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<https://escholarship.org/uc/item/28m2248v>

Journal

PEDIATRIC INFECTIOUS DISEASE JOURNAL, 35(2)

ISSN

0891-3668

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Publication Date

2016

DOI

10.1097/INF.0000000000000946

Peer reviewed

Safe and Effective Prophylaxis with Bimonthly Intravenous Pentamidine in the Pediatric Hematopoietic Stem Cell Transplant Population

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Background: Without prophylaxis, *Pneumocystis jiroveci* pneumonia (PCP) develops in 5%–15% of pediatric hematopoietic stem cell transplant (HCT) patients with mortality above 50%. Trimethoprim–sulfamethoxazole is a standard PCP prophylaxis; pentamidine is frequently used as second-line prophylaxis because of trimethoprim–sulfamethoxazole’s potential for cytopenias. Monthly intravenous (IV) pentamidine has variable efficacy with PCP infection rates of 0%–10% in pediatric patients, and higher breakthrough rates in those younger than 2 years. We hypothesized that bimonthly (twice monthly) pentamidine might have equivalent safety and improved efficacy; therefore, we conducted a retrospective analysis of bimonthly pentamidine PCP prophylaxis. **Methods:** We retrospectively reviewed records of all pediatric HCT patients who received bimonthly IV pentamidine between December 2006 and June 2013, and collected data regarding demographics, clinical course, prophylaxis rationale, laboratory values and adverse events.

Results: Between December 2006 and June 2013, 111 pediatric HCT patients received bimonthly IV pentamidine (574 doses, 8758 patient-days); 31 patients were younger than 2 years at initiation. In the majority (53% of courses), pentamidine was initiated because of cytopenias. Fourteen patients (12.6% of patients, 2.4% of doses) experienced a side-effect prompting discontinuation, including 3 patients with infusion-related hypotension/anaphylaxis and 3 with acute pancreatic dysfunction. No patients [0% (95% confidence interval: 0–3.2)] developed PCP during or after bimonthly IV pentamidine prophylaxis.

Conclusions: Bimonthly IV pentamidine for PCP prophylaxis in the HCT pediatric population has comparable safety to monthly IV pentamidine and was highly effective, including in the very young. Bimonthly IV pentamidine should be considered in pediatric patients as second-line PCP prophylaxis.

Key Words: pediatric, stem cell transplant, PCP prophylaxis, intravenous pentamidine

(*Pediatr Infect Dis J* 2016;35:135–141)

In the absence of prophylaxis, *Pneumocystis jiroveci* pneumonia (PCP) develops in 5%–15% of pediatric hematopoietic stem cell transplant (HCT) patients and has a mortality rate higher than 50%.^{1–3} Trimethoprim–sulfamethoxazole (TMP–SMZ) is standard

and validated prophylaxis in the vast majority of adult and pediatric oncologic patients.^{4–8} Recent meta-analyses have demonstrated high efficacy of TMP–SMZ prophylaxis in pediatric HCT populations with disease risk reduction of 0.09 and very low PCP breakthrough (0%–0.2%).⁷ However, some pediatric patients cannot tolerate TMP–SMZ because of bone marrow suppression, allergy, side effects or inability to use oral medications; in these patients, atovaquone, dapsone or pentamidine are considered acceptable second-line prophylaxis.^{7,8} Because of the lack of high-quality data, national recommendations conflict regarding second-line prophylaxis in pediatric patients, and consequently, practice varies according to institutional preference.^{7–14}

In patients undergoing HCT, second-line prophylaxis is frequently used because TMP–SMZ is thought to contribute to bone marrow suppression in patients with ongoing cytopenias.¹² Pentamidine is often thought preferable to dapsone and atovaquone as second-line in the HCT population because both require patients to tolerate oral intake; in addition, dapsone has been implicated in hematologic toxicities in HCT patients, and atovaquone may potentiate liver dysfunction.^{8,15–17} In pediatric populations, intravenous (IV) pentamidine is often preferred over aerosolized pentamidine because of concerns for effective aerosolized delivery, particularly in younger children, who are less likely to be compliant.^{3,7,14,18–20} Monthly IV pentamidine is an attractive choice because of ease of delivery and its relatively benign side-effect profiles in children.^{3,7,14,18–22} In recent pediatric HCT literature, adverse events prompting discontinuation of monthly IV pentamidine have been reported between 6% and 10% of patients, with major events like hypotension or anaphylaxis reported in 2%–5% of patients.^{14,18,19,23} Importantly, IV pentamidine has not been associated with cytopenias or delayed engraftment.^{14,19,24}

