MMTN
MEDICAL MYCOLOGY TRAINING NETWORK

How do I diagnose and manage chronic pulmonary aspergillosis?

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ASIA FUNGAL WORKING GROUP
an ISHAM working group

Chronic pulmonary aspergillosis (CPA)

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Disclosure

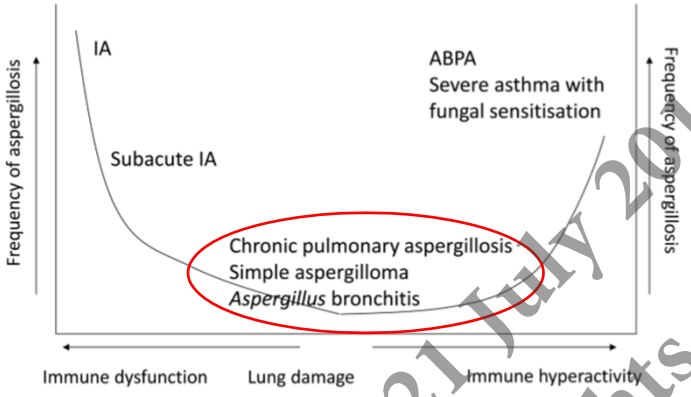
NO CONFLICT OF INTEREST

CPA

- First reported as fatal disease in 1842 in Edinburgh, UK
- Now:
  - a serious long term, chronic pulmonary disease
  - A devastating disease with previous infection (TB or non TB) & has complex clinical and radiological picture, drug interactions, toxicities & intolerances
  - Caused by Aspergillus spp. esp. *A. fumigatus* which releases its spores (conidia) to the air

Maghrabi & Denning. Curr Fungal Infect Rep (2017) 11:242–51

Interaction between *Aspergillus* & host



The pulmonary response is based on immune status

Modified from Kosmidis & Denning BMJ 2014

Term	Definition
Simple aspergilloma	Single pulmonary cavity containing a fungal ball, with serological or microbiological evidence implicating *Aspergillus* spp. in a non-immunocompromised patient with minor or no symptoms and no radiological progression over at least 3 months of observation.
CCPA	One or more pulmonary cavities (with either a thin or thick wall) possibly containing one or more aspergillomas or irregular intraluminal material, with serological or microbiological evidence implicating *Aspergillus* spp. with significant pulmonary and/or systemic symptoms and overt radiological progression (new cavities, increasing pericavitary infiltrates or increasing fibrosis) over at least 3 months of observation.
CFPA	Severe fibrotic destruction of at least two lobes of lung complicating CCPA leading to a major loss of lung function. Severe fibrotic destruction of one lobe with a cavity is simply referred to as CCPA affecting that lobe. Usually the fibrosis is manifest as consolidation, but large cavities with surrounding fibrosis may be seen.
***Aspergillus* nodule**	One or more nodules which may or may not cavitate are an unusual form of CPA. They may mimic tuberculoma, carcinoma of the lung, coccidioidomycosis and other diagnoses and can only be definitively diagnosed on histology. Tissue invasion is not demonstrated, although necrosis is frequent.
SAIA	Invasive aspergillosis, usually in mildly immunocompromised patients, occurring over 1–3 months, with variable radiological features including cavitation, nodules, progressive consolidation with "abscess formation". Biopsy shows hyphae in invading lung tissue and microbiological investigations reflect those in invasive aspergillosis, notably positive *Aspergillus* galactomannan antigen in blood (or respiratory fluids).

Denning et al Eur Respir J 2016; 47: 45–68 | DOI: 10.1183/13993003.00583-2015

CPA: epidemiology

- affect > 3 million people worldwide,
- ~1.2 million have had tuberculosis.

(Denning – LIFE)

CPA in Asia

- TB burden: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh & South Africa
- the high number of PTB's prevalence in Asia, makes us think that the prevalence of CPA is also high
- In resource limited setting: often misdiagnosed as recurrent TB
- Often the laboratory result of acid fast bacilli is negative but continue treated as PTB

WHO report 2018
Kosmidis & Denning . Thorax 2015;70:270–7

The 23rd European Congress of Clinical Microbiology and Infectious Diseases — Abstract No. 3393

Burden of serious fungal infections in China

Liping Zhu, Jiqin Wu, David S. Perlin, David W. Denning
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LEADING INTERNATIONAL FUNGAL EDUCATION

Introduction

The incidence of serous fungal infections has been increasing over the past several decades as a result of the expanding number of immunocompromised patients with risk factors such as HIV infection, transplantation, immunosuppressive therapy, corticosteroid therapy, and broad-spectrum antibiotic medication, etc. Despite the availability of newer and potent antifungal agents, the morbidity and mortality of invasive fungal infections remain high. Understanding of the burden of fungal infections is crucial to both better disease prevention and treatment. In China, with the largest population in the world, population-based surveillance on various fungal infections is still lacking. However, data from specific high risk populations and some cities has increasingly been reported. We have attempted to estimate the burden of serious fungal infection in China through literature review.

