ERS/ESCMID Clinical Practice Guidelines: chronic pulmonary aspergillosis

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### Aspergillus Guideline: Chronic Pulmonary Aspergillosis

### Joint ESCMID and ERS guidelines

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#### **Chronic Pulmonary Aspergillosis - subsets**

- Simple/single Aspergilloma
- Aspergillus nodule(s)
- Chronic Cavitary Pulmonary Aspergillosis / Complex Aspergilloma (CCPA)
- Chronic Fibrosing Pulmonary Aspergillosis (CFPA)
- Subacute invasive(SIA)/Semi-Invasive / Chronic Necrotizing Pulmonary Aspergillosis (CNPA)
- Note fungal balls (aspergilloma) may be seen in any of these conditions, except *Aspergillus* nodule

### Different patterns of CPA



Aspergillus nodule



Simple aspergilloma



Chronic cavitary pulmonary aspergillosis

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Chronic fibrosing pulmonary aspergillosis

### Single (simple) aspergilloma



Figure 2 Simple aspergilloma which developed within a post-tuberculous cicatricial atelectasis of the left upper lobe with saccular bronchiectasis. Surgical resection by VATS was done because of recurrent hemoptysis and a requirement for anticoagulant therapy.

> Courtesy Dr Beigelman, Lausanne, Switzerland

### Spiculated nodule - aspergillosis



Figure 13 - Nodule of the right upper lobe with irregular and slightly spiculated borders that was surgically resected and proven to be an *Aspergillus* nodule.



### Multiple Aspergillus nodules



Figure 6 – Aspergillus nodules of variable size and borders and fungus ball filling a cavity with a wall of variable thickness in a patient with preexisting bronchiectasis and cicatricial atelectasis of the middle lobe. Successive axial views with lung windows.



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#### Aspergillus nodule



Patients may have 1, 2 or more nodules Cough and dyspnoea are common, 30% weight loss, occcasional haemoptysis.

57% had positive IgG antibody



### CCPA without a fungal ball



Figure 3 - Chronic cavitary pulmonary aspergillosis showing marked progression. Chest X-rays prior to 2007 (1990's) showed 'upper lobe fibrosis', without a firm diagnosis. A large cavity with pleural thickening on the left. In 2012, bilateral large cavities with pleural thickening and atelectasis of both upper lobes, with some pleural thickening.

Neither cavity contains a visible fungal ball.



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## Irregular cavity walls - very characteristic of fungal growth in the cavity





### Chronic cavitary pulmonary aspergillosis







# Pleural thickening and early aspergilloma formation



Figure 10 - Cavity with irregular edge and aspergilloma presenting as a coarse and irregular network in a patient with a previous left upper lobe resection. Note apical pleural thickening.



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### **Radiological diagnosis of CPA**

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Features of cavitation, fungal ball, pleural thickening and/or upper lobe fibrosis	Raise suspicion of CPA for physicians	Radiological report must mention possible CPA	A	II	Roberts, 1987; Kim, 2000; Franquet, 2001; Denning, 2003; Greene, 2005; Kobashi, 2006; Godet, 2014	CPA is often missed for years and patients mismanaged. Microbiological testing required for confirmation High quality CT with vessel visualisation

### CCPA + 1 aspergilloma & multiple cavities



Figure 4 - Chronic cavitary pulmonary aspergillosis (CCPA). Multiple cavities with a fungus ball lying within the largest one. The wall of the cavities cannot be distingushed from the thickened pleura nor the neighboring alveolar consolidation.

The extra pleural fat is hyperattenuated (yellow arrows). Dilated oesophagus = yellow star.



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# Bilateral aspergillomas in CCPA - related to NTM infection



**Courtesy Pr Khalil- Pr Cadranel, Tenon Hospital, France** 

# Bilateral aspergillomas in CCPA - related to NTM infection



Figure 8 – CCPA in a smoker with previous infection to *Mycobacterium kansasii*, undernutrition and cirrhosis. Severe hemoptysis.
Typical bilateral fungus balls (stars) almost filling the cavities on the left side.
Irregular walls of the cavity on the right side.
Enhanced thickened pleura (yellow arrows).

