Jurnal Biologi Tropis

Original Research Paper

Diagnosis and Treatment of Aspergillosis

Baiq Fanindya Harliza[1*] & Prima Belia Fathana[2]

[1]Program Studi Pendidikan Dokter, Fakultas Kedokteran Universitas Mataram dan Ilmu Kesehatan, Universitas Mataram, Mataram, Nusa Tenggara Barat, Indonesia;

[2]Program Studi Pendidikan Dokter, Fakultas Kedokteran Universitas Mataram dan Ilmu Kesehatan, Universitas Mataram, Mataram, Nusa Tenggara Barat, Indonesia;

Article History

Received : Agustus 28th, 2024

Revised : September 19th, 2024

Accepted : October 03th, 2024

*Corresponding Author:
Baiq Fanindya Harliza,
Program Studi Pendidikan Dokter, Fakultas Kedokteran dan Ilmu Kesehatan, Universitas Mataram, Nusa Tenggara Barat, Indonesia;
Email: fanindyaliza@gmail.com

Abstract: Aspergillosis is an infection caused by the fungus *Aspergillus* , which typically affects individuals with weakened immune systems. One of the more serious forms of this infection is chronic pulmonary aspergillosis, which has a mortality rate of over 50%. This infection is estimated to affect approximately 3 million people worldwide, making it a significant global health issue. Accurate diagnosis and effective management are crucial to reducing morbidity and mortality. This article aims to explore the diagnosis and management of aspergillosis. The method employed is a literature review, with data obtained from various scientific articles through databases such as PubMed, Google Scholar, and ScienceDirect, with a publication limit of the last 10 years. Diagnosis of aspergillosis is based on clinical manifestations and supported by laboratory, radiological, and mycological examinations. Management of aspergillosis includes the administration of oral corticosteroids, antifungal drugs, surgery, and immunomodulatory therapy. Diagnosis is established based on clinical symptoms and relevant supporting examinations, while treatment is adjusted according to the severity of the infection and the patient's overall health condition. The conclusion of this article emphasizes the importance of early diagnosis and appropriate management in reducing the mortality rate associated with aspergillosis.

Keywords: Aspergillosis, diagnosis of aspergillosis, treatment of aspergillosis.

Introduction

Pulmonary mycosis is an infection, colonization, or hypersensitivity reaction of fungi that causes disorders in the lungs. This disease is increasingly common due to increasing risk factors such as widespread use of antimicrobials, increasing cases of immunodeficiency, and increasing patients with lung disease. One of the pulmonary mycoses that most frequently found is aspergillosis (Guanabara *et al.*, 2021). Aspergillus is a widely distributed fungus that can spread indoors and outdoors. This fungus can cause pulmonary disease, namely aspergillosis, which is caused mainly by *Aspergillus fumigatum* (Tong *et al* ., 2021) . Aspergillosis can be transmitted through inhaled conidia. Aspergillosis is a dangerous disease with *a case fatality rate of* 30.22% (Sun *et al.*, 2017). In another study, patients with chronic pulmonary aspergillosis had a high *mortality rate of more than 50% (Tong et al* ., 2021).

According to a study conducted in India in 2002 to 2003 with sputum culture of patients who were positive for chronic pulmonary tuberculosis and had received treatment, it was found that out of 500 patients, 200 patients suffered from fungal infections (46%) (Hayes and Novak-Frazer, 2016). The most common types of fungi are *Aspergillus fumigatus, Aspergillus niger, Histoplasma capsulatum, and Cryptococcus neoforman 6* . The incidence of aspergillosis in the world was reported at 13,456 cases in the period 2006–2015, an increase of 38.2% from the previous period (Paulussen *et al.* , 2017).

Risk factors for aspergillosis infection include patients with immune disorders, patients receiving immunosuppressive therapy, cancer patients undergoing chemotherapy or radiotherapy, long-term use of corticosteroids, DM and patients undergoing long ICU care, patients with chronic diseases or *destroyed lung* , in this condition there is damage to the local bronchopulmonary defense mechanism (Soedarsono and Widoretno, 2019). Aspergillosis infection is estimated to affect 3 million people worldwide, making it a significant health problem worldwide. With significant morbidity and mortality rates and prolonged treatment strategies, aspergillosis infection is described as a challenging disease for patients and healthcare professionals (Hayes and Novak-Frazer, 2016).

In 2019, aspergillosis treatment focused on the use of antifungals, which were selected based on the type of aspergillosis suffered by the patient (Bazaz et al., 2019). However, in 2022 and 2023, triazoles began to be used as the first-line choice in antifungal therapy for aspergillosis. The use of immunosuppressants is also permitted, but must be done with caution and under close supervision (Lamoth et al., 2022; Stemler et al., 2023). This article aims to review the diagnostic process and effective treatment steps in treating this disease. Accurate diagnosis plays an important role in determining the success of therapy. Effective treatment can significantly reduce the risk of complications and mortality in patients infected with aspergillosis. The expected benefits of this article are to increase knowledge and assist readers in diagnosing and treating aspergillosis in Indonesia.

Materials and Methods

The method used is iterature review, which processes information and data from various related articles to obtain conclusions. The articles used are related to the diagnosis and management of aspergillosis obtained through searches in databases such as *PubMed, Google Scholar, and Sciencedirect.* The publication year limit used in this article is at least 10 years.

Results and Discussion

Definition

Fungi are one of the microorganisms that are widely used in everyday life. However, not all types of fungi provide positive benefits in human life. There are several types of fungi that are dangerous because they can cause disease in humans. *Aspergillus* is a type of fungus that belongs to the *Ascomycetes class* and is in the form of long, branched filaments (Hasanah, 2017). This fungus is a saprophytic conidial fungus that is widely found in soil, construction dust and hospitals and is cosmopolitan because its spores are easily spread by wind and easily grow on organic materials and agricultural products (Kanj *et al*, 2018). *Aspergillus* requires warm temperatures, humidity and organic material to be able to reproduce (Hasanah, 2017). Tropical countries like Indonesia have natural conditions that are suitable for the growth of *Aspergillus* which is a fungus that can live in media with high acidity and sugar levels (Praja and Yudhana, 2017).

Aspergillus is one of the fungi that is often used in everyday life, especially in the fields of biotechnology, industry and education (Hasanah, 2017). However, in addition to providing benefits, *Aspergillus* can also cause disease in humans called Aspergillosis. Aspergillosis is often also called *Brooder Pneumonia* , *Mycotic Pneumonia* or *Pneumomycosis* (Hasanah, 2017). Aspergillosis can occur due to inhalation of *Aspergillus spores* by humans. However, in order to cause disease, individuals who inhale the spores usually have special body conditions such as immune system disorders or lung disease (Guanabara *et al.* , 2021; Kanj, Abdallah and Soubani, 2018; Arastehfar *et al.* , 2021). The types of *Aspergillus* that most often cause disease in humans are *Aspergillus fumigatus* , *Aspergillus flavus* , *Aspergillus terreus* and *Aspergillus niger* (Arastehfar *et al.*, 2021)

The most common Aspergillosis is *Pulmonary Aspergillosis* , a type of opportunistic infection and usually occurs due to *Aspergillus fumigatus infection* (Hasanah, 2017). *Pulmonary Aspergillosis* is one of the most common types of pulmonary mycosis or pulmonary fungal infection (Guanabara *et al.* , 2021). There are three main types of *Pulmonary Aspergillosis* , namely *Allergic Bronchopulmonary*

Aspergillosis (ABPA) which occurs due to a hypersensitivity reaction to the *Aspergillus antigen* and usually occurs in patients with moderate to severe asthma or *cystic fibrosis* , *Chronic Pulmonary Aspergillosis* (CPA) which is a problem in the form of infection with a presentation of local infection and usually occurs in patients with chronic lung disease and *Invasive Pulmonary Aspergillosis* (IPA) which occurs in patients with neutropenia or non-neutropenia or immunodeficiency (Kanj, Abdallah and Soubani, 2018).

Etiology

Aspergillosis is caused by infection with fungi of the genus *Aspergillus*. There are around 24 species *of Aspergillus* that have the ability to become pathogens, but in Indonesia, *Aspergillus fumigatus is found* to be the most common cause of aspergillosis, followed by *Aspergillus flavus, Aspergillus glaucus, Aspergillus niger,* and *Aspergillus versicolor* (CDC, 2019; Praja and Yudhana, 2017).

Figure 1. *Aspergillus fumigatus* as the most common cause of aspergillosis (CDC, 2019)

Aspergillus fungi reproduce asexually by spores (conidia). a wide spectrum of diseases because it can live on a wide substrate in a variety of conditions due to its good adaptability and competitiveness (Palmieri et al., 2022). *Aspergillus* can be found in open spaces such as growing on plants, decaying organic matter, soil, animals, and water. In addition, it can live in closed spaces such as building surfaces, heating ducts, air-conditioned rooms, and so on (Hasanah, 2017; Paulussen et al., 2017).

Aspergillus spores are transmitted to humans through the air and then enter the respiratory tract through inhalation (CDC, 2019; Palmieri et al., 2022). In healthy individuals, *Aspergillus* that enters will be cleared by innate immunity, alveolar macrophages, and ciliated epithelium of the respiratory tract. In individuals with chronic respiratory diseases or with impaired immunity, these clearance mechanisms are not optimal, giving the fungus the opportunity to infect and form colonies in the respiratory tract, especially in the lungs (CDC, 2019; Fosses Vuong and Waymack, 2020; Palmieri et al., 2022). Therefore, *Aspergillus infections* are often found in individuals with weak immune systems or with lung disease.

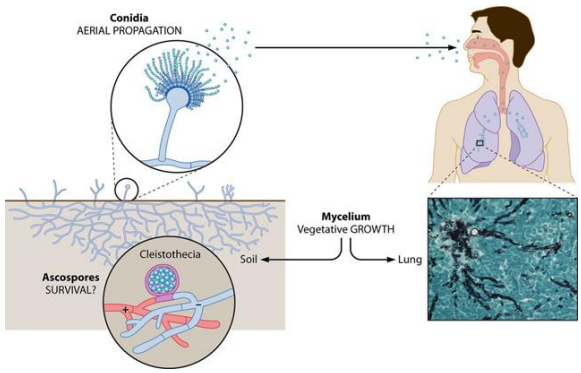

Figure 2. *Aspergillus.s p transmission* (Latge and Chamilos, 2019)

Classification aspergillosis

In general, the term aspergillosis covers a group of diseases involving the lungs due to the way it enters through inhalation of *Aspergillus spores* into the human respiratory tract. Aspergillosis is divided into:

1. Non-Invasive Aspergillosis

a. Allergic Bronchopulmonary Aspergillosis (ABPA)

Allergic bronchopulmonary aspergillosis (ABPA) is a condition commonly found in patients with asthma and *cystic fibrosis.* This condition is a reaction of the body's response to aspergillus so that there is usually mucus in the patient's lungs (Kanj, Abdallah and Soubani, 2018).

b. Chronic Pulmonary Aspergillosis (CPA)

Chronic pulmonary aspergillosis (CPA) is usually found in people who have lung diseases, such as tuberculosis, bronchiectasis, sarcoidosis, pneumoconiosis or ankylosing spondylitis. Patients who experience CPA can

also experience pulmonary aspergilloma or *fungus ball* is a solid and shapeless mass of fungal mycelium that is often found in the upper part of the lung lobe (Kanj, Abdallah and Soubani, 2018).

c. Invasive Pulmonary Aspergillosis (IPA)

Invasive pulmonary aspergillosis (IPA) is usually found in people with a weak immune system, for example patients with AIDS, leukemia patients, patients receiving corticosteroid treatment, cytotoxic chemotherapy, and patients with chronic granulomatous diseases (Kanj, Abdallah and Soubani, 2018) .

Diagnosis Enforcement

In patients with suspected pulmonary Aspergillosis, the diagnosis can be made by looking at the clinical manifestations and several examinations such as radiological examinations, laboratory examinations, and mycological examinations. Radiological examinations include chest X-rays and chest CT scans. The first and main chest X-ray examination is performed on patients with suspected lung abnormalities. The chest X-ray image seen in patients with suspected pulmonary Aspergillosis is the presence of a solid mass that is round or oval like a ball (*fungus ball*) in the cavity. This fungus ball will move when the patient changes position (Soedarsono and Widoretno, 2019). Another radiological examination that can be performed if the chest X-ray image is less supportive is a chest CT scan. The image that can be seen from the CT scan results is the presence of gas bubbles in *the fungus ball* (Senja *et al*, 2020). CT angiography can also be performed on patients with coughing up blood to identify hypertrophy in the bronchial arteries that supply blood to the cystic aspergilloma wall (Soedarsono and Widoretno, 2019).

General laboratory tests also need to be carried out routinely to see an increase in the number of eosinophils that usually occurs in patients with allergic pulmonary mycosis, such as ABPA (Guanabara *et al.*, 2021). In addition, mycological examinations including microscopic examination, isolation, and identification of fungi in cultures and serological tests can also be carried out to confirm the diagnosis to be made (Guanabara *et al.* , 2021). Sputum culture examination can also be carried out because this organism can be found in it. Another examination that can be done is the precipitin test. This precipitin test is carried out by precipitating antibodies to the *Aspergillus antigen* in the serum which aims to help distinguish aspergillosis from other lung diseases, such as lung cancer, blood clots that previously existed in the cavity, lung abscesses, and ruptured hydatid cysts. A lung biopsy can be performed if the diagnosis is still uncertain (Soedarsono and Widoretno, 2019).

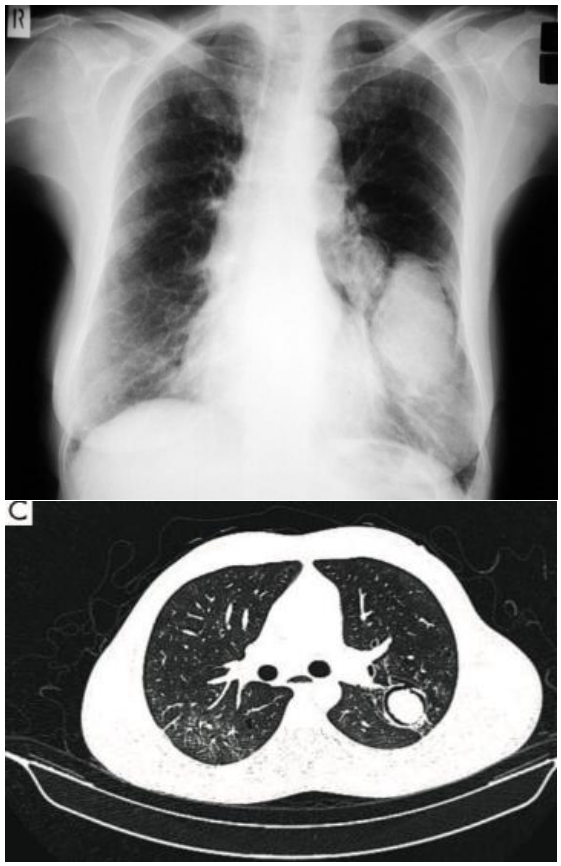

Figure 3. Results of thorax photo and thorax CT scan (Soedarsono and Widoretno, 2019)

The diagnostic criteria for systemic mycosis are known as three terms, namely *proven, probable,* and *possible.* These diagnostic criteria are determined by three things, namely host factors, clinical features, and mycological examination results. Host factors consist of risk factors and underlying diseases (eg diabetes mellitus and chronic obstructive pulmonary disease). The clinical picture is determined from clinical symptoms and examinations. Mycological examinations include fungal identification, serology, and molecular-based examinations (Guanabara *et al.* , 2021).

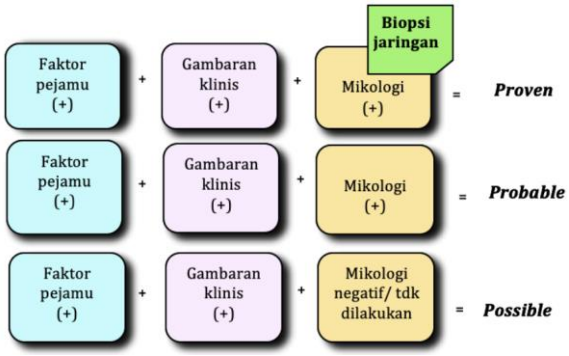

Figure 4. Diagnostic criteria for pulmonary mycosis (Guanabara, E. *et al.* 2021)

Governance

Treatment of aspergillosis infection depends on the severity of the infection and the underlying medical condition, so that treatment and medication for aspergillosis infection can be done in the following ways:

1. Oral corticosteroids: aim to suppress the hyperimmune inflammatory response. In patients with acute *Allergic bronchopulmonary aspergillosis* (ABPA), prednisolone is generally given as an oral agent for a total duration of three to five months at a dose of 0.5 mg daily for two weeks. Corticosteroids can be combined with antifungal drugs to reduce the dose of steroids and improve lung function (Ritesh Agarwal, et al, 2018). The use of immunosuppressive therapy such as corticosteroids should be considered very carefully in a multidisciplinary approach to avoid graft rejection, Graft versus host disease (GVHD) or worsening of the underlying immune disease (Lamoth et al., 2022).
2. Antifungal drugs: These drugs are the standard treatment for invasive pulmonary aspergillosis. The most effective treatment is antifungal drugs. Three classes of AF drugs are currently licensed for the treatment of aspergillosis: polyenes (amphotericin B formulations), triazoles (voriconazole, posaconazole, isavuconazole, itraconazole) and echinocandins (anidulafungin, caspofungin, micafungin) (Lamoth and Calandra, 2022). Triazol oral merupakan landangan pengobatan CPA. Itrakonazol digunakan sebagai lini pertama karena biaya terjangkau dan dan aman (Denning *et al.*, 2016). Vorikonazzol dapat diberikan pada penyakit yang yang lebih parah. Pasien dengan terapi triazol jangka panjang harus melakukan kontrol dermatologis rutin (setiap 6 bulan) untuk deteksi kanker kulit (Lamoth et al., 2022; Stemler et al., 2023).
3. Surgery may be required to remove the aspergilloma and should be considered in cases of hemoptysis. Surgery is most effective in patients with a single lesion and not disseminated disease. Therapeutic embolization to control hemoptysis is another way to manage symptoms although it does not cure the disease. In cases of small aspergilloma that do not compromise blood vessels, watchful waiting is appropriate without antifungal therapy if there is no increase in cavity size over six to twenty-four months (Vuong, Hollingshead and Waymack, 2024).

Conclusion

Pulmonary Aspergillosis is one of the most common types of pulmonary mycosis or fungal lung infection. The diagnosis of this disease can be established from the clinical manifestations experienced by the patient and several supporting examinations that have been determined. After the diagnosis is established, the treatment carried out will be based on the severity of the infection suffered and other underlying health conditions.

Acknowladmen

The author would like to express his deepest gratitude to all parties involved, both directly and indirectly, in the research and preparation of this paper, so that this research can be completed properly.

Reference

Arastehfar, A., Carvalho, A., Houbraken, J., Lombardi, L., Garcia-Rubio, R., Jenks, J. D., ... & Hoenigl, M. (2021). Aspergillus fumigatus and aspergillosis: From basics to clinics. *Studies in mycology*, *100*(1), 100115-100115. 10.1016/j.simyco.2021.100115.

Bazaz, B.R. and Denning, D.W. (2019) 'Aspergillosis : causes , types and

treatment', pp. 1–16.

CDC (2019). *Sources of Aspergillosis | | Aspergillosis | Types of Fungal Diseases | Fungal Diseases | CDC* . [online] www.cdc.gov. Available at: https://www.cdc.gov/fungal/diseases/aspergillosis/causes.html .

Centers for Disease Control and Prevention, 2014. CDC - Clinical Features of aspergillosis .

Centers for Disease Control and Prevention (2015) 'Symptoms of Aspergillosis', *Centers for Disease Control and Prevention* , pp. 4–6. Available at: https://www.cdc.gov/fungal/diseases/aspergillosis/symptoms.html%0Ahttps://www.cdc.gov/fungal/diseases/aspergillosis/definition.html.

Denning, D.W., Cadranel, J., Beigelman-aubry, C., Ader, F., Chakrabarti, A., Blot, S. and Ullmann, A.J. (2016) 'Chronic pulmonary aspergillosis : rationale and clinical guidelines for diagnosis and management', pp. 45–68. Available at: https://doi.org/10.1183/13993003.00583-2015.

Fosses Vuong, M. and Waymack, J.R. (2020). *Aspergillosis* . [online] PubMed. Available at: https://www.ncbi.nlm.nih.gov/books/NBK482241/.

Guanabara, E. *et al.* (2021) *General Guidelines for Clinical Practice of Pulmonary and Respiratory Diseases* . 1st edn. Edited by ADS Alvin Kosasih, Yusup Subagio Sutanto. Jakarta.

Hasanah, U. (2017) 'Understanding Aspergillosis, Fungal Infection of the Genus Aspergillus', *Journal of Healthy and Prosperous Families* , 15(2), pp. 76–86. doi: 10.24114/jkss.v15i2.8777.

Hayes, G.E. and Novak-Frazer, L. (2016) 'Chronic pulmonary aspergillosis—Where are we? And where are we going?', *Journal of Fungi* , 2(2), pp. 1–34. doi: 10.3390/jof2020018.

Kanj, A., Abdallah, N. and Soubani, AO (2018) 'The spectrum of pulmonary aspergillosis', *Respiratory Medicine* , 141(June), pp. 121–131. doi: 10.1016/j.rmed.2018.06.029.10.1016/j.rmed.2018.06.029.

Lamoth, F. and Calandra, T. (2022) 'Pulmonary aspergillosis: diagnosis and treatment', *European Respiratory Review*, 31(166), pp. 1–15. doi:10.1183/16000617.0114-2022.

Latgé, J.-P. and Chamilos, G. (2019). Aspergillus fumigatus and Aspergillosis in 2019. *Clinical Microbiology Reviews* , [online] 33(1). doi: https://doi.org/10.1128/cmr.00140-18.

Palmieri, F., Koutsokera, A., Bernasconi, E., Junier, P., Garnier, C. Von and Ubags, N. (2022) 'Recent Advances in Fungal Infections : From Lung Ecology to Therapeutic Strategies With a Focus on Aspergillus spp .', 9(March), pp. 1–20. Available at: https://doi.org/10.3389/fmed.2022.832510 .

Paulussen, C., Hallsworth, J.E., Álvarez-Pérez, S., Nierman, W.C., Hamill, P.G., Blain, D., Rediers, H. and Lievens, B. (2017) 'Ecology of aspergillosis: insights into the pathogenic potency of Aspergillus fumigatus and some other Aspergillus species', *Microbial Biotechnology*, 10(2), pp. 296–322. Available at: https://doi.org/10.1111/1751-7915.12367.

Praja, RN and Yudhana, A. (2017) 'Isolation and identification of Aspergillus Spp from the lungs of native chicken which sell in Banyuwangi Market', *Jurnal Medik Veteriner* , 1(1), pp. 6–11.

Senja, M., Medison, I. and Russilawati, R. (2020) 'Pulmonary Aspergilloma; A Case Report', *YARSI Medical Journal* , 28(2), pp. 032–040. doi: 10.33476/jky.v28i2.1421.

Soedarsono, S. and Widoretno, ETW (2019) 'Aspergilloma in Pulmonary Tuberculosis', *Journal of Respiration* , 3(2), p. 58. doi: 10.20473/jr.v3-i.2.2017.58-65.

Stemler, J., Többen, C., Lass-flörl, C., Steinmann, J., Ackermann, K., Rath, P., Simon, M., Cornely, O.A. and Koehler, P. (2023) 'Diagnosis and Treatment of Invasive Aspergillosis Caused'.

Sun, K.S., Tsai, C.F., Chen, S.C.C. and Huang, W.C. (2017) 'Clinical outcome and prognostic factors associated with invasive pulmonary aspergillosis: An 11-year follow-up report from Taiwan', *PLoS ONE*, 12(10), pp. 1–10. Available at:

https://doi.org/10.1371/journal.pone.0186422.

Tong, X., Liu, T., Jiang, K., Wang, D., Liu, S., Wang, Y. and Fan, H. (2021) 'Clinical Characteristics and Prognostic Risk Factors of Patients With Proven Invasive Pulmonary Aspergillosis: A Single-Institution Retrospective Study', *Frontiers in Medicine*, 8(December), pp. 1–8. Available at: https://doi.org/10.3389/fmed.2021.756237