

Pentamidine in *Pneumocystis jirovecii* prophylaxis in heart transplant recipients

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Abstract

Despite advances in transplantation techniques and the quality of post-transplantation care, opportunistic infections remain an important cause of complications. *Pneumocystis jirovecii* (*P. jirovecii*) is an opportunistic organism, represents an important cause of infections in heart transplantation patients. Almost 2% to 10% of patients undergoing cardiac transplantation have *Pneumocystis pneumonia*. Prophylaxis is essential after surgery. Various prophylaxis regimes had been defined in past and have different advantages. Trimethoprim/sulfamethoxazole (TMP/SMX) has a key role in prophylaxis against *P. jirovecii*. Generally, although TMP/SMX is well tolerated, serious side effects have also been reported during its use. Pentamidine is an alternative prophylaxis agent when TMP/SMX cannot be tolerated by the patient. Structurally, pentamidine is an aromatic diamidine compound with antiprotozoal activity. Since it is not effectively absorbed from the gastrointestinal tract, it is frequently administered *via* the intravenous route. Pentamidine can alternatively be administered through inhalation at a monthly dose in heart transplant recipients. Although, the efficiency and safety of this drug is well studied in other types of solid organ transplantations, there are only few data about pentamidine usage in heart transplantation. We sought to evaluate evidence-based assessment of the use of pentamidine against *P. jirovecii* after heart transplantation.

Key words: Pentamidine; Prophylaxis; Trimethoprim; Heart transplantation; *Pneumocystis pneumonia*; *Pneumocystis jirovecii*; *Pneumocystis carinii*

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Core tip: Trimethoprim/sulfomethoxazole (TMP/SMX), the first-line drug for pneumocystis pneumonia prophylaxis following heart transplantation, is well tolerated, however; serious side effects have also been reported during its use. Pentamidine is an alternative prophylaxis agent when TMP/SMX cannot be tolerated following solid organ transplantations. Although there are various studies evaluating the efficiency and safety of pentamidine in these groups, merely reports were found about its usage in heart transplantation recipients. This review aims to evaluate the use of pentamidine against *Pneumocystis jirovecii* following heart transplantation.

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INTRODUCTION

Infection is a major determinant of survival among many others in patients undergoing cardiac transplantation^[1,2]. *Pneumocystis jirovecii* (*P. jirovecii* or *P. carinii*), an opportunistic organism, represents an important cause of infections in this group of patients. The objective of the present review was to provide a comprehensive and evidence-based assessment of the use of pentamidine against *P. jirovecii*, which is a potential threat in patients undergoing cardiac transplantation who require very close monitoring during all stages of the peri-operative care.

OPPORTUNISTIC PULMONARY INFECTIONS IN PATIENTS UNDERGOING CARDIAC TRANSPLANTATION

Despite advances in transplantation techniques and the quality of post-transplantation care, opportunistic infections remain an important cause of complications. As compared non-respiratory infections, pneumonia represents a more serious threat when one considers its incidence and severity. A classification scheme for pneumonia based on the temporal occurrence proposes that pneumonia within the first post-transplant period is referred to as nosocomial, while those occurring between post-transplant months 1 and 6 are considered opportunistic, and those occurring thereafter can be considered as community-acquired pneumonia. Despite this general classification scheme, certain specific patient groups experience an increased risk of opportunistic infections even 6 mo after the procedure^[3-6].

Other than the bacterial infections, *Aspergillus*

spp, *Candida* spp, CMV, *Nocardia* spp and PCP represent the causative organisms that are most frequently associated with pulmonary disease. Invasive pulmonary aspergillosis is a serious condition with high mortality^[7], and introduction of the lipid formulations of amphotericin B, echinocandins, and novel azole antifungals resulted in an increased chance of successful treatment in patients with this condition^[8].

