J. Mycopathol. Res. 53(2) : 185-190, 2015; (ISSN 0971-3719)

REVIEW

Penicillium marneffei Segretain : An emerging mysterious fungal pathogen of humans

MAHENDRA PAL[1], PRATIBHA DAVE[2], ANIL KUMAR MANNA[3] AND NIRMALENDU SAMAJAPATI[3]

[1]Department of Microbiology, Immunology and Public Health, College of Veterinary Medicine and Agriculture, Addis Ababa University,P.B.No.34, Debre Zeit, Ethiopia

[2] Welfare Hospital and Research Center, Bharauch 392001,Gujarat

[3]Department of Botany, University of Calcutta, Kolkata 700019

Received : 24.12.2014 Accepted : 24.04.2015 Published : 27.10.2015

In recent years, fungi have emerged as a major public health problem both in developed and developing nations of the world. They have the potential to produce superficial to life threatening invasive infection. Among such fungi, *Penicillium marneffei* Segretain, the principal cause of penicillosis, is a dimorphic fungus, which is endemic in Southeast Asia, and has emerged as one of most common infections in HIV infected patients. In India, *P.marneffei* is isolated from HIV infected patients, and also from rodents.The infection due to *P.marneffei* is rarely recorded in domestic animals. The source of infection is exogenous. Though bamboo rats are considered as reservoir of *P.marneffei*, there is hardly any conclusive evidence of direct transmission of infection from rat to man. The epidemiology of disease is mysterious, as it is not clear how rat and human acquire this thermo-regulated pathogenic fungus. The natural history, and transmission dynamics of the pathogen are not clearly elucidated. The mycological, histopahological, immunological, and molecular techniques are employed to confirm the diagnosis of *P.marneffei* infection.The disease should be differentiated from blastomycosis, cryptococcosis, histoplasmosis, and tuberculosis. A number of drugs such as amphotericin B, itraconazole, and voriconazole are tried in the management of disease. It is emphasized that the role of *P.marneffei* should be further investigated in various clinical disorders of humans and animals. Additional studies on the epidemiology particularly the source, reservoir and mode of transmission will be highly rewarding. The cytological examination of Wright stained smears from clinical materials may be helpful to make a presumptive diagnosis of *P.marneffei* infection in the Primary Health Centres where the laboratory facilities for mycological culture are non-existent.

Key words: Dimorphic fungus, HIV, human, *Penicillium marneffei*, South East Asia

INTRODUCTION

In recent years, several infectious diseases have emerged causing a serious impact on public health and economy of many countries of the world (Pal, 2013). These diseases cause high morbidity and mortality, and are recorded from developed as well as developing nations (Pal,2014; Pal *et al.*,2014a).Among such diseases, penicilliosis chiefly caused by *Penicillium marneffei* Segretain has emerged as one of the most common infections in HIV infected patients residing in endemic areas of Southeast Asia (Drouhet, 1993; Samson *et al.*, 1995). The risk of infection is not restricted to those living in endemic areas, as HIV infected

*Email : palmahendra2@gmail.com

individuals who travel to Southeast Asia also became infected by *P. marneffei* (Julander and Petrini, 1997).The infections by other members of the genus *Penicillium* are rarely recorded in humans and animals (De Hoog *et al.*, 2000; Pal,2007).

Most cases of penicilliosis are disseminated infections, clinically resembling to other diseases such as histoplasmosis, cryptococcosis, blastomycosis, and tuberculosis (Imwidthaya, 1994). The common clinical features include fever, weight loss, anaemia, generalized lymphadenopathy, hepatosplenomegaly, pulmonary involvement, mucosal ulcers, and skin lesions (Supparatpinyo *et al.*, 1992; Tsui *et al.*, 1992; Vanittanakom *et al.*,2006). Infected tissues can show a mixture of reactions, including necrosis, suppuration, and granuloma formation (Deng and Connor, 1985; Bhoopat *et al.*, 1994). *Penicillium marneffei* infections in domestic animals are very occasionally encountered (Pal,2007).

Definitive diagnosis is usually made by culture of the fungus from blood, skin biopsy, bone marrow, or lymph nodes, or by histopathological demonstration of the characteristic morphologic findings of this fungus in biopsy material (Supparatpinyo *et al.*, 1994; Viviani and Tortorano, 1998).The detailed microscopic morphology of fungal isolates can be studied in Narayan stain developed by Pal (2004). Apart from mycological cultures, a number of serological tests have been described in recent years for the diagnosis of penicilliosis, and other endemic mycoses. In order to provide a more rapid and accurate diagnosis, a TaqMan real-time PCR has been used to detect and identify *P. marneffei* DNA coding for 5.8S rRNA in purified yeast DNA and clinical samples (Sakorn *et al.*, 2009).