Methods

All published epidemiology papers reporting fungal infection rates from China were identified. If few data existed, we used specific populations at risk and fungal infection frequencies in those populations to estimate national incidence or prevalence. Population (2009), HIV (2011) and TB (2011) data were from WHO. Asthma, ABPA and CPA rates were from Denning, Bull WHO 2011, Med Mycol 2013 (ahead of print) and Ma, 2011. COPD admissions were from Tan, Respirology, 2009. Cryptococcal meningitis (CM) estimate in HIV was assumed to be 1% of late stage HIV patients, and the rate of CM in other cases on the ratios reported by Chen, Mycopathologia, 2012. Pneumocystis jiroveci pneumonia (PCP) rates were based in Hong Kong rates in HIV and in non-HIV on Wang, J Med Microbiol, 2011. Penicillium marneffei infection rate was based in HK data, adjusted for regional differences in HIV prevalence. Tinea capitis rate was on a report from Shanghai (Zhu, Mycopathologia, 2010). Keratitis rate was based on Xu in Qingdao (Chin Med J, 2012).

Results

Of the 1,363M population, 20% are children (0-14 years) and 12% are >60 years old. 20M Chinese (age 15-50) women are estimated to get recurrent vaginal thrush (4+ times annually). Of the 740,000 estimated HIV positive patients in 2011, 92,227 are not on ARVs (CD4 <350). Of these an estimated 83,000 develop oral thrush, 50,000 oesophageal candidiasis, 461 CM, 16,140 PCP and 1,383 P. marneffei infection. We estimate a 5-year period prevalence of 256,534 CPA cases (assuming 15% annual mortality), 80% from 893,121 cases of pulmonary TB, 20% other conditions. Asthma prevalence in adults is estimated at nearly 20M and assuming 2.5% of asthmatics have ABPA, 491,721 patients with ABPA are likely and 648,300 have severe asthma with fungal sensitisation (SAFS). The rate of candidemia was estimated at 5/100,000 population (68,150 cases) and Candida peritonitis at 19,982 cases. Invasive aspergillosis (IA) in >100,000 haematological patients is estimated at 8,178 cases and in the COPD 154,000 cases (11.9M admissions). IA numbers in renal and liver transplantation and numerous other fungal diseases were not estimated.

Infection	Number of infections per underlying disorder per year					Total burden	Rate /100K
	None	HIV/AIDS	Respiratory	Cancer/Tx	ICU		
Oesophageal candidiasis	-	50,834	-	-	-	50,834	3.7
Candidaemia	-	-	-	20,445	47,705	68,150	5.0
Candida peritonitis	-	-	-	-	19,082	19,082	1.4
Recurrent vaginal candidiasis (4x/year +)	19,959k	-	-	-	-	19,959	2,939
Allergic bronchopulmonary aspergillosis (ABPA)	-	-	491,721	-	-	491,721	36.1
Severe asthma with fungal sensitisation (SAFS)			648,300			648,300	47.6
Chronic pulmonary aspergillosis (CPA)	-	-	265,534	-	-	265,534	19.5
Invasive aspergillosis	-	-	-	8,178	154,155	162,333	11.9
Mucormycosis	-	-	-	2,726	-	2,726	0.2
Cryptococcal meningitis	922	461	-	922	-	2306	0.17
Pneumocystis jiroveci pneumonia (PCP)	-	16,140	?	8,070	-	24,210	1.8
Penicillium marneffei infection	?	1,383	-	-	-	1,383	0.1
Fungal keratitis	17,038	-	-	-	-	17,038	1.3
Tinea capitis	34,075	-	-	-	-	34,075	2.5
Total burden estimated	20,010k	151,822	1,405,555	37,615	221k	21,829k	

Conclusion

Without any national surveys of fungal disease in China, uncertainty surrounds all these estimates. But the burden of fungal disease is almost certainly one of the greatest in the world. Epidemiological studies are urgently required to validate or modify these estimates.

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CPA in Asia: India

Table 2. Pulmonary tuberculosis (TB) estimates in the Indian population.

