Published in final edited form as:
*Pediatr Blood Cancer*. 2008 April ; 50(4): 779–783. doi:10.1002/pbc.21287.

# Intravenous Pentamidine Is Effective as Second Line *Pneumocystis* Pneumonia Prophylaxis in Pediatric Oncology Patients

**Su Young Kim, MD, PhD**[1], **Alix A. Dabb, PharmD**[2], **Donald J. Glenn, MPH**[2], **Kristen M. Snyder, MD**[1], **Meredith K. Chuk, MD**[1], and **David M. Loeb, MD, PhD**[1,*]

[1]Division of Pediatric Oncology, Department of Oncology, The Johns Hopkins Hospital, Baltimore, Maryland [2]Division of Pediatric Oncology, Department of Pharmacy, The Johns Hopkins Hospital, Baltimore, Maryland

## Abstract

**Background—***Pneumocystis jirovecii*, formerly *carinii*, pneumonia (PCP) poses a life-threatening risk to oncology patients. The use of trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis virtually eliminates the risk of infection; however, many patients cannot tolerate TMP-SMZ. We performed a retrospective analysis to determine the PCP breakthrough rate in pediatric oncology patients receiving intravenous pentamidine as second line PCP prophylaxis.

**Procedure—**We conducted a retrospective chart review of pediatric oncology patients who received intravenous pentamidine from 2001 to 2006 at our institution. The diagnosis, age and bone marrow transplant (BMT) status were determined. A subset of patients had review of their records to determine the justification for discontinuing TMP-SMZ. Children who developed symptoms of pneumonia with a clinical suspicion of PCP underwent bronchoscopy, allowing for identification of *Pneumocystis*.

**Results—**A total of 232 patients received 1,706 doses of intravenous pentamidine and no toxicities were identified. The main reasons for discontinuing TMP-SMZ were bone marrow suppression and drug allergy. Three children developed PCP, equating to a breakthrough rate of 1.3%. Two of these children had undergone BMT (1.9% breakthrough rate) and both were under the age of two (6.5% breakthrough rate).

**Conclusions—**The use of intravenous pentamidine as PCP prophylaxis results in a breakthrough rate of 1.3%. TMP-SMZ is the first choice for PCP prophylaxis. However, when necessary, the use of intravenous pentamidine has an acceptably low failure rate, even in high-risk BMT patients. Other options should be considered for children less than 2 years of age.



*Correspondence to: David M. Loeb, Assistant Professor, Oncology and Pediatrics, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Bunting-Blaustein Cancer Research Building, Room 254, 1650 Orleans Street, Baltimore, MD 21231. loebda@jhmi.edu.

This study has been presented in part at the 2006 Annual ASCO Conference as an abstract. Chuk MK, et al. 2006. The use of IV pentamidine as second line prophylaxis for pneumocystis pneumonia. *Journal of Clinical Oncology*. 24 supplement: #9043.

### Keywords

pentamidine; *Pneumocystis* pneumonia; prophylaxis

## INTRODUCTION

*Pneumocystis jirovecii* (formerly *carinii*) is a very common pathogen with over two-thirds of children demonstrating antibodies by the age of 4, usually from asymptomatic infections [1]. *Pneumocystis* infections have serious implications for immuno-compromised patients. In pediatric oncology patients, the mortality rate associated with *P. jirovecii* pneumonia (PCP) is 24% despite early diagnosis and appropriate treatment [2]. Fortunately, the widespread use of trimethoprim-sulfamethoxazole (TMP-SMZ) prophylaxis has virtually eliminated all cases of PCP [3]. However, there are many children who cannot tolerate TMP-SMZ due to myelosuppression, drug allergy, or inability to take or absorb oral medications.

Aerosolized pentamidine is a common second line prophylactic agent. In adult bone marrow transplant (BMT) patients, the use of aerosolized pentamidine results in PCP breakthrough rates ranging from 1.2% to 2.7%, demonstrating its effectiveness as a second line prophylactic agent in a high-risk population [4,5]. Several smaller studies in pediatric oncology patients have confirmed the efficacy of aerosolized pentamidine in children [6–8]. However, the administration of aerosolized pentamidine requires specialized equipment and personnel that may not be available at all centers. There is also the concern that younger children may not receive an adequate amount of the drug due to difficulties in delivery. Therefore, many institutions, including our own, utilize intravenous pentamidine as prophylaxis, even though there are no published data to support its efficacy in the pediatric oncology population.

