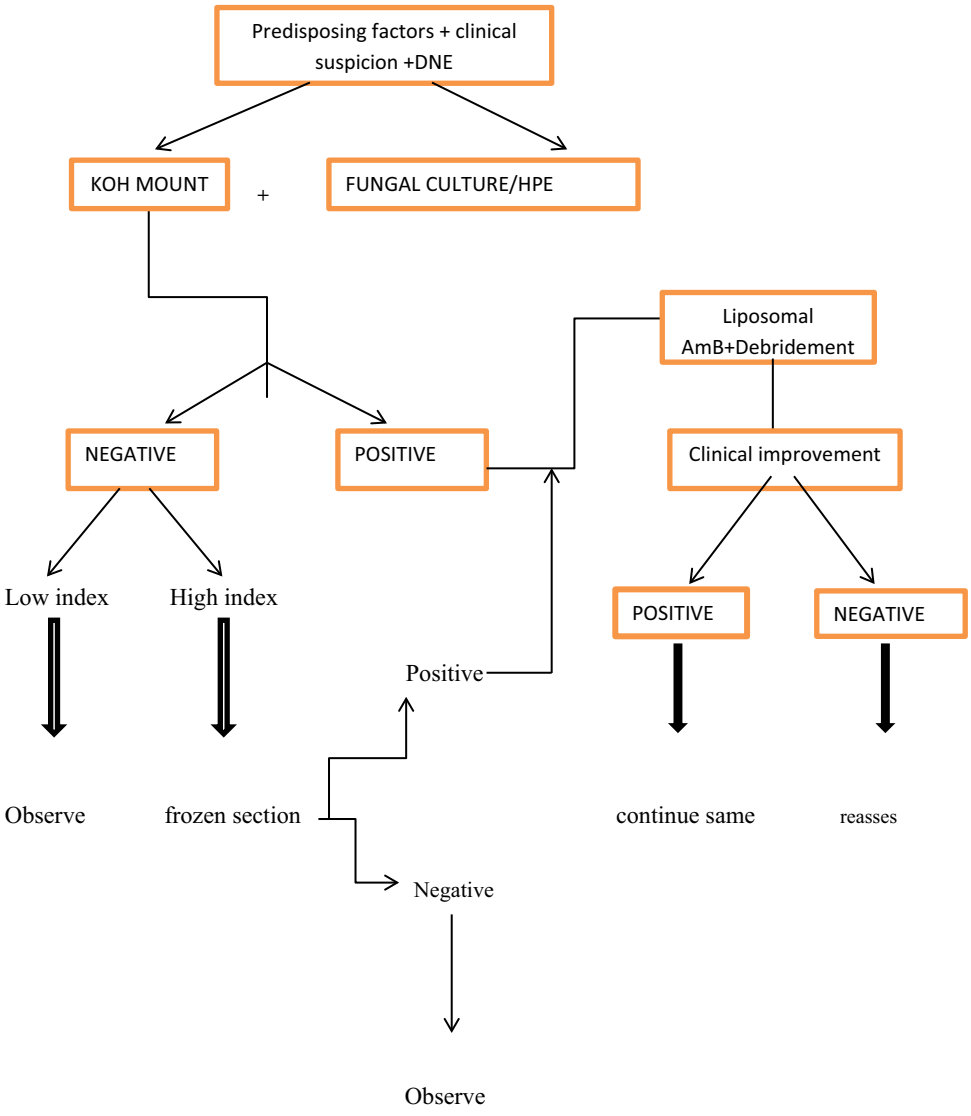
Fig. 3 Orbital complications

to suspect the disease entity and efficient sample collection and reporting may be life saving for the patient.

Hence in any suspecting individuals, a battery of tests is done. KOH mounts acts a screening test alone and fungal culture is required, which is time consuming [3, 8]. Fungal culture results are compromised by the reduced viability of zygomycetes hyphae; hence it is isolated only in few patients. Hence pathological evidence of tissue invasion and identification of fungal hyphae was taken into account. This was aided by frozen section or routine HPE. In our study, HPE could identify fungal aetiology in 100% cases. Early identification of aetiology is crucial and thereafter a systematic protocol was followed in all patients (Fig. 3).

All the patients underwent endonasal debridement as the latest studies support improved outcomes with endonasal approach. Kasapoglu et al. [3] in his series has reported better survival rates for patients undergoing endonasal surgery (90%) when compared to open surgery (57.1%). Selected patients underwent debridement via transpalatal or transzygomatic, in addition to endonasal route. The rationale behind the same was to reduce the fungal load and increase drug penetrance. Endoscopic debridement was

Fig. 4 Management protocol



preferred to radical surgery as the patients were constantly monitored; and equivalent or better results were achieved with less morbidity. However no comparative studies was undertaken simultaneously. An average of 2.6 g of Liposomal amphotericin B was given for all patients. Kiran Bala et al. [7] have reported an improved survival with liposomal amphotericin B (88%) over conventional (66%). AmB is licensed by the US Food and Drug administration [10] as the first line drug for invasive fungal sinusitis and hence was selected as the drug of choice in our study. Posacanazole has been reportedly used as a salvage therapy [1] in cases of refractory mucor and it has been successfully used in patient VIII of our study. Other options like capsofungin has been used by Kazak et al. [11] but the lack of data from randomised controlled studies, adequate response of our patients to AmB and azole groups and the high cost involved limited their usage. The good results of our study may be attributed to the facts that almost all cases were identified in its nascent stage and were primarily sino-nasal with or without orbital/palatal involvement. None of the patients had intracranial extent of the disease. Parikh et al. [12] also reported an overall lower mortality rates compared to other studies and attributed the intracranial spread to be the highest predictor of mortality. Great care was taken to start the medical and surgical treatment simultaneously. Serial DNE and inpatient analysis was meticulously done for at least a month to detect any resurgence of the disease. There was no hesitation in considering a second de Kock no debridement if the mucosa showed unsatisfactory healing. Neutropenia was not detected at any stage of our treatment. Many studies including Cho et al. [13] has attributed neutropenia to increasing mortality rates (Fig. 4).

The absence of clinical improvement within 48 h of initiation of treatment should be approached with caution. The possibilities being inadequate debridement, lower dosage of drug, possible co-infection, underlying trigger is not addressed to or the patient may be in sepsis. Serial DNE and imaging guided further plan of action.

Conclusion

A cookie cutter treatment is definitely not applicable to every patient, but a streamlined protocol-wise approach has achieved good results. A high index of suspicion and aggressive medical and surgical treatment is essential. Multiple endoscopic debridement supplemented by site specific debridement have brought good results. A good histopathological and microbiological support is needed to guide treatment.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and or national research committee and with 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This was a retrospective chart review and thus informed consent was not required by our human ethics board.

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