Note hypertrophic systemic arteries (red arrows).

**Courtesy Pr Khalil- Pr Cadranel, Tenon Hospital, France** 

### Consolidation with cavitation



Figure 11 - Chronic cavitary pulmonary aspergillosis of the right upper lobe. Mediastinal window shows cavitary alveolar consolidation delimited inferiorly by fissures. Note the dense extrapleural fat.



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# Large nodules is a rare manifestation of CPA



Figure 14 - Chronic pulmonary aspergillosis presenting as bilateral upper lobe lung masses. Partly necrotic and cavitary on the left.



### Progression of CCPA to chronic fibrosing pulmonary aspergillosis



1992

1994 on no Rx

1997 still on no Rx



#### Chronic pulmonary aspergillosis caused by *A. calidoustus* with rapid progression to CFPA



#### November 2008

#### December 2008



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### Subacute invasive/chronic necrotising



Figure 7 - Subacute invasive aspergillosis complicating hepatocellular carcinoma being treated with sorafinib. Cavitary lesion developed with multiple symptoms over 6 weeks. He presented with unresectable hepatocellular carcinoma. Note the almost normal lung background.



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## Clinical phenotypes of chronic Aspergillus spp diseases



### Underlying diseases in patients with CPA (%)

	<u>Smith</u>	<u>Others</u>
Classical tuberculosis	17	31-81
Atypical tuberculosis	16	?
ABPA	14	12
COPD/emphysema	33	42-56
Pneumothorax	17	12-17
Lung cancer survivor	10	?
Pneumonia	22	9-12
Sarcoidosis (stage II/III)	7	12-17
Thoracic surgery	14	8-11
Rheumatoid arthritis	4	2
Asthma / SAFS	12	6-12
Ankylosing spondylitis	4	2-11
None	1	15

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#### Chronic Pulmonary Aspergillosis – Diagnostic criteria

Required:

1.1 Characteristic CT appearance of a fungus ball in a pulmonary or pleural cavity, or dilated bronchus,

AND

1.2 Any direct or indirect microbiological evidence of Aspergillus infection (see below).





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1.2 Any direct or indirect microbiological evidence of *Aspergillus* infection (see below). OR

Required:

2.1 Radiological features consistent with chronic pulmonary aspergillosis (including cavity(ies), pleural thickening, extensive fibrosis or nodule) AND

2.2 Clinical or radiological evidence of at least 3 months disease (sometimes inferred) [Note shorter durations of disease may be seen in SIA/CNPA, which becomes CPA because of its chronicity],

AND

2.3 Histological or microbiological or immunologic evidence of *Aspergillus* infection (e.g. histological evidence of *Aspergillus*-like hyphae in lung biopsy or *Aspergillus* culture from a percutaneous cavity aspiration; strongly positive BAL antigen; positive IgG antibody/precipitins). Respiratory tract culture or PCR positive for *Aspergillus* is supportive.





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Required:

Exclusion of histoplasmosis, coccidioidomycosis and paracoccidiodomycosis in endemic areas or those with pertinent travel history; actinomycosis.

Active bacterial infection, including mycobacterial infection and/or malignancy may occur concurrently. Mycobacterial infections or malignancy may mimic CPA.



#### **Strength of Recommendation – Definition**

Grade of Recommendation	Definition
Grade A	ESCMID (EFISG) and ECMM strongly support a recommendation for use
Grade B	ESCMID (EFISG) and ECMM moderately support a recommendation for use
Grade C	ESCMID (EFISG) and ECMM marginally support a recommendation for use
Grade D	ESCMID (EFISG) and ECMM support a recommendation <u>against</u> use

Ullmann AJ, Cornely OA, et al. Clin Microb Infect 2012.



#### **Quality of Evidence – Level Definition**

Level of Evidence	Definition
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

Ullmann AJ, Cornely OA, et al. Clin Microb Infect 2012.



#### **Added Index – Definition**

Added Index	Source of Level II Evidence
r	Meta-analysis or systematic review of RCT
t	Transferred evidence i.e. results from different patients' cohorts, or similar immune-status situation
h	Comparator group: historical control
u	Uncontrolled trials
а	For published abstract presented at an international symposium or meeting

Ullmann AJ, Cornely OA, et al. Clin Microb Infect 2012.





