**Name of Journal: *World Journal of Transplantation***

**ESPS Manuscript NO: 21739**

**Manuscript Type: MINIREVIEWS**

**Pentamidine in *Pneumocystis jirovecii* prophylaxis in heart transplant recipients**

Diken AI *et al*. Pentamidine and heart transplantation

**Adem Ilkay Diken, Ozlem Erçen Diken, Onur Hanedan, Seyhan Yılmaz, Ata Niyazi Ecevit, Emir Erol, Adnan Yalçınkaya**

**Adem Ilkay Diken, Seyhan Yılmaz, Emir Erol, Adnan Yalçınkaya**, Department of Cardiovascular Surgery, Hitit University Faculty of Medicine, 19100 Corum, Turkey

**Ozlem Erçen Diken**, Department of Chest Diseases, Hitit University Faculty of Medicine, 19100 Corum, Turkey

**Onur Hanedan, Ata Niyazi Ecevit**, Department of Cardiovascular Surgery, Turkiye Yuksek Ihtisas Hospital, 06100 Ankara, Turkey

**Author contributions:** All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

**Conflict-of-interest** **statement:** Any author has conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Adem Ilkay Diken, MD, Assistant Professor,** Department of Cardiovascular Surgery, Hitit University Faculty of Medicine, Camlik Caddesi No: 2, Bahcelievler Mahallesi, 19100 Corum, Turkey. ademilkay@gmail.com

**Telephone:** +90-530-6873315

**Received:** July 22, 2015

**Peer-review started:** August 6, 2015

**First decision:** October 13, 2015

**Revised:** October 21, 2015

**Accepted:** December 7, 2015

**Article in press:**

**Published online:**

**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/sulfomethoxazole (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 antiprotozal 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:** Heart transplantation; Pentamidine; Trimethoprim; Prophylaxis; Pneumocystis pneumonia; *Pneumocystis jirovecii*; *Pneumocystis carinii*

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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

Diken AI, Diken OE, Hanedan O, Yılmaz S, Ecevit AN, Erol E, Yalçınkaya A. Pentamidine in *Pneumocystis jirovecii* prophylaxis in heart transplant recipients. *World J Transplant* 2015; In press

**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 anti-fungals 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 QuantilFERON 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 Chzeck 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. jiroveci*, *P. jirovecii* and *P. carini* 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.

**THI 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 immuno-suppressor 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 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[21]. 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, atavoquone 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 was the first to provide evidence for its efficiency against PCPin 1987[41]. Structurally, pentamidine is an aromatic diamidine compound with antiprotozal 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. Neprotoxicity 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 Altıntaş *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 PC P prophylaxis is used, generally after the hematopoetic 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-linetherapy. 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, Vasconselles *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.

**REFERENCES**

1 **Baumgartner WA**, Borkon AM, Achuff SC, Baughman KL, Traill TA, Reitz BA. Organization, development and early results of a heart transplant program. The Johns Hopkins Hospital experience. *Chest* 1986; **89**: 836-839 [PMID: 3519108]

2 **Hunt SA**. Complications of heart transplantation. *J Heart Transplant* 1983; **3**: 70-74

3 **Fishman JA**. Infection in solid-organ transplant recipients. *N Engl J Med* 2007; **357**: 2601-2614 [PMID: 18094380]

4 **Fishman JA**, Issa NC. Infection in organ transplantation: risk factors and evolving patterns of infection. *Infect Dis Clin North Am* 2010; **24**: 273-283 [PMID: 20466270 DOI: 10.1016/j.idc.2010.01.005]

5 **Garrido RS**, Aguado JM, Díaz-Pedroche C, Len O, Montejo M, Moreno A, Gurguí M, Torre-Cisneros J, Pareja F, Segovia J, Garcia M, Lumbreras C. A review of critical periods for opportunistic infection in the new transplantation era. *Transplantation* 2006; **82**: 1457-1462 [PMID: 17164717]