Mycobacterium tuberculosis is a bacterial agent and infections caused by this organism are closely related with demographic characteristics of the patient groups. Globally, *Mycobacterium tuberculosis* has been reported to occur in 0.35% to 15% of the cases undergoing solid organ transplantation^[9]. This organism may be expected to play a greater role in the future both in the community in general and in immunocompromised individuals in particular (particularly in Anatolia and Europe), considering the mass migrations and conflicts influencing the populations across the Middle East region. In areas with high endemicity, the potential for prophylaxis may be evaluated using purified protein derivative (PPD) or QuantiferON tests in high-risk individual^[10].

Pneumocystis carinii (*P. carinii*) was initially described in rats and humans. This organism has been re-named as *P. jirovecii* in honor of the Czech parasitologist Otto Jirovec in order to differentiate other variants of *Pneumocystis* found in other species from this organism, which was first described in 1976 in humans^[11]. Although initially thought to be a protozoan, further studies ascertained that it is actually a yeast-like single cell fungus^[12]. Although the International Code of Nomenclature for Algae, Fungi, and Plants (ICNafp) recommended the use of the name with two "i"s, i.e., *P. jirovecii*, for academic publications, currently *P. jirovecii*, *P. jirovecii* and *P. carinii* are frequently used synonymously^[13]. The term PCP is widely accepted as the acronym for pneumocystis pneumonia.

This organism is ubiquitous in the nature. The probable route of transmission is through respiration. The infection caused by this organism takes the form of diffuse bilateral pneumonitis with a mortality of 90% to 100% and 35% for untreated and treated cases, respectively. The clinical course is closely associated with the age of the patients. Most common signs and symptoms associated with the disease include tachypnea, cough, and hypoxia resulting from pneumocyte injury.

THE INCIDENCE OF PCP IN PATIENTS UNDERGOING CARDIAC TRANSPLANTATION

Almost 2% to 10% of patients undergoing cardiac transplantation have PCP^[14-18]. The divergence in the reported figures reflects the differences between centers and populations examined. Also, there may be

an increased frequency and severity of PCP in centers where seasonal clustering of *P. jirovecii* is observed^[17].

The incidence of PCP may vary depending on the type of the immunosuppressive treatment administered after transplantation. Recent evidence suggests that after the introduction of the effective immunosuppressor mycophenolate mofetil (MMF) there has been a decrease in the frequency of PCP, despite the absence of data involving cardiac transplant patients^[19-21]. For instance, Oz *et al.*^[20] showed a decreased incidence of PCP with MMF in rat models of immunosuppression. Virus-free Sprague Dawley rats were immunosuppressed by tacrolimus, sirolimus, dexamethasone and/or MMF in study models and no PCP development was observed in any of the rats treated with MMF. Another team of investigators led by Husain *et al.*^[21] reviewed 4 separate clinical studies in which patients received MMF, and found no cases of PCP in patients receiving MMF among a group of 1068 subjects. In contrast, 1.8% of the patients who did not receive MMF had PCP. Although the exact mechanisms of this protective effect conferred by MMF are unknown, blockade of the replication of the microbial genetic material at one step of microbial growth has been proposed. In contrast with these positive findings for MMF, Arichi *et al.*^[22] suggested that administration of MMF may represent a risk factor for PCP in patients undergoing renal transplantation due to strong immunosuppression.

Cardenal *et al.*^[23] compared 72 CT patients with a group of subjects representative of the normal population during an average follow up duration of 5 years and showed a similar frequency of PCP in both groups. While the causative agent was associated with opportunistic infections, it was associated with subclinical infection in the normal subjects^[23].