### **Respiratory specimen diagnosis of CPA**

Test	Strength of Recommendation	Quality of Evidence
Direct microscopy for hyphae <sup>a</sup>	А	II
Fungal culture (sputum or BAL) <sup>b</sup>	А	III
Histology	A	II
Fungal culture (transparietal aspiration)	В	II
Aspergillus PCR (respiratory secretion) <sup>c</sup>	C	II
Bacterial culture (sputum or BAL)	C	IIt

### Molecular detection of *Aspergillus* spp. in sputum

Laboratory result	СРА
Culture positive for <i>A. fumigatus</i>	7/42 (16.7%)
qPCR positive for <i>Aspergillus</i> spp	30/42 (71.4%)



Denning et al. Clin Infect Dis 2011;52:1123

### Aspergillus IgG in blood Key diagnostic test



#### Falling levels is good, but takes months or years





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ERS EUROPEAN RESPIRATORY SOCIETY Aspergillus antibody diagnosis of CPA

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Cavitary or nodular pulmonary infiltrate in non- immunocompromise	Diagnosis or exclusion of CPA	Aspergillus IgG antibody	A	II	Guitard, 2012; Baxter, 2012; Van Toorenenbergen, 2012	IgG and precipitins test standardisation incomplete
d patients		Aspergillus precipitins	A	II	BTS,1970; Uffredi, 2003; Kitasato, 2009; Ohba, 2012; Baxter, 2012	Most in house tests poorly validated, with uncertain sensitivity the
		antibody	D	Ш	Brouwer, 1988;	Sensitivity for
		Aspergillus IgA antibody	D	Ш	Schonheyder 1987; Nimomiya, 1990;	Aspergillus nodule uncertain
In context of asthma/ABPA/CF		Aspergillus IgE antibody	В	II	Denning, 2003; Agarwal, 2012	

### Aspergillus IgG serology



0.972 0.902 0 Area under ROC curve results

Comparison of 4 commercial assays using 250 patients with CPA in Manchester and normal controls from Uganda





# Frequency of Aspergillus antibodies after TB

- UK
- Japan
- India
- Brazil

- 1970 34%
- 1989 20%
- 2001 27%
- 1988 21%

Iwata et al. *Kekkaku*. 1989;64:7–13. Shahid et al. *Indian Journal of Medical Microbiology*. 2001;19:201–5. Kurhade et al. *Indian Journal of Medical Microbiology*. 2002;20:141–4. Ferreira-da-Cruz et al. *Memórias do Instituto Oswaldo Cruz*.1988;83:357–60.





### **Antigen diagnosis of CPA**

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Cavitary or nodular pulmonary infiltrate in non- immunocompromised patients	Diagnosis or exclusion of CPA	Antigen (BAL) Antigen (serum) Antigen (sputum)	B C No data	11	Izumikawa, 2012 Izumikawa, 2012; Kono, 2013; Shin, 2014	Antigen studied in BAL and serum, but not sputum.



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Nam Int J Infect Dis 2010;14:e479; Ohba et al, Resp Med 2012; 106:724





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### **Oral triazole therapy for CPA**

Antifungal agent and dose	Strength of	Quality of Evidence
	Recommendation	
Itraconazole 200 mg bid, adjust with TDM	А	Ш
Voriconazole <sup>a</sup> 150-200 mg bid, adjust with TDM	А	II
Posaconazole 400 mg bid (liquid); 300mg od (tablets)	В	II

a Lower doses advised in those over 70 years, low weight, significant liver disease and those of NE Asian descent who may be slow metabolisers TDM = therapeutic drug monitoring

## Impact of oral itraconazole therapy for chronic pulmonary aspergillosis after TB over 6 months



**Oral itraconazole** 



Agarwal R et al, Mycoses 2013; 56:559.





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### **Duration of antifungal therapy for CPA**

Population	Intention	Intervention	SoR	QoE	Reference	Comment
CPA patients on antifungal therapy	Control of infection, arrest of pulmonary fibrosis, prevention of haemoptysis, improved quality of life.	6 mo antifungal therapy Long term antifungal therapy, depending on status and drug tolerance	B	11	Agarwal, 2013: Yoshida, 2012; Nam, 2010: Felton, 2010; Camuset, 2007: Jain, 2006: Cadranel, 2012 Felton, 2010; Camuset, 2007; Jain, 2006; Cadranel, 2012	Optimal duration of therapy in CPA is unknown, indefinite suppressive therapy may be appropriate in selected patients
Subacute IA/CNPA	Cure	6 mo	В	II	Camuset, 2007 Cadranel, 2012	

## Chronic pulmonary aspergillosis - response to itraconazole after 6 months therapy and follow up



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Agarwal R et al, Mycoses 2013; 56:559.

### Chronic cavitary pulmonary aspergillosis



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Patient RW June 2002

Stable, asymptomatic, normal inflammatory markers, just detectable Aspergillus precipitins

Itraconazole stopped after 5 years

www.aspergillus.org.uk

#### Chronic cavitary pulmonary aspergillosis - relapse



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Patient RW January 2003

Marked change, with new cough, weight loss, *CRP/ESR* and *Aspergillus* precipitins

Itraconazole restarted

www.aspergillus.org.uk

#### Chronic cavitary pulmonary aspergillosis an example of radiographic <u>failure</u>





#### Patient SS April 2004

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Patient SS July 2004, despite receiving itraconazole for 3 months

www.aspergillus.org.uk





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### **Alternative intravenous therapy for CPA**

Population	Intention	Intervention	SoR	QoE	Reference	Comment
CPA patients with progressive disease, who fail, are intolerant of triazoles or have triazole resistance	Control of infection	Micafungin 150mg/d	В	II	Kohno, 2011; Kohno, EJCMID 2013; Saito, 2009; Kohno, 2011; Kohno , 2004; Izumikawa, 2007; Yasuda, 2009; Nam, 2009	
		Amphotericin B deoxycholate 0.7-1.0mg/kg/d	С	III	Denning, 2003	
		Liposomal AmB 3mg/kg/d	В	lla	Newton, 2014	
		Caspofungin 50-70mg/d	С	lla	Kier, 2014; Kohno 2013	





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### Local cavity therapy for CPA

Population	Intention	Intervention	SoR	QoE	Reference	Comment
CPA with aspergilloma, unwilling or unable to take oral therapy, multi- azole resistance and inoperable	Control of infection	Instillation of amphotericin B deoxycholate into cavity	С	II	Giron, 1998; Kravitz, 2013	Experimen tal





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#### Follow up of Aspergillus nodule and after resection surgery

Population	Intention	Intervention	SoR	QoE	Reference	Comment
Aspergillus nodule not treated with antifungal therapy	To identify progression early and/or carcinoma of lung if multiple lesions	3-6 mos clinical follow up with (low dose) imaging, inflammatory markers and Aspergillus IgG/precipitins	A	III	Farid, 2013; Muldoon, 2014	Not necessary if entire single nodule resected
Post- lobectomy/pneumonect omy	To detect recurrence early	3-6 mos then 6 monthly for 3 years with inflammatory markers and Aspergillus IgG/precipitins	A	111	Farid, 2013.	No predictors of recurrence yet described. Full re- evaluation if consistent increase in Aspergillus IgG titres.

### CPA guildeines

- Evidence base strong for radiology and Aspergillus antibody
- Strong experiential evidence for resection of single aspergillomas – caution in multi-cavity disease
- Evidence base weak on treatment, although 3 RCTs done
- Basic pathogenesis not well understood
- Natural history of Aspergillus nodule not well documented
- Immune deficits common long term therapy generally recommended.
- Azole resistance now a major problem







Primary prophylaxis of invasive fungal infections in patients with haematologic malignancies. 2014 update of the recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology.

Aspergillus pragensis sp. nov.







## 7тн ADVANCES AGAINST ASPERGILLOSIS

3 - 5 March 2016

Manchester Central Convention Complex Manchester United Kingdom

www.AAA2016.org