6 **Cervera C**, Fernández-Ruiz M, Valledor A, Linares L, Antón A, Ángeles Marcos M, Sanclemente G, Hoyo I, Cofán F, Ricart MJ, Pérez-Villa F, Navasa M, Pumarola T, Moreno A. Epidemiology and risk factors for late infection in solid organ transplant recipients. *Transpl Infect Dis* 2011; **13**: 598-607 [PMID: 21535336 DOI: 10.1111/j.1399-3062.2011.00646.x]

7 **Trullas JC**, Cervera C, Benito N, de la Bellacasa JP, Agustí C, Rovira M, Mas A, Navasa M, Cofan F, Ricart MJ, Pérez-Villa F, Moreno A. Invasive pulmonary aspergillosis in solid organ and bone marrow transplant recipients. *Transplant Proc* 2005; **37**: 4091-4093 [PMID: 16386634]

8 **Silveira FP**, Husain S. Fungal infections in solid organ transplantation. *Med Mycol* 2007; **45**: 305-320 [PMID: 17510855]

9 **Montoya JG**, Giraldo LF, Efron B, Stinson EB, Gamberg P, Hunt S, Giannetti N, Miller J, Remington JS. Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. *Clin Infect Dis* 2001; **33**: 629-640 [PMID: 11486285]

10 **Singh N**, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. *Clin Infect Dis* 1998; **27**: 1266-1277 [PMID: 9827281]

11 **Stringer JR**, Beard CB, Miller RF, Wakefield AE. A new name (Pneumocystis jiroveci) for Pneumocystis from humans. *Emerg Infect Dis* 2002; **8**: 891-896 [PMID: 12194762]

12 **Stringer JR**, Beard CB, Miller RF. Spelling Pneumocystis jirovecii. *Emerg Infect Dis* 2009; **15**: 506 [PMID: 19239784 DOI: 10.3201/eid1503.081060]

13 **Redhead SA**, Cushion MT, Frenkel JK, Stringer JR. Pneumocystis and Trypanosoma cruzi: nomenclature and typifications. *J Eukaryot Microbiol* 2006; **53**: 2-11 [PMID: 16441572]

14 **Hofflin JM**, Potasman I, Baldwin JC, Oyer PE, Stinson EB, Remington JS. Infectious complications in heart transplant recipients receiving cyclosporine and corticosteroids. *Ann Intern Med* 1987; **106**: 209-216 [PMID: 3541723]

15 **Austin JH**, Schulman LL, Mastrobattista JD. Pulmonary infection after cardiac transplantation: clinical and radiologic correlations. *Radiology* 1989; **172**: 259-265 [PMID: 2544923]

16 **Dummer JS**. Infectious complications of transplantation. *Cardiovasc Clin* 1990; **20**: 163-178 [PMID: 2404597]

17 **Grossi P**, Ippoliti GB, Goggi C, Cremaschi P, Scaglia M, Minoli L. Pneumocystis carinii pneumonia in heart transplant recipients. *Infection* 1993; **21**: 75-79 [PMID: 8491524]

18 **Muñoz P**, Muñoz RM, Palomo J, Rodríguez-Creixéms M, Muñoz R, Bouza E. Pneumocystis carinii infection in heart transplant recipients. Efficacy of a weekend prophylaxis schedule. *Medicine* (Baltimore) 1997; **76**: 415-422 [PMID: 9413427]

19 **Haddad F**, Deuse T, Pham M, Khazanie P, Rosso F, Luikart H, Valantine H, Leon S, Vu TA, Hunt SA, Oyer P, Montoya JG. Changing trends in infectious disease in heart transplantation. *J Heart Lung Transplant* 2010; **29**: 306-315 [PMID: 19853478 DOI: 10.1016/j.healun.2009.08.018]

20 **Oz HS**, Hughes WT. Novel anti-Pneumocystis carinii effects of the immunosuppressant mycophenolate mofetil in contrast to provocative effects of tacrolimus, sirolimus, and dexamethasone. *J Infect Dis* 1997; **175**: 901-904 [PMID: 9086147]