The infection responds to antifungal treatment, but untreated cases, especially in immunocompromised patients, are usually fatal (Supparatpinyo *et al.*,1994). Hence, identification of possible sources of the infection is clinically important. Currently, the therapy of choice for invasive infection appears to be intravenous amphotericin B followed by oral itraconazole. The present paper highlights the growing significance of *P.marneffei* as an emerging systemic pathogen especially in AIDS/HIV infected patients.

ETIOLOGY

Currently, the genus *Penicillim* contains about 200 species (Pitt,1988).They are widely distributed in nature and are ubiquitous as sabrobe on a wide variety of materials and many species thrive in habitats with low water activity (Pitt,1988; De Hoog *et al.*, 2000).They are found in the soils, on decaying vegetables, on wood etc (Pal,2007). Most of the species of *Penicillium* are unable to grow at 37°C. *Penicillium marneffei*, being unique among the members of *Penicillium* by its thermoregulated dimorphism, is the only species known to be a primary pathogen of humans and animals (Vanittanakom *et al.*, 2006; Chaiwun *et al.*, 2011). Occasionally, other species of *Penicillium* such as *P. brevicompactum, P. chrysogenum, P. citrinum, P. commune, P.cyclopium, P. decumbens, P.griseofulvum, P.lilacium ,P.oxalicum*, and *P.verrucosum* are isolated from the clinical materials of humans and animals (De Hoog *et al.*,2000; Pal,2007).

HOST RANGE

Penicillium species have been isolated from humans, cats, dogs, horses, buffaloes, parrots, parakeets, and rodents (Harvey,1984; Pal, 2007).However, *P. marneffei* has been identified in humans, bamboo rats, and dogs (Chariyalertsak *et al.*,1996a; Chaiwun *et al.*,2011).Most infections due to *P.marneffei* are recorded in humans as compared to other hosts (Doung, 1996; Pal, 2007).

TRANSMISSION

Hitherto, exact mode of transmission of *P.marneffei* to humans remain unclear.Animal reservoirs in Northern Thailand, the bamboo rat (*Rhizomyces sinensis*), the hoary bamboo rat (*R. pruinosus*), the large bamboo rat (*R. sumatrensis*), and the small bay bamboo rat (*Cannomys badius*) are identified as animal reservoir of *P.marneffei* (Li *et al.*, 1989; Ajello *et al.*,1995; Chariyalertsak *et al.*, 1996 b). Infected rats appear healthy (Deng *et al.*, 1986) and therefore, a carrier may not appear ill. While bamboo rats are a natural reservoir, these animals are generally not in contact with humans, and there is no firm evidence of direct transmission from rat to man (Deng *et al.*, 1986). Although unproven, humans are assumed to become infected by inhaling aerosolized infectious conidia originating from thus far unidentified environmental sources (Vanittanakom *et al.*, 2006). However, bamboo rats and HIV-positive patients have been found to share genetically similar strains of *P. marneffei*, suggesting rat-to-human transmission might be possible or co-infection from a common but still

unidentified source (Gugnani *et al.*, 2004). One scenario is that death of the bamboo rat results in the production of large quantities of spores, thereby, serving as an amplifying host for human *P. marneffei* infections (Gugnani *et al.,* 2004). Alternatively, transmission could be indirect, with some other animal serving as an intermediate between the bamboo rats and humans. The accidental inoculation of pathogen caused skin lesions in a scientist in the laboratory (Segretain, 1959). This indicates that the skin may serve as a portal of entry for *P.marneffei* (Pal, 2007). However, further studies are warranted to elucidate the transmission dynamics of *P.marneffei* infection in humans.

