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MEDICAL MYCOLOGY
TRAINING NETWORK

Chronic pulmonary aspergillosis – diagnosis and management in resource-limited setting

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Chronic pulmonary aspergillosis (CPA) – diagnosis & management in resource-limited setting

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Chronic Pulmonary Aspergillosis

- Long-term aspergillosis in the lung, a slowly progressive & destructive disease
- Caused by: *A. fumigatus* (>), *A. niger* & *A. flavus* (<)
- IDSA guideline:
 - Simple aspergilloma: cavity with a fungus ball inside
 - Chronic cavitary pulmonary aspergillosis (CCPA) – complex aspergilloma
 - chronic necrotizing pulmonary aspergillosis (CNPA)
- Untreated may develop fibrosis – worsening of the disease

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

Term	Definition
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).

CPA: epidemiology

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

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(Denning – LIFE)

CPA: pathogenesis

- Underlying condition that accommodates cavity formation or causes tissue damaged
- A fertile site for the grow of *Aspergillus*
- *Aspergillus* destroys lung tissues by invasion, production of proteolytic enzymes, toxins and other metabolites that make things worse

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)
- Prolonged use of low-dose oral or inhaled corticosteroids
- Absence of or presence of very little vascular invasion

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	2	4	9	4
Systemic conditions				
Diabetes	3	2	2	2
Steroid usage	2	0	2	0
Other systemic conditions	4	0	3	8
Smoking (>20 y)	5	2	7	2
Malnutrition (BMI <18.5)	4	4	3	1

Signs & symptoms

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

Symptoms of patients with chronic aspergillosis

	CNPA (n=7)	Group A (n=5)	CCPA (n=8)	SA (n=7)
Sex; male/female	6/4	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)
BMI; mean (range)	18 (13-21)	17 (14-19)	20 (16-26)	21 (18-24)
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 y 4 m)	24 m (6 m-4 y)

Table was modified from Izumikawa et al. J Infect Chemother 2014
 Hedayati et al. Eur J Clin Microbiol Infect Dis. 2015;34;1759–1765

CPA: Diagnosis

- Symptoms lasting > 3 months, usually are weight loss, fatigue, cough, haemoptysis & breathlessness
- CX-rays showing cavities ≥ 1 or nodules (early)
- Key diagnostic: precipitin test to detect antibody (IgG) anti *Aspergillus* in serum/ other body fluid

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CPA: Diagnosis

- Laboratory investigation:
 - Sputum
 - Direct: branched hyphae
 - culture: positive rate ~ 25%
 - PCR: more sensitive, but many remains negative
- Biopsy:
 - Conventional mycology (direct & culture)
 - histopathology

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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

Resource limited setting

- History: underlying condition, treatment
- Clinical presentation:
 - PTB sequelae or misdiagnosed with PTB or
 - Co – infection with PTB
 - Other underlying condition