We performed a 5-year retrospective analysis to determine the efficacy of intravenous pentamidine, administered monthly, in preventing PCP in pediatric oncology patients. We calculated a breakthrough infection rate of 1.3% (or 0.18% per patient-months of treatment). Analysis of patients who underwent bone marrow transplantation revealed a breakthrough rate of 1.9%, which is similar to adult transplant patients who received aerosolized pentamidine [4,5]. These results suggest that the use of intravenous pentamidine is effective as second line PCP prophylaxis, even in high-risk BMT patients.

## METHODS

### Patient Population

The Division of Pediatric Oncology at The Johns Hopkins Hospital is a tertiary pediatric oncology and bone marrow transplantation center. The majority of patients undergoing active treatment receive PCP prophylaxis. The standard regimen consists of TMP-SMZ, given twice daily on two or three consecutive days every week. Patients undergoing bone marrow transplantation receive TMP-SMZ twice daily during the preparetive regimen, after

which it is resumed on Day +28 of the transplant. Patients who cannot tolerate TMP-SMZ receive intravenous pentamidine (4 mg/kg) administered monthly.

### Administration of Intravenous Pentamidine

Pentamidine (4 mg/kg) is diluted in Dextrose 5% water to a final concentration of 6 mg/ml. The drug is administered over a period of 2 hr under nursing supervision in the pediatric oncology outpatient clinic or the pediatric oncology inpatient unit. Patients are monitored for adverse effects during the infusion.

### Data Collection

The Johns Hopkins Hospital Pharmacy Order Entry System records all medication requests including the date and time of distribution. This system was used to identify pediatric oncology patients who received intravenous pentamidine between January 1, 2001 and May 31, 2006, and to determine the number of doses that were dispensed. Each patient's age, diagnosis and whether or not they had undergone BMT were determined by review of the Electronic Patient Record database. The medical records of patients who had received intravenous pentamidine from January 1, 2005 to November 30, 2005 were reviewed to determine the reason for discontinuing TMP-SMZ. The number of patients who were diagnosed with PCP during the 65-month study period allowed us to calculate the breakthrough infection rate.

### Diagnosis of PCP

All patients with a clinical suspicion of PCP underwent bronchoalveolar lavage or open lung biopsy. Samples were inspected for the presence of foamy alveolar casts by modified H+E and later stained with methenamine silver or Gram–Weigart stain to verify PCP. The pathology database was referenced to cross check the number of patients with a diagnosis of PCP.

## RESULTS

### Patient Characteristics

Two hundred thirty-two pediatric oncology patients received at least one dose of intravenous pentamidine from January 2001 to May 2006. No significant toxicities related to the administration of pentamidine were identified and no patient discontinued its use due to intolerance. The total number of doses that these children received was 1,706. The mean number of doses per patient was 7.4, with a range from 1 to 44, and a median of 5 doses.

The diagnoses of our patient population are given in Table I. Fifty percent of patients had leukemia (27% acute lymphoblastic leukemia, 17% acute myelogenous leukemia, 5% other). Children with brain tumors accounted for 11% of our population and those with sarcomas comprised 10%. The number of diagnoses exceeds the number of patients because six children had two oncologic diagnoses.

### TMP/SMZ Intolerance

A subset of patients who received pentamidine from January 1, 2005 to November 30, 2005 was evaluated to determine the reasons that TMP-SMZ was discontinued (Table II). The medical records of 92 children were examined. Fifty-three percent of patients developed myelosuppression, 13% had a drug allergy, 7% could not take oral medications, 7% were noncompliant, and 4% had mucositis.

### PCP Breakthrough Rates

Three of 232 patients who were receiving intravenous pentamidine developed PCP during the study period. This equates to a breakthrough rate of 1.3% (Table III). One thousand seven hundred six total doses were administered to these patients, resulting in a rate of 0.18% per patient-months of treatment. Two of the patients diagnosed with PCP were infants. One had undergone his second matched unrelated BMT for recurrence of bilineage leukemia and the other had undergone autologous BMT for stage IV neuroblastoma. This prompted us to examine our patient population for BMT status and young age.

There were 106 BMTpatients (79 allogeneic and 18 autologous). Nine patients received high-dose cyclophosphamide without exogenous reconstitution for the treatment of aplastic anemia and are included in the transplant group. These patients had received 577 doses of intravenous pentamidine. The PCP breakthrough rate for this high-risk population was 1.9% (2 cases of 106 patients) and 0.35% per patient-months. A correlation between the type of preparative regimen received and the development of PCP could not be made because the two BMT patients who developed PCP received different regimens (cyclophosphamide/total body irradiation and carboplatin/topotecan/thiotepa).

