

Chronic pulmonary aspergillosis (CPA)

Retno Wahyuningsih

Department of Parasitology, Faculty of Medicine, Universitas Indonesia,
Department of Parasitology, Faculty of Medicine, Universitas Kristen Indonesia ,
Jakarta, Indonesia

Disclosure

- Grant from the government to do research

Aspergillus

- A eukaryote, belong to Ascomycota
- A largely saprophytic filamentous fungi
- Ca. 250 spp. only 20 known associated with disease in human
- Genetically closely related to vertebrates
- Named after aspergillum, a holy water sprinkler, by Michelli, a priest & botanist
- modern taxonomist: toilet bowl brush

Rokas A. Curr Biol. 2013; 23: R187

Two side of a coin

Benefit

- The “cell factories”, use in industry:
 - Fermentation in food production: soya, sake
 - *A. niger*: citric acid
- Drug: *A. terreus*, source of the cholesterol lowering agent lovastatin.
- Recycling environmental carbon & nitrogen

Harm

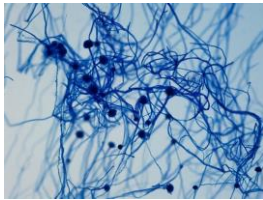
- aflatoxin produced by *A. flavus*
 - Turkey X disease
 - Billion dollar of crop (food) losses
 - Cancer in human
- Diseases:
 - lethally lung infection – acute invasive aspergillosis & chronic debilitating infection)
 - Other anatomic sites
 - Allergy - ABPA

Rokas A. Curr Biol. 2013; 23: R187

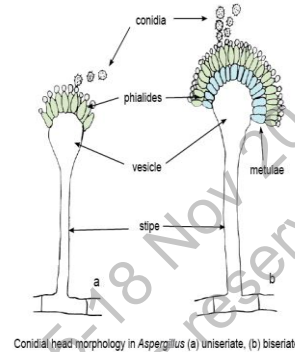
Page et al., Med Mycol, 2015; 53:417–39

Aspergillus morphology

- A beautifully made structure consisting of hyphae, head & spore
- True hyphae forming web called mycelium



Mycelium



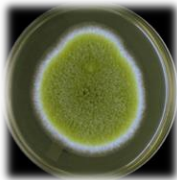
Conical head morphology in *Aspergillus* (a) uniseriate, (b) biseriate.

[http://www.mycology.adelaide.edu.au/Fungal_Descriptions/Hyphomycetes_\(hyaline\)/Aspergillus/](http://www.mycology.adelaide.edu.au/Fungal_Descriptions/Hyphomycetes_(hyaline)/Aspergillus/)
<http://thunderhouse4-yuri.blogspot.com/2012/02/aspergillus-flavus.html>

Aspergillus morphology

culture

- Colorful filamentous fungi
- Different color, different species



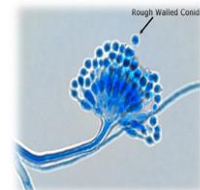
A. flavus



A. niger

microscopy

- True hyphae
- Vesicle
- Conidiophore
- sterigma
- spores



<http://thunderhouse4-yuri.blogspot.com/2012/02/aspergillus-flavus.html>
<http://www.scind.org/269/Science/some-commercially-important-microbial-species-.html>

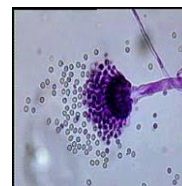
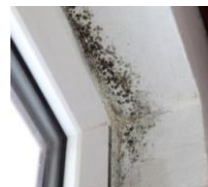
reproduction

- A complicated way of reproduction
- Comprising of asexual, sexual and parasexual stages
- The important for medical mycology is the result of the processes which produce a very tiny spore that release to the air and easily inhale to our respiratory system.

Gibbons & Rokas, *Trends Microbiol* 2013

Where it grows

- Ubiquitous in nature
- Grow in soil (mainly)
- grow in organic (grain, rice) & inorganic materials (wall of building)
- Its spore is largely distributed in the air
- Mode of dissemination is wind



<http://www.marvistavet.com/aspergillus.pml>

How it release its spore

- No special mechanism own by the fungi to release the spores
- By mechanical releasing mechanism then distributed by the wind
- small size; easily inhaled to the respiratory system
- In immunocompetent host, the inhaled spores are easily eliminated by ciliary activity of bronchial epithelium