21 **Husain S**, Singh N. The impact of novel immunosuppressive agents on infections in organ transplant recipients and the interactions of these agents with antimicrobials. *Clin Infect Dis* 2002; **35**: 53-61 [PMID: 12060875]

22 **Arichi N**, Kishikawa H, Mitsui Y, Kato T, Nishimura K, Tachikawa R, Tomii K, Shiina H, Igawa M, Ichikawa Y. Cluster outbreak of Pneumocystis pneumonia among kidney transplant patients within a single center. *Transplant Proc* 2009; **41**: 170-172 [PMID: 19249506 DOI: 10.1016/j.transproceed.2008.10.027]

23 **Cardenal R**, Medrano FJ, Varela JM, Ordoñez A, Regordan C, Rincon M, Martinez A, Calderon EJ. Pneumocystis carinii pneumonia in heart transplant recipients. *Eur J Cardiothorac Surg* 2001; **20**: 799-802 [PMID: 11574228]

24 **Frenkel JK**, Good JT, Shultz JA. Latent Pneumocystis infection of rats, relapse, and chemotherapy. *Lab Invest* 1966; **15**: 1559-1577 [PMID: 5297332]

25 **Smulian AG**, Sullivan DW, Linke MJ, Halsey NA, Quinn TC, MacPhail AP, Hernandez-Avila MA, Hong ST, Walzer PD. Geographic variation in the humoral response to Pneumocystis carinii. *J Infect Dis* 1993; **167**: 1243-1247 [PMID: 8486964]

26 **Vargas SL**, Hughes WT, Wakefield AE, Oz HS. Limited persistence in and subsequent elimination of Pneumocystis carinii from the lungs after P. carinii pneumonia. *J Infect Dis* 1995; **172**: 506-510 [PMID: 7622894]

27 **Kostakis ID**, Sotiropoulos GC, Kouraklis G. Pneumocystis jirovecii pneumonia in liver transplant recipients: a systematic review. *Transplant Proc* 2014; **46**: 3206-3208 [PMID: 25420860 DOI: 10.1016/j.transproceed]

28 **Martin SI**, Fishman JA. Pneumocystis pneumonia in solid organ transplant recipients. *Am J Transplant* 2009; **9** Suppl 4: S227-S233 [PMID: 20070684 DOI: 10.1111/j.1600-6143.2009.02914.x]

29 **Wang EH**, Partovi N, Levy RD, Shapiro RJ, Yoshida EM, Greanya ED. Pneumocystis pneumonia in solid organ transplant recipients: not yet an infection of the past. *Transpl Infect Dis* 2012; **14**: 519-525 [PMID: 22571389 DOI: 10.1111/j.1399-3062.2012.00740.x]

30 **Sarwar S**, Carey B, Hegarty JE, McCormick PA. Low incidence of Pneumocystis jirovecii pneumonia in an unprophylaxed liver transplant cohort. *Transpl Infect Dis* 2013; **15**: 510-515 [PMID: 23930824 DOI: 10.1111/tid.12117]

31 **Celik T**, Gedik E, Kayabas U, Bayindir Y, Gulbas G, Firat AK, Togal T. A heart transplant recipient lost due to Pneumocystis jiroveci pneumonia under trimethoprim-sulfamethoxazole prophylaxis: case report. *Exp Clin Transplant* 2010; **8**: 325-328 [PMID: 21143101]

32 **Hoyo I**, Sanclemente G, Cervera C, Cofán F, Ricart MJ, Perez-Villa F, Navasa M, Marcos MA, Puig de la Bellacasa J, Moreno A. Opportunistic pulmonary infections in solid organ transplant recipients. *Transplant Proc* 2012; **44**: 2673-2675 [PMID: 23146490 DOI: 10.1016/j.transproceed.2012.09.067]

33 **Fernàndez-Sabé N**, Cervera C, López-Medrano F, Llano M, Sáez E, Len O, Fortún J, Blanes M, Laporta R, Torre-Cisneros J, Gavaldà J, Muñoz P, Fariñas MC, María Aguado J, Moreno A, Carratalà J. Risk factors, clinical features, and outcomes of listeriosis in solid-organ transplant recipients: a matched case-control study. *Clin Infect Dis* 2009; **49**: 1153-1159 [PMID: 19751149 DOI: 10.1086/605637]