However, monthly IV pentamidine prophylaxis in pediatric patients has variable efficacy in preventing PCP. In the past decade, several studies using monthly dosing of IV pentamidine in broad cohorts of immunocompromised children reported PCP infection rates between 5% and 10%, with higher infectious breakthrough in the HCT patients (as opposed to oncology patients) particularly in the <2-year-old population.^{14,18–20,25–27} Higher breakthrough in younger patients may be related to the type of immunodeficiencies seen in children of this age or to increased drug metabolism in younger patients.^{19,20} In addition, pharmacokinetic studies demonstrate a 10-to-14-day elimination half-life, suggesting that monthly dosing may be inferior to more frequent administration.²⁸

Pediatric HCT institutions across the country have varying protocols for IV pentamidine administration: a 2009 survey revealed that 20 of 25 HCT centers in the Primary Immune Deficiency Treatment Consortium employ IV pentamidine as a second-line agent, with 10 of 20 administering it every 4 weeks, 3 of 20 every 3 weeks and 7 of 20 every 2 weeks (Cowan, 2009, personal communication). Given efficacy concerns and pharmacokinetic studies, the University of California San Francisco (UCSF) Benioff Children’s Hospital San Francisco administers prophylactic IV pentamidine every 2 weeks (bimonthly) to pediatric HCT patients requiring second-line PCP prophylaxis. We hypothesized that bimonthly IV pentamidine would

Accepted for publication September 23, 2015.

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This work was supported by University of California, San Francisco and Clinical and Translational Science Institute (CTSI) Biostatistical Consulting Resident Research Funding Grant: UCSF-CTSI Grant Number UL1 TR000004. The authors have no conflicts of interest or to disclose.

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ISSN: 0891-3668/16/3502-0135

DOI: 10.1097/INF.0000000000000946

have a similar side-effect profile and increased prophylactic efficacy in comparison with previous reports for monthly pentamidine. To demonstrate this, we performed a retrospective review to quantify the efficacy and toxicities of bimonthly IV pentamidine PCP prophylaxis in our pediatric HCT population.

MATERIALS AND METHODS

UCSF's Pediatric Blood and Marrow Transplant Program treats a diverse group of children, who need transplant for a variety of oncologic, hematologic, metabolic and immunologic illnesses. The standard posttransplant regimen includes initiation of PCP prophylaxis with TMP-SMZ (twice a day, 3 times weekly) at day +21. If the patient is still neutropenic at day +21, bimonthly pentamidine is initiated in the place of TMP-SMZ, with the goal of transition to TMP-SMZ when neutrophil recovery occurs (as demonstrated by absolute neutrophil count $>500/\text{mm}^3$ for 3 days without granulocyte colony stimulating factor). If posttransplant patients who have been initiated on TMP-SMZ, become neutropenic (absolute neutrophil count <500) during recovery because of oncologic relapse or other marrow suppression, pentamidine is initiated at that time as alternative PCP prophylaxis. IV pentamidine is the only alternative (second-line) prophylaxis that is used in the UCSF pediatric HCT population as per our standard operating protocol; all other forms of alternative prophylaxis are considered third-line and would only be used in the rare event of pentamidine failure or contraindication. Standard pentamidine dosing is 4 mg/kg IV every 2 weeks (bimonthly); UCSF pediatric HCT patients typically do not receive aerosolized pentamidine. In patients greater than 40 kg, the pentamidine dilution is 6 mg/mL; this same dilution was also used for patients less than 40 kg before January 2012. The standard concentration was changed in January 2012 to 2 mg/mL for patients less than 40 kg. Transplant patients remain on some form of PCP prophylaxis for at least 6 months and until demonstrated CD4 cell count recovery to $>200/\text{mm}^3$ with a functional T-cell response to phytohemagglutinin of $>50\%$ of the lower limit of control. If patients must be transitioned off pentamidine and TMP-SMZ is contraindicated, there is no standard third-line PCP prophylaxis, and choice is left to clinician discretion. Before transplant, most oncology and primary immunodeficiency patients receive TMP-SMZ, whereas patients with other nonmalignant conditions, who are not immunodeficient are generally not taking PCP prophylaxis.