Rokas A. Curr Biol. 2013; 23: R187

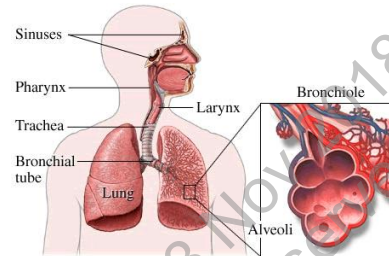
A. fumigatus

- Grows in soil, compost, & other inorganic materials
- Survive in high temperature, e.g. peak temperature of compost production
- Can survive human body temperature
- Small conidia (2 to 3 μm), easily inhale & reach the lowest portion of the lung
- Consider the most pathogenic

Latge JP. CMR 1999; 12: 310-50

How conidia reach our respiratory system

- conidia are blown by the wind
- Its small size facilitates inhalation
- the smaller the size of conidia, the easier it will reach the alveoli
- Depends on the condition of the immune system: eliminated or causes disease



<http://ripasofacile.blogspot.com/2017/09/riassunto-apparato-respiratorio.html>
Schaffner et al., J. Clin. Investig. 1982;69:617-31

Innate immunity activity in the elimination of *A. fumigatus* conidia

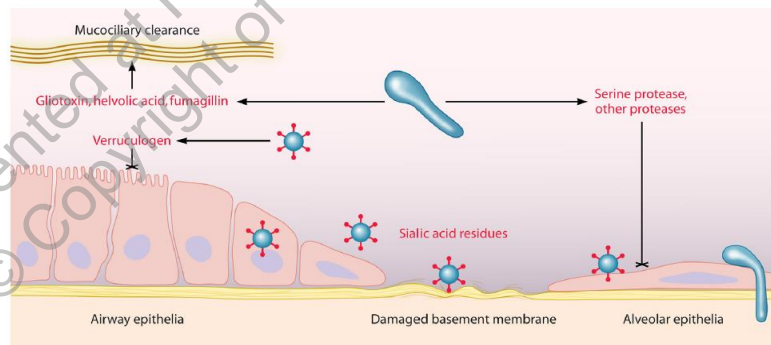
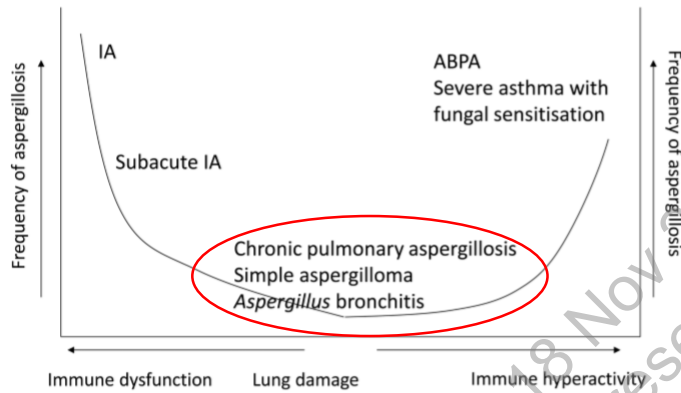


FIG. 2. Interaction of *A. fumigatus* with respiratory epithelia. Following inhalation, *A. fumigatus* encounters airway epithelia (lining trachea, bronchi, and bronchioles), the mucus and fluid lining the upper respiratory tract, and, ultimately, the alveolar space. Fungal products (shown in red) may enhance colonization through tissue injury (cross-haired line) and attachment to epithelial cells or damaged basement membrane. Conidia may also germinate and invade the surrounding lung tissue via the basement membrane or following ingestion by epithelial cells.

Dagenais & Keller CMR 2009;22: 447-65

Interaction between *Aspergillus* & host



The response is based on immune status

Modified from Kosmidis & Denning BMJ 2014

Aspergillus Pulmonary infection

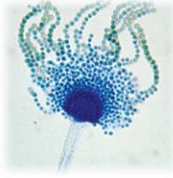
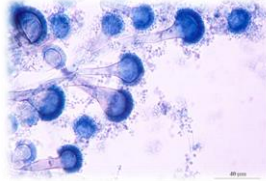
- Acute pulmonary infection
- Chronic pulmonary infection
- Aspergiloma

CHRONIC PULMONARY CPA

CPA: epidemiology

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

(Denning – LIFE)

A. flavus*A. fumigatus**A. niger*

Other: *A. flavus* & *A. niger*, *A. terreus*

THE MAIN CAUSE: *A. FUMIGATUS*

Kosmidis & Denning. Thorax 2015;70:270–277
Maghrabi & Denning. Curr Fungal Infect Rep 2017; 11:242–251

<http://www.life-worldwide.org/assets/uploads/images/>
<https://www.inspq.gc.ca/node/484>
<http://medicinenews.blogspot.com/2013/02/microscopic-morphology-of-aspergillus.html>