EPIDEMIOLOGY

Penicillosis caused by *P.marneffei* is endemic in Thailand, Hongkong, India, Vietnam, China, and Taiwan (Vanittanakam *et al.*,2006; Pal,2007). The epidemiology of penicilliosis due to *P.marneffei* is still mysterious, though the fungus was isolated for the first time in 1956 from a captive bamboo rat (Pal,2007). The bamboo rats are the only animals known to be naturally infected by this fungus, though this animal is not considered to be a reservoir host of the fungus, nor does it play a role in causing human infections. It is believed that *P. marneffei* is a natural part of the flora inhabiting vegetation, and soil. The fungus is present in internal organs of rats with an infection rate varying with the species. How rats are colonized or infected, is still not clearly elucidated. Human *P.marneffei* was first described in 1959 as a laboratory acquired infection when Segretain, a French Researcher, accidentally pricked his finger with a needle with *P.marneffei* that was used to inoculate the laboratory animal (Segretain,1959).The first naturally occurring human case of *P. marneffei* was reported by Di Salvo and collaborators in 1973. The patient was an American with Hodgkin disease, and was living in Southeast Asia. How the humans get the infection, is still remained an unresolved mystery. However, a case control study could not establish exposure to bamboo rats as a risk factor for acquiring penicilliosis (Chariyalertsak *et al.*, 1997).The exposure to the soil, particularly during the rainy season has been suggested to be critical risk factor (Chariyalertsak *et al.*,1997; Vanittanakom *et al.*,2006). The portal of entry of infection in humans may probably be the lung. Evidence exists for seasonality in penicilliosis infections ,as increased number of cases are recorded during the rainy months (Chariyalertsak *et al.*, 1996 b).

The disease is described in immunocompetent hosts, and patients with other immunocompromising conditions (Wong *et al.*, 2001). However, the majority of the cases are observed in patients co-infected with HIV. In Southeast Asia, penicilliosis is considered to be an AIDS-defining illness. In Thailand, penicilliosis is the third commonest opportunistic infection in AIDS patients following tuberculosis, and cryptococcal meningitis (Supparatpinyo *et al.*, 1994). In Hong Kong, 7.7% of AIDS patients developed penicilliosis during the course of the infection. Imported cases of *Penicillium marneffei* are reported from Australia, Canada, Japan, Europe and USA in immunocompromised patients, mainly with AIDS having a past history of travelling in South East Asia (Drouhet, 1993).

CLINICAL SPECTRUM

The common clinical manifestations in humans include fever, anaemia, weight loss, weakness, and generalized skin papules with central umbilication resembling molluscum contagiosum (Supparatpinyo *et al.,* 1994; Ranjana *et al.*,2002;). Cutaneous penicilliosis lesions commonly appear on the face, ears, extremities, and occasionally the genitalia. Involvement of other organs, such as the central nervous system, bone marrow, lymph node, lung, liver, and intestine has been reported. Patients with hepatic penicilliosis have fever, abdominal pain, hepatomegaly, and a marked increase in serum alkaline phosphatase levels (Kantipong *et al.*, 1998).

DIAGNOSIS

As clinical signs are not pathognomonic, the help of laboratory is imperative to establish an unequivocal diagnosis of disease.Definitive diagnosis is usually made by culture of the fungus from the skin biopsy, bone marrow, or lymph nodes, or by histopathological demonstration of the characteristic morphologic findings of this fungus in biopsy material by Griedly fungus (GF) or Gomori methanamine silver (GMS) techniques (Pal,2007). *P. marneffei* exibits dimorphic growth in culture. At 25°C, the fungus grows as a mould, demonstrating characteristic colonies that include a flat green surface ,and underlying deep red colour. At 37°C, the fungus grows as white colonies of yeast (Vanittanakom *et al.,* 2006).

Suspicious lesions should always be biopsied for microbiological and histopathological investigations. The yeast cells in biopsies have a distinctive morphology in tissue sections. They may resemble the tissue phase of another dimorphic fungus *Histoplasma capsulatum*. However, *P. marneffei* yeasts divide by fission instead of budding as seen in *H. capsulatum*.The result is that a transverse septum is seen in between two *P. marneffei* cells. An early presumptive diagnosis can be made several days before the results of fungal cultures are available by microscopic examination of Wright-stained samples of skin scrapings, bone marrow aspirate, or lymph node biopsy specimens. Many intracellular and extracellular basophilic, spherical, oval, and elliptical yeast-like organisms can be seen, some with clear central septation, which is a characteristic feature of *P. marneffei* (Supparatpinyo *et al.*, 1994).In some patients, the fungus can be identified by microscopic examination of a Wright's stained peripheral blood smear (Supparatpinyo and Sirisanthana,1994). The direct demonstration of oval, elongated, yeast-like cells under light microscope of Wright stain smear from cutaneous lesions of a labourer from Manipur State was very useful to make a presumptive diagnosis of *P.marneffei infection*.This helped us to start antifungal therapy with itraconazole (P.Dave, Personal Communication). The demonstration of thermal dimorphism of the fungus cultures, the presence of a diffusible red pigment in the mould culture, and the typical microscopic morphology of the mould phase all help to confirm the identity of this pathogenic fungus (Viviani and Tortorano, 1998).