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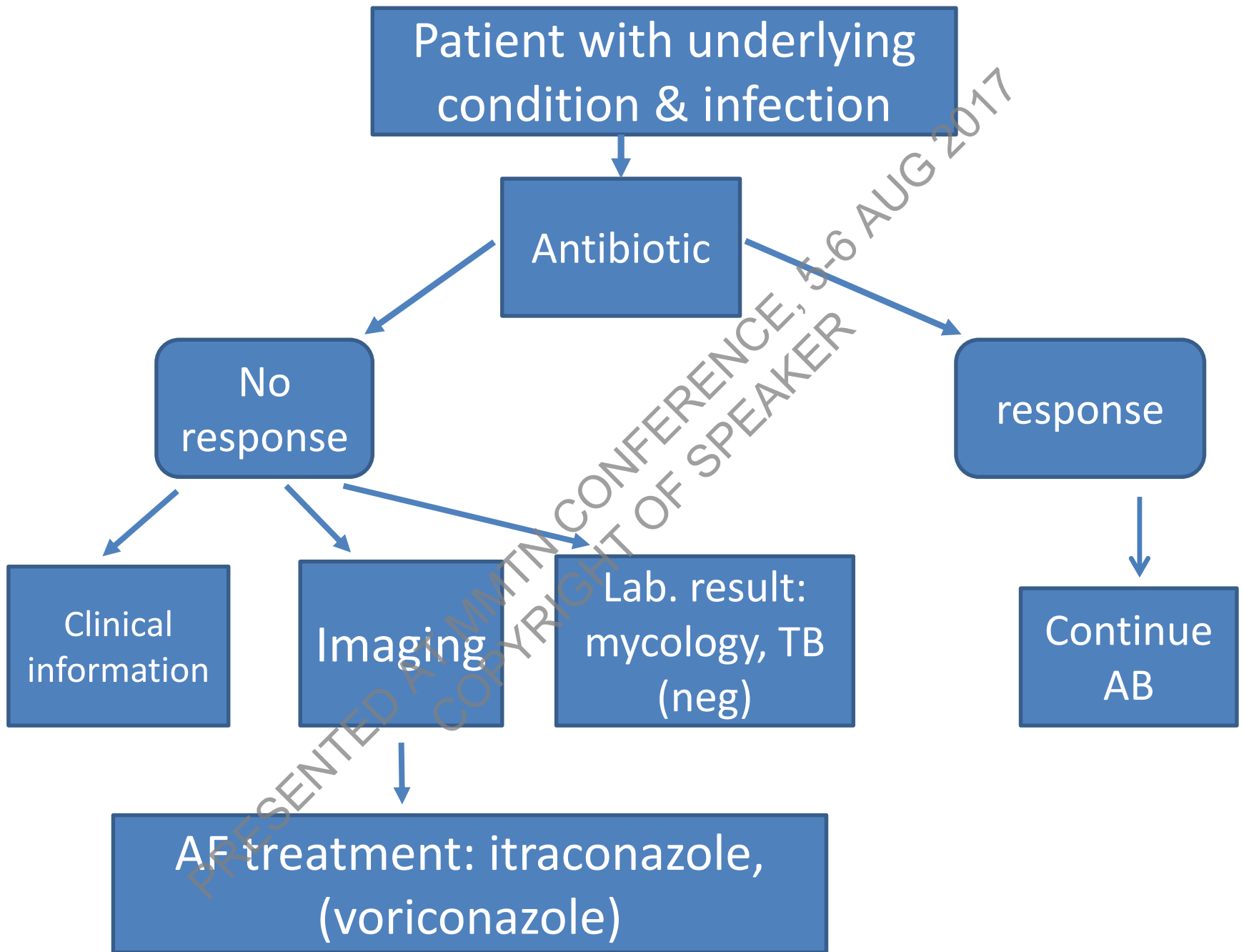
Resource limited setting

- Diagnosis: usually the conventional (direct investigation & culture) mycology test are available
 - weakness sensitivity & specificity
 - Contamination? Colonization?

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Resource limited setting: Treatment

- Voriconazole
- Itraconazole:
 - Widely used anti-fungal either for invasive infections such as aspergillosis as well as superficial infections
 - Emergence of resistant strains to itraconazole
 - Wide use for treatment of superficial & systemic mycoses
 - Use of azole derivative in agriculture



Patient with underlying condition & infection

Antibiotic

No response

response

Clinical information

Imaging

Lab. result: mycology, TB (neg)

Continue AB

AF treatment: itraconazole, (voriconazole)

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.
- What we can do is to halt the progressive lung tissue destruction

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Chronic cavitary pulmonary aspergillosis

CASE REPORT

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Case report: physical examination

looked ill and
cachectic

loss weight during
the last 10 years

A 60 year old lady
with recurrent
hemoptysis

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History

1998: pulmonary TB, clinical signs, chest X ray, sputum acid fast bacilli (+)

Anti TB six month, sputum was cleared from acid fast bacilli

D/pulmonary TB

2003: sputum acid fast bacilli (+).

Category II of anti TB - 9 months, declared cured, no acid fast bacilli.

D/ relaps pulmonary TB

2007: cough & blood streak for the 1st time.

Acid fast bacilli negative.

One week AB, symptoms were disappeared.

Diagnosis: residual symptoms of TB.

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History:

February 2010

profuse hemoptysis, admitted to the hospital.

chest CT scan - right lung : rough broncho-vascular pattern, bronchiectasis, fibrosis, cavities on top.

Acid fast bacilli (-)

Pulmonary lesion: residual process of former TB.

AB was given, clinical symptoms were disappeared.

March 2011

profuse hemoptysis, admitted to the hospital for one week, acid fast bacilli (-)

CXR was unchanged

Diagnosis: infected bronchiectasis, prev. TB and recurrent hemoptysis,

Discharged: cough almost everyday, blood streak (+/-).

AB and symptomatic treatment:
no response

Work and family history

No other diseases and no significant family history.

Civil servant since a long period of time.

2007, her office was moved to an old, dump bldg because her previous office was being renovated.

3-4 months later: 1st hemoptysis.

Almost a year in the dump building, moved back to her newly renovated building office. None of her colleagues have such a complaint.

Lab investigation

May 2011:
sputum 3 days,
C. albicans,
Aspergillus antibody
(+)

July 2011:
sputum 3 days,
A. niger ,
Aspergillus antibody
(+).

August 2011:
hemoptysis +
spt. *A. fumigatus*,
susceptible to
itraconazole and
voriconazole, SDD to
amphotericine B.

September 2011 PCP was identified, but no treatment was given, the patient feel well and clinically looks good.

Imaging



CXR 2010

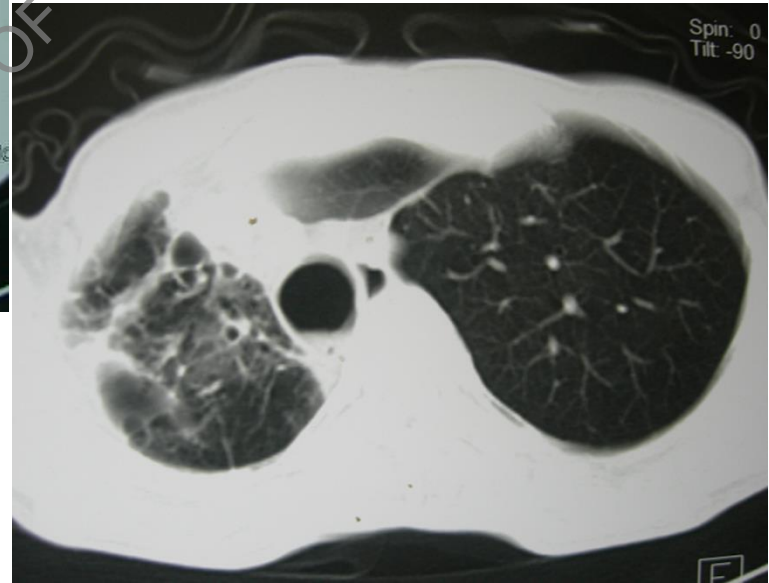
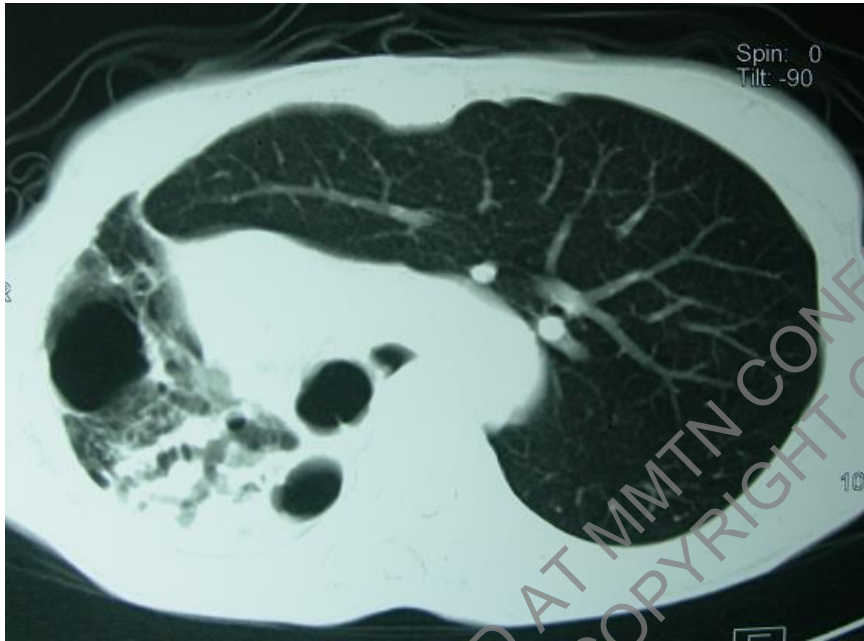


CXR 2011

The result of both CXR of 2010 & 2011 are the same

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CT scan Augusts 2011



The result shows right lung destruction

Based on Chest CT scan and previous lab investigations, the diagnosis were

- Chronic cavitary pulmonary aspergillosis (CCPA)
- Post TB
- destroyed right lung
 - Bronchiectasis, atelectasis
 - Multiple bullae
 - Fungus ball

Treatment (2011)



Itraconazole, 400 mg/day for 10 days, cont by 200 mg/day for one week.
Erythromycin 250 mg/day as anti inflammatory agent for her bronchiectasis, with good response, patient feel much better

Itraconazole was given because **antibody against Aspergillus was positive**, eventhough sputum investigations yield *C. albicans*

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Treatment (2011)

A month later a sputum investigation (3X) was done

A. niger was isolated and antibody against *Aspergillus* remain +

The patient feels much better

400 mg itraconazole/day was added and clinically looks well

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Lab. investigation and imaging

August 2011: hemoptysis, *A. fumigatus* was isolated; susceptible to itracon & voricon, amphotericine B is SDD

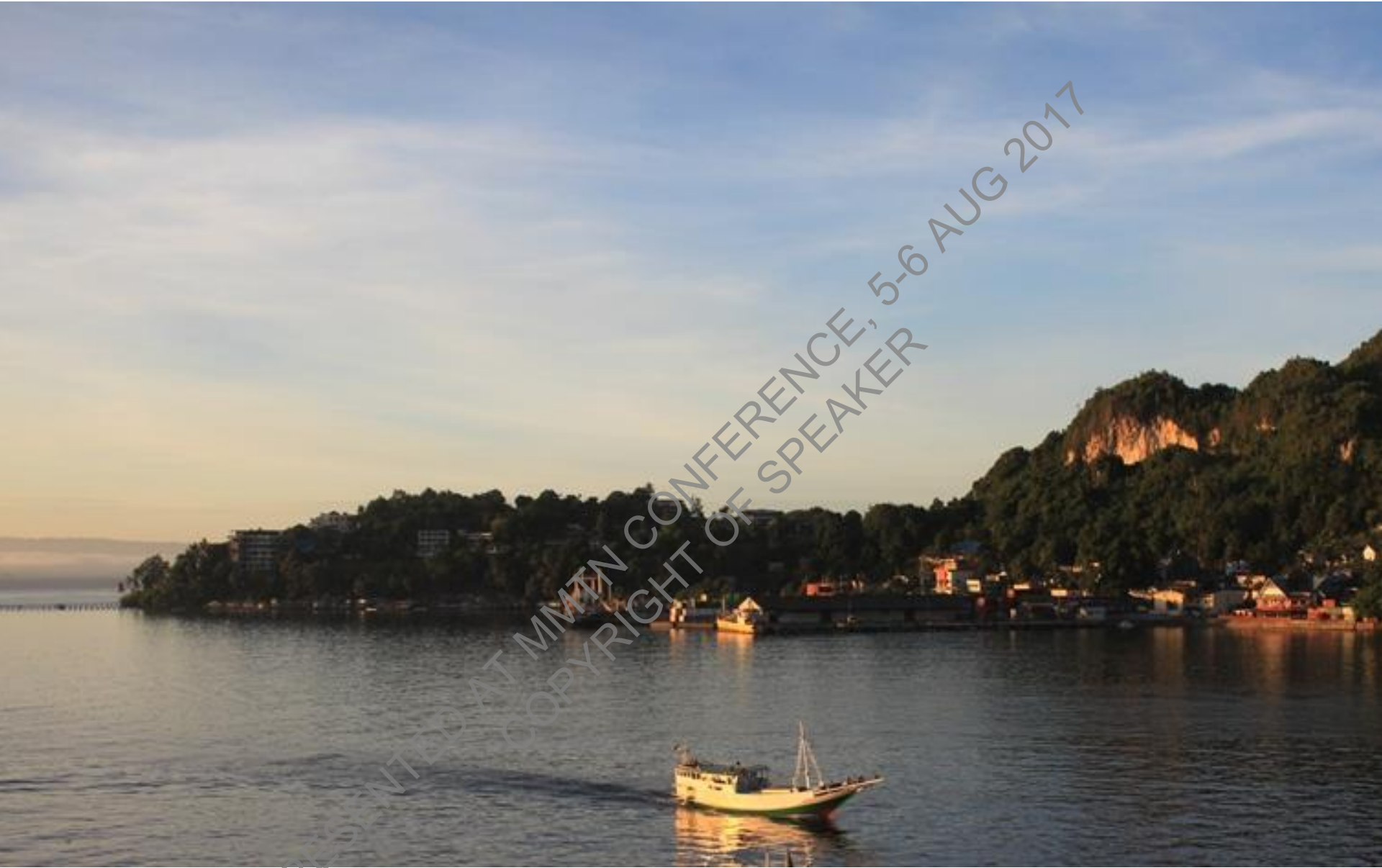
Chest CT scan: right destroyed lung (bronchiectasis, athelectasis, multiple bullae with possibility of fungus balls).

Treatment: itraconazole 200 mg/day for 2 weeks

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Thank you

MMTN Kuala Lumpur August 6, 2017

Early morning in Jayapura, Papua, Indonesia