Brighton and Sussex University Hospitals NHS Trust

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Guideline for the Management of Adult Aspergillus Related Lung Disease

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Target audience:	Clinicians managing Aspergillus related lung disease

Contents

1. Introduction

The guideline has been developed in order to standardise advice to clinicians in the diagnosis of Aspergillus related lung disease, prescription of antifungal medications, monitoring of these drugs to ensure adequate therapeutic levels and to avoid drug induced toxicity.

2. Key Terms

i. IA - Invasive Aspergillosis; A rapidly progressing (<1 month clinical symptoms) fungal lung infection in immunocompromised patients

ii. SAIA - Subacute Invasive Aspergillosis; An invasive aspergillosis found in mildly immunocompromised patients with symptoms over 1-3 months.

iii. CCPA - Chronic Cavitatory Pulmonary Aspergillosis; 1 more pulmonary cavities containing one or more aspergillomas with serological or microbiological evidence of aspergillus with increasing symptoms and radiological features of expanding thick wall cavities over at least 3 months.

iv. CCFA - Chronic Cavitatory Fibrosing Aspergillosis; The end stage of CCPA with fibrotic destruction of at least 2 lung lobes.

v. ABPA - Allergic Bronchopulmonary Aspergillosis; An allergic clinical picture to aspergillus moulds mainly affecting patients with asthma, cystic fibrosis or bronchiectasis with evidence of pulmonary infiltrates and central bronchiectasis on radiology.

vi. Aspergilloma; A single pulmonary cavity containing a fungal ball, with serological or microbiological evidence of Aspergillus in an immunocompetent patient who is asymptomatic and without progression over at least 3 months.

vii. ALT - Alanine Aminotransferase

viii. LFT - Liver Function Tests

ix. U&E - Urea & Electrolytes

3. Purpose

1. Provide an overview of aspergillus related lung disease and the appropriate use of diagnostics available.
2. Provide prescription advice in order to ensure appropriate prescription of antifungals.
3. Provide monitoring advice in order to ensure safe management of patients related to potential drug toxicity
4. Provide monitoring advice to ensure appropriate therapeutic levels.

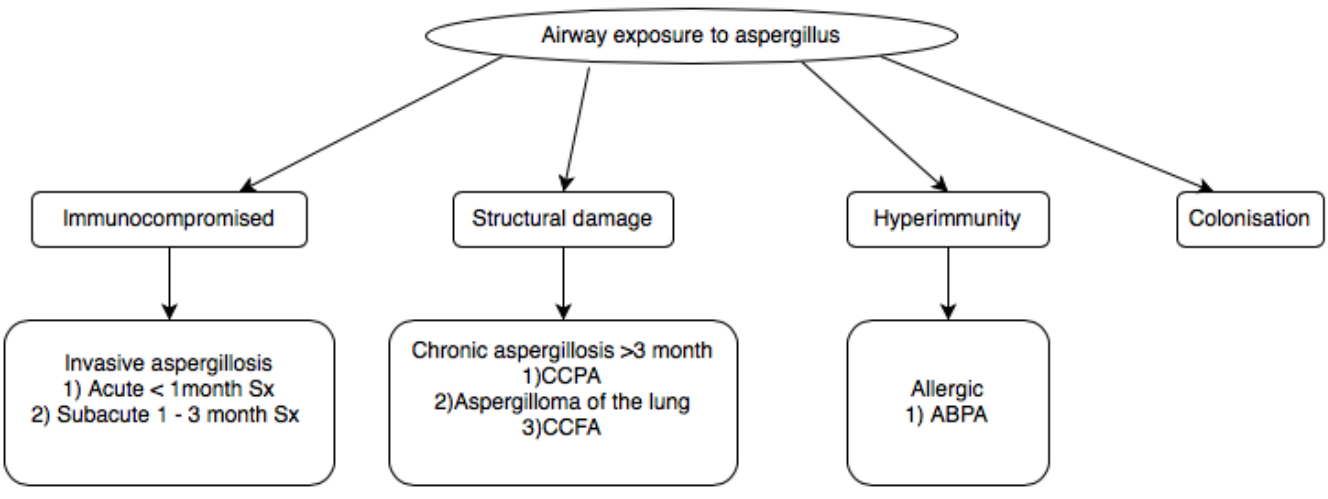
4. Background & Classification

Aspergillus is a mould that is ubiquitous in the environment. It produces spores that are inhaled by humans and in a healthy person will rarely cause disease. In susceptible people this mould can develop into disease mainly involving the respiratory system. This group of diseases is called Aspergillosis. Aspergillis fumigatus is the most common pathogenic mould to humans.