MECHANISM OF PNEUMOCYSTIS JIROVECI INFECTION

Currently two different hypotheses have been put forward to explain how *P. jirovecii* may lead to development of an infectious disease in cardiac transplant patients while not causing any infections despite common presence in healthy individuals. According to the first hypothesis, after the initial infection (primary infection) with *P. jirovecii*, the organisms enter a latent phase in the pulmonary tissue and are activated after immunosuppression as to cause PCP^[24]. The strongest piece of evidence for this hypothesis comes from the detection of antigens against this pathogen in healthy young individuals^[25]. On the other hand, several studies found no evidence of this pathogen up to one year after PCP^[26]. The second hypothesis proposes that the pathogen that is associated with *P. jirovecii* infection is actually of exogenous origin. A low incidence of PCP during the initial months where immunosuppression is

most severe as well as a prolonged duration of time between the transplantation and occurrence of PCP are supportive of the second hypothesis. Currently there is no conclusive evidence, both for the first hypothesis proposing a latent source of infection, and for the hypothesis offering a more likely explanation of an exogenous source.

REQUIREMENT FOR PROPHYLAXIS

Regardless of the source of *P. jirovecii* infections, currently no consensus exists on the need for primary prophylaxis (PP) in all solid organ transplantations^[27]. On the other hand, most authors advocate the use of PP in CT patients^[28]. In a Vancouver based study involving patients undergoing a variety of different solid organ transplantation procedures (657 kidney, 436 liver, 44 kidney/pancreas, 104 lung and heart/lung), prolonged prophylaxis has been recommended on the basis of the occurrence of late PCP more than 1 year after post-transplantation^[29].

In studies where it has been reported that there may be no need for prophylaxis in a variety of patients with immunosuppression, a recommendation to administer selective prophylaxis has been made, in addition to drawing attention to the possibility that PCP may have a more severe clinical course^[30]. When one considers studies reporting occurrence of PCP even under trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis, the need for prophylaxis in CT patients becomes even more important^[31].

Among patients undergoing cardiac transplantation, those receiving MMF may be considered as those with the least need of PCP prophylaxis. As mentioned earlier, the anti-microbial properties of MMF, the mechanisms of which have not been clearly elucidated, and the supporting evidence, though few in number^[20,21], suggest that prophylaxis may not be necessary in this patient group. Yet, there is no consensus regarding the use of prophylaxis in this patient group.

AGENTS USED FOR PROPHYLAXIS

One of the first agents utilized for PP for *P. jirovecii* was TMP/SMX. It is one of the most commonly used agents for this indication since 1988, when it was first introduced for use in PP. While in the initial years, a recommendation to use TMP/SMX for the first 3 or 13 mo was made, after 1997 the recommended duration of prophylaxis has been extended as to include a prophylaxis of several years to life-long prophylaxis^[19]. TMP/SMX has been shown to reduce the risk of PCP by more than 90%^[32]. This agent is also effective against listeriosis and toxoplasmosis^[32-36]. Although it is generally accepted that the incidence of PCP is reduced after one year, cases with late-onset PCP have also been reported. Majority of these cases occurred during phases of acute rejection^[29,32]. Some authors have advocated more prolonged use of TMP/SMX in

association with this condition^[28].

Except for some isolated reports, numerous studies have established the efficacy and safety of TMP/SMX prophylaxis^[23,37,38]. Generally, although TMP/SMX is well tolerated, serious side effects have also been tolerated during its use^[39,40]. Some of the side effects may be associated with its mechanism of action involving the folate metabolism. Agents that may be administered through non-systemic routes such as the inhalational route instead of this agent are warranted, particularly in patients undergoing bone marrow transplantation who are prone to adverse effects involving the myeloproliferative system.

After year 2000, atavouone has been introduced for *P. jirovecii* prophylaxis in patients who were not considered suitable for TMP/SMX or pentamidine prophylaxis. This agent is not only effective for protection against *P. jirovecii*, but also against *Toxoplasma gondii*. Alternatively, oral combinations of pyrimethamine and sulfadoxine or agents such as dapson may be utilized^[19].