Total population in 2011	1,210,569,573
Incident TB cases	2,130, 602
Annual pulmonary TB case alive at 1 year	1,438,157
Estimated annual CPA cases after Pulmonary TB	92,042
5-year estimated CPA prevalence	290,147
5-year estimated CPA prevalence rate (per 100,000)	24

CPA: chronic pulmonary aspergillosis.

India is one of Asian countries with high TB prevalence, an important underlying factor for the development of CPA.

Agarwal et al., PLoS ONE 2014; 9(12): e114745.
doi:10.1371/journal.pone. 0114745

CPA in Asia: Indonesia

- Jakarta & surrounding cities:
  - 56 patients with TB (32 male, age range: 17-78 years), 10 patients (17.9%) met criteria for CPA.
- Manado (Celebes):
  - 72 patients post TB, 25 (34.7 %) proven as CPA

Setianingrum et al., Poster, ISHAM meeting – Amsterdam 2018
Kurniawan et al., free paper Petri meeting, Bandung Oct 2018

CPA in Asia: Malaysia

Table 1. Estimated annual cases and total burden of serious fungal infections in Malaysia.

Fungal Infection	Number of Infections per Underlying Disorder per Year					Total Burden	Rate/100,000
	None	HIV/AIDS	Respiratory	Cancer/Tx	ICU		
Oesophageal candidiasis	-	5850	-	-	-	5850	19
Candidaemia	-	-	-	1073	460	1533	5
Candida peritonitis					230	230	0.8
Recurrent vaginal candidiasis (>4×/year)	501,138	-	-	-	-	501,138	4800 *
ABPA	-	-	30,062	-	-	30,062	98
SAFS	-	-	39,682			39,682	130
Chronic pulmonary aspergillosis	-	-	7635	-	-	7635	24.9
Invasive aspergillosis	-	-		184	834	1018	3.3
Cryptococcal meningitis	47	700	-	108	-	855	2.8
Pneumocystis pneumonia	-	1286	-	-	-	1286	4.2
Histoplasmosis		175				175	0.6
T. marneffei infection		350				350	1.1
Fungal keratitis	400					400	1.3
Total burden estimated	501,585	8361	77,379	1365	1524	590,214	

Velayuthan et al., J. Fungi. 2018, 4, 38

Chronic Pulmonary Aspergillosis

- long-term pulmonary aspergillosis, a slowly progresive & destructive disease, with never been improvement
- individuals with a relatively normal immune system with chronic pulmonary disease
- from simple aspergilloma to chronic cavitary pulmonary aspergillosis (CCPA)
- ca. 5% are silent & have no pulmonary disorder

Maghrabi & Denning. Curr Fungal Infect Rep 2017; 11:242–251
Godet et al. Respiration 2014;88:162–174

CPA: pathogenesis

- underlying condition that accomodates cavity formation or causes tissue damaged
- a fertile site for the grow of Aspergillus
- Aspergillus destroyes lung tissues by invasion, production of protelytic enzymes, toxins and other metabolites that make things worse

Izumikawa et al. J Infect Chemother 2014

CPA: underlying condition

- Use of alcohol, tobacco abuse, suffer diabetes: deterioration in local or systemic defenses against infection
- bronchopulmonary disease – presence of cavity:
  - **active PTB/ residual PTB**
  - bronchial dilatation,
  - Sarcoidosis
  - COPD
  - Surgically treated lung cancer
- prolonged use of low-dose oral or inhaled corticosteroids
- absence of or presence of very little vascular invasion

Camuset et al., Chest 2017; 131: 1435-41; Izumikawa et al. J Infect Chemother 2014
Smith & Denning. Eur. Respir. J. 2011; 37, 865–72.

- CPA almost always associated with chronic pulmonary disorders.
- persons with pre-existing chronic pathologic process in the lung are at risk of suffering from CPA

CONCLUSION:

Smith & Denning. Eur Respir J 2011;37:865–72

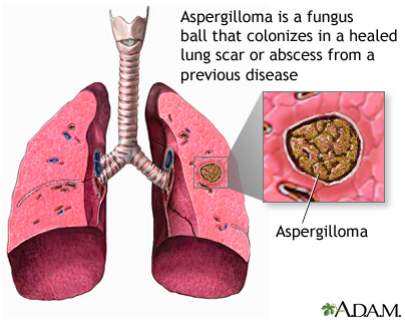
CPA diagnosis (imaging)

- Aspergiloma
- Chronic cavitary pulmonary aspergillosis (CCPA- most common
- Chronic fibrosing pulmonary aspergillosis (CFPA)
- Sub acute invasive aspergillosis (SAIA)
- Aspergillus nodule
- Pleural thickening