Risk factors for Aspergillosis are:

Immunocompromised	Immunocompetent with lung tissue damage	Hyperimmunity /Allergy
High dose steroids	TB	Asthma
Neutropenia inducing chemotherapy	NTM	
Stem cell transplant	ABPA	
Haematological malignancy	COPD	
Solid organ transplantation	Bronchiectasis	
Advanced HIV	Cystic Fibrosis	
Chronic granulomatous disease	Prior Pneumothorax	
Drug induced T-cell dysfunction i.e. Anti-TNF	Treated Lung Cancer	
	Fibrocavitatory sarcoid	
	Pneumoconiosis	
	Sillicosis	

FLOW CHART 1 – CLASSIFICATION OF ASPERGILLUS



5. Guideline: Diagnostics

Radiology			
Clinical diagnosis	**Radiology recommended**	**Findings**	**F/U scanning once diagnosis established**
IA	HRCT <48 hour of suspicion	Nodules, (halo sign, nodule>1cm surrounded by ground glass opacity), consolidate lesions, wedge shaped infarcts, pleural effusions, air crescents (late), cavities (late), bronchioalveolar wall destruction, centrilobular micronodules, tree-in-bud	Minimal interval of 2 weeks after started treatment unless clinical deterioration
SAIA	HRCT	Usually an absence of prior cavitatory lesion. Starts with single area of progression consolidation in an upper lobe progressing over days/weeks. Often thin walled cavities. Nodules. Pleural thickening, fungal balls, pneumothorax, pleural effusion possible. Air-crescent sign.	Minimal interval of 2 weeks after started treatment unless clinical deterioration
CCPA	HRCT	Likely underlying bronchopulmonary disruption. Starts out in the apices. 1 or more new/or expanding cavity of variable wall thickness, with 1 or more with intracavity aspergilloma, pleural thickening, [parenchymal destruction.	3 months/clinical deterioration
CCFA	HRCT	The end stage of CCPA with severe fibrotic destruction of at least 2 lobes of lung.	3 months/clinical deterioration
Aspergilloma	HRCT	Single fungal ball within a single lung cavity	3 months

Radiology			
Clinical diagnosis	**Radiology recommended**	**Findings**	**F/U scanning once diagnosis established**
ABPA	HRCT	Pulmonary infiltrates and centrilobular bronchiectasis	1 - 3 months

Investigations					
Clinical diagnosis	**Bronchoscopy**	**Sputum**	**Bloods**	**Histology/Cytology**	**Differential to exclude**
IA	BAL MC&S (bacterial & fungal)* hyphae Galactomannan BAL PCR/(1-3)-β-D-Glucan - Consider if above tests negative.	MC&S	Consider serum Galactomannan & (1-3)-β-D-Glucan	Percutaneous/ excision biopsy showing hyphae invading lung parenchyma	AFB & Mycobacterium culture (BAL & sputum) Acute invasive fungal infections
SAIA	BAL MC&S - hyphae Galactomannan & (1-3)-β-D-Glucan BAL PCR - in conjunction with these tests if clinical suspicion but negative microscopy	MC&S	Aspergillis IgG	Percutaneous/ excision biopsy showing hyphae invading lung parenchyma	AFB & Mycobacterium culture (BAL & sputum) Acute invasive fungal infections

CCPA	BAL MC&S - hyphae Galactomannan	MC&S	Aspergillis IgG	Septate hyphae with a chronic inflammatory reaction. Occasionally a granuloma & fibrosis	AFB & Mycobaterium (BAL & Sputum) Culture for bacteria Cytology for Lung Malignancy Vasculitis Rheumatoid
CCFA	BAL MC&S - hyphae Galactomannan	MC&S	Aspergillis IgG	Septate hyphae with a chronic inflammatory reaction. Occasionally a granuloma & fibrosis	AFB & Mycobaterium (BAL & Sputum) Culture for bacteria Cytology for Lung Malignancy Vasculitis Rheumatoid
Aspergilloma	-		Aspergillis IgG		AFB & Mycobaterium (BAL & Sputum) Culture for bacteria Cytology for Lung Malignancy Vasculitis Rheumatoid
ABPA	BAL MC&S - hyphae Galactomannan		Total IgE Aspergillis IgE Bloods eosinophills		

* Aspergillis IgG may be positive in ABPA

** When sending BAL please label clearly with ?invasive aspergillosis, plus tick fungal as well as bacterial culture on form, that will trigger SAB plates to be set up and incubated at 30 and 37 degrees for fungal growth.