Thirty-one of our patients were children less than 2 years of age and they received 184 doses of intravenous pentamidine. These patients had a breakthrough rate of 6.5% and 1.09% per patient-months. The breakthrough rate for infants who had undergone BMT was 9.1% and 1.92% per patient-months of treatment. Thus, while intravenous pentamidine appears to be as effective as the aerosolized form in the BMT population, young children, and especially young BMT patients, appear to represent a particularly high-risk population for whom intravenous pentamidine may be insufficient PCP prophylaxis.

## DISCUSSION

We present the first report of the use of intravenous pentamidine as routine second line PCP prophylaxis. Our results show a very low breakthrough rate of 1.3% over a 65-month period. The break-through rate in BMT patients was 1.9%, which is similar to the rate in adult BMT patients receiving aerosolized pentamidine [4,5]. These findings suggest that intravenous pentamidine is effective as second line PCP prophylaxis.

Aerosolized pentamidine is often used for PCP prophylaxis in patients who are not able to tolerate TMP-SMZ. Retrospective studies in adult BMT patients have shown breakthrough infection rates between 1.2% and 2.7% [4,5]. Aerosolized pentamidine has also been used in pediatric oncology patients. There are several reports that show no PCP in this setting [6–8]. However, all of these studies were very small and the patient population would not be

defined as high-risk, suggesting that this may be an overestimate of the effectiveness of aerosolized pentamidine in children. The data for the use of intravenous pentamidine as prophylaxis in children are limited to small retrospective studies in HIV patients [9,10].

Atovaquone has been compared to aerosolized pentamidine in the HIV setting. Breakthrough rates in this population were 22% and 17% respectively, suggesting that these agents are equally efficacious as second line prophylaxis [11]. A prospective randomized trial comparing atovaquone with TMP-SMZ following autologous BMT showed that 0 of 16 patients who received atovaquone developed PCP [12]. The infection rate in the TMP-SMZ arm could not be determined due to early discontinuation of the trial due to high intolerance levels. More recently, a retrospective study of children with leukemia at St. Jude Children's Hospital showed no PCP in 86 patients who received daily atovaquone over a median of 1.5 years, including 37 patients who had undergone bone marrow transplantation [13]. This result is slightly better than what we report, however, the sample size is smaller, making it difficult to compare the two regimens.

Two of the patients in our study who succumbed to PCP were infants who had undergone bone marrow transplantation. Recent autopsy findings of immunocompetent infants, most of whom died in automobile accidents, showed that all (79 of 79) had *P. jirovecii* in their lungs as determined by PCR analysis [14]. This suggests that infants are the natural reservoir for *P. jirovecii*. The absence of PCP in immunocompetent children suggests that children eventually clear the organism as their immune systems develop. Children with cancer are immunosuppressed secondary to chemotherapy, preventing them from clearing the organisms as their peers do. Infants who undergo bone marrow transplantation are continuously immunosuppressed and have a higher likelihood of still being colonized. Therefore, this group constitutes the highest risk population.

Even when PCP is identified early and treated appropriately with high-dose TMP-SMZ, there is a high mortality rate [2]. This seems to conflict with the observation that prophylaxis with TMP-SMZ has virtually eliminated PCP infections [3]. One theory to explain this discrepancy is that *P. jirovecii* develops resistance to TMP-SMZ. Because the organism cannot be cultured, this hypothesis cannot be tested directly, but there are molecular and epidemiologic studies that support this hypothesis. Sulfonamides inhibit folate biosynthesis by targeting the product of the dihydropteroate synthase (DHPS) gene. Use of the *Saccharomyces cerevisiae* homolog to DHPS in an *Escherichia coli* complementation model shows that DHPS mutations cause increased sulfonamide resistance [15]. The use of TMP-SMZ as PCP prophylaxis in HIV patients leads to DHPS mutations in the organism, with a trend toward increased mortality from infection [16]. In contrast, Beard et al. [14] did not find DHPS mutations in *P. jirovecii* in any of the 79 infants found to be colonized. We therefore hypothesize that infants are colonized with *P. jirovecii* at the time of their cancer diagnosis and have difficulty clearing the organism due to the immunosuppressive effects of chemotherapy. Prophylactic TMP-SMZ can induce mutations in the DHPS gene and when the infant develops PCP, it is due to a resistant organism. Reports that some patients respond to treatment with pentamidine, despite a failure in clinical improvement with intravenous TMP-SMZ lends support to this hypothesis [2].