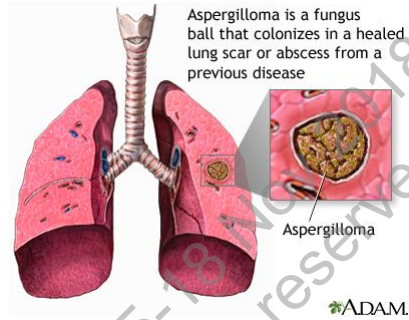
Chronic Pulmonary Aspergillosis

- long-term pulmonary aspergillosis, a slowly progressive & 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

Aspergilloma

- Saprophytic fungi, that grow in the existing cavity causes by other diseases, mostly PTB
- *Aspergillus* is the common cause .



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

Aspergilloma – fungus ball

- The fungus grow as mass of hyphae embeded in protein-matrix , a connection with air way will stimulates formation of *Aspergillus* head ultimately produces sporulation
- Usually symptomless, but the common symptom if any is hemophtysis that can be fatal

Latge JP. CMR 1999; 12: 310-50

TABLE 3 Diagnostic criteria for different management of chronic pulmonary aspergillosis (CPA)

Term	Definition	Types
Simple aspergilloma	Single pulmonary cavity containing a fungal ball, with serological or microbiological evidence implicating <i>Aspergillus</i> 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 <i>Aspergillus</i> 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.	
<i>Aspergillus</i> 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 <i>Aspergillus</i> galactomannan antigen in blood (or respiratory fluids).	

Denning et al. EJR Express 2015

CPA: pathogenesis

- underlying condition that accomodates cavity formation or causes tissue damaged
- a fertile site for the grow of *Aspergillus*
- *Aspergillus* destroys 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
Smith & Denning. Eur. Respir. J. 2011; 37, 865–72.

Table 2
Underlying conditions of CPA patients.

	CNPA (n = 7)	Group A (n = 5)	CCPA (n = 8)	SA (n = 7)
Respiratory conditions				
Prior tuberculosis	2	1	3	4
Bronchiectasis	1	3	2	3
Prior pneumonia	3	4	0	2
Pneumothorax or bullae	1	3	2	2
COPD or emphysema	5	0	1	0
Prior thoracic surgery	2	2	1	1
Other respiratory conditions ^a	2	4	9	4
Systemic conditions				
Diabetes Mellitus	3	2	2	2
Steroid usage	2	0	2	0
Other systemic conditions ^b	4	0	3	8
Smoking (>20 y)	5	2	7	2
Malnutrition (BMI <18.5)	4	4	3	1

CNPA, chronic necrotizing pulmonary aspergillosis; CCPA, chronic cavitary pulmonary aspergillosis; SA, simple pulmonary aspergilloma

Izumikawa et al. J Infect Chemother 2014

- 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

Clinical presentation

- Aspergiloma
- Chronic cavitary pulmonary aspergillosis (CCPA)
- 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

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

Symptoms of patients with chronic aspergilosis

	CNPA (n = 7)	Group A (n = 5)	CCPA (n = 8)	SA (n = 7)
Sex; Male/Female	6/1	4/1	7/1	3/4
Age; mean (range)	59.1 (45–75)	67.0 (50–77)	69.7 (58–80)	56.6 (40–68)
Body mass index; mean (range)	18.0* (13.0–21.4)	16.9* (13.9–18.8)	20.2 (15.7–25.7)	21.3 (18.0–23.9)
Symptoms				
Cough	5	5	7	4
Sputum	5	2	3	3
Hemoptysis	1	5	6	4
Dyspnea	3	1	2	0
Fever	4	2	0	0
Malaise	3	0	0	0
Weight loss	1	2	0	0
Duration; median (range)	3 m (1 m–6 y)	24 m (17 m–6 y)	29 m (6 m–5 y4 m)	24 m (6 m–4 y)

modified from Izumikawa et al. J Infect Chemother 2014

Hedayati et al. Eur J Clin Microbiol Infect Dis. 2015; 34:1759–1765

Table 1. CPA: diagnosis criteria and definitions [3]

1	Chronic pulmonary or general symptoms including at least 1 of the following (for a minimum of 3 months in duration): weight loss, productive cough or haemoptysis
2	A progressive formation and expansion of single or multiple pulmonary cavitations surrounded by a wall and possible pleural thickening on radio-imaging [20, 27]
3	A positive result for a serum <i>Aspergillus</i> spp. precipitins test or an isolation of <i>Aspergillus</i> spp. from the pulmonary or pleural cavity
4	Increased biological inflammatory syndrome markers (C-reactive protein, plasma viscosity or erythrocyte sedimentation rate)
5	The exclusion of all other causes that could imitate the symptoms (bronchial carcinoma, TB and atypical mycobacteria)
6	No overt immunocompromising conditions (HIV-infection, leukaemia and chronic granulomatous disease)

