નં.SHSRC/કોવિડ/મ્યુકોરમાઇકોસીસ/માર્ગદર્શિકા/
૨૦૨૧/૬૦૮-૬૪૮
કમિશ્નરશ્રી, આરોગ્ય તબીબી સેવાઓ અને તબીબી
શિક્ષણ (આ.વિ), બ્લોક ન.૫, ડો. જીવરાજ મહેતા
ભવન, ગાંધીનગર
તા.૧૧/૦૫/૨૦૨૧

વિષયઃ- Advisory on Screening, Diagnosing Management & Treatment Protocol for Mucormycosis in COVID- 19 Adult Patients ની માર્ગદર્શિકા મોકલાવવા બાબત.

હાલમાં કોરોનાથી સાજા થયા બાદ કેટલાક દર્દીઓમાં એક પ્રકારનો ફંગસનો રોગ – મ્યુકોરમાઇકોસીસ જોવા મળી રહયો છે. આ રોગનું નિદાન કરવામાં અથવા સારવાર આપવામાં વિલંબ થાય તો તે ઝડપથી પ્રસરે છે અને જીવલેણ પણ બની શકે છે. મ્યુકોરમાઇકોસીસનાં સ્ક્રિનિગ, તપાસ, નિદાન અને સારવાર માટે ICMR ધ્વારા એડવાઇઝરી બહાર પાડવામાં આવેલ છે તેમજ બી.જે.મેડીકલ કોલેજ અને સિવિલ હોસ્પિટલ, અમદાવાદના નિષ્ણાંતો ધ્વારા આનો ટ્રીટમેન્ટ પ્રોટોકોલ બનાવવામાં આવેલ છે. જે આપની જાણ સારૂ તેમજ આપના કક્ષાએથી ઘટતી કાર્યવાહી કરવા આ સાથે સામેલ છે.

અધિક નિયામક(જ.આ.)	અધિક નિયામક(ત.સે.)	અધિક નિયામક(ત.શિ.)
ગાંધીનગર	ગાંધીનગર	ગાંધીનગર

બિડાણ –

(૧) Advisory on Screening, Diagnosing & Management of Mucormycosis

(૨) Treatment Protocol for Mucormycosis in Adult Patients

પ્રતિ,

- ડીનશ્રી, સરકારી મેડીકલ કોલેજ, GMERS મેડીકલ કોલેજ, સ્વનિર્ભર મેડીકલ કોલેજ, તમામ
- મેડીકલ સુપ્રિન્ટેન્ડેટશ્રી, સરકારી અને GMERS મેડીકલ કોલેજ સંલગ્ન હોસ્પિટલ, તમામ
- મુખ્ય જિલ્લા તબીબી અધિકારીશ્રી સહ સિવિલ સર્જનશ્રી, સિવિલ હોસ્પિટલ, તમામ
- મુખ્ય જિલ્લા આરોગ્ય અધિકારીશ્રી, જિલ્લા પંચાયત, તમામ
- સુપ્રિન્ટેન્ડેટશ્રી, સબ ડિસ્ટ્રીકટ હોસ્પિટલ, તમામ

નકલ સવિનય રવાના –

- અગ્રસચિવશ્રી, આરોગ્ય અને પરિવાર કલ્યાણ વિભાગ, બ્લોક નં.૭/૭,માળ, સચિવાલય, ગાંધીનગર
- કમિશ્નરશ્રી, આરોગ્ય, તબીબી સેવાઓ અને તબીબી શિક્ષણ(આ.વિ.), બ્લોક નં.૫/૧ માળ, ડૉ.જીવરાજ મહેતા ભવન, ગાંધીનગર
- મિશન ડાયરેકટરશ્રી(એન.એચ.એમ.), બ્લોક નં. ૫/૨ માળ, ડૉ.જીવરાજ મહેતા ભવન, ગાંધીનગર

નકલ રવાના

- એકઝીકયુટીવ ડાયરેકટરશ્રી, સ્ટેટ હેલ્થ સીસ્ટમ રીસોર્સ સેન્ટર, એન.એચ.એમ. ભવન, ગાંધીનગર
- વિભાગીય નાયબ નિયામકશ્રી, વિભાગીય નાયબ નિયામકશ્રીની કચેરી, તમામ.