34 **Martina MN**, Cervera C, Esforzado N, Linares L, Torregrosa V, Sanclemente G, Hoyo I, Cofan F, Oppenheimer F, Miro JM, Campistol JM, Moreno A. Toxoplasma gondii primary infection in renal transplant recipients. Two case reports and literature review. *Transpl Int* 2011; **24**: e6-12 [PMID: 20955469 DOI: 10.1111/j.1432-2277.2010.01173.x]

35 **Soave R**. Prophylaxis strategies for solid-organ transplantation. *Clin Infect Dis* 2001; **33** Suppl 1: S26-S31 [PMID: 11389519]

36 **Fernàndez-Sabé N**, Cervera C, Fariñas MC, Bodro M, Muñoz P, Gurguí M, Torre-Cisneros J, Martín-Dávila P, Noblejas A, Len O, García-Reyne A, Del Pozo JL, Carratalà J. Risk factors, clinical features, and outcomes of toxoplasmosis in solid-organ transplant recipients: a matched case-control study. *Clin Infect Dis* 2012; **54**: 355-361 [PMID: 22075795 DOI: 10.1093/cid/cir806]

37 **Olsen SL**, Renlund DG, O'Connell JB, Taylor DO, Lassetter JE, Eastburn TE, Hammond EH, Bristow MR. Prevention of Pneumocystis carinii pneumonia in cardiac transplant recipients by trimethoprim sulfamethoxazole. *Transplantation* 1993; **56**: 359-362 [PMID: 8356591]

38 **Hughes WT**. Limited effect of trimethoprim-sulfamethoxazole prophylaxis on Pneumocystis carinii. *Antimicrob Agents Chemother* 1979; **16**: 333-335 [PMID: 315754]

39 **Jick H**. Adverse reactions to trimethoprim-sulfamethoxazole in hospitalized patients. *Rev Infect Dis* 1982; **4**: 426-428 [PMID: 6981160]

40 **Kocak Z**, Hatipoglu CA, Ertem G, Kinikli S, Tufan A, Irmak H, Demiroz AP. Trimethoprim-sulfamethoxazole induced rash and fatal hematologic disorders. *J Infect* 2006; **52**: e49-e52 [PMID: 15996741]

41 **Goa KL**, Campoli-Richards DM. Pentamidine isethionate. A review of its antiprotozoal activity, pharmacokinetic properties and therapeutic use in Pneumocystis carinii pneumonia. *Drugs* 1987; **33**: 242-258 [PMID: 3552596]

42 **Prabhavalkar S**, Masengu A, O'Rourke D, Shields J, Courtney A. Nebulized pentamidine-induced acute renal allograft dysfunction. *Case Rep Transplant* 2013; **2013**: 907593 [PMID: 23401840 DOI: 10.1155/2013/907593]

43 **Green PT**, Reents S, Harman E, Curtis AB. Pentamidine-induced torsades de pointes in a renal transplant recipient with Pneumocystis carinii pneumonia. *South Med J* 1990; **83**: 481-484 [PMID: 2321077]

44 **Nathan SD**, Ross DJ, Zakowski P, Kass RM, Koerner SK. Utility of inhaled pentamidine prophylaxis in lung transplant recipients. *Chest* 1994; **105**: 417-420 [PMID: 8306738]

45 **Miller R**, Steel S. Nebulized pentamidine as prophylaxis for Pneumocystis carinii pneumonia. *J Antimicrob Chemother* 1991; **27**: 153-157 [PMID: 2055807]

46 **Barkholt L**, Ericzon BG, Tollemar J, Malmborg AS, Ehrnst A, Wilczek H, Andersson J. Infections in human liver recipients: different patterns early and late after transplantation. *Transpl Int* 1993; **6**: 77-84 [PMID: 8447929]