A number of serological tests have been described for the diagnosis of penicilliosis, and other mycotic diseases (Yuen *et al.*, 1994; Pal, 2007; Pal *et al.*, 2014b). However, the specificities of most assays that use polyclonal antibodies and antigens are limited by cross-reactions with other human pathogens. Desakorn and co-investigators (1999) used polyclonal hyperimmune sera raised from rabbits immunized with whole arthroconidia of *P. marneffei* in an ELISA for the detection of *P. marneffei* antigen in urine. A significant proportion of patients with infections other than penicilliosis (e.g., other systemic mycoses and melioidosis) also had positive results, at a lower titer. Wheat and others (1997) also noticed cross-reactivity between penicilliosis and histoplasmosis in urinary antigen detection by a rabbit immunoglobulin G-based assay for *Histoplasma capsulatum* var. *capsulatum*. Similarly, the galactomannan of *Aspergillus fumigatus* cross-reacts with *P. marneffei* in a latex agglutination test and immunohistochemical staining (Van Cutsem *et al.*,1990). These antigen or antibody based tests might be of utility for the diagnosis of mycoses in areas of low endemicity (e.g., for the diagnosis of suspected infections in returning travellers), whereas for residents of areas of endemicity, background titers could be an important consideration in interpreting the test results. ELISA with Mp1p represents another approach to the serodiagnosis of systemic mycoses: the use of mono-specific antigens and antibodies. An indirect immunofluorescent assay for antibody detection in the patients with penicilliosis has been reported (Yuen *et al.,* 1994). Subsequently, a novel gene,*MP*, was cloned, which was found to encode an immunogenic mannoprotein, Mp1p (Cao *et al.*, 1998).

Diagnosis of penicilliosis may be difficult when few yeast cells are present, while a gold standard diagnosis technique requires long-term culture. In order to provide a more rapid and accurate diagnosis, a TaqMan real-time PCR has been used to detect and identify *P. marneffei* DNA coding for 5.8S rRNA in purified yeast DNA and clinical samples (Sakorn *et al.*, 2009).

TREATMENT

The clinical response to antifungal therapy of opportunistic fungal infections is associated with factors related to the host immune status and/or underlying disease rather than with antifungal susceptibility of the mould, and pharmacokinetics of the therapeutic agent (Bossche *et al.,* 1994). Lack of an appropriate cell mediated immune response can both predispose to and result in perpetuation of the infection. Furthermore, oral absorption of ketoconazle varies among different individuals and there is also concern, based on experience with mice, the subsequent use of amphotericin B may be antagonized (Bennett, 2000).

The current recommended treatment regimen is to give amphotericin B, 0.6 mg/kg/day for 2 weeks, followed by itraconazole, 400 mg/day orally in two divided doses for the next 10 weeks (Sirisanthana *et al*,. 1998). After initial treatment, the patient should be given itraconazole, 200 mg/ day, as secondary prophylaxis for life) (Supparatpinyo *et al*,. 1998).

Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for 8 weeks (Supparatpinyo and Schlamm, 2007), followed by 200 mg/day for prevention of recurrence. Itraconazole capsule is better absorbed when taken with or immediately after a meal.

The alternative drug for primary treatment in the hospital is IV voriconazole, 6 mg/kg every 12 hours on day 1 and then 4 mg/kg every 12 hours for at least 3 days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day 1, and then 200 mg twice daily for 12 weeks (Supparatpinyo and Schlamm, 2007).The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied so far.Very little information is available on the treatment of penicillosis in domestic animals (Pal,2007).

PREVENTION AND CONTROL

As the source of infection and mode of transmission are not clearly understood,the appropriate effective measures for the control of *P.marneffei* infection are not well indicated. However,the patients with advanced HIVdisease are advised to avoid visiting *P.marneffei* endemic regions, and particularly the rural areas. Any injury on the skin of immunocompromised patients needs immediate medical care. Itraconazole (200 mg daily orally) or fluconazole (400 mg once weekly orally) can be used as an effective prophylaxis in HIV infected patients living in endemic areas to reduce the occurrence of *P.marneffei* infection (Supparatpinyo *et al.*, 1998; Chariyalertsak *et al.*, 2002; Chaiwarith *et al.*,2011).