ICMR INDIAN COUNCIL OF MEDICAL RESEARCH
Serving the nation since 1911

mygov मेरी सरकार

Evidence Based Advisory in the Time of COVID-19

Screening, Diagnosis & Management of **Mucormycosis**

Mucormycosis, if uncared for, may turn fatal

Mucormycosis is a fungal infection that mainly affects people who are on medication

Sinuses or lungs of such individuals get affected after fungal spores are inhaled

This can lead to serious disease with warning sign & symptoms as follows:

- Pain and redness around eyes and/or nose
- Fever
- Headache
- Coughing
- Shortness of breath
- Bloody vomits
- Altered mental status

icmr
INDIAN COUNCIL OF MEDICAL RESEARCH
Serving the nation since 1911

mygov
मेरी सरकार

Evidence Based Advisory in the Time of COVID-19

Screening, Diagnosis & Management of **Mucormycosis**

What Predisposes

- Uncontrolled diabetes mellitus
- Immunosuppression by steroids
- Prolonged ICU stay
- Co-morbidities – post transplant/malignancy
- Voriconazole therapy

icmr
INDIAN COUNCIL OF MEDICAL RESEARCH
Serving the nation since 1911

mygov
मेरी सरकार

Evidence Based Advisory in the Time of COVID-19

Screening, Diagnosis & Management of **Mucormycosis**

Dos

- Control hyperglycemia
- Monitor blood glucose level post COVID-19 discharge and also in diabetics
- Use steroid judiciously – correct timing, correct dose and duration
- Use clean, sterile water for humidifiers during oxygen therapy
- Use antibiotics/antifungals judiciously

icmr
INDIAN COUNCIL OF MEDICAL RESEARCH
Serving the nation since 1911

mygov
मेरी सरकार

Evidence Based Advisory in the Time of COVID-19

Screening, Diagnosis & Management of **Mucormycosis**

Don'ts

- Do not miss warning signs and symptoms
- Do not consider all the cases with blocked nose as cases of bacterial sinusitis, particularly in the context of immunosuppression and/or COVID-19 patients on immunomodulators
- Do not hesitate to seek aggressive investigations, as appropriate (KOH staining & microscopy, culture, MALDITOF), for detecting fungal etiology
- Do not lose crucial time to initiate treatment for mucormycosis

ICMR
INDIAN COUNCIL OF MEDICAL RESEARCH
Serving the nation since 1911

mygov
मेरी सरकार

Evidence Based Advisory in the Time of COVID-19

Screening, Diagnosis & Management of **Mucormycosis**

How to Manage (1/2)

- Control diabetes and diabetic ketoacidosis
- Reduce steroids (if patient is still on) with aim to discontinue rapidly
- No antifungal prophylaxis needed

ICMR
INDIAN COUNCIL OF MEDICAL RESEARCH
Serving the nation since 1911

mygov
मेरी सरकार

Evidence Based Advisory in the Time of COVID-19

Screening, Diagnosis & Management of **Mucormycosis**

How to Manage (2/2)

Extensive Surgical Debridement - to remove all necrotic materials
Medical treatment

- Install peripherally inserted central catheter (PICC line)
- Maintain adequate systemic hydration
- Infuse Normal saline IV before Amphotericin B infusion
- Antifungal Therapy, for at least 4-6 weeks

Monitor patients clinically and with radio-imaging for response and to detect disease progression

Treatment Protocol For Mucormycosis In Adult Patients
- By Expert Committee of Civil Hospital, Ahmedabad

Institutional Strategies

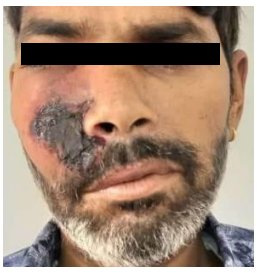
1. All mucormycosis cases will be primarily admitted and managed pre & post operatively in respective surgical specialty (ENT, Oral and maxillofacial surgery, Ophthalmology, Neurosurgery etc.)
   After admission every patient is to be examined by Department of Medicine, ENT, and Oral and Maxillofacial Surgery; and by Ophthalmology & Neurosurgery as and when indicated.
2. Uncontrolled medical illness would be managed by respective medical units.
3. Independent second opinion of senior / another faculty from respective emergency unit may be taken if required.
4. Separate ward, OT or extra OT day are to be managed as per clinical load.
5. Day care treatment may be offered even post operatively whenever feasible.
6. The focus will be on early diagnosis & rapid initiation of antifungal therapy and aggressive "early" surgical debridement of necrotic lesions with optimal correction of co- morbidities.