In summary, we report the efficacy of intravenous pentamidine as PCP prophylaxis in patients intolerant of TMP-SMZ. We observed a PCP breakthrough rate of 1.3% with the use of intravenous pentamidine administered monthly in pediatric oncology patients. BMT patients who are at high risk of developing infection have a similarly low rate of 1.9%, justifying the use of intravenous pentamidine as second line prophylaxis. Infants, who would benefit most from non-oral and non-aerosolized therapy, have a higher breakthrough rate of 6.5%. The actual and theoretical concerns that are associated with PCP infection in this population suggest that TMP-SMZ prophylaxis should be continued for as long as possible, even in circumstances that might warrant discontinuation of the drug in older patients.

Due to the limitations inherent to a retrospective study, we were not able to compare our breakthrough rates with a group given prophylaxis with aerosolized pentamidine. In addition, since this was a single institution study, it is unclear if our rates underestimate or overestimate national incidence rates. Although historical data provides an estimate of infection rates, this does not account for changes in therapy that have occurred over the years. All of these variables make it difficult to establish the current PCP breakthrough rate with second line agents in pediatric oncology patients. These questions can only be answered by performing a randomized trial comparing intravenous pentamidine versus aerosolized pentamidine or atovaquone in a multi-institution setting. This approach would lead to the enrollment of more patients, allowing for stratification according to diagnosis, while eliminating single institution bias. The greatest benefit of such a national study would be the ability to collect the samples of patients who progress while on prophylaxis. Molecular analysis of these strains may then be able to help us understand the pathophysiology of *Pneumocystis* that breaks through prophylaxis.

## REFERENCES

1. Pifer LL, Hughes WT, Stagno S, et al. Pneumocystis carinii infection: Evidence for high prevalence in normal and immunosuppressed children. Pediatrics. 1978; 61:35–41. [PubMed: 400818]
2. Hughes WT, Feldman S, Chaudhary SC, et al. Comparison of pentamidine isethionate and trimethoprim-sulfamethoxazole in the treatment of Pneumocystis carinii pneumonia. J Pediatr. 1978; 92:285–291. [PubMed: 304478]
3. Hughes WT. Five-year absence of Pneumocystis carinii pneumonitis in a pediatric oncology center. J Infect Dis. 1984; 150:305–306. [PubMed: 6332155]
4. Vasconcelles MJ, Bernardo MVP, King C, et al. 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. [PubMed: 10707997]
5. Marras TK, Sanders K, Lipton JH, et al. Aerosolized pentamidine prophylaxis for Pneumocytis carinii pneumonia after allogeneic marrow transplantation. Transpl Infect Dis. 2002; 4:66–74. [PubMed: 12220242]
6. Weinthal J, Frost JD, Briones G, et al. Successful Pneumocystis carinii pneumonia prophylaxis using aerosolized pentamidine in children with acute leukemia. J Clin Oncol. 1994; 12:136–140. [PubMed: 8270969]
7. Mustafa MM, Pappo A, Cash J, et al. Aerosolized pentamidine for the prevention of Pneumocystis carinii pneumonia in children with cancer intolerant or allergic to trimethoprim/sulfamethoxazole. J Clin Oncol. 1994; 12:258–261. [PubMed: 8113834]
8. O'Sullivan BP, Spaulding R. The use of aerosolized pentamidine for prophylaxis of Pneumocystis carinii pneumonia in children with leukemia. Pediatr Pulmonol. 1994; 18:228–231. [PubMed: 7838621]

9. Ena J, Amador C, Pasquau F, et al. Once-a-month administration of intravenous pentamidine to patients infected with human immunodeficiency virus as prophylaxis for Pneumocystis carinii pneumonia. Clin Infect Dis. 1994; 18:901–904. [PubMed: 8086550]
10. Gupta M, Stephenson K, Gauar S, et al. Intravenous pentamidine as an alternate for Pneumocystis carinii pneumonia prophylaxis in children with HIV infection. Pediatr Pulmonol Suppl. 1997; 16:199–200. [PubMed: 9443273]
11. Chan C, Montaner J, Lefebvre EA, et al. Atovaquone suspension compared with aerosolized pentamidine for prevention of Pneumocystis carinii pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. J Infect Dis. 1999; 180:369–376. [PubMed: 10395851]
12. Colby C, McAfee SL, Sackstein R, et al. Aprospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as Pneumocystis carinii pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 1999; 24:897–902. [PubMed: 10516703]
13. Madden RM, Pui CH, Hughes WT, et al. Prophylaxis of Pneumocystis carinii pneumonia with atovaquone in children with leukemia. Cancer. 2007; 109:1654–1658. [PubMed: 17345613]
14. Beard CB, Fox MR, Lawrence GG, et al. Genetic differences in Pneumocystis isolates recovered from immunocompetent infants and from adults with AIDS: Epidemiological implications. J Infect Dis. 2005; 192:1815–1818. [PubMed: 16235182]
15. Iliades P, Meshnick SR, Macreadie IG. Analysis of Pneumocystis jirovecii DHPS alleles implicated in sulfamethoxazole resistance using an Escherichia coli model system. Microb Drug Resist. 2005; 11:1–8. [PubMed: 15770087]
16. Crothers K, Beard CB, Turner J, et al. Severity and outcome of HIV-associated Pneumocystis pneumonia containing Pneumocystis jirovecii dihydropteroate synthase gene mutations. AIDS. 2005; 19:801–805. [PubMed: 15867494]