Hayes & Novak-Frazer. J. Fungi. 2016
Muldoon et al. BMC Pulmonary Med. 2016; 16:123

Aspergilloma

- Saprophytic fungi, that grow in the existing cavity causes by other diseases, mostly PTB
- *Aspergillus* is the common cause .
- Usually symptomless; fatal complication is massive hemoptysis



Latge JP. CMR 1999; 12: 310–50
http://pennstatehershey.adam.com/content.aspx?productId=112&pid=28&gid=000130

CPA: Signs & symptoms

- Pulmonary disease that most of the time could not differ from other pulmonary infection
- need other diagnostic information:
  - Imaging: cavity, nodule, pleural thickening
  - mycology investigations: culture, serology (precipitin test)

Muldoon et al. BMC Pulmonary Med. 2016; 16:123

CPA diagnosis: clinical

- Symptoms lasting > 3 months, usually are weight loss, fatigue, cough, haemoptysis & breathlessness
- CX-rays showing cavities ≥ 1 or nodules (early)
- Often misdiagnose as recurrent TB

Godet et al. Respiration 2014;88:162–174
Maghrabi & Denning. Curr Fungal Infect Rep 2017; 11:242–251

CPA diagnosis: Laboratory investigation

- Sputum
  - Direct: branched hyphae
  - culture: positive rate ~ 25%
  - PCR: more sensitive
- **Key diagnostic**: precipitin test to detect Ab-IgG anti *Aspergillus*) in serum/other body fluid
- Biopsy:
  - Conventional mycology (direct & culture)
  - histopathology

Godet et al. Respiration 2014;88:162–174
Maghrabi & Denning. Curr Fungal Infect Rep 2017; 11:242–251

CPA diagnosis: Laboratory investigation

- Obtaining sputum:
  - Sometimes difficult
  - Induced sputum
- if obtain sputum is difficult, may be bronchoscopy needed to get BAL
- Investigation of acid fast bacilli is also important in addition of looking for *Aspergillus*

Langridge et al. BMC Pulm Med. 2016;16(1):23.,
Richardson & Denning. J Infect Secur.2016;72(2):240–9.

Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management

David W. Denning[1], Jacques Cadranel[2], Catherine Beigelman-Aubry[3], Florence Ader[4,5], Arunaloke Chakrabarti[6], Stijn Blot[7,8], Andrew J. Ullmann[9], George Dimopoulos[10] and Christoph Lange[11–14] on behalf of the European Society for Clinical Microbiology and Infectious Diseases and European Respiratory Society

Test	Strength of recommendation	Quality of evidence
Direct microscopy for hyphae[#]	A	II
Fungal culture (sputum or BAL)[¶]	A	III
Histology	A	II
Fungal culture (transthoracic aspiration)	B	II
Aspergillus PCR (respiratory secretion)[+]	C	II
Bacterial culture (sputum or BAL)	C	III

BAL: bronchoalveloar lavage. [#]: positive microscopy is a strong indicator of infection; [¶]: bacterial culture plates are less sensitive than fungal culture plates; [+]: PCR more sensitive than culture.

Eur Respir J 2016; 47: 45–68 | DOI: 10.1183/13993003.00583-2015

Conclusion: method of diagnosis

Table 2. Mandatory diagnostic tests for patients suspected of having CPA.

Immunology/Serology	Sputum Microbiology	Radiology
Aspergillus IgG/precipitins	Microscopy	CXR
Immunoglobulins and electrophoresis	Culture (including fungal culture)	
Functional antibody testing (*Tetanus*, *Haemophilus*, *Pneumococcus*)	Sensitivity (including resistance testing of any isolated *Aspergillus* spp.)	
Mannose binding lectin levels	Sputum *Aspergillus* PCR	CT thorax