*** Total IgE & Aspergillis IgE pay be positive in CCPA/SAIA/CCFA

6. Guideline: Antifungal Prescribing

Treatment			
Clinical diagnosis	**First Line**	**Second Line**	**Duration**
IA/SAIA **-**Treatment initiated while diagnostics carried out	**Voriconazole** **Initially** 6 mg/kg IV 12 hourly for 1 day, followed by 4 mg/kg IV 12 hourly **<u>Oral switch (day 10-14)</u>** If HRCT improved & resolution of neutropenia If >40kg, **Voriconazole** 200mg PO bd If <40kg, **Voriconazole** 100mg PO bd If HRCT worsened at day 10-14 for **Liposomal amphotericin (Ambisome)** 3mg/kg IV od (round dose to nearest 50mg) -Note 1mg test dose over 10 minutes	If Voriconazole contraindicated **Caspofungin** 70mg IV day one followed by 50mg IV OD If weight >80kg continue 70mg IV OD	6-12 weeks dependent on degree & duration of immunosuppression, disease site and clinical improvement
CCPA/CCFA	Asymptomatic -observed with f/u every 3-6 months Symptomatic **-Itraconazole** oral solution 200mg PO BD	**Voriconazole** If<40kg 200mg PO BD then 100mg PO BD IF>40kg 400mg PO BD then 200mg PO BD ***Posaconazole tablets** 400mg PO BD is third line if voriconazole resistance ****Cyclical Caspofungin** can be considered in triazole intolerant disease under Specialist Respiratory opinion	Minimum 4 – 9 months

Treatment			
Clinical diagnosis	**First Line**	**Second Line**	**Duration**
Aspergilloma	Asymptomatic -observation over 6-12 months Symptomatic and fit -Surgery Symptomatic and unable for surgery **-Itraconazole** oral solution PO 200mg BD	**Voriconazole** If<40kg 200mg PO BD then 100mg PO BD IF>40kg 400mg PO BD then 200mg PO BD If azole intolerant:- **Caspofungin** 70mg IV day one followed by 50mg IV OD If weight >80kg continue 70mg IV OD **Third Line** **Posaconazole tablets** 400mg PO BD if voriconazole resistance	6-9 months
ABPA	**Itraconazole** oral solution 200mg PO BD		

7. Guideline: Prescribing guidance & Therapeutic Drug Monitoring

Prescribing guidance

Voriconazole

Voriconazole is an antifungal medication with risk of liver toxicity, phototoxicity and squamous cell carcinoma of the skin.

1. Liver function monitoring

    1. Check LFT's before starting voriconazole. If mild to moderate derangement or cirrhosis, proceed with caution on a risk/benefit basis.

    2. Weekly LFT's for first month followed by monthly monitoring if LFT's within normal parameters.

    3. Stop voriconazole if ALT levels double or remain elevated on successive monitoring. Increase frequency of monitoring to weekly if deranged at any point. Hepatotoxicity is usually reversible on discontinuation.

2. Phototoxicity/Squamous Cell Carcinoma

    1. Patients should be advised to avoid sunlight exposure, wear protective clothing and SPF50 sunscreen in sunlight. Any phototoxicity should be referred to dermatology, and consideration of stopping voriconazole.

    2. Close monitoring of skin for pre-cancerous skin lesions if any phototoxicity occurs. Stop voriconazole if any pre-cancerous or squamous cell carcinoma.

3. Women of child-bearing potential must always use effective contraception during treatment with voriconazole.

Itraconazole & Posaconazole

1. Liver Function Tests

    1. Check LFT's before starting itraconazole or posaconazole and then monthly during treatment

    2. If mild to moderate derangement or cirrhosis, proceed with caution on a risk/benefit basis. Stop itraconazole / posaconazole if ALT levels double or remain elevated on successive monitoring. Increase frequency of monitoring to weekly if deranged at any point. Hepatotoxicity is usually reversible on discontinuation.

Caspofungin

1. Liver function Tests

    1. Check LFT's before starting Caspofungin then monthly during treatment

    2. Reduce maintenance dose to 35mg od in moderate hepatic impairment. Avoid if severe.

Ambisome

1. Liver & Renal Function, Magnesium & Full Blood Count

    1. U&E's, magnesium, LFT's & FBC should be monitored during treatment. This should be twice weekly initially and no less than weekly for the remainder of the treatment period.

Therapeutic Drug Monitoring

Requires 1-2mL serum taken at appropriate times and clearly labelled.

Ensure all high-risk samples are clearly marked.

Laboratory turnaround times are from receipt of sample.

All reports are sent by first class mail. Urgent results can be telephoned to laboratories on request if you've provided an appropriate contact name and current telephone number on the request form.

Use the following form to submit all clinical samples.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/746859/PHE_Y2_issue_03.pdf.pdf

Itraconazole

A trough level (pre-dose) should be measured pre-dose, 1-2 weeks post starting oral treatment (i.e. at steady state).

Trough levels should be re-measured 7 days post any dose changes or changes to medication that can potentially interact.

Target levels

- ***>0.5 mg/L but < 4mg/L***
- *Turnaround is estimated at 3 days*

Voriconazole

A trough level (pre-dose) should be measured between day 3 - 5 of treatment (PO or IV). Trough levels should be re-measured 7 days post any dose changes or changes to medication that can potentially interact.

Target levels

- ***>2.0 mg/L and < 6mg/L (****levels >5.5mg are associated with hepatotoxicity and neurotoxicity)*
- *Turnaround 1-2 days*

Posaconazole

A trough level (pre-dose) should be measured after 5 days of treatment.

Target levels

- ***>1mg/L***
- *Turnaround time 2-3 day*

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