CONCLUSION

Penicillosis caused by *P.marneffei* , is an opportunistic mycotic disease in Southeast Asian countries including India. In Thailand, it is the third most common infection in AIDS patients following tuberculosis and cryptococcosis. *P.marneffei* can cause cutaneous and systemic infections in humans.The skin lesions are commonly observed on the face, ears, and extremities. Cultural isolation of the fungus from clinical materials is pertinent to establish an unequivocal diagnosis of disease. Microscopic examination of smears of fine needle aspirate from the cutaneous lesions, and lymph nodes are helpful to demonstrate the fungus. Hitherto, the exact mode of transmission of *P.marneffei* infection in humans is not clearly elucidated .Primary treatment with amphotericin B. and prophylaxis with itraconazole is said to be effective. The patients who do not receive the appropriate antifungal treatment have a poor prognosis. Hence, early diagnosis, and adequate antifungal therapy is imperative to avoid the complications. The etiologic role of *P.marneffei* should be studied in domestic, pet, farm, and wild animals.

ACKNOWLEDGEMENT

We are very grateful to Prof.Dr.R.K.Narayan for critically going through our manuscript. Thanks are also due to Tewodros for proving some references related with the subject,and Anubha for excellent computer work.

REFERENCES

Ajello, L., Padhye, A., Sukroongreung, S., Nilakul, C. and Tantimavanic, S. 1995. Occurrence of *Penicillium marneffei* infections among wild bamboo rats in Thailand. *Mycopathologia*, **131**:1–8.

Bennett, J. L. 2000. Antifungal agents. In: Mandell GL, Douglas L, Bennett JE (eds), *Principles and Practise of Infectious Disease*. 4th edn. New York: Churchill Livingstone, Pp. 448–59.

Bhoopat, L., Thamprasert, K., Chaiwun, B., Attasiri, C., Vithayasai, P. and Chaimongkol, B. 1994. Histopathologic spectrum of AIDS associated lesions in Maharaj Nakorn Chiang Mai Hospital. *Asian Pacific Journal of Allergy and Immunology* **12**:95–104.

Bossche, H. V., Warnock, D. and Dupont, B. 1994. Mechanisms and clinical impact of antifungal drug resistance. *Journal of Medical Veterinary Mycology* **32** (Suppl.1): 189–202.

Cao, L., Chan, C. M., Lee, C., Wong, S. S. Y. And Yuen, K. Y. 1998. *MP1* encodes an abundant and highly antigenic cell wall mannoprotein in the pathogenic fungus *Penicillium marneffei*. *Infection and Immunity* **66**:966–973.

Chaiwarith, R., Fakthongyoo, A., Praparattanapan, J., Boonmee, D., Sirisanthana, T. and Supparatpinyo, K. 2011. Itraconazole vs fluconazole as a primary prophylaxis for fungal infections in HIV-infected patients in Thailand. *Current HIV Research* **9:** 334-338.

Chaiwun, B., Vanittanakom, N., Jiviriyawat, Y. and Thorner, P. 2011. Investigation of dogs as a reservoir of *Penicillium marneffei* in northern Thailand. *International Journal of Infectious Disease* **15:**236-239.

Chariyalertsak, S., Vanittanakom, P., Nelson, K., Sirisanthana, T. and Vanittanakom, N. 1996a. *Rhizomys sumatrensis* and *Cannomys badius*, new natural animal hosts of *Penicillium marneffei*. *Journal of Medical Veterinary Mycology* **34**:105–110

Chariyalertsak, S., Sirisanthana, T., Supparatpinyo, K. and Nelson, K.E. 1996b. Seasonal variation of disseminated *Penicillium marneffei* infections in northern Thailand: a clue to the reservoir? *Journal of Infectious Disease* **173:**1490-1493.

Chariyalertsak, S., Sirisanthana, T., Supparatpinyo, K., Praparatanapan, J. and Nelson, K. E. 1997. Case control study of risk factors for *Penicillium marneffei* infection in Human Immunodeficiency Virus-infected patients in northern Thailand. *Clinical Infectious Disease* **24**:1080-1086.