47 **Neumann UP**, Langrehr JM, Kaisers U, Lang M, Schmitz V, Neuhaus P. Simultaneous splenectomy increases risk for opportunistic pneumonia in patients after liver transplantation. *Transpl Int* 2002; **15**: 226-232 [PMID: 12012043]

48 **Singh N**, Gayowski T, Wagener M, Marino IR, Yu VL. Pulmonary infections in liver transplant recipients receiving tacrolimus. Changing pattern of microbial etiologies. *Transplantation* 1996; **61**: 396-401 [PMID: 8610349]

49 **Torre-Cisneros J**, De la Mata M, Pozo JC, Serrano P, Briceño J, Solórzano G, Miño G, Pera C, Sánchez-Guijo P. Randomized trial of weekly sulfadoxine/pyrimethamine vs. daily low-dose trimethoprim-sulfamethoxazole for the prophylaxis of Pneumocystis carinii pneumonia after liver transplantation. *Clin Infect Dis* 1999; **29**: 771-774 [PMID: 10589886]

50 **Singh N**, Gayowski T, Wagener MM, Marino IR. Pulmonary infiltrates in liver transplant recipients in the intensive care unit. *Transplantation* 1999; **67**: 1138-1144 [PMID: 10232564]

51 **Trotter JF**, Levi M, Steinberg T, Lancaster J. Absence of Pneumocystis jiroveci pneumonia in liver transplantation recipients receiving short-term (3-month) prophylaxis. *Transpl Infect Dis* 2008; **10**: 369-371 [PMID: 18482201 DOI: 10.1111/j.1399-3062.2008.00318.x]

52 **Altintas G**, Diken AI, Diken OE, Hanedan O, Kucuker SA. Inhaled pentamidine for Pneumocystis jiroveci prophylaxis in a heart transplant recipient with allergy for trimethoprim sulfamethoxazole. *Exp Clin Transplant* 2011; **9**: 72-73 [PMID: 21605028]

53 **Marras TK**, Sanders K, Lipton JH, Messner HA, Conly J, Chan CK. Aerosolized pentamidine prophylaxis for Pneumocystis carinii pneumonia after allogeneic marrow transplantation. *Transpl Infect Dis* 2002; **4**: 66-74 [PMID: 12220242]

54 **Montgomery AB**. Prophylaxis of Pneumocystis carinii pneumonia in patients infected with the human immunodeficiency virus type 1. *Semin Respir Infect* 1989; **4**: 311-317 [PMID: 2697054]

55 **DeMasi JM**, Cox JA, Leonard D, Koh AY, Aquino VM. Intravenous pentamidine is safe and effective as primary pneumocystis pneumonia prophylaxis in children and adolescents undergoing hematopoietic stem cell transplantation. *Pediatr Infect Dis J* 2013; **32**: 933-936 [PMID: 23538522 DOI: 10.1097/INF.0b013e318292f560]

56 **Kim SY**, Dabb AA, Glenn DJ, Snyder KM, Chuk MK, Loeb DM. Intravenous pentamidine is effective as second line Pneumocystis pneumonia prophylaxis in pediatric oncology patients. *Pediatr Blood Cancer* 2008; **50**: 779-783 [PMID: 17635000]

57 **Machado CM**, Macedo MC, Medeiros RS, Massumoto C, Silva AC, Castelli JB, Silva RL, Ostronoff M, Dulley FL. Primary Pneumocystis carinii prophylaxis with aerosolized pentamidine after bone marrow transplantation. *Acta Haematol* 1998; **99**: 54-56 [PMID: 9490570]

58 **Vasconcelles MJ**, Bernardo MV, King C, Weller EA, Antin JH. Aerosolized pentamidine as pneumocystis prophylaxis after bone marrow transplantation is inferior to other regimens and is associated with decreased survival and an increased risk of other infections. *Biol Blood Marrow Transplant* 2000; **6**: 35-43 [PMID: 10707997]

**P-Reviewer:** Zielinski T **S-Editor:** Ji FF **L-Editor: E-Editor:**