PENTAMIDINE IN PROPHYLAXIS

Although pentamidine was originally used for the treatment of trypanosomiasis and leishmaniasis in 1930s, it was first licensed in 1950s. Goa *et al*^[41] was the first to provide evidence for its efficiency against PCP in 1987. Structurally, pentamidine is an aromatic diamidine compound with antiprotozoal activity. Since it is not effectively absorbed from the gastrointestinal tract, it is frequently administered *via* the intravenous route. It may cause mild and generally reversible nephrotoxicity or hypoglycemia, while pancreatitis represents its most common side effect. Nephrotoxicity may cause acute allograft dysfunction, particularly in renal transplant patients^[42]. Hypotension, hypocalcemia, and cardiac dysrhythmia are other side effects that can be observed. A patient developing torsades des pointes during inhaled pentamidine treatment in a renal transplant patient has also been reported^[43]. These side effects may be assumed to occur less frequently during inhaled use. Due to its potent efficacy against pneumocytosis and toxoplasmosis, it has been included in the 2013 Model List of Essential Medicines issued by the World Health Organization (WHO).

In patients who cannot tolerate TMP/SMX due to side effects after cardiac transplantation, pentamidine is an alternative agent and is frequently administered through inhalation at a monthly dose of 150 mg or 300 mg. It is diluted with 6 mL of water for preparation and is administered *via* a 20 min nebulization. During the administration, the patient has to be positioned in the sitting position and the patient should perform a deep inspiration after each 4 to 5 normal inspiratory activity^[44]. The device that has been reported to be most commonly used in for the delivery of the inhalational drug is Respirgard II nebulizer (Marquest,

Englewood, Colo, United States). Once or twice monthly dose-regimens do not differ significantly in terms of efficacy^[45]. Administration of bronchodilators with nebulizer prior to the procedure may allow better tolerance of the drug by reducing cough and bronchospasm. Due to its method of administration, some patients may require hospitalization. The terms used to describe the inhalational treatment in literature include "inhaled", "aerolized", or "nebulized" treatment.

As compared to studies in liver transplant patients^[46-51], studies examining the role of pentamidine in PCP prophylaxis in patients undergoing cardiac transplantation are relatively scarce in number. Except for Altintas *et al*^[52], who showed safe use of inhaled pentamidine in a cardiac transplant patient developing allergic reaction to TMP/SMX, no other studies in this patient group have been identified in the literature. In that study, due to the absence of established guidelines regarding the route and dosage of administration of pentamidine in CT patients, the use of this agent in that patient was based on the use in other patient groups with immunosuppression^[53,54]. Since the publication this study in 2011, no other studies have been published. The scarcity of reports may be due to the fact that PCP occurs at a relatively low frequency in CT patients after introduction of the widespread use of TMP/SMX as well as due to the generally good safety profile of TMP/SMX.

When the use of pentamidine in other patient groups with immunosuppression is examined, it is evident that intravenous route is also used for its administration. In certain centers, intravenous PCP prophylaxis is used, generally after the hematopoietic stem cell transplantation in children or adolescents^[55], and initial results with this route of administration suggest that pentamidine may be used as a first-line therapy. In the study by Kim *et al*^[56], it was considered as a safe second-line agent after TMP/SMX in a similar patient population. Again, in a study involving patients undergoing bone marrow transplantation, the authors recommended that inhaled pentamidine may be used as a second-line agent based on positive results with this agent^[57]. On the other hand, Vasconcelles *et al*^[58] found high rates of failure with inhaled pentamidine in bone marrow transplant patients.

CONCLUSION

Despite an ever decreasing incidence of PCP in cardiac transplant patients, in patients who are unable to receive treatment with TMP/SMX for PP, there is a need for effective second-line agent(s). In the absence of large-scale studies in CT populations, pentamidine distinguishes itself as a safe and effective potential second-line agent based on the results in other patient groups with immunosuppression. In a specific patient group such as those undergoing CT, large-scale studies are warranted to establish reliable therapeutic algorithms.

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