Chariyalertsak, S., Supparatpinyo, K., Sirisanthana, T. and Nelson,

K.E. 2002. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. *Clinical Infectious Disease* **34**:277-284.

De Hoog, G.S., Guarro, J., Gene, J.L. and Figueras, M.J. 2000. *Atlas of Clinical Fungi.* 2nd Ed. Centraalbureau voor Schimmelcultures,The Netherlands, pp.814–845.

Deng, Z. and Connor, D. 1985. Progressive disseminated penicilliosis caused by *Penicillium marneffei.* Report of eight cases and differentiation of the causative organism from *Histoplasma capsulatum. American Journal of Clinical Pathology* **84**:323–327.

Deng, Z., Yun, M. and Ajello, L. 1986. Human penicilliosis and its relation to the bamboo rat (*Rhizomys pruinosus*), *Journal of Medical Veterinary Mycology* **24**:383–389.

Desakorn, V., Smith, M. D., Walsh, A. L., Simpson, A. J. H., Sahassananda, D., Rajanuwong, A., Wuthiekanun, V., Howe, P., Angus, B. J., Suntharasamai, P. and White, N. J. 1999. Diagnosis of *Penicillium marneffei* infection by quantitation of urinary antigen by using an enzyme immunoassay. *Journal of Clinical Microbiology* **37**:117–121.

Di Salvo, A.F., Fickling, A.M. and Ajello, L.1973. Infection caused by Penicillium marneffei, description of first natural infection in man.*American Journal of Clinical Pathology* **59**: 259-263.

Drouhet, E. 1993. Penicillosis due to *Penicillium marneffei*: a new emerging systemic mycosis in AIDS patients travelling or living in Southeast Asia. *Journal of Mycology Medical* **4**: 195–224.

Duong, T. A. 1996. Infection due to *Penicillium marneffei,* an emerging pathogen: review of 155 reported cases. *Clinical Infectious Disease* **23**:125-130.

Gugnani, H., Fisher, M.C. and Paliwal-Johsi, A. 2004. Role of *Cannoms badius* as a naural animal host of *Penicillium marneffei* in India. *Journal of Clinical Microbiology* **42**:5070.

Harvey, C. 1984. Nasal aspergillosis and penicilliosis in dogs: results of treatment with thiabendazole. *Journal of American Veterinary Medical Association* **184**:48–50.

Imwidthaya, P. 1994. Systemic fungal infections in Thailand. *Journal of Medical Veterinary Mycologyy* **32**:395–399.

Julander, I. and Petrini, B. 1997. *Penicillium marneffei* infection in a Swedish HIV-infected immunodeficient narcotic addict. *Scandinavian Journal of Infectious Diseases* **29**:320–322.

Kantipong, P., Panich, V., Pongsurachet, V. and Watt, G. 1998. Hepatic penicilliosis in patients without skin lesions. *Clinical Infectious Disease* **26:**1215-1217.

Li, J., Pan, L. and Wu, S. 1989. Mycologic investigation on *Rhizomys pruinous senex* in Guangxi as natural carrier with *Penicillium marneffei. Chinese Medical Journal* **102**: 477–485.

Pal, M. 2004. Efficay of Narayan stain for morphological studies of moulds,yeasts and algae. *Revista Iberoamericana de Micologia* **21:** 219.

Pal, M. 2007. *Veterinary and Medical Mycology.*1st Ed. Indian Council of Agricultural Research, New Delhi, India.

Pal, M.2013. Public health concern due to emerging and re-emerging zoonoses. *International Journal of Livestock Research* **3**: 56-62.

Pal, M.2014. *Cryptococcus gattii*: An emerging global mycotic pathogen of humans and animals. *Journal of Mycopathological Research* **52**:1-7.

Pal, M., Dave, P. and Mahendra, R.2014a.Ebola haemorrahagic fever: An emerging highly contagious and fatal viral zoonosis. *International Journal of Multidisciplinary Research* **2:** 1-2.

Pal, M., Dave, P. and Manna,A.K.2014b. Emerging role of *Aspergillus flavus* in human and animal disorders. *Journal of Mycopathological Research* **52**: 211-216.

Pitt, J.I. 1988. *A Laboratory Guide to Common Penicillium species.*North Ryde, Australia.

Ranjana, K.H., Priyokumar, K., Singh,T.J.,Gupta, C.H.C., Sharmila, L., Singh, P.N. and Chakrabtari, A. 2002. Disseminated *Peicillium marneffei* infection among HIV infected patients in Manipur state, India. *Journal of Infection* **45:**268-271.

Sakorn, P., Jutarat, P., Chantana, K., Sudjai, P., Parichat, P., Tanawan, S., Pranee, L. and Khunchai, S.2009. Development of TaqMan real-time polymerase chain reaction for the detection and identification of *Penicillium marneffei. Mycoses* **52**:487–492

Samson, R.A., Hoekstra, E.S., Frisvad, J.C. and Filtenborg, O. 1995. *Introduction to Food-borne Fungi.* 4th Ed. Centraalbureau voor Schimmelcultures, The Netherlands. Pp.170–171.

Segretain, G.1959. *Penicillium marneffei* n.sp.,agent d'une mycose du systeme reticuloendothelial. *Mycopathologia Mycologia et Applicata* **11**:327-353.

Sirisanthana, T., Supparatpinyo, K., Perriens, J., and Nelson, K.E. 1998. Amphotericin B and itraconazole for treatment of disseminated *Penicillium marneffei* infection in human immunodeficiency virusinfected patients. *Clinical Infectious Diseases* **26**:1107-1110.

Supparatpinyo, K. and Schlamm, H.T. 2007. Voriconazole as therapy for systemic *Penicillium marneffei* infections in AIDS patients. *American Journal of Tropical Medicine and Hygiene* **77**: 350-353.

Supparatpinyo, K. and Sirisanthana, T. 1994. Disseminated *Penicillium marneffei* infection diagnosed on examination of a peripheral blood smear of a patient with human immunodeficiency virus infection. *Clinical Infectious Diseases* **18:** 246-247.

Supparatpinyo, K., Chiewchanvit, S., Hirunsri, P., Uthammachai, C., Nelson, K. and Sirisanthana, T. 1992. *Penicillium marneffei* infection in patients infected with human immunodeficiency virus. *Clinical Infectious Disease* **14**: 871–874.

Supparatpinyo, K., Khamwan, C., Baosoung, V., Nelson, K.E., and Sirisanthana, T. 1994. Disseminated *Penicillium marneffei* infection in Southeast Asia. *Lancet* **344**:110-113.

Supparatpinyo, K., Perriens, J., Nelson, K.E., and Sirisanthana, T. 1998. A controlled trial of itraconazole to prevent relapse of *Penicillium marneffei* infection in patients infected with the human immunodeficiency virus. *New England Journal of Medicine* **339:**1739-1743.

Tsui, W., Ma, K. and Tsang, D. 1992. Disseminated *Penicillium marneffei* infection in HIV-infected subject. *Histopathology* **20**: 287–293.

Van Cutsem, J., Meulemans, L., van Gerven, F., and Stynen, D. 1990. Detection of circulating galactomannan by Pastorex *Aspergillus* in experimental invasive aspergillosis. *Mycoses* **33**:61–69.

Vanittanakom, N., Cooper, C.R. Jr., Fisher, M.C. and Siristhanthana, T. 2006. *Penicillium marneffei* infection and recent advances in the epidemiology and molecular biology aspects. *Clinical Microbiology Reviews* **19**: 95–110.

Viviani, M. A. and Tortorano, A. M. 1998. *Penicillium marneffei. In:* Ajello L., *and* Hay R. J. *(Eds.) Medical mycology, Topley and Wilson's Microbiology and Microbial Infections,* 9th ed. *Vol.***4**, Arnold, London, United Kingdom. pp.409-419.

Wheat, J., Wheat, H., Connolly, P., Kleiman, M., Supparatpinyo, K., Nelson, K., Bradsher, R.,and Restrepo, A. 1997. Cross reactivity in *Histoplasma capsulatum* variety *capsulatum* antigen assays of urinary samples from patients with endemic mycoses. *Clinical Infectious Dissease* **24**: 1169–1171.

Wong, S.S., Wong, K.H. and Hui, W.T. 2001. Differences in clinical and laboratory diagnostic characteristics of *penicilliosis marneffei* in human immunodeficiency virus (HIV) - and non-HIV-infected patients. *Journal of Clinical Microbiology* **39**: 4535-4540.

Yuen K. Y., Wong, S. S. Y., Tsang, D. N. C. and Chau, P. Y. 1994. Serodiagnosis of *Penicillium marneffei* infection. *Lancet* **344**: 444–445.