## TABLE I

The Diagnosis of Patients Receiving Intravenous Pentamidine

| | | | Number of patients[a] | |
|---|---|---|---|---|
| **Category** | **% of patients** | **Diagnosis** | **All** | **BMT** |
| Total | | | 238 | 112 |
| Leukemias | 50% | Acute lymphoblastic | 65 | 18 |
| | | Acute myelogenous | 41 | 29 |
| | | Bilineage | 7 | 6 |
| | | Chronic myelogenous | 3 | 3 |
| | | Biphenotypic | 2 | 1 |
| Brain tumors | 11% | Medulloblastoma | 8 | 2 |
| | | Astrocytoma | 5 | 1 |
| | | Glioblastoma multiforme | 3 | 1 |
| | | Other | 10 | 2 |
| Sarcomas | 10% | Osteosarcoma | 10 | 0 |
| | | Ewing's sarcoma | 7 | 0 |
| | | Rhabdomyosarcoma | 4 | 0 |
| | | Other | 2 | 1 |
| Others | 10% | Neuroblastoma | 14 | 13 |
| | | Wilm's tumor | 3 | 2 |
| | | Germ cell tumor | 2 | 1 |
| | | Nasopharyngeal carcinoma | 2 | 0 |
| | | Hepatoblastoma | 1 | 0 |
| | | Renal medullary carcinoma | 1 | 0 |
| Lymphomas | 6% | Hodgkin's | 7 | 6 |
| | | Burkitt's | 4 | 1 |
| | | Other | 4 | 2 |
| Myelodysplasias | 6% | Aplastic anemia | 12 | 9 |
| | | Fanconi anemia | 1 | 1 |
| | | Kostmann's congenital neutropenia | 1 | 1 |
| | | Paroxysmal nocturnal hemoglobinuria | 1 | 1 |
| Immunodeficiencies | 3% | Autoimmune disorders | 4 | 4 |
| | | Various disorders | 4 | 3 |
| Histiocytoses | 2% | Hemophagocytic lymphohistiocytosis | 4 | 1 |
| | | Langerhans' cell histiocytosis | 1 | 0 |
| Lymphoproliferation | 1% | Post-transplantation lymphoproliferation | 2 | 1 |
| | | Lymphoproliferative disorder | 1 | 0 |
| Mucopolysaccharides | 1% | Hurler syndrome | 2 | 2 |

[a] Six patients had two oncological diagnoses, resulting in more diagnoses than patients.

**TABLE II**

Reasons for Discontinuation of TMP-SMZ

| **92 Patients from January 1, 2005 to November 30, 2005** | |
|---|---|
| Myelosuppression | 53% |
| Drug allergy | 13% |
| Inability to take oral medications | 7% |
| Noncompliance | 7% |
| Mucositis | 4% |
| Transferred from another institution | 2% |
| Elevated liver function tests | 1% |
| Liver fibrosis | 1% |
| Liver failure | 1% |
| Congenital neutropenia | 1% |
| G6PD deficiency | 1% |
| Autoimmune enteropathy | 1% |
| Insurance | 1% |
| Unknown | 7% |

**TABLE III**

PCP Breakthrough Rates

| | Number of patients | Pentamidine doses | PCP diagnoses | Infection rate (%) | Infection rate per dose (%) |
|---|---|---|---|---|---|
| All patients | 232 | 1706 | 3 | 1.3 | 0.18 |
| BMT patients | 106 | 577 | 2 | 1.9 | 0.35 |
| Infant patients[a] | 31 | 184 | 2 | 6.5 | 1.09 |
| Infant BMT patients[a] | 22 | 104 | 2 | 9.1 | 1.92 |

[a]Infants are patients less than 2 years of age.