This study included all HCT patients at UCSF Benioff Children's Hospital San Francisco who received IV pentamidine between December 2006 and June 2013 and were younger than 21 years at the time of pentamidine administration. Patients were identified through the electronic medication administration database in our hospital and cross-referenced with the UCSF pediatric HCT database. HCT patients who were identified as having received bimonthly pentamidine were selected for further detailed chart review. A subgroup analysis was performed for the subset of patients who were initiated on bimonthly pentamidine when younger than 2 years in consideration of prior reports that this population may be at highest risk for breakthrough during monthly IV pentamidine.^{20,24} Patient details were abstracted until resumption of alternative prophylaxis, or for those who did not resume alternative prophylaxis, at least 14 days beyond the last pentamidine dose. Discrete pentamidine courses were defined by separation with another form of PCP prophylaxis or discontinuation of prophylaxis for greater than 1 month. Detailed chart review included demographics (age, ethnicity and primary diagnosis), clinical course (time to transplant, transplant regimen, stem cell source, major illnesses particularly respiratory illnesses, relapse and death) and rationale for pentamidine initiation as per clinician report. Many of the

patients were on alternative PCP prophylaxis before and after pentamidine initiation, so detailed information was collected about the transition between modes of prophylaxis.

Toxicities of pentamidine were assessed in 2 ways for each 2-week pentamidine dosing period: (1) baseline and peak laboratory values for creatinine, aspartate aminotransferase and alanine transaminase were abstracted directly from laboratory records; (2) examination of clinician daily progress notes for adverse symptoms attributed to pentamidine were recorded qualitatively by transcribing the clinician's wording. Adverse symptoms data included both short-term infusion reactions (anaphylaxis, arrhythmia, confusion/hallucination, hypotension, shortness of breath, local skin reaction, skin numbness/tingling and nausea/vomiting) and chronic side effects (hepatotoxicity, nephrotoxicity, pancreatitis, dysgeusia, anemia, thrombocytopenia or rash). Concurrent medications that might be hepatotoxic or nephrotoxic as determined by our transplant pharmacist (L.M.) were also recorded for each 2-week period to account for possible confounding for significant hepatotoxicity or nephrotoxicity.

All patients included in the study who had respiratory symptoms underwent work-up guided by clinical discretion. For patients in whom there was clinical suspicion of PCP, bronchoalveolar lavage or open lung biopsy were performed. Bronchoalveolar lavage samples were inspected by UCSF pathology for the presence of foamy alveolar casts with methenamine silver or Gram-Weigert stain to verify PCP.

A descriptive analysis using means, medians, variances and standard deviation (SD) was performed to analyze qualitative and quantitative data. *P* values for demographics and toxicity were calculated by Fisher exact analysis. Confidence intervals (CI) for efficacy proportions were computed using the exact binomial method. *P* values for efficacy comparison with other prior reported PCP incidences with pentamidine prophylaxis were calculated by Fisher exact tests. Side effects that our patient population experienced, both in total and the subset prompting discontinuation, were compared with the most current side effects reported in a standardized pharmacy database Lexicomp (Philadelphia, PA). Statistical analyses were performed by a biostatistical consultant at the UCSF Clinical & Translational Science Institute. This study was approved by the institutional review board at UCSF with a waiver of consent.

RESULTS

Patient Characteristics

Between December 2006 and June 2013, 332 individual patients had a collective total of 366 transplants. One hundred and twenty-seven patients (38%) received pentamidine prophylaxis as some point during their treatment course, 16 of whom were excluded from the study because of a variety of alternative dosing or route (1 of these patients was excluded for aerosolized pentamidine). One hundred and eleven pediatric HCT patients (with a total of 141 transplants) received bimonthly IV pentamidine and were included in the study. Thirty-one patients were in the younger than 2 years subgroup at the time of pentamidine initiation (with a total of 40 transplants in these patients; Fig. 1). One (1%) patient received 4 transplants, 6 (5%) patients received 3 transplants (4 with planned triple tandem autologous transplants), 15 (14%) received 2 transplants and 89 (80%) patients received 1 transplant. The average age was 6.9 years (SD, 6.0) with median age 4.5 years (first quartile median, 1.8; third quartile median, 11.7). The characteristics of the included patients are summarized in Table 1. Of the 111 included patients, the majority had leukemia (37%) or immunodeficiency (27%) as their reason for HCT.