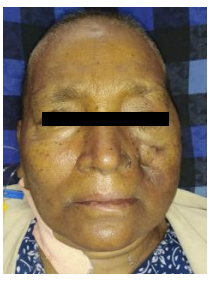
Introduction:

- Mucormycosis or Zygomycosis is a fungal disease caused by fungi of order Mucorales.
- High risk group- Diabetes mellitus, diabetic ketoacidosis, steroid, cytotoxic drug therapy, HIV, immunosuppression, malignancy or haematological disorder including iron overload states.
- New corona virus SARS COV 2 itself may serve as a risk factor - chronic respiratory disease, corticosteroid therapy, intubation /mechanical ventilation, deranged glucose metabolism, which may lead to secondary fungal infection.
- Overall mortality: Pulmonary mucormycosis: 50-70%, Rhinocerebral: 30 - 70%, CNS involvement: >80%, Disseminated: > 90%, AIDS: almost 100%

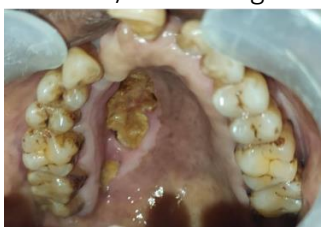
Presenting features:

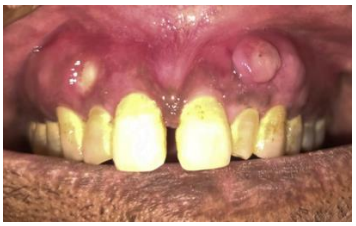
- Facial findings:
  Facial swelling / Paresthesia / Sinus tract on face/ Discolouration of skin (necrosis)/ Infection in dangerous area of face



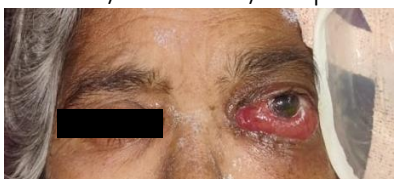


- Nasal findings:
  Foul smelling nasal discharge/Nasal congestion/ Sinusitis/ Erythematous to violaceous to black necrotic eschar in nasal cavity
- Intraoral findings:
  Halitosis/ Intraoral pus discharge/ Ulceration & Blackening of mucosa/ Exposed palatal bone/ Sinus tract/ Loosening of teeth/ Unhealed tooth socket/ Mobility of maxilla





- Orbital findings:
  Vision loss/ Peri orbital cellulitis/ Chemosis/ Exophthalmos(Proptosis)/ Opthalmoplegia



- CNS findings:
  Headache/ Cranial nerve involvement/ Rapidly progressive neurological deficit
- Pulmonary findings:
  Fever/ Cough/ Chest pain/ Dyspnea/ Hemoptysis
- Gastrointestinal findings:
  Abdominal pain/ Nausea/ Vomiting/ Gastrointestinal bleeding

Specific points to be observed in history:

- H/o COVID infection (Immunosuppressive drugs/ Ventilatory care, etc.)
- Co morbid conditions: Diabetes mellitus/ Malignancy/ HIV/ Chronic kidney disease / Obesity/ Other systemic illness
- Local factors (H/O tooth extraction or any other oral/surgical procedure/ Head injury)

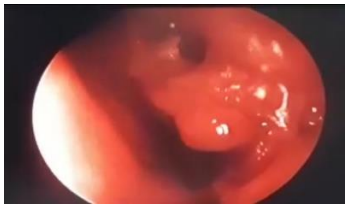
Investigations:

1) Lab parameters:

CBC/ ESR/ FBS, PPBS, HbA1C/ LFT/ RFT with electrolytes/ HIV, HbsAg / CSF (if indicated)

2) Nasal endoscopic examination

Black necrotic eschar tissue

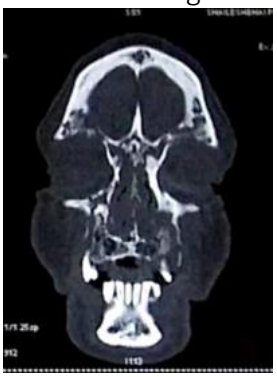


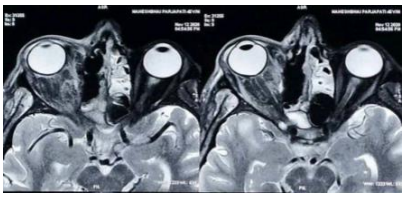
3) Radiographic Examination:

X- Ray PNS and OPG may be normal

Contrast enhanced CT scan with 3D Reconstruction findings:

- Erosion and thinning of Hard tissues
- Mucosal thickening of sinuses
- Enlargement of masticatory muscle
- Changes in Fat Planes





MRI with contrast findings:

- Optic neuritis
- Cavernous sinus thrombosis
- Intracranial involvement
- Infratemporal fossa involvement

4) Biopsy:

Oral cavity: Biopsy from deeper portion of extracted tooth socket/exposed bone
Nasal Cavity: Nasal endoscopy and crust sampling
Direct microscopy of bronchoalveolar lavage & transbronchial biopsy

Test	Sample to be collected in	To diagnose
KOH	Saline	Presence of Fungi
Fungal culture	Saline	Type of Fungi
Histopathology	10%Formalin	Fungus/Bony lesions/ malignancy
Frozen section	Saline	Extension of disease/ fungus intraoperatively if available
Squash and imprint cytology preparation	Saline	Presence of fungi

Treatment:

Medical management:

1. Mucormycosis should be treated with antifungal Injectable Amphotericin B for 2-3 weeks on clinical suspicion & as per severity even while awaiting diagnostic and culture reports.
2. Duration of pre operative Amphotericin therapy may be considered as per clinical severity and early need for surgical intervention.
3. Oral antifungal: Overlap with Injectable for 3-4 days before step down and to be continued 1 week after endoscopic biopsy is negative.
4. Liposomal amphotericin is preferred in cases having Renal complication due to Amphotericin and in case of cerebral parenchymal involvement.

1) First line antifungal therapy:

- **Inj Amphotericin B Deoxycholate(C-AmB):**

Dose: 1.0-1.5 mg/kg once per day, IV: infused over 4 - 6 hours

- **Half-life**:
  Biphasic: Initial 15 to 48 hr, Terminal 15 days
- **Disadvantages**:
  Highly toxic, Poor CNS penetration
  To avoid infusion-related immediate reactions, premedicate with:
  1. NSAID and/or diphenhydramine **or** acetaminophen with diphenhydramine **or** hydrocortisone
  2. Pre-infusion administration of 500 to 1,000 mL of normal saline
- **Dosing**:
  1) Renal Impairment: Daily total dose can be decreased by 50% or the dose can be given every other day- Haemodialysis or CRRT.
  2) Hepatic Impairment: No dosage adjustment

Adverse Reactions:

Systemic: >10%:

Hypersensitivity: Anaphylaxis, Infusion reactions

Cardiovascular: Hypotension

Central nervous system: Chills, malaise, pain & headache (less frequent with I.T.)

Endocrine & metabolic: Hypokalemia, hypomagnesemia

Gastrointestinal: Anorexia, diarrhoea, epigastric pain, heartburn, nausea (less frequent with I.T.), stomach cramps, vomiting (less frequent with I.T.)

Hematologic & oncologic: Anemia (normochromic-normocytic)

Local: Pain at injection site (with or without phlebitis/ thrombophlebitis –incidence may increase with peripheral infusion of admixtures)

Renal: Renal function abnormality (including azotemia, renal tubular acidosis, nephrocalcinosis [>0.1 mg/ml]), renal insufficiency

Respiratory: Tachypnea

Miscellaneous: Fever 1% to 10%:
Cardiovascular: Flushing, hypertension
Central nervous system: Arachnoiditis, delirium, neuralgia (lumbar; especially with Intrathecal therapy), paresthesia (especially with intrathecal therapy)
Genitourinary: Urinary retention
Hematologic & oncologic: Leukocytosis

- Watch for: Urine output , Renal function Test (pH, Bl. Urea, S. Creatinine, Electrolytes)

Cockcroft-Gault formula for estimating creatinine clearance (CrCl)

CrCl (male) = ([140-age] × weight in kg)/(serum creatinine × 72)
CrCl (female) =([140-age] × weight in kg)/(serum creatinine × 72) × 0.85
In case of nephrotoxicity
Crcl <10 ml/min: 0.5-0.7 mg/kg IV q24-48hr
Consider other antifungal agents that may be less nephrotoxic
Intermittent hemodialysis: 0.5-1 mg/kg IV q24hr after dialysis session
Continuous renal replacement therapy: 0.5-1 mg/kg IV q24hr

- Inj Liposomal amphotericin B (LAmB):
  - Dosage: 5 mg/kg per day and in CNS mucormycosis dose is 7.5 – 10 mg/kg per day
  - Advantages: Less nephrotoxic, better CNS penetration than AmB or ABLC
  - Disadvantage: Expensive
  - Contraindication : Hypersensitivity
- Inj Amphotericin B lipid complex (ABLC) :
  - Dosages:5 mg/kg/day
  - Advantages and Supporting Studies: Less nephrotoxic than AmB deoxycholate
  - Disadvantage: Expensive, Possibly less efficacious than LAmB for CNS infection

2) Second line- AZOLE Derivatives (Step Down or Salvage Therapy)

Step-down therapy — Posaconazole and isavuconazole are broad-spectrum azoles available in both parenteral and oral formulations

Posaconazole or isavuconazole for oral step-down therapy. Alternatively IV parenteral formulations can be used as salvage regimen in case of unresponsiveness to AmB

- Isavuconazole:

Dosage:
- 200 mg of isavuconazole (372 mg of isavuconazonium sulfate), load q8h * 6 followed by once-daily dosing

Advantages and Supporting Studies:
- Efficacy similar to that of LAmB in mouse models
- FDA-approved
- Rational empirical option when septate mold vs mucormycosis is not yet established

Disadvantage:
- Much less clinical experience
- Clinical study supporting approval is small and historically controlled

- Posaconazole:

Dosage:
- 200 mg four times per day
- Alternatively, posaconazole delayed-release tablets (300 mg every 12 hours on first day, then 300 mg once daily) taken with food.

Advantages and Supporting Studies:
- In vitro activity against the Mucorales
- Lower MICs than isavuconazole
- Retrospective data for salvage therapy in mucormycosis

Disadvantage:
- Substantially lower blood levels than isavuconazole,
- No data on initial therapy for mucormycosis
- No evidence for combination therapy with posaconazole
- Limited use for salvage therapy, hyperglycemia, hypokalemia, pruritus
- Contraindicated with Statin group of drugs

3) Combination therapy

a. Lipid polyenes (both ABLC and LAmB) plus echinocandins(e.g. caspofungin, micafungin, and anidulafungin) :

- Improves survival rate among disseminated mucormycosis including CNS disease better outcome than monotherapy with polyenes.

Advantages and Supporting Studies:

- Favorable toxicity profile
- Synergistic in murne disseminated mucormycosis
- superior outcomes for rhino-orbial-cerebral mucormycosis.

Disadvantage: Limited data

b. Lipid polyenes plus azole (Posaconazole or Isavuconazole)

Advantages and Supporting Studies:

- Favorable toxicity profile

Disadvantage:

- No convincing data to support any form of combination therapy
- Not recommended in major treatment guidelines.

c. Triple therapy (Lipid polyene plus echinocandin plus azole)

Advantages and Supporting Studies:

- Maximal Aggressiveness

Disadvantage:

- No available evidence of superiority vs. monotherapy or dual therapy

Duration of therapy:

- Inj antifungal 2-3 weeks or more depending on clinical severity
- Liposomal antifungal may be used if AmB toxicity develops
- Overlap of injectable and oral antifungals for 3-4 days followed by oral antifungals.
- Oral antifungal to be continued 1 week after biopsy is negative.
- Regular follow up initially monthly for 3 months then SOS.

4) Treatment of comorbidities

5) Other treatment:

- Use of blood & blood components should be judicious to maintain the hemoglobin level >10 gm%.
- Iron chelating agent may be useful in iron overload conditions like patient on multiple blood transfusion

Surgical Management:

ENT surgeon/ Oral and Maxillofacial surgeon/ Ophthalmologist/ Plastic surgeon/ Neuro surgeon

SITUATION	APPROACH	SURGICAL DEBRIDEMENT	RECONSTRUCTION	INTERVENTION BY
1) If nasal and sinus involvement is present without bony erosion of maxilla/ zygoma and orbital floor	-	Endoscopic sinus surgery (ESS) by ENT surgeon	-	-

2) Maxilla involvement without involvement of intraoral soft tissue	Intraoral crevicular incision	Maxillectomy (partial/ total)	Primary closure	Surgical debridement of the involved structures by Maxillofacial surgeon/ Plastic surgeon Endoscopic clearance of sinuses(ESS) by ENT
3) Maxilla involvement with involvement of intraoral soft tissue	Intraoral crevicular incision	Maxillectomy (partial/ total)	Depending on size of the defect: 1) 1 or 2 teeth involvement - Buccal fat pad 2) More than 2 teeth or central portion of palate- Temporalis muscle/ other flaps 3) Involvement of Infra temporal fossa/ necrosis of Temporalis muscle- STG/ other flaps 4) Obturator/ Zygomatic implants	Surgical debridement of the involved structures by Maxillofacial surgeon/ Plastic surgeon Endoscopic clearance of sinuses(ESS) by ENT
3) Maxilla + Minimal zygoma involvement	Intraoral crevicular incision	Maxillectomy (partial/ total) + Zygoma debridement	As above	Intra oral surgical debridement by Maxillofacial surgeon/ Plastic surgeon Endoscopic clearance of sinuses (ESS) by ENT
4) Maxilla +zygoma +orbit	A) Weber ferguson with Dieffenbach's modification incision	Maxillectomy (partial/ total) + Zygoma debridement + Debridement of Orbital floor/ walls + Localised debridement of necrosed tissue in early	As above Reconstruction of floor of orbit+ walls of orbit and	Surgical debridement of the involved structures by Maxillofacial surgeon/ Plastic surgeon Endoscopic clearance of sinuses by ENT Orbital region debridement/ exenteration by Ophthalmologist

	B) Trans-conjunctival approach	localised orbital disease **Exenteration of eye** in case of: **1)** Vision loss **2)** Total ophthalmoplegia **3)** Chemosis **4)** Necrosis of orbital tissues **NOTE:-** Loss of vision in not always the indication of exenteration	orbital shelf with temporalis muscle/ other flaps	
5) Frontal bone and skull base	Coronal approach	**A)** Anterior table:- Debridement Posterior table:- Cranialization **B)** Debridement if Osteomyelitic skull bone and involvement of the cerebral parenchyma	-	Endoscopic clearance of sinuses & skull base by ENT and neurosurgeon Safe maximum resection by Neurosurgeon

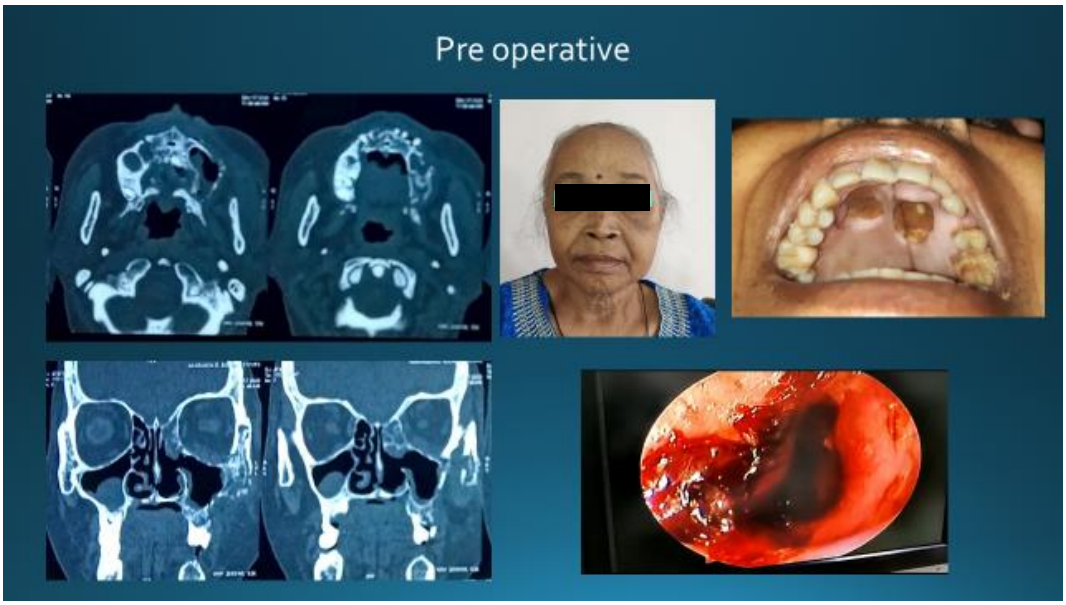
References:

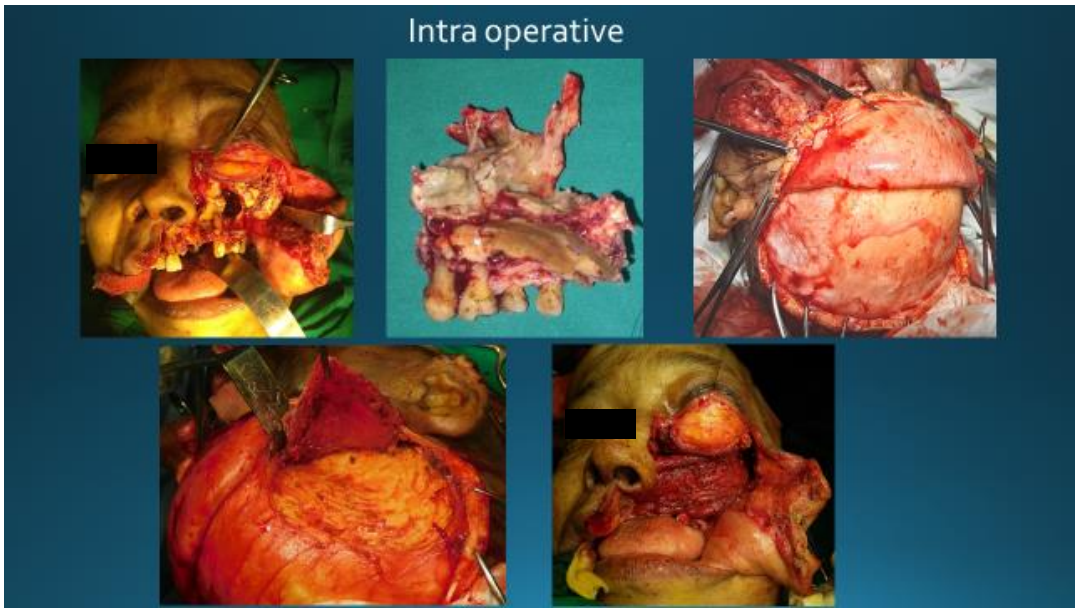
1. Harrison's Principles of Internal Medicine – 20th Edition. 213: Mucormycosis: Page no:1537
2. Cornely OA al: ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013.Clin Microbiol Infect 20(S3):5, 2014
3. Kontoyiannis DP et al: Prospective antifungal therapy (PATH) alliance: Focus on mucormycosis Mycoses 57:240, 2014
4. Spellberg B et al: Novel Perspective on mucormycosis: Pathophysiology, Presentation, and management. Clin Microbiol Rev 18:556, 2005
5. Spellberg B et al: Combination therapy for mucormycosis: Why, what, and how? Clin infect Dis 54(S1):S73, 2012
6. Spellberg B et al: Risk factor for mortality in patients with mucormycosis. Med Mycol 50:611, 2012
7. www.cdc.gov
8. Clin Infect Dis. 2009;48(12):1743
9. Am J Transplant. 2009;9(9):2166. Epub 2009 Jul 22. Transplantation. 2010;90(1):85
10. Theory and Practice of Histological techniques; *Bancroft 6TH Edition*; Chap 9; Pg 121 – 134.
11. District laboratory practice in tropical countries", Monica Cheesbrough 2003 (part-1 & 2)
12. Koss's Diagnostic Cytology& its Histopathologic Bases, 1616, 5th edition
13. Comprehensive Cytology, Marluce Bibbo 32:881-906, 1991
14. Theory and Practice of Histological techniques; *Bancroft 6TH Edition*
15. Vankatesh Anehosur- JOMS 2019
16. Dimitrios P Kontoyiannis, How I treat mucormycosis BLOOD (2011)

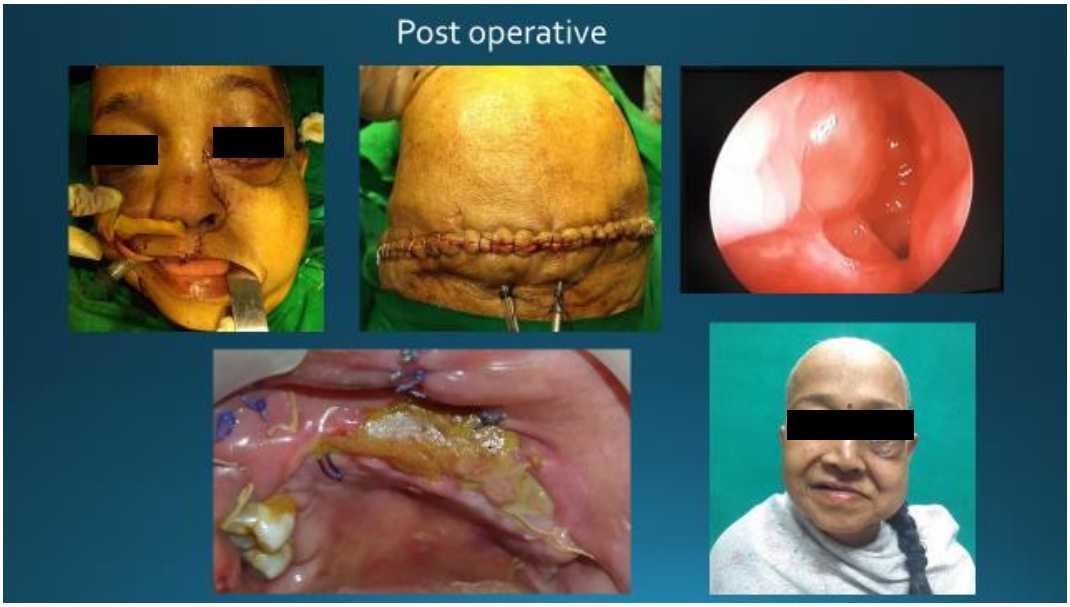
17. B.Rammaert, Diabetes and mucormycosis: A complex interplay, Diabetes & Metabolism (2012)
18. Kiran Bala, International society for human and medical mycology, Medical Mycology (2015)

Faculties in the Expert Committee:

1) Dr. Kamlesh Upadhyay: (Professor and Head, General medicine)
2) Dr. Ila Upadhya: (Professor and Head, ENT)
3) Dr. Sonal Anchlia: (Professor and Head, Oral and maxillofacial surgery)
4) Dr. Hansa Thakkar: (Professor and Head, Ophthalmology)
5) Dr. Jaimin Shah: (Professor and Head, Neurosurgery)
6) Dr. Jayesh Sachde: (Professor and Head, Plastic surgery)
7) Dr. Pranay Shah: (Professor and Head, Microbiology)
8) Dr. Hansa Goswami: (Professor and Head, Pathology)






Post operative