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Diagnosis and treatment of pneumocystis pneumonia - a review article

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Abstract: This study aims to comprehensively evaluate the literature on recent advances in the diagnosis and treatment of Pneumocystis Pneumonia (PCP). A thorough review of relevant literature was conducted. Data were sourced from electronic databases such as PubMed, Scopus, Google Scholar, and Medline, focusing on articles published within the last ten years. The review included 41 articles. The diagnosis of PCP has evolved with the development of molecular techniques, advanced imaging modalities, and artificial intelligence models. Trimethoprim-sulfamethoxazole (TMP-SMX) remains the mainstay of treatment. Corticosteroid adjunctive therapy (CAT) has demonstrated efficacy in improving outcomes, while emerging research suggests a potential role for immunomodulatory agents. Chemoprophylaxis with TMP-SMX remains the main stay of prevention in populations at risk. Despite advances in diagnostic technologies, treatment options for PCP have largely remained unchanged. There are currently no vaccines, and chemoprophylaxis remains the mainstay of prevention. Practical Immediate treatment is essential. New ELISA techniques are viable, while real-time PCR proves superior to nested PCR. Clinical judgment plays a critical role in supporting laboratory diagnoses. High-resolution CT scans may be warranted for evaluating immunosuppressed patients with suspected pneumonia when chest X-rays appear normal. Radiomics can assist in distinguishing PCP from other types of pneumonia in non-HIV patients. Trimethoprim-sulfamethoxazole remains the preferred treatment, with alternative options including dapsone with trimethoprim, clindamycin with primaquine, atovaquone, or pentamidine. Corticosteroid adjunct therapy (CAT) is beneficial in treating PCP, and chemoprophylaxis is essential for high-risk populations.

Keywords: *AIDS, Immunocompromised, Pneumocystis jirovecii, Pneumocystis pneumonia.*

1. Introduction

Pneumocystis jirovecii, often abbreviated as P. jirovecii, is an opportunistic fungus that leads to a severe lung condition known as pneumocystis pneumonia (PCP) [1]. PCP, attributed to P. jirovecii, predominantly affects immunocompromised individuals, including those with HIV/AIDS, hematologic malignancies, solid organ transplant recipients, and those receiving immunosuppressive therapy [2, 3]. PCP poses a significant threat to the health and survival of immunocompromised patients [4, 5]. Those with malignancies, recipients of solid organ transplants, and individuals undergoing treatment with immunosuppressive drugs are particularly vulnerable to this fungal infection [6,7, 8]. Furthermore, certain health conditions such as diabetes and severe malnutrition heighten the susceptibility to PCP [9, 10]. Dyspnoea on exertion is a hallmark symptom of PCP, often progressing rapidly to respiratory distress, reflecting the severity of lung involvement [11]. Patients commonly present with a non-productive cough, which may be associated with low-grade fever and malaise [12]. Hypoxemia is a frequent finding in PCP and may present as refractory hypoxemia, necessitating supplemental oxygen therapy or mechanical ventilation in severe cases [13]. PCP can occasionally involve extrapulmonary sites, such as the central nervous system, leading to symptoms like headache, altered mental status, and

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focal neurological deficits [14]. This study aims to thoroughly evaluate the literature on the current advances in the diagnosis and treatment of PCP.

2. Methodology

This study was carried out after a thorough evaluation of the pertinent literature. The data was searched through electronic databases like PubMed, Scopus, Google Scholar, and Medline to find articles that had just been published in the last ten years. The search was conducted using the terms "pneumocystis carinii," " pneumocystis jiroveci," "diagnosis," and "treatment." Analysis has been done through only English-language research that focused on diagnosis and treatment of pneumocystis pneumonia.

3. Results of PCP Diagnosis

Today, PCP can be diagnosed via different methods, depending on laboratory conditions, available resources, and type and quality of samples obtained from patients [15, 17]. In a 2-year Australian retrospective cohort study of patients with clinically suspected PJP, P jirovecii PCR on nasopharyngeal swab samples showed perfect specificity, however sensitivity was low [18].

3.1. Traditional Tests

Traditional diagnostic methods like staining techniques have limitations in sensitivity and specificity. Molecular techniques such as polymerase chain reaction (PCR) have revolutionized PCP diagnosis, offering higher sensitivity and specificity, particularly in bronchoalveolar lavage samples [19].

3.2. Serological Tests

Recently, serological assays, including enzyme-linked immunosorbent assays (ELISA), have shown promise in detecting specific antibodies against Pneumocystis, aiding in diagnosis, especially in resource-limited settings [20]. These new methods may be used as a screening test for PCP, decreasing the need for biological specimens obtained by invasive techniques, which is a major benefit to the patient's care and an improvement in the clinical management of the disease [21]. Furthermore, a multicenter study evaluated the performance of a novel ELISA assay in differentiating PCP from other respiratory infections. The assay demonstrated high specificity and positive predictive value, indicating its potential for accurate PCP diagnosis in clinical practice [22].

3.3. Molecular Tests

Study by Parian et. al, evaluated the clinical utility of PCR in guiding the initiation and duration of antimicrobial therapy for PCP. The study found that PCR-guided therapy led to more timely initiation of treatment and reduced unnecessary antibiotic exposure, highlighting the potential role of PCR in optimizing patient management [23]. In a recent study by Miriam et. al, nested and quantitative real-time PCR methods for the amplification of the P. jiroveci DHPS (dihydropteroate synthase) gene were evaluated in a cohort of 71 microscopically confirmed PCP cases and 70 negative cases, the sensitivities and specificities were 94% and 81% for nested PCR and 94% and 96% for real-time PCR, respectively [24].

3.4. Metagenomic Next-Generation Sequencing (mNGS)

In a study by Lu et al, Metagenomic next-generation sequencing (mNGS) was compared with routine detection assays, including Gomori methenamine silver (GMS) stain and polymerase chain reaction (PCR) technique. Specimens of 4 bronchoalveolar lavages (BAL) and 1 lung tissue samples were obtained from 4 non-HIV patients from our hospitals. Although both GMS and mNGS were positive for P. jirovecii with PCR as positive control, the testing time of mNGS was obviously shorter than GMS. Compared with the traditional GMS method, mNGS has absolute advantages [25].

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3.5. Imaging Modalities

High-resolution computed tomography (HRCT) scans play a crucial role in diagnosing PCP immunosuppressed patients with suspected pneumonia and normal chest radiographic findings by revealing characteristic findings such as ground-glass opacities and cystic lesions, nodules, cysts, and spontaneous pneumothorax also can develop [26].

3.6. Radiomics:

Radiomics exhibited promising diagnostic efficacy in distinguishing PCP from various pneumonia types in individuals without HIV. Integrating radiomics with serum β-D-glucan presents a prospective, precise, and non-invasive approach to assess PCP infection risk among non-HIV patients displaying pneumonia manifestations on CT scans [27].

3.7. Artificial Intelligence

PCP diagnostic model in patients with severe pneumonia using four easily available and noninvasive clinical indicators. With satisfying diagnostic performance and good clinical practicability, this model may help clinicians to make early diagnosis of PCP, reduce the delays of treatment and improve the prognosis among these patients [28].

4. Results of PCP Treatment

4.1. Background

In general, efforts should be made to confirm the diagnosis of PCP before the initiation of treatment or prophylaxis. This is because (a) all drugs have some toxicity, and (b) patients with PCP may worsen before they get better [29].

4.2. Antimicrobial Therapy

Trimethoprim-sulfamethoxazole (TMP-SMX) remains the first-line treatment for PCP due to its efficacy and cost-effectiveness. However, alternative agents like pentamidine, atovaquone, and clindamycin-primaquine are reserved for patients who are intolerant to TMP-SMX or those with severe adverse reactions [30].

4.3. Corticosteroids Adjunctive Treatment (CAT)

It is possible that corticosteroids adjunctive treatment is also beneficial for HIV-infected patients with mild hypoxaemia due to PCP [31]. A meta-analysis by Ding et al, suggests that among non-HIV PCP patients with respiratory failure, CAT use may be associated with better clinical outcomes, and it may be associated with increased mortality in unselected non-HIV PCP population [32]. In infants with a clinical diagnosis of PJP, early use of steroids in addition to conventional TMP/SMX therapy significantly reduced mortality in hospital and 6 months after discharge [33].

4.4. Immunomodulatory Agents

A promising avenue of treatment is the use of combination therapy to treat PCP. It was recently shown that a cocktail of antibody and sulfasalazine leads to a dramatic improvement in the severity of PCP in a mouse model compared to single therapy methods; however, the mechanism by which this occurs needs further investigation [34]. Emerging research suggests a potential role for immunomodulatory agents like monoclonal antibodies targeting specific cytokines or immune pathways in the management of severe PCP, warranting further investigation [35].

5. Results of PCP Prevention

5.1. Vaccination

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Some current results are promising for utilizing whole organisms in developing a vaccine against PCP; however, a major issue in this technique is the inability to culture Pneumocystis in vitro, limiting this approach from being effective on a large scale. Overall, while immunization with whole Pneumocystis organisms has been shown to be quite effective in animal models [36, 37, 38]. The above limitation has led to the exploration of subunit-based vaccines, but the results are not yet clinically applied [39].

5.2. Prophylactic Agents

Prophylaxis against PCP is paramount in high-risk populations, with TMP-SMX remaining the preferred agent. Alternative agents such as dapsone, atovaquone, and aerosolized pentamidine offer options for TMP-SMX intolerant patients. However, some reviews underscore the significance of evidence-based approaches in PCP prophylaxis, as demonstrated through RCTs [40, 41].

6. Conclusion

Despite advances in real-time PCR, mNGS, imaging, and radiomics technologies, treatment for PCP using TMP-SMX, dapsone with trimethoprim, clindamycin with primaquine, atovaquone, or pentamidine has largely remained unchanged. There are currently no vaccines, and chemoprophylaxis with TMP-SMX remains the primary method of prevention.

7. Practical Implications

- Staining techniques and microscopy may lead to delays in treatment and worse prognosis; therefore, empiric treatment should be initiated as soon as PCP is suspected.
- New ELISA techniques are inexpensive and require a non-invasive specimen with improvement in the patient's care and clinical management.
- Real-time PCR has a better specificity than nested PCR and is likely to generate fewer false positives.
- The mNGS can be used to quickly and accurately diagnose PJP, but a combination of clinical judgement of symptoms, laboratory testing, and imaging examination is required to make a comprehensive judgment along with mNGS test results.
- High-resolution CT may be indicated for evaluation of immunosuppressed patients with suspected pneumonia and normal chest radiographic findings.
- Radiomics showed good diagnostic performance in differentiating PCP from other types of pneumonia in non-HIV patients.
- Trimethoprim/sulfamethoxazole for 21 days is the treatment of choice in adults and children. Alternative treatment regimens include dapsone with trimethoprim, clindamycin with primaquine, atovaquone, or pentamidine.
- Patients with moderate to severe disease should receive CAT. The use CAT is beneficial for patients with HIV PCP patients and non-HIV PCP patients without hypoxemia. CAT use should be withheld in non-HIV PCP patients without hypoxemia.
- There are no vaccines in clinical trials for the prevention of PCP, and significant obstacles exist that have slowed development, including host range specificity, and the inability to culture Pneumocystis spp. Therefore, chemoprophylaxis against PCP is paramount in high-risk populations, with TMP-SMX remaining the preferred agent.

8. Recommendations

- Future research to address antimicrobial resistance, understand host immune responses.
- Emerging monoclonal antibodies are promising but need further studies and trials in human.

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