CHAPTER 7.4 Pneumocystis jirovecii

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1 Epidemiology

Pneumocystis jirovecii (PJP) is a potentially life-threatening infection in immunocompromised individuals [1]. Pneumocystis is transmitted via the airborne route. New infections in humans are most likely acquired through person-to-person spread [2]. Individuals with normal immune systems may be asymptomatically colonised in the lungs and serve as a reservoir for the spread of Pneumocystis to immunocompromised hosts [3].

2 Risk factors

Patients with human immunodeficiency virus (HIV) and a low CD4 count are at the highest risk of PJP. For patients without HIV, the most significant risk factors are glucocorticoid treatment and defects in cell-mediated immunity [4]. Glucocorticoids increase the risk of developing PJP by suppressing cell-mediated immunity and altering lung surfactant. Other specific risk factors include taking other immunosuppressive medications, having had a solid organ transplant, undergoing treatment for organ rejection or certain inflammatory conditions (particularly rheumatological diseases), having a primary immunodeficiency (e.g., severe combined immunodeficiency) and being severely malnourished.

In the absence of prophylaxis, approximately 5 to 15% of patients who undergo solid organ transplantation develop PJP [5]. Rates are lowest among renal transplant recipients and highest among lung and heart-lung transplant recipients. The period of highest risk for PJP following solid organ transplantation is one to six months post-transplant if prophylaxis is not administered.

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Several clusters or outbreaks of PJP in solid organ transplant recipients, primarily kidney transplant recipients, have been reported [2, 6]. Hospitalised patients with PJP should be cared for using standard precautions; however, they should not share a room with other immunocompromised individuals due to the potential for person-to-person transmission.

3 Clinical manifestations

Patients with PJP may present with fulminant respiratory failure, accompanied by fever and a dry cough. However, as clinical awareness of PJP has increased and laboratory diagnosis has improved, patients more commonly present with mild to moderate PJP, experiencing less severe and more indolent dyspnoea and cough. Almost all patients with PJP will experience either hypoxaemia at rest or during exertion, or an increased alveolar–arterial oxygen tension gradient.

The typical *radiographic features* of PJP are diffuse, bilateral interstitial infiltrates. If the chest radiograph is normal, high-resolution computed tomography scanning may reveal extensive ground-glass opacities or cystic lesions.

4 Diagnosis

A diagnosis of PJP should be considered for patients with risk factors for PJP who present with pneumonia and radiographic findings that are suggestive of the condition. Prompt evaluation is warranted. Diagnosis includes microbiological identification of the organism in a sample of induced sputum or bronchoalveolar lavage (BAL) fluid, when possible. The most rapid and least invasive method of diagnosing PJP is analysis of sputum induced by inhaling hypertonic saline [1]. If PJP is not identified using this method, bronchoscopy with BAL should be performed. Detection of the organism in respiratory specimens is most commonly achieved by microscopy with staining of an induced sputum specimen or BAL fluid. Staining is necessary because Pneumocystis cannot be cultured. Several PCR assays have been developed to detect Pneumocystis in induced sputum, bronchoalveolar lavage (BAL) fluid, blood or nasopharyngeal aspirates. These assays are particularly useful for patients without HIV, as the sensitivity of microscopy with staining is substantially lower in this group. BAL and induced sputum samples demonstrate the highest sensitivity and specificity. However, when BAL or induced sputum samples are unavailable, PCR can be

performed on upper respiratory tract samples (e.g., nasopharyngeal aspirates or oral washes), although false positives and negatives can occur [7]. When PCR is used to diagnose lower respiratory tract infection in samples from the upper respiratory tract, it is important to distinguish between a positive result due to colonisation or infection.

5 Treatment

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended medication for treating PJP in patients without HIV [8, 9]. For patients with normal renal function, the recommended dose of TMP-SMX is 15 to 20 mg/kg body weight per day, administered intravenously or orally in three or four divided doses. However, several studies have suggested low-dose TMP-SMX (7.5 mg/kg to 15 mg/kg) may be safer and just as effective at treatment of PJP [9]. The dosage is based on the TMP component. The dose may need to be adjusted if creatinine clearance changes during therapy. Patients should receive intravenous therapy until they are clinically stable and have a functioning gastrointestinal tract. The usual duration of therapy is 21 days. After completing the course of treatment, patients should be considered for secondary prophylaxis with a reduced dose of the same antimicrobial therapy to prevent recurrent infection. The antimicrobial regimens used for secondary prophylaxis are the same as those used to prevent the initial infection (see below). When TMP-SMX cannot be used for the treatment of PJP, alternative drugs include clindamycin plus primaquine, trimethoprim plus dapsone, atovaquone and pentamidine administered intravenously (IV).

Adjunctive glucocorticoids are recommended for patients with severe disease, for example an arterial blood gas measurement showing a partial pressure of oxygen of less than 70 mmHg, an alveolar-arterial oxygen gradient of at least 35 mmHg, or hypoxaemia on pulse oximetry, while breathing room air. The recommended dosing algorithm is as follows: 40 mg of prednisolone per 1.73 m^2 body surface area orally twice daily for five days, followed by 40 mg per 1.73 m^2 orally once daily for five days, then 20 mg per 1.73 m^2 orally once daily for 11 days.

6 Prophylaxis

PJP is a potentially life-threatening infection that is difficult to treat. PJP prophylaxis is therefore recommended for all paediatric kidney transplant recipients during the first 6–12 months post-transplant, as this almost completely prevents PJP. TMP-SMX is the recommended first-line agent for PJP prophylaxis due to its proven efficacy. TMP-SMX is generally well tolerated in patients without HIV infection, as a meta-analysis found that adverse events necessitating cessation of therapy (leukopenia, thrombocytopenia, or severe dermatologic reactions) occurred in only 3.1% of adults [10].

Indications for prophylaxis:

- Universal prophylaxis for all paediatric kidney transplant recipients for the first 6 months post-transplant
- Following treatment for an acute rejection episode by glucocorticoid pulse therapy or a lymphocyte-depleting antibody (e.g., thymoglobulin or ATG, especially in cases where the CD4+ T cell count is below 150/µL); administer TMP-SMX prophylaxis for 6 months
- After rituximab therapy, administer TMP-SMX prophylaxis for the duration of B-cell depletion, typically for 12 months.
- All patients with CMV viremia, for as long as CMV viremia persists.

Recommended dosing for prophylactic TMP-SMX:

- Children up to 13 years: 150 mg of trimethoprim per m^2 of body surface area per day and 750 mg of sulfamethoxazole per m^2 per day, taken orally in two daily doses three times per week on alternating days, e.g., on Monday, Wednesday, and Friday. The maximum absolute dose is 160 mg of trimethoprim and 800 mg of sulfamethoxazole.
- Adolescents aged over 13 years: 160 mg of trimethoprim and 800 mg of sulfamethoxazole in one dose, three times per week on alternate days (e.g., Monday, Wednesday, and Friday).

Reducing the dose of TMP-SMX in cases of renal insufficiency:
eGFR 15–30 mL/min/1.73 m^2: reduce the dose by 50%.
For eGFR < 15 mL/min/1.73 m^2, administration is not recommended.

For patients who cannot take TMP-SMX (e.g., those with a history of severe allergic reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis),

we recommend either dapsone (with pyrimethamine if Toxoplasma prophylaxis is required) or atovaquone. For patients for whom haematological toxicity is not a concern, we prefer dapsone as it is cheaper than atovaquone. Patients should undergo testing for glucose-6-phosphate dehydrogenase deficiency prior to taking dapsone.

Another option for PJP prophylaxis is *aerosolised pentamidine,* for example for patients with an eGFR of less than 15 ml/min/1.73 m^2. However, this method is less effective than other regimens, requires specialised equipment and has been associated with the transmission of Mycobacterium tuberculosis. Furthermore, it only has a local effect; if the aerosol does not reach all areas of the lungs, untreated areas remain at risk of PJP.

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