Godet et al. Respiration 2014;88:162–174

CPA: Diagnosis

- Symptoms lasting > 3 months, usually are weight loss, fatigue, cough, hemoptysis & 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* (differential diagnosis)

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

Conclusion: method of diagnosis

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

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

Hayes & Novak-Frazer. J. Fungi. 2016

CPA: treatment

- No codified treatment yet
- 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 treatment

- Voriconazole is the first line for Aspergillosis therapy, but the obstacle is expensive & has many side effects
- Itraconazole is preferred since for financial reason is more affordable
- Isavuconazole: no published data yet

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.

Itraconazole

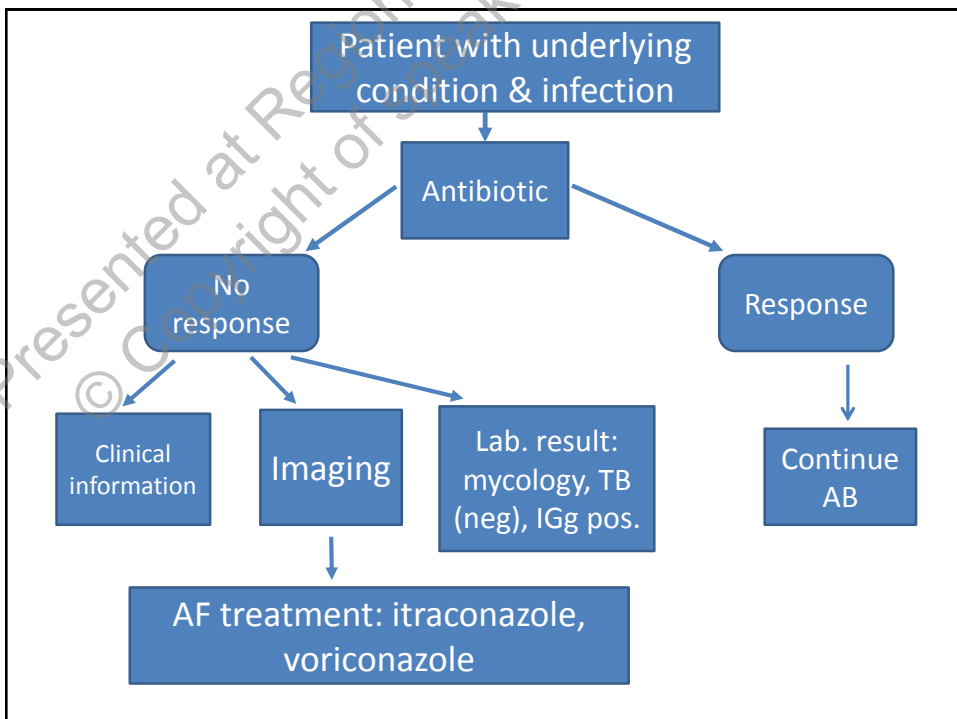
- The best choice, but long term use is challenging,
- widely use for the treatment of aspergillosis,
- but difficult to absorb; with high fat meal & carbonated drinks
- antagonist to many drugs esp. with anti TB rifampicin
- Liver function monitoring
- relapse is also complicates treatment

Alastruey-Izquierdo A et al. Respiration 2018;96:159–170

Case

- A 60 yo lady with CCPA, post TB, hemoptysis diagnosis was established based on clinical, laboratory (precipitin pos, Aspergillus isolated), CXR showed multiple cavity & bronchiectasy
- treated with 400 mg itraconazole/day for 6 months, clinically patient getting better, but
- Relaps after we stop the treatment

Wahyuningsih et al AFWG 2017



Prognosis

- CPA is often diagnosed late leads to improper treatment
- progresses toward worsening in line with pulmonary tissue destruction
- Mortality rate is ca. 15-30% in the first six months after diagnosis.
- Large volume hemoptysis is life threatening
- What we can do is to halt the progressive lung tissue destruction

Kosmidis & Denning . Thorax 2015;70:270-7
Kosmidis & Muldoon. Med Mycol. 2017; 55: 63-8

TB in Asia

- Asian countries, known for the high number of TB patients & the most is PTB.
- India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Bangladesh (4%)
- Damage lung tissue due to PTB is the fertile ground for the grow of *Aspergillus*
- PTB is known to be the most important underlying disease for CPA

Global TB report, WHO 2018

CPA in Asia

- 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

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
Huashan Hospital, Fudan University, Shanghai 200040 China; Public Health Research Institute, Newark, NJ, USA and The University of Manchester in association with the LIFE program at www.LIFE-worldwide.org



Introduction

The incidence of serious 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 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 the 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, Respiriology, 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 jirovecii pneumonia (PCP) rates were based on Hong Kong rates in HIV and 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 4,383 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 (63,150 cases) and candida peritonitis at 19,952 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
Candidemia	--	--	--	20,445	47,705	68,150	5.0
Candida parositis	--	--	--	--	19,082	19,082	1.4
Recurrent vaginal candidiasis (4x/year+)	19,959h	--	--	--	--	19,959	2.929
Allergic bronchopulmonary aspergillosis (ABPA)	--	--	491,721i	--	--	491,721	36.1
Chronic asthma with fungal sensitisation (SAFS)	--	--	648,300	--	--	648,300	49.6
Chronic pulmonary aspergillosis (CPA)	--	--	256,534	--	--	256,534	19.6
Invasive aspergillosis	--	--	--	8,178	154,155	162,333	11.3
Mucormycosis	--	--	--	2,726	--	2,726	0.2
Cryptococcal meningitis	922	461	--	922	--	2,306	0.17
Pneumocystis jirovecii pneumonia (PCP)	--	16,140	7	8,070	--	24,210	1.8
Penicillium marneffei infection	7	1,383	--	--	--	1,383	0.1
Fungal keratitis	17,036	--	--	--	--	17,036	1.3
Tinea capitis	34,075	--	--	--	--	34,075	2.5
Total burden-estimated	20,010h	151,820	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.

corresponding author:
Dr. Li-ping Zhu,
Email: zhulp@fudan.edu.cn



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

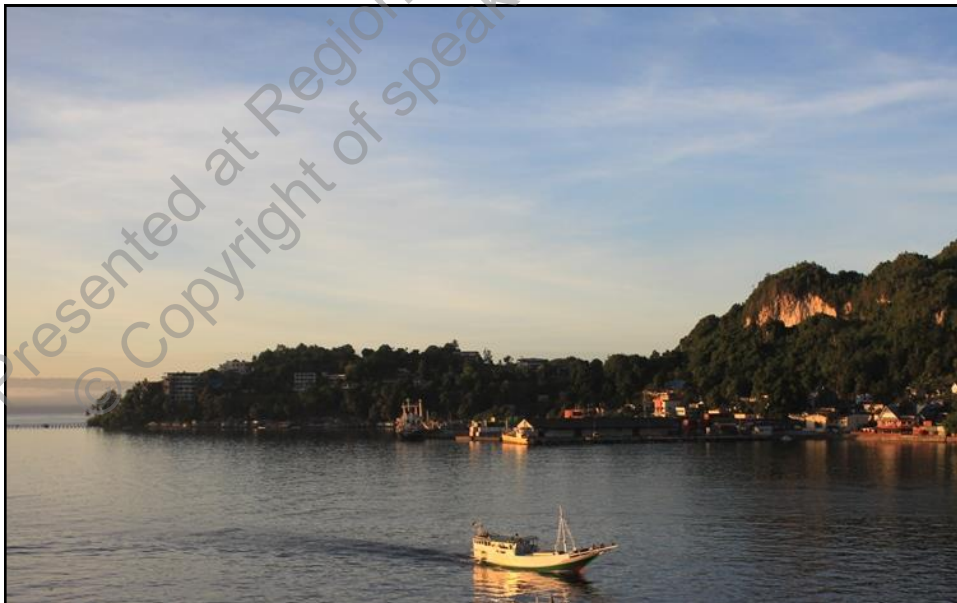
- Jakarta & surrounding cities:
 - 56 patients with TB (32 male, age range: 17-78 years), 10 patients (17.9%) met criteria for CPA.
- Manado (Celebes):
 - 72 patients post TB, 25 (34.7 %) proven as CPA



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

Conclusion

- CPA is debilitated infection of the lung, which never show any clinical improvement
- Underlying condition is important in the development of CPA
- In Asia, PTB is an important underlying disease
- Since PTB prevalence in Asia is high, there should be more attention to CPA
- Improvement alertness of doctors & laboratory skill



Thank you

MMTN Taipei November 15-18, 2018

Early morning in Jayapura, Papua, Indonesia