**UCSF BENIOFF CHILDRENS HOSPITAL
December 2006-June 2013**

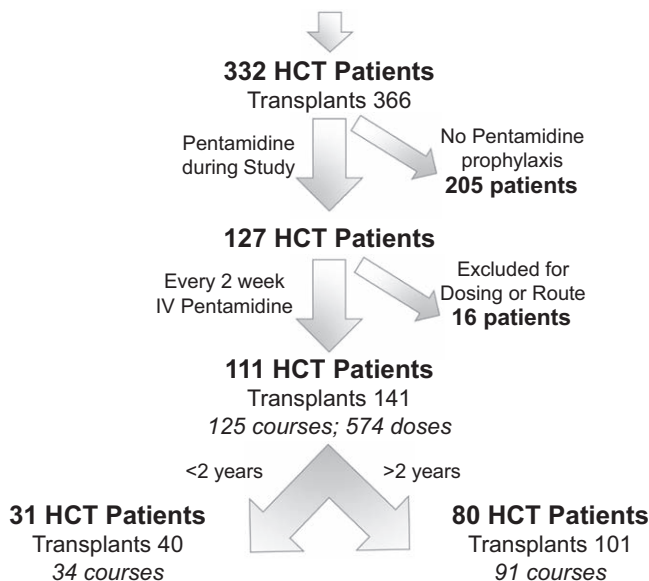


FIGURE 1. Study population. One hundred and twenty-seven HCT patients received pentamidine during the study period, meeting initial criteria. Of those, 111 patients were included, whereas 16 were excluded based on dosing or route.

Dosing and Pentamidine Course Information

One hundred and eleven patients received 125 discrete pentamidine courses with a total of 574 doses (8758 patient-days) of pentamidine. There were 34 pentamidine courses initiated in HCT patients younger than 2, 2 of these patients also had a later pentamidine course when they were older (included in the >2-year-old course numbers). The average length of pentamidine course was 70 days (4.6 doses) with a SD of 78.5 days (5.1 doses); range, 14–449 days (1–30 doses). The average length of pentamidine in the <2-year-old population was 80.7 days (5.4 doses) with a SD of 87.4 days (5.9 doses); range, 14–440 days (1–30 doses). Thirty-four courses consisted of only 1 administration with replacement prophylaxis starting subsequently (at the 2-week mark).

Pentamidine Initiation

Rationales regarding TMP–SMZ discontinuation and pentamidine initiation for the discrete 125 courses are summarized in Figure 2. The most common reason for pentamidine initiation was myelosuppression [67 (53%) courses], and the second most common reason for initiation was intolerance of oral medications [16 (13%) courses]. The majority of time pentamidine was initiated for myelosuppression, and it was following transplant after an initial failure of TMP–SMZ trial (63%), although 34% of courses were initiated without a trial of TMP–SMZ (because of anticipated prolonged bone marrow recovery). Sixty-four (51.2%) pentamidine courses were initiated within 30 days of transplant, 38 (30.4%) were initiated in the 31-to-90-day period, and 23 (18.4%) were initiated longer than 91 days post transplant.

Pentamidine Discontinuation and Toxicities

Pentamidine discontinuation rationale for the 125 individual courses is shown in Table 2. The most common discontinuation reasons were resolution of myelosuppression (allowing reinstitution of TMP–SMZ). When replaced with alternative prophylaxis, the

TABLE 1. Patient Characteristics

Demographics	Total (%)	Age < 2 (%)
Primary diagnosis	111 (100)	31 (28)
Leukemias	41 (37)	3 (10)
Lymphomas	2 (2)	0 (0)
Myelodysplastic syndrome	5 (5)	0 (0)
Brain tumors	6 (5)	2 (6)
Neuroblastoma	9 (8)	1 (3)
Bone marrow failure	10 (9)	1 (3)
Immunodeficiency/HLH	31 (28)	20 (65)
Other*	7 (6)	4 (13)
Ethnicity	111	
Caucasian	46 (41)	
Hispanic	36 (32)	
Black	3 (3)	
Asian	20 (18)	
Other	6 (5)	
Gender	111	
Male	66 (59)	
Female	45 (41)	
Transplant type	141	
Autologous	27 (19)	
Haploidentical	24 (17)	
Matched related donor	29 (21)	
Unrelated donor	61 (43)	
Stem cell source	141	
Cord blood	13 (9)	
Marrow	37 (26)	
PBSC	91 (65)	
Conditioning intensity	141	
Non-myeloablative	17 (12)	
Reduced intensity	28 (20)	
Myeloablative	96 (68)	

Demographic data for all included patients, including diagnosis, ethnicity, gender, transplant, stem cell source and conditioning intensity.

*Sarcoma, hurlers, hunters, sickle cell and porphyria.

HLH indicates hemophagocytic lymphohistiocytosis; PBSC, peripheral blood stem cells (90 patients PBSC only, 1 patient combined with bone marrow).

majority of pentamidine, 74% of courses, was replaced by TMP–SMZ. Five patients were transitioned to third-line alternative prophylaxis, 4 (3% of courses) replaced with atovaquone and 1 (1% of courses) with dapsone. Of these, 4 had experienced an adverse effect of second-line pentamidine (see below); the fifth was restarted on atovaquone by outside providers after transition back into their care.

Fourteen patients (11.2% courses, 12.6% of patients) experienced an adverse effect prompting discontinuation of pentamidine (2.4 for every 100 pentamidine doses or 0.16 for every 100 patient-days; Table 2). Two of the 14 discontinued courses occurred after only 1 pentamidine dose. An additional 7 patients (5.6% of courses; 6.3% of patients) experienced a side effect which clinicians attributed as possibly related to pentamidine but did not lead to pentamidine discontinuation. Side effects that our patient population experienced both in total and the subset prompting discontinuation are compared with the most current side effects reported in a standardized pharmacy database Lexicomp in Figure 3.²³

Four patients (3.6% patients; 0.7% of all 574 doses) experienced hypotension and hemodynamic instability during an infusion; 3 of these patients (2.7%) had pentamidine discontinued after the episode. The fourth patient was continued on pentamidine with careful monitoring during subsequent doses as she was intubated in the intensive care unit and had multiple reasons for hemodynamic instability at the time of the infusion; she did not have any recurrence with subsequent infusions. Two of the patients were younger than 2 years with severe combined immunodeficiency (SCID), a third patient was younger than 3 years with SCID and the fourth

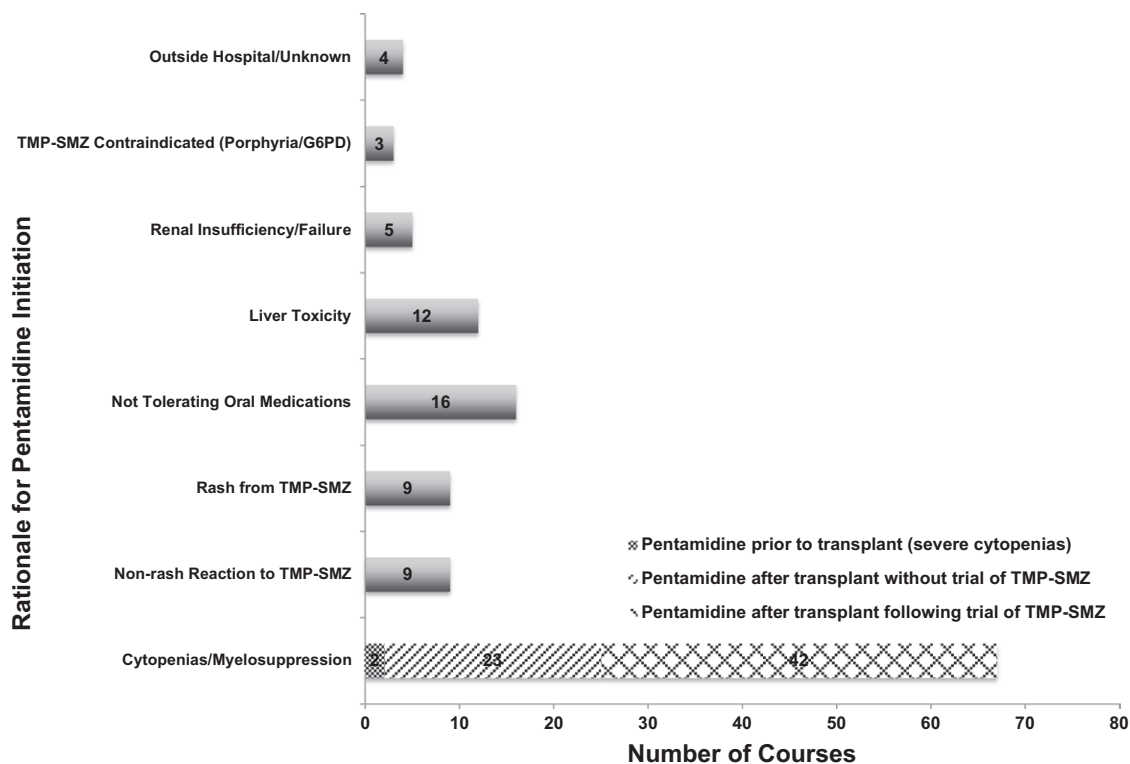


FIGURE 2. TMP-SMZ discontinuation and pentamidine initiation. Clinician rationale for pentamidine initiation. If a clinician listed cytopenia/myelosuppression as rationale for initiating pentamidine, we further categorized by timing of this initiation in relationship to transplant timing (before transplant, after transplant without TMP-SMZ trial because of prolonged bone marrow recovery and after transplant following trial of TMP-SMZ).

TABLE 2. Pentamidine Discontinuation

	N (%)
Resumption of first-line prophylaxis	86 (68.9)
Resolved myelosuppression	52 (41.6)
Tolerating oral medications	12 (9.6)
Improved transaminitis	7 (5.6)
TMP-SMZ initiated for another infection/indication	3 (2.4)
Other or unknown reason	12 (9.6)
Changed to monthly pentamidine (via outside provider)	3 (2.4)
No further prophylaxis required	22 (17.6)
Patient death	10 (8.0)
CD4/immune reconstituted	10 (8.0)
Hospice	2 (1.6)
Adverse reaction to pentamidine	14 (11.2)
Infusion reaction	10 (8.0)
Hypotension	3 (2.4)
Dyspnea/tachycardia	1 (0.8)
Abdominal pain/nausea/vomiting	2 (1.6)
Rash/pruritus	2 (1.6)
Perioral numbness/tingling	2 (1.6)
Pancreatic dysfunction	3 (2.4)
Hepatotoxicity	1 (0.8)
Nephrotoxicity	0 (0.0)
Total courses	125 (100.0)

Pentamidine discontinuation categories included resumption of TMP-SMZ (first-line prophylaxis) for a variety of reasons, changing dosing to an alternative dosing pattern rather than bimonthly, cessation of prophylaxis or adverse reaction. For patients who had an adverse reaction, we categorized the type and severity of reaction.

was 15 years old and had acute myeloid leukemia. Patients with SCID were more likely to develop hypotension/hemodynamic instability from pentamidine administration when compared with

non-SCID patients ($P = 0.009$). Notably, there was no statistical difference in comparing patients <2 to those >2 years old for development of hypotension ($P = 0.31$). Each episode responded to fluid and supplemental oxygen, and none resulted in cardiac arrest or respiratory failure requiring intubation, although 1 patient was temporarily transferred to the intensive care unit.

Four patients (3.6% patients) developed pancreatic dysfunction and/or pancreatitis. In all 4 patients, multiple medications were simultaneously stopped, and in 3 of the 4, this included pentamidine (2.7%). The fourth patient's pancreatitis resolved before being able to tolerate oral medications. Three of these 4 patients had been diagnosed and treated for acute lymphocytic leukemia (ALL), whereas the remaining patient was receiving a transplant for SCID. Patients with prior ALL were more likely to develop pancreatitis while on IV pentamidine ($P = 0.009$).

Noninfusion-related reactions also included hepatotoxicity and nephrotoxicity and were additionally assessed by laboratory values. One patient (0.9%; 0.9% discontinued) developed hepatotoxicity, both quantitatively (transaminitis) and by clinician report, which was attributed to pentamidine and prompted discontinuation. One patient (0.9%; 0% discontinued) developed renal insufficiency, which was partially attributed to pentamidine but resolved without pentamidine discontinuation; this patient was simultaneously on carboplatin and a fluoroquinolone antibiotic.

There was no statistical difference in an adverse reaction prompting discontinuation in the <2 versus >2 -year-old patient population ($P = 0.10$) or by primary diagnosis ($P = 0.75$) when compared with other diagnoses. Patients, who received autologous transplants, were statistically less likely to experience side effects than other patients ($P = 0.02$).