Clinical presentation is important

Hayes & Novak-Frazer. J. Fungi. 2016

The role of galactomannan

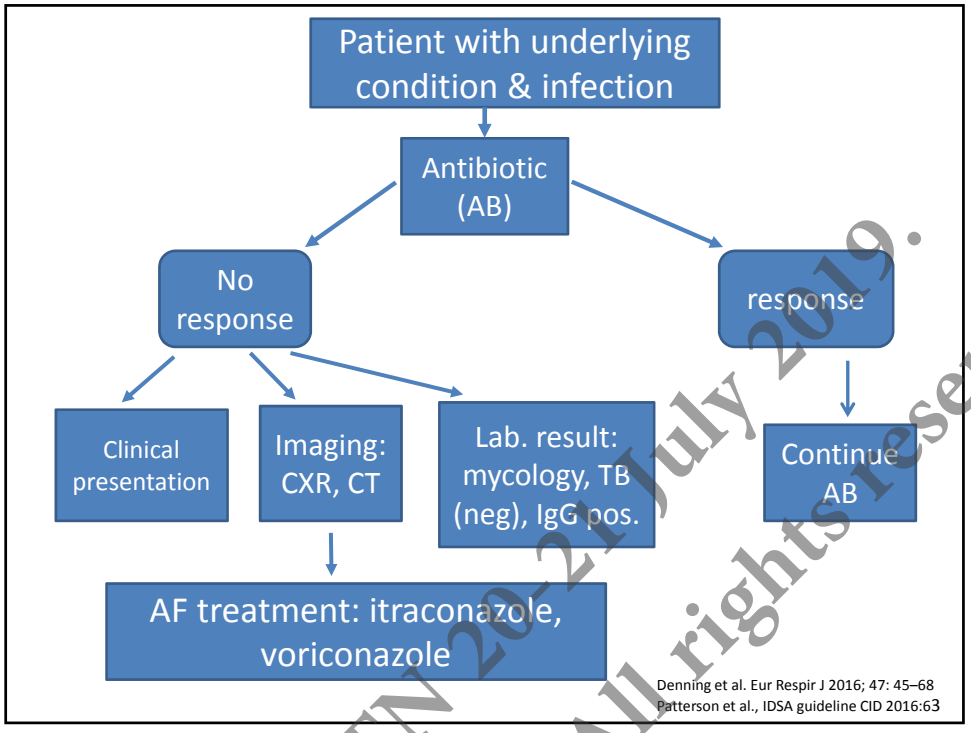
- GM in BAL has sensitivity ranging from 23% to 85% with cut off level 0.4.
- GM in serum 66,7 % & 63.5% with cut off level 0.7
- BAL is better

Shin et al J Infect 2014; 68: 494-9; Kono et al. Respir Med 2013; 107: 1094-100

CPA: treatment

- Bronchial artery embolization for hemoptysis
- Surgery: impairment of respiratory function or severity of comorbid does not allow surgery plus high morbidity & mortality.
- Antifungal:
  - Itraconazole, voriconazole (older)
  - Posaconazole, isavuconazole (newer)

Glimp & Bayer Arch Intern Med 1983; 143:303– 308;
Park & Jheon Eur J Cardio Thorac Surg 2002;21:918–23
Regnard et al. Ann Thorac Surg 2000; 69:898–903
Patterson et al., IDSA guideline CID 2016:63
Agarwal et al. Mycoses. 2013;56(5):559–70.



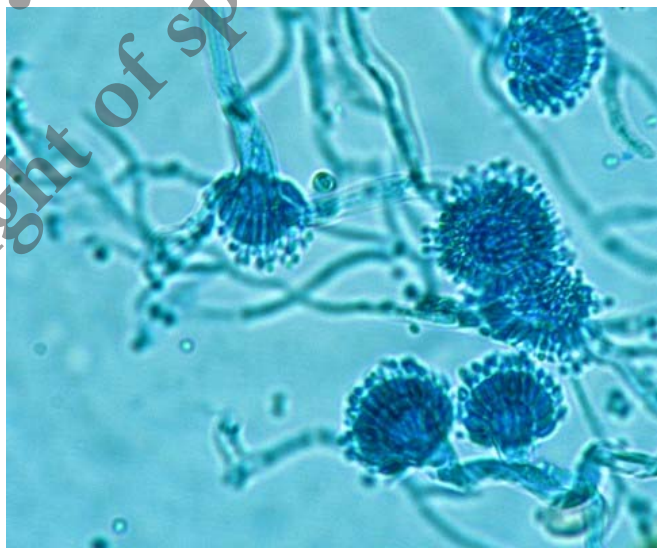
CPA diagnosis in resource limited setting

- diagnosis is based on clinical presentation,
- risk factors,
- Chest X Ray
- result of mycology lab. investigations

Source: personal opinion

Conclusion

- High prevalence of CPA in Asia
- No clinical improvement
- Proper diagnosis help patient to gain a better quality of life
- Underlying condition is important clue of diagnosis
- Use all possible diagnostic tool (clinical data, imaging, mycology conventional method, & antibody test)



Thank you

MMTN Malaysia, July 20-21, 2019

Aspergillus flavus
LPCB slide, 400× magnification, personal photo