EPIDEMIOLOGICAL, CLINICAL, LABORATORY AND THERAPY FEATURES OF 118 CASES OF *PENICILLIUM MARNEFFEI* INFECTION IN HIV PATIENTS ADMITTED IN THE HOSPITAL FOR TROPICAL DISEASES

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INTRODUCTION

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1. PROBLEMS OF STUDY

- *P.marneffei* (P.M) was first described in 1956 at the Pasteur Institute of Dalat, Viet Nam.
- Southeast Asia and Southern part of China are where the disease was suspected to be endemic.
- During the outbreak of AIDS, disseminated P.M infections began to be observed and has emerged in HIV/AIDS patients who were living in the endemic area.

In Viet Nam,

- **The first AIDS patient with disseminated P.M infection was reported on July 7th, 1996, in the Hospital for Tropical Diseases, HCMC.**
- **The number of penicilliosis marneffei in HIV-infected patients has been reported increasingly and this infection is life-threaten disease.**

Therefore, it is necessary to performed study on epidemiology, clinical feature, laboratory and treatment of *P.M infection in HIV patients* → *suitable treatment and prevention measures.*

2. AIMS OF STUDY

Judge epidemiological, clinical, laboratory features and ability of treatment of P.M infection in HIV patients admitted in The Hospital for Tropical Diseases.

Specific aims

- Judge epidemiological features of P.M infection in HIV patients admitted in The Hospital for Tropical Diseases.

- Determine ratio of P.M infection in HIV patients admitted in The Hospital for Tropical Diseases.

- Determine ratio of HIV patients in *Penicilliosis marneffei* cases who are in – patients in The Hospital for Tropical Diseases and have developed AIDS.

Specific aims

- Describe clinical, laboratory features of P.M infection in HIV patients admitted in The Hospital for Tropical Diseases.

- Judge treatment of P.M infection in HIV patients admitted in The Hospital for Tropical Diseases.

OBJECTS AND METHODS OF STUDY

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1. Objects

All HIV – infected patients with P.M infection admitted to the Hospital for Tropical Diseases from July 7th, 1996 to December 30th, 2003.

- *Inclusion criteria*

HIV – infected patients with confirmed P.M infection.

- *Exclusion criteria*

HIV – infected patients with past history of P.M infection.

2. Methodology

- Design

Case-series study

- Location

Hospital for Tropical Diseases, HCMC

- Size N = 118

3. Collect data

- Method

Collection retrospectively patients' files

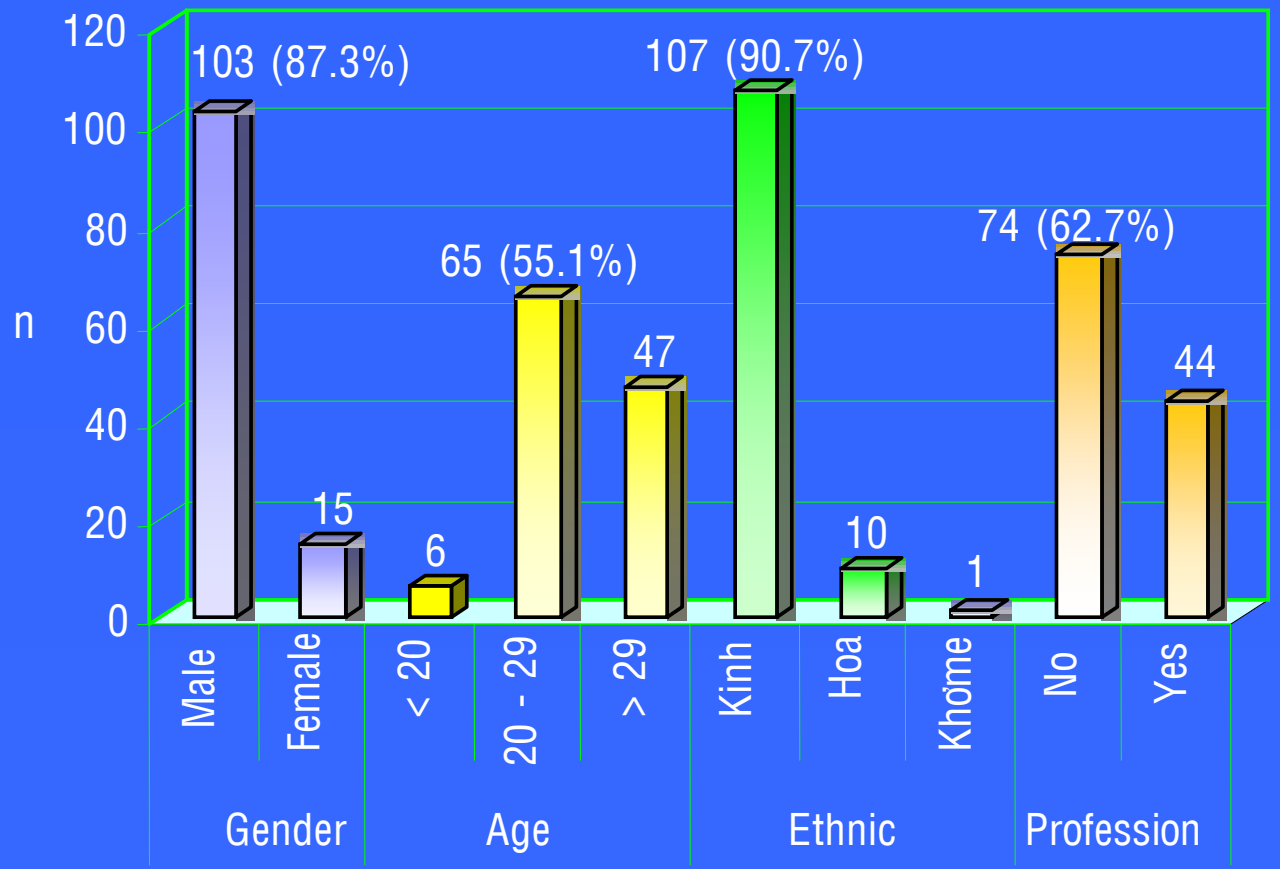
- Tool

Table of data sources

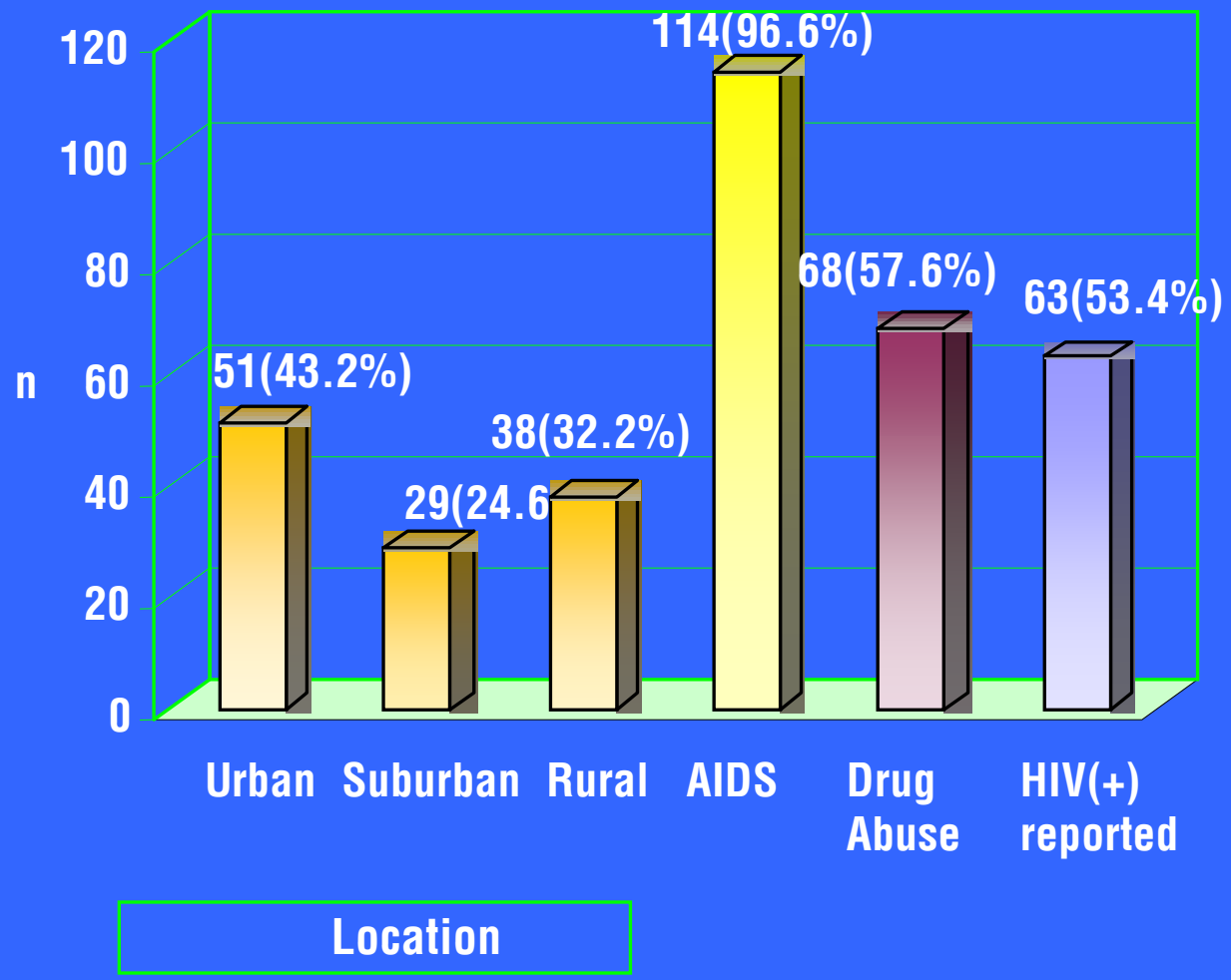
RESULTS

EPIDEMIOLOGICAL FEATURES

1. Population Society of sample

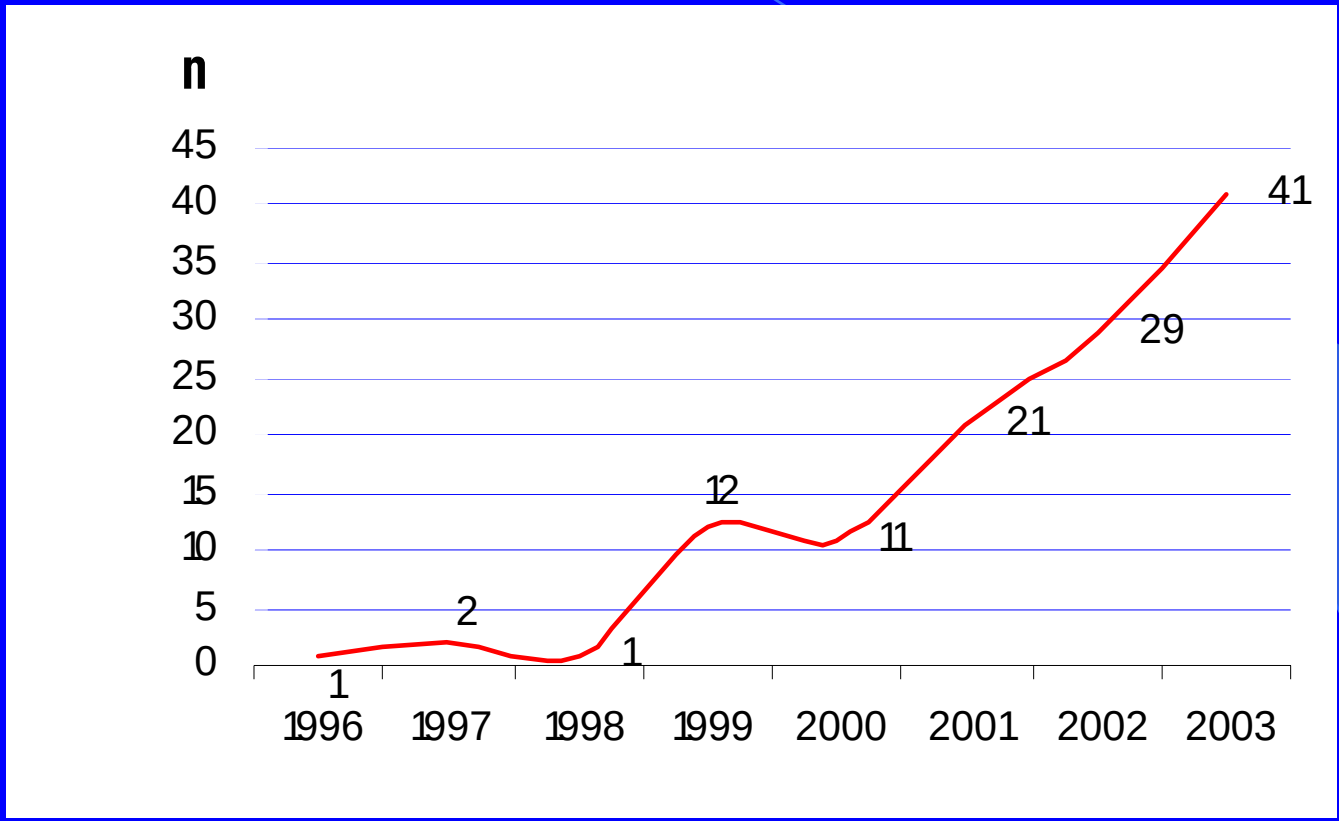


1. Population Society of sample



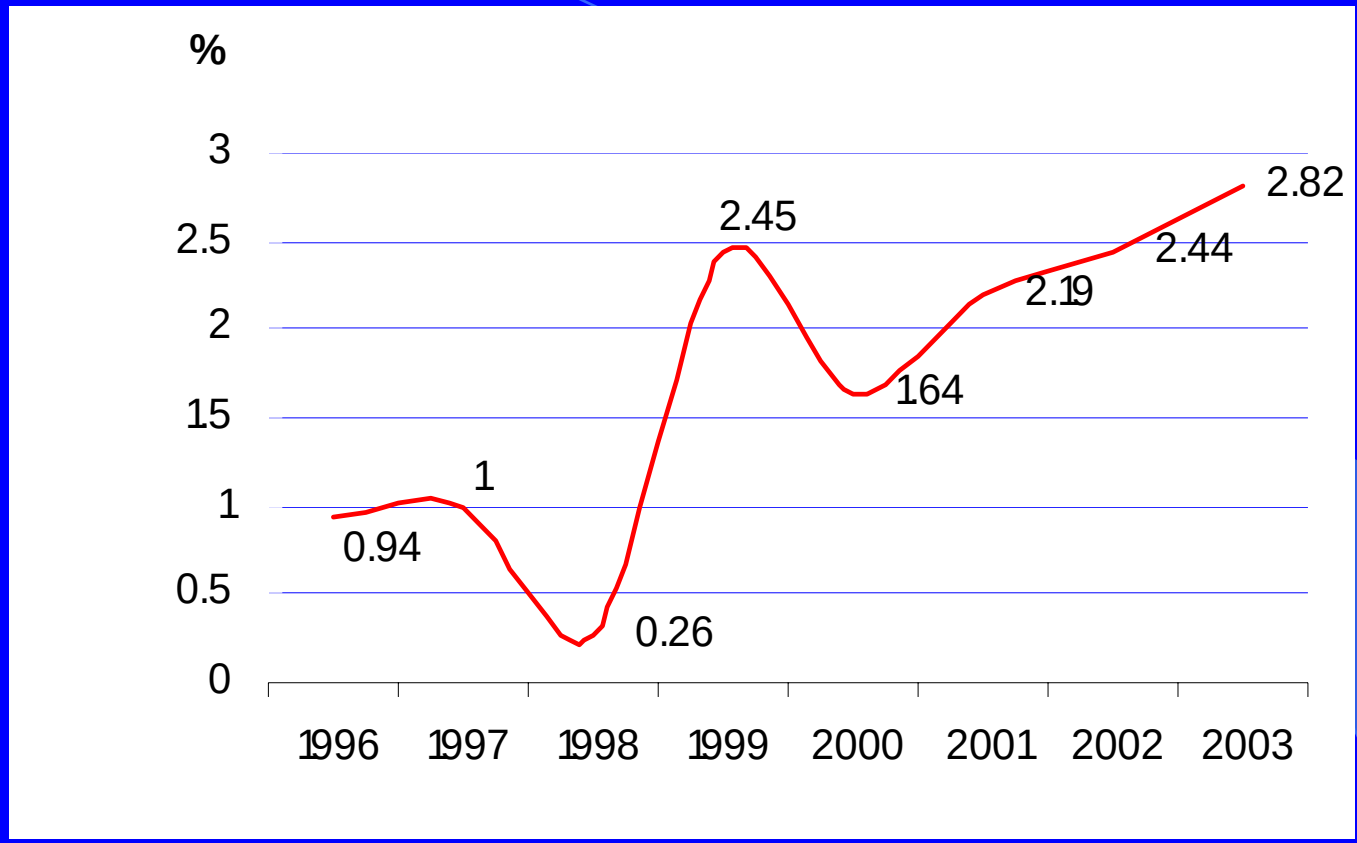
2. Distribution of disease by time

2.1 Distribution of disease per year



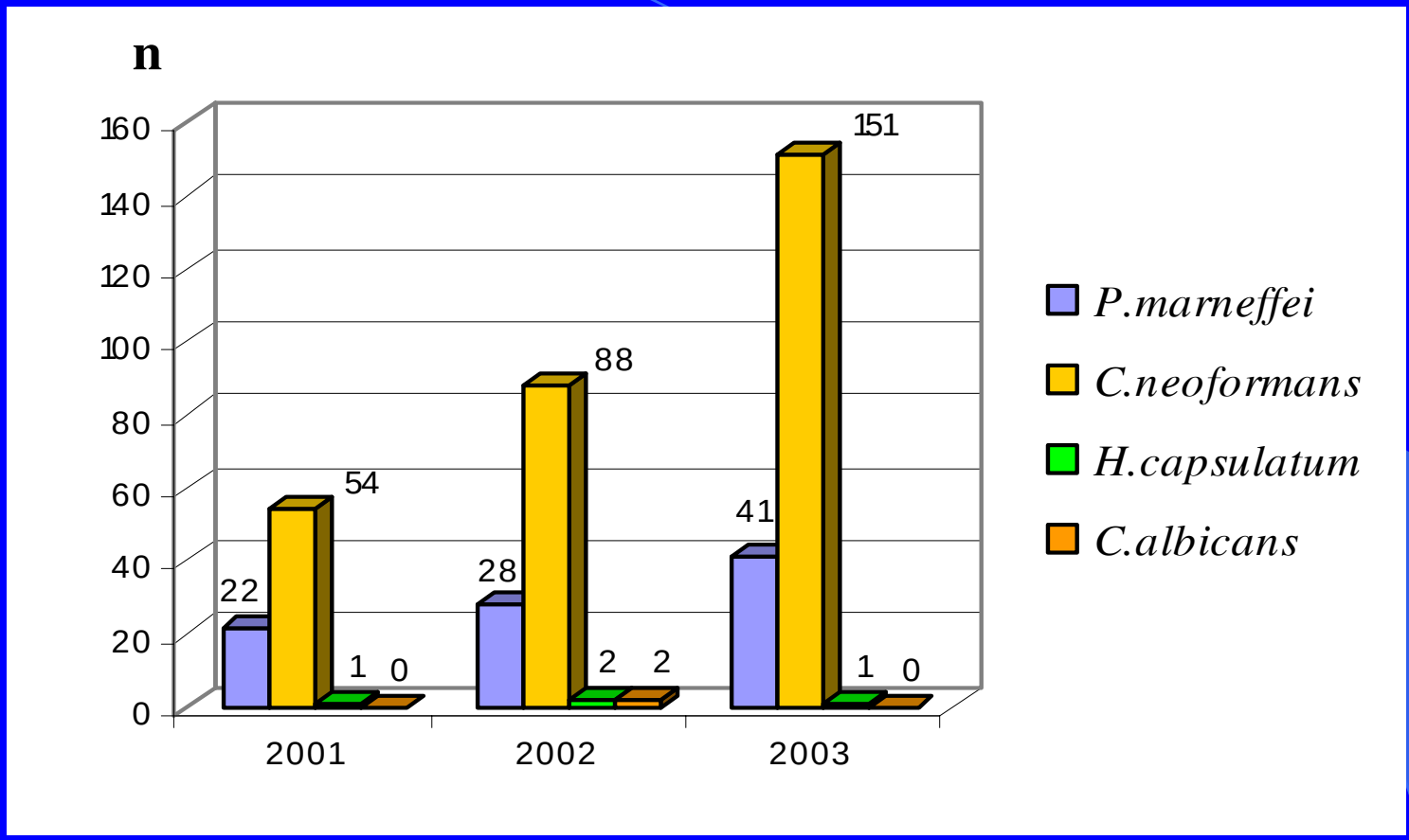
Number of cases of *P. marneffei* infection in HIV patients per year (1996 – 2003)

2.1 Distribution of disease per year



Ratio of *P. marneffei* infection in HIV patients per year (1996 – 2003)

2.1 Distribution of disease per year



Distribution of deep-seated mycosis in HIV patients in H.T.D

2.2 Distribution of disease by season

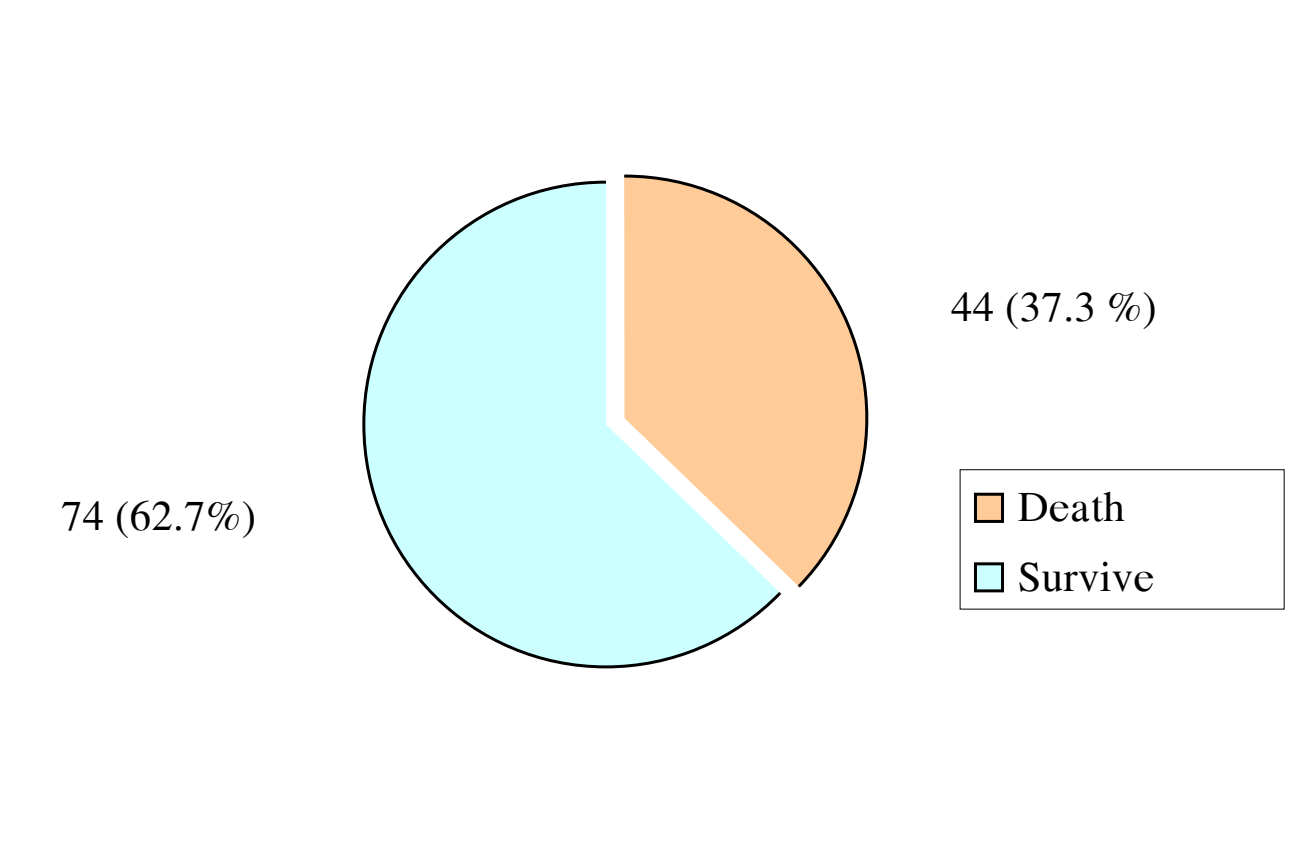
Season	2001	2002	2003	Total
Rainy	12	16	23	51
Dry	09	13	18	40
Total	21	29	41	91

Frequency of P.M infection by season in year

Year	OR	KTC 95%	P
2001	1.37	0.53 – 3.56	0.48
2002	1.30	0.59 – 2.89	0.49
2003	1.41	0.73 – 2.76	0.35
2001, 2002, 2003	1.36	0.88 – 2.11	0.18

Relation between P. M infection and season

3. Case – fatality rate: 44/118 = 37.3%

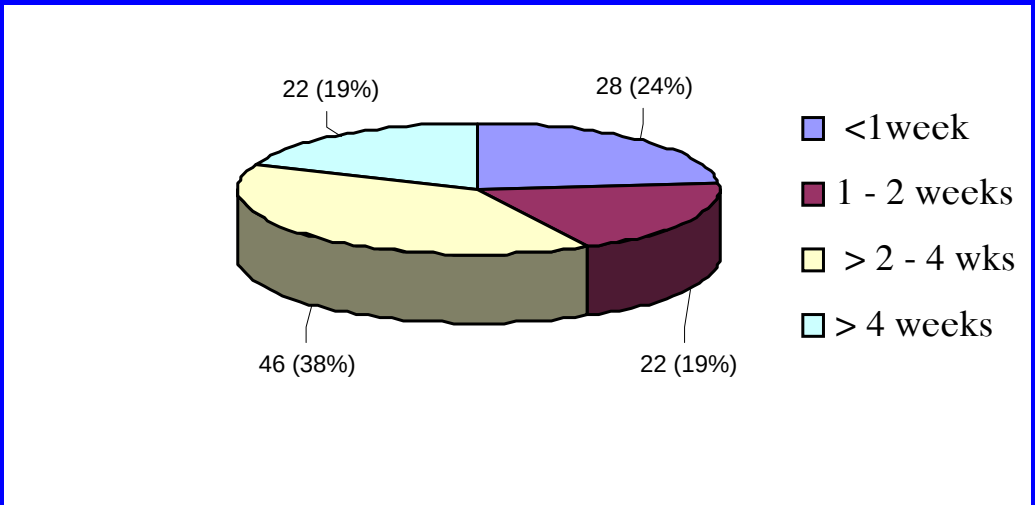


CLINICAL FEATURES

1. Hospitalization reason

- High fever: 51.7%
- Fatigue: 13.6%
- 12/16 cases who hospitalized due to fatigue would have bad outcome (die or dying)

2. The time of illness before going to hospital



3. Clinical features (N=118)

	n	%
Fever	108	91.5
Anemia	102	68.6
Debilitation, weigh loss	95	80.5
Hepatomegaly	83	70.3
Skin lesions	70	59.3
Splenomegaly	65	55.0
Cough	52	44.0
Tachypnea	51	43.2
Lymphoadenopathy	51	43.2
Diarrhea	47	39.8
Bleeding	15	12.7

Specific skin lesions of *P. marneffei* infection in HIV patients (papules with central necrotic, umbilication)

- 51 cases with tachypnea and 39/51 case died. There was statistical relation between tachypnea and death ($p < 0.001$)

4. Accompanied diseases

- 97 cases (82.2%) had other accompanied diseases.
- 45 cases had ≥ 2 accompanied diseases.
- Majority of accompanied diseases are infectious diseases:

* Lingual fungal infection	57 cases
* Tuberculosis	21 cases
* Viral hepatitis	21 cases
* Pneumonia	20 cases
* Sepsis	07 cases

LABORATORY FEATURES

1. HCT(%), WBC, lymphocyte, platelet, CD4(/mm3)

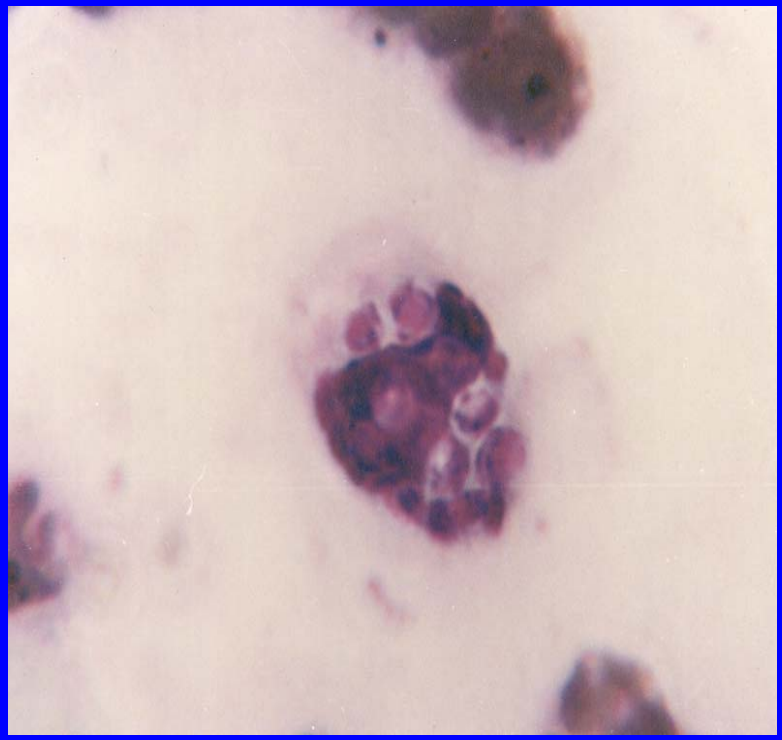
	Mean	SD	Min	Max	Median
Hct	26	8.6	6.4	51	26.4
WBC	6086	6251	330	52700	4990
Lymphocyte	1190	2835	50	24000	468
Platelet	107602	80437	11000	491000	88.500
CD4	10	11	1	50	7

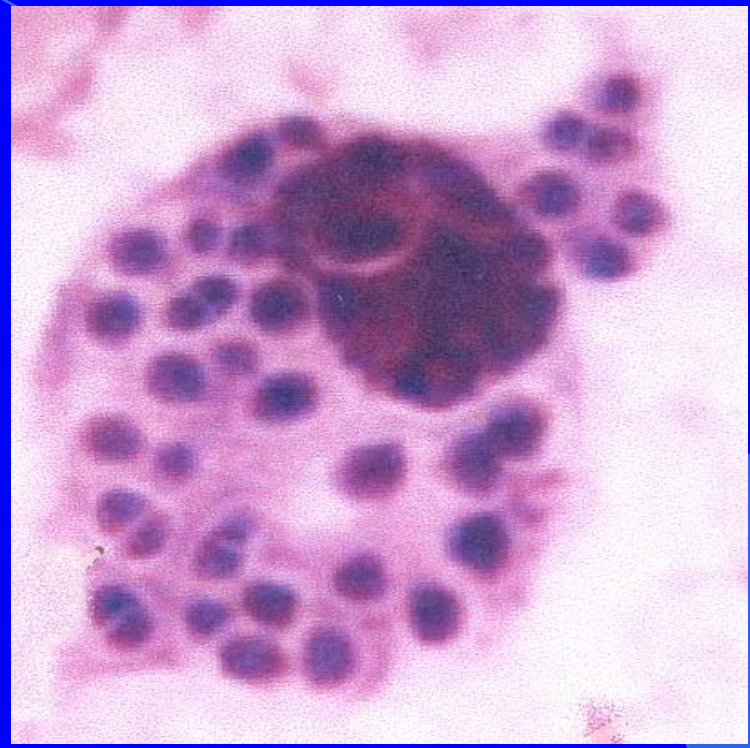
2. Chest X-ray

- 57 cases (48.3%) had lung lesions:
    * in alveolars: 40 cases
    * in interstitial- alveolar spaces: 11 cases
    * in interstitial spaces: 6 cases
- 12 cases had lung lesions on chest X-ray without respiratory symptoms (functional and physical).
- However, the aetiology of these lung lesions was unknown because at it had not yet available facility for isolation P.M and other agents from sputum (except *Mycobacterium*). Unfortunately, we could not exclude P.M pneumonia in some those cases.

3. Microscopic examination, culture and identification

- Could be observed on microscopic examination of touch smears of a skin biopsy specimen, blood smear, lymph node biopsy specimen or bone marrow aspirate.
- Could be quickly suggested diagnosis by observed yeast-like cells inside of macrophage on microscopic examination.
- Culture of the specimen obtained from skin biopsy was the highest sensitivity (94.7%), followed by blood culture (91.5%) and it could take 5 - 6 days before the results of fungal culture were available.





Yeast-like cells inside of macrophage on microscopic examination

37°C
BHI blood

25°C
Sabouraud

Segretain, IP, 1959: *Penicillium marneffei*

Photo from Prof K Y Yuen

***P.marneffei* : thermal dimorphism from cultures**

ANTIFUNGAL TREATMENT

1. Antifungal treatment

- 83 cases (70.3%) were recommended antifungal therapy.
- The rest was not treated (due to early died, discharged hospital by themselves or transferred to an other hospital before the diagnosis of P.M infection was reported).
- Most of antifungal drugs are usually chosen in the first 02 weeks :
    * Itraconazole, 400mg/day (57 case)
    * Amphotericin B, 0.6 - 0.7 mg/kg/day, (9 case)

      or Amphotericin B plus Itraconazole (2 cases)

The next 10 weeks: Itraconazole 400mg/day as monotherapy.

2. Results of treatment

- The mortality of initial treatment with Amphotericin B or Amphotericin B plus Itraconazole was: 9% (1/11 cases).

- The mortality of initial treatment with Itraconazole was: 24.56% (14/57 cases).

- Generally, the mortality of antifungal treatment was: 23%

2. Results of treatment

- Without antifungal treatment:

  * The mortality was: 71.4%

  * Unknown outcome was: 28.6% (discharged hospital by themselves or transferred to an other hospital before the diagnosis of P.M infection was reported)

- 12 recurrent cases within 6 months later due to not adherence to prophylaxis therapy.

DISCUSSIONS

1. Epidemiological features

- The features of population-society in this sample are similar to the ones in HIV patients in Viet nam.
- Almost patients were urban population suggested that P.M transmitted through respiratory tract.
- Number of patients and ratio of P.M infection in HIV patients tend to increase every year; case – fatality rate is high.

⇒ P.M infection in HIV patients is an important opportunistic fungal disease and more and more increases.

- 96.6% among Penicilliosis marneffei are associated with AIDS.

⇒ P.M.infection in HIV patients is the index of an acquired immunodeficiency syndrome (AIDS).

2. Clinical, laboratory features

- The time of illness before going to hospital suggests that P.M. infection was a subacute disease.

- The variety of clinic and laboratory shows that a lot of organs are injured but unspecified. So it could be the manifestations of accompanied diseases or AIDS.

- Because specific skin lesions (papules with central necrotic, umbilication) to diagnosis were seen in 59.3% cases, the diagnosis would be difficult.

2. Clinical, laboratory features

- Tachypnea is a bad prognostic factor.

- The severe status of immune-deficiency with Low CD4+ T cell count is an opportunity for P.M causing infection.

⇒ ARV therapy is active and effective prevention for opportunistic infectious diseases including P.M infection in HIV patients.

- P.M could be isolated from many kinds of specimens of patients

⇒ P.M caused disseminated infection.

3. Diagnosis and Treatment

- It is necessary to diagnosis quickly of P.M infection in AIDS patients and to treat with antifungal agents.

- Yeast-like cells inside of macrophage could be observed on microscopic examination and suggested diagnosis. Confirmed diagnosis is based on fungal culture.

- Amphotericin B or Itraconazole is the first of choice.

- Secondary therapy and primary prophylaxis are necessary.

CONCLUSIONS AND RECOMMENDATION

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1. Conclusions

- *P.marneffei* infection in HIV patients is an important opportunistic fungal disease. It more and more increases in Viet Nam.

- The respiratory tract is more likely a portal of entry of *P. marneffei* and *P. marneffei* infection has been considered an acquired immunodeficiency syndrome (AIDS)-defining disease.

- *P. marneffei* usually causes an subacute, invasive disseminated disease with variable clinical and laboratory manifestation that can be mistaken by accompanied diseases or AIDS.

1. Conclusions

- A more specific finding is skin lesions and may be suggest diagnosis of P.M infection. It is more difficult to diagnose P.M infection if there were not skin lesions.

- Tachypnea is risk factor because there was statistical relation between tachypnea and death.

- Confirmed diagnosis is based on the growth of P.M characterized by its thermal dimorphism from cultures (blood cultures, skin lesion cultures usually have high sensitivity).

1. Conclusions

- The current recommended treatment regimen is antifungal therapy.

- The suggested schedule therapy in our study is according to the guideline of The Ministry of Health (March 2005): Amphotericin B or Itraconazole.

- Secondary therapy and primary prophylaxis are necessary.

2. Recommendation

- It is necessary to have further studies on *Penicillium marneffei* (with greater power design, bigger sample size, multi centre studies) to gain more information about epidemiological, clinical manifestation, laboratory and treatment features of P.M. infection in HIV patients.

- Microscopic examination of blood smears and fungal blood cultures should be done routinely on AIDS patients with prolong fever, anemia, splenomegaly, hepatomegaly or lymphadenopathy

2. Recommendation

- Fungal infection should be suspected on AIDS patients with chronic pneumonia. It is necessary to have a bronchoalveolar lavage specimen by fiberoptic endoscopy for aetiology investigating.

- It is necessary to have training courses for doctors, technicians about clinical manifestations, laboratory procedures for detection and identification of opportunistic fungal infections in HIV/AIDS patients.

- It is necessary to develop serological diagnostic tests for P.M. infection.

2. Recommendation

- Provide enough ARV agents because ARV therapy is actively and effectively useful in prevention for opportunistic infectious diseases including P.M infection in HIV patients

- It is necessary to have infection control measures in health care settings for HIV/AIDS patients to prevent the transmission of respiratory infection agents from patient to patient, to relatives and to health care workers.

2. Recommendation

- Studying on antifungal agents for prevention of opportunistic fungal infections in HIV/AIDS patients in Viet Nam (*C.neoformans, P.marneffei).*

- Screening for *P.marneffei* in patients with severe immunodeficiency status (not due to HIV).