Management and role of antifungals in Aspergilloma / fungal mycetoma

Aspergillosis refers to a spectrum of disease caused by *Aspergillus* species. In immunocompromised and critically ill patients' invasive pulmonary aspergillosis (IPA) is relatively common and often fatal. In non-immunocompromised patients' chronic pulmonary aspergillosis (CPA) (including those with an aspergilloma) may occur in those who have suffered a pulmonary insult such as tuberculosis, sarcoidosis, pneumothorax etc.

Within the spectrum of CPA are simple aspergilloma, chronic cavitatory pulmonary aspergillosis, chronic fibrosing pulmonary aspergillosis and Aspergillus nodule.

Surgical treatment is the mainstay of management for symptomatic patients with simple aspergilloma. Surgical results are excellent. However, there are many patients with extensive multi cavitatory CPA who fail medical therapy and in whom surgery is contemplated. The results of surgical treatment for this group are not so good.

The perioperative management of post-surgical patients with pulmonary aspergillosis can be challenging.

The aims of antifungal therapy are to prevent Aspergillus empyema and to prevent recurrence of CPA post-surgery, or at least progression, if residual disease remains.

Adjuvant antifungal pharmacotherapy does not improve the results of surgical treatment for isolated pulmonary aspergillosis where a full curative resection has been carried out. [1]

Aspergilloma

Single uncomplicated "aspergilloma" is defined as a single pulmonary cavity containing a fungal ball in a non-immunocompromised patient with microbiological or serological evidence of *Aspergillus* sp. with minimal or no symptoms and no radiographic progression over at least 3 months.

An aspergilloma is described radiographically as an approximately spherical shadow with surrounding air, also called a fungal ball, in a pulmonary cavity, with evidence that *Aspergillus* sp. is present in the material as below. [2]

- Fungal culture & direct microscopy (DM) - from a biopsy/BAL sample following bronchoscopy-if possible

- In non-immunocompromised patients – Aspergillus total antibodies by precipitin test, Aspergillus IgG antibodies by ELISA & Aspergillus galactomannan antigen by ELISA
- In immunocompromised patients- Aspergillus galactomannan antigen by ELISA

Aspergillus fumigatus is the usual cause. Fungal balls of the lung may rarely be caused by other fungi, such as *A. flavus* or other moulds like *Scedosporium* sp.

Single aspergilloma represents a manifestation of CPA with a favourable prognosis and is usually not rapidly progressive so that management decisions are not usually acute, unless severe haemoptysis has occurred. [2]

What are the management options for an *Aspergillus* fungal ball of the lung (Aspergilloma)?

Recommendations.

- asymptomatic patients with a single aspergilloma and no progression of the cavity size over 6–24 months should continue to be observed.
- patients with symptoms, especially significant haemoptysis, with a single aspergilloma, should be resected, if there are no other contraindications.
- preoperative, perioperative /postoperative antifungal therapy gives less postoperative complications with better prognosis. Antifungal therapy with voriconazole (or another mould-active azole) or amphotericin B (deoxycholate / liposomal) is suggested to prevent postoperative *Aspergillus* empyema.[2]

Pre-operative

An evaluation of risk of spillage at surgery needs to be made based on the difficulty of separating the cavity containing the fungal ball from the chest wall. Extra-pleural dissection over the apex may be required but may be followed by bleeding from collateral arterial vessels crossing the pleura from the chest wall.

Perform BAL / serum Aspergillus galactomannan antigen levels,

If it is higher than normal values (may be slightly high sometime as the fungal ball is well walled off)

OR

If it is likely or possible that the cavity will be opened during the surgical procedure, leading to pleural contamination then,

antifungal therapy with voriconazole (or another mould-active azole such as itraconazole) or amphotericin B (depending on the clinical situation) should be given.[2]

Standard practice is to start oral voriconazole (drug of choice for aspergillosis) 2 weeks before surgery, perform liver function tests, if they are normal start oral voriconazole 400 mg 12 hours apart on day 1 (loading dose) followed by oral voriconazole 200 mg twice daily for two weeks alternatively, oral itraconazole 200 mg twice daily for two weeks while monitoring liver function tests weekly.[1]

Numerous drug interactions need to be considered, including marked prolongation of sedation post-operatively.[1] Use of voriconazole may alter the preferred anaesthetic approach, as prolongation of benzodiazepine sedation is problematic with voriconazole.[2] If patients are on an azole prior to surgery and there is a risk of azole resistance, consider amphotericin B pre- and perioperatively. [1]

Peri-operative

If spillage does occur, some clinicians advise washing out the pleural space with amphotericin B to prevent Aspergillus empyema, although evidence to support this approach is minimal.[2] Aspergillus empyema is a difficult to treat entity, probably requiring long term antifungal therapy and may lead to pleural fibrosis and a significant restrictive pulmonary defect if only a lobectomy or wedge resection is done. [1]

Antifungal therapy should be continued postoperatively, and a Microbiologist/Mycologist involved in care to monitor therapy and determine the length of treatment. [2]

Continue IV antifungal therapy through the peri-operative period.[1]

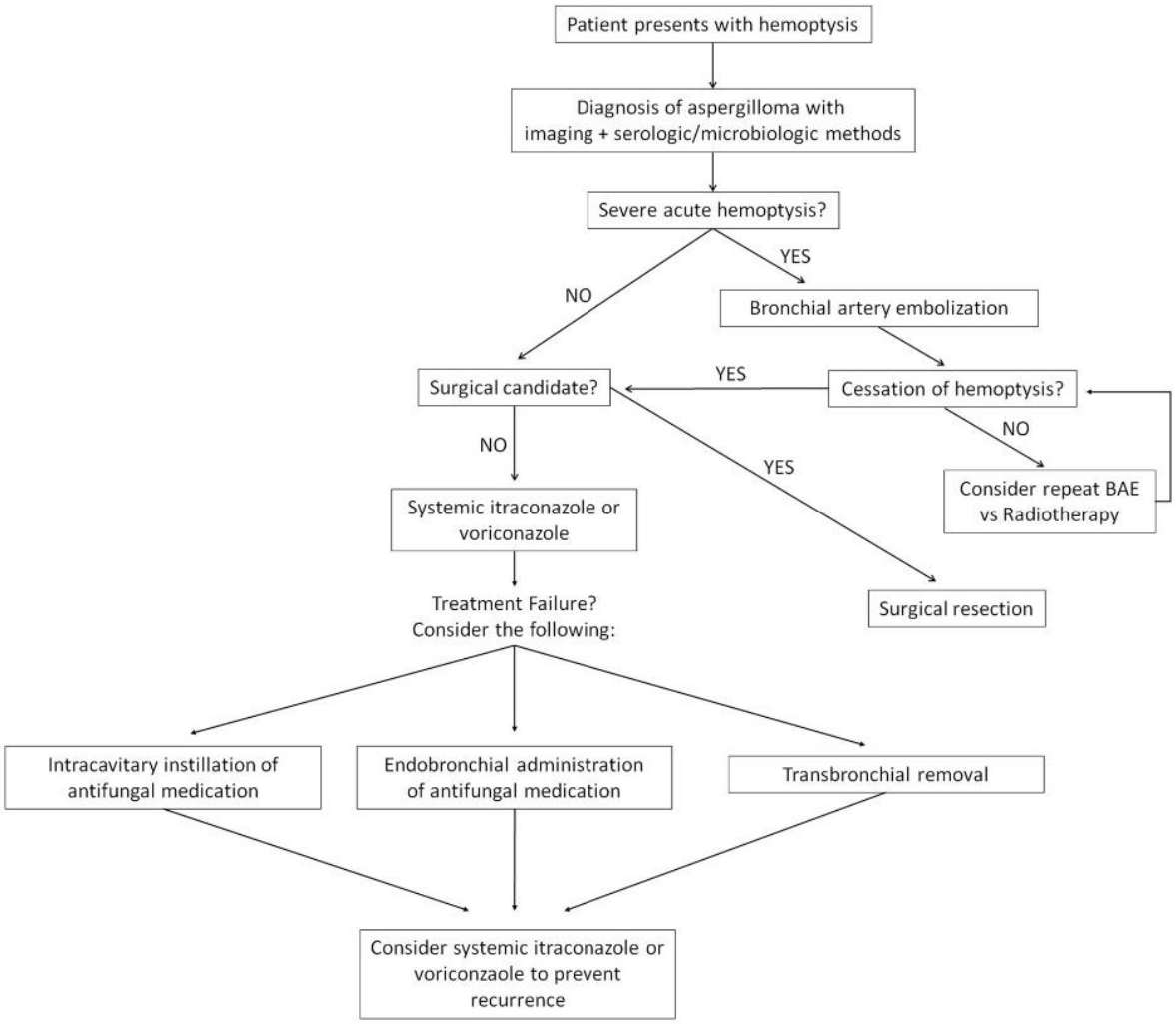
Post-operative

If there is no evidence of infection following spillage during surgery, a minimum of 4 weeks of therapy is typically recommended.

For patients with spillage, active follow-up (typically at 4-6-month intervals) assessing radiographic change, inflammatory markers, and Aspergillus galactomannan antigen titers for 3 years is advised.

If spillage has not occurred, then active follow-up is not advised, unless there is ongoing active pulmonary disease.[2] If patients have residual cavitatory disease, treat post-operatively long term to prevent recurrence, just as in patients who do not undergo surgery.[1]

Proposed treatment algorithm for patients with pulmonary aspergilloma [3]



Less commonly used methods [3]

1) **Intracavitary instillation of antifungal medication**

Direct delivery of antifungal medication to the cavity increases aspergilloma penetration. Lung function is preserved in the process of treatment, making this a good alternative to surgery for

patients with limited pulmonary reserve. Length of hospital stay is significantly shorter for patients receiving intracavitary instillation of amphotericin B (ICAB) than those who were treated by surgery. Furthermore, intracavitary instillation of antifungals can be done on an outpatient basis.

Despite good clinical outcome in most patients, radiographic clearance of the fungal ball, however, was achieved in approximately 30% of cases. The reason of this is unclear but may be due to:

1) delayed radiographic improvement compared to clinical symptom resolution,

2) remnant mass on imaging represents dead cells, and

3) ICAB was only able to prevent invasion of the fungal ball into surrounding lung parenchyma rather than clearance of the infection.

The total dose of amphotericin B required for aspergilloma clearance is unclear;

Amphotericin B 50 mg daily for 10 - 15 days has been used in previous studies.

Potential complications - pneumothorax or subcutaneous emphysema

2) **Endobronchial instillation of antifungal medication** – poorly studied
3) **Transbronchial removal of aspergilloma** – Recent technique with promising results
4) **Treatment for hemoptysis**

4.1 Bronchial artery embolization

For patients who are poor surgical candidates or have extensive disease, bronchial artery embolization (BAE) can be an important treatment option for short-term control of hemoptysis. Immediate clinical success is attainable in 73%–99%. Recurrence of hemoptysis, however, occur in 10–55% of cases. BAE appears to be a safe and effective procedure for the acute management of life-threatening hemoptysis in patients with pulmonary aspergillosis.

4.2 Radiotherapy

When BAE is not successful at managing hemoptysis in patients who are poor surgical candidates, radiotherapy may be considered. Radiotherapy leads to occlusion of the vessels that line the aspergilloma cavity without affecting the growth of the fungus.

4.3 Radiofrequency ablation

Minimally invasive thermal technique used predominately for lung cancer treatment. *Aspergillus* species can generally grow up to 50 ℃ and can be killed via heat exposure beyond 70 ℃.

Fungal balls / mycetoma due to fungi other than *Aspergillus* species

Aspergillus species cause most pulmonary mycetomas. Other fungi such as *Pseudallescheria boydii*, *Mucoraceae*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Sporothrix schenckii*, *Blastochizomyces capitatus* and *Candida albicans* have been reported as causes of pulmonary mycetoma .[4]

Antifungal management of these fungal mycetomas caused by different fungi depends on the causative agent.

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Annexure

Instructions for drug usage

Instructions for Voriconazole use (Sanford guide 2021)

IV dosing

- D1- Loading dose = 6mg/kg q12h x 2 doses
- D2 onwards = 4mg/kg q12h

Oral dosing

Weight >40kg: D1- Loading dose = 400mg q12h x 2 doses

D2 onwards = 200mg q12h

Weight <40 kg: D1- Loading dose = 200mg q12h x 2 doses

D2 onwards = 100mg q12h

Special notes

- Advice the patient to take oral dose 1 hour before or 1 hour after meals
- If CrCl <50 – Switch to oral drug (normal dose) to prevent accumulation of IV vehicle (cyclodextrin) or discontinue
- In mild to moderate hepatic impairment (Child-Pugh Class A and B) – Standard loading dose is recommended but the maintenance dose should be halved. No recommendations for patients with severe hepatic impairment are available.
- Use ideal body weight in obese patients to avoid supratherapeutic concentrations

Adverse effects

- Hepatic toxicity (monitor LFT)
- Rash (20%), photosensitivity and rarely Stevens-Johnson, hallucinations and anaphylactoid infusion reactions with fever and hypertension
- QT prolongation, ventricular tachycardia – one case
- Transient visual disturbances (21%) – altered/enhanced visual perception, blurred or coloured visual change or photophobia within 30-60 minutes. Visual changes resolve within 30-60 min. after administration and are attenuated with repeated doses (do not drive at night). Persistent visual changes occur rarely. Cause unknown.

- Painful periostitis with prolonged use due to elevated serum fluoride levels

Concurrent use of following drugs is contraindicated with voriconazole due to drug interactions.

- Carbamazepine
- Eplerenone
- Ergot alkaloids
- Naloxegol
- Phenobarbitol
- Pimozide
- Qunidine
- Rifabutin
- Rifampin
- Sirolimus
- St.John's wort
- Tolvaptan

Instructions for Itraconazole use (Sanford guide 2022)

IV formulations – Not available

- Adult dose - 200mg bd x 4 doses, then 200mg q12-24h

Oral formulations

Conventional capsule:

- Adult dose - 200mg q12h [2] (maximum dose 600mg/day)
- Paediatric dose – 5-10mg/kg/day (divided q12-24h) (maximum dose 600mg/day)

Hepatic adjustment dose

Prolonged elimination in hepatic impairment is expected, but limited data are available to guide dosing. Close monitoring is advised

Adverse effects

- Most common effects are dose related nausea (10%), diarrhoea (8%), vomiting (6%) and abdominal discomfort (5.7%)
- Allergic rash (8.6%), increase in bilirubin (6%), oedema (3.5%), hepatitis (2.7%)
- Increased doses may produce hypokalemia (8%) and increased blood pressure (3.2%)
- Delirium, neuropathy
- Cardiac function impairment
- Severe liver failure

Special notes

- Capsules are given with food and acidic drinks (lime juice, lemon juice etc.) to obtain highest plasma concentrations
- Pregnancy category – C

Major interactions

Amitriptyline, antacids, calcium channel blockers, carbamazepine, H_2 blockers, isoniazid, midazolam, oral hypoglycemics, phenytoin, protease (HIV) inhibitors, proton pump inhibitors, rituximab, simvastatin, tacrolimus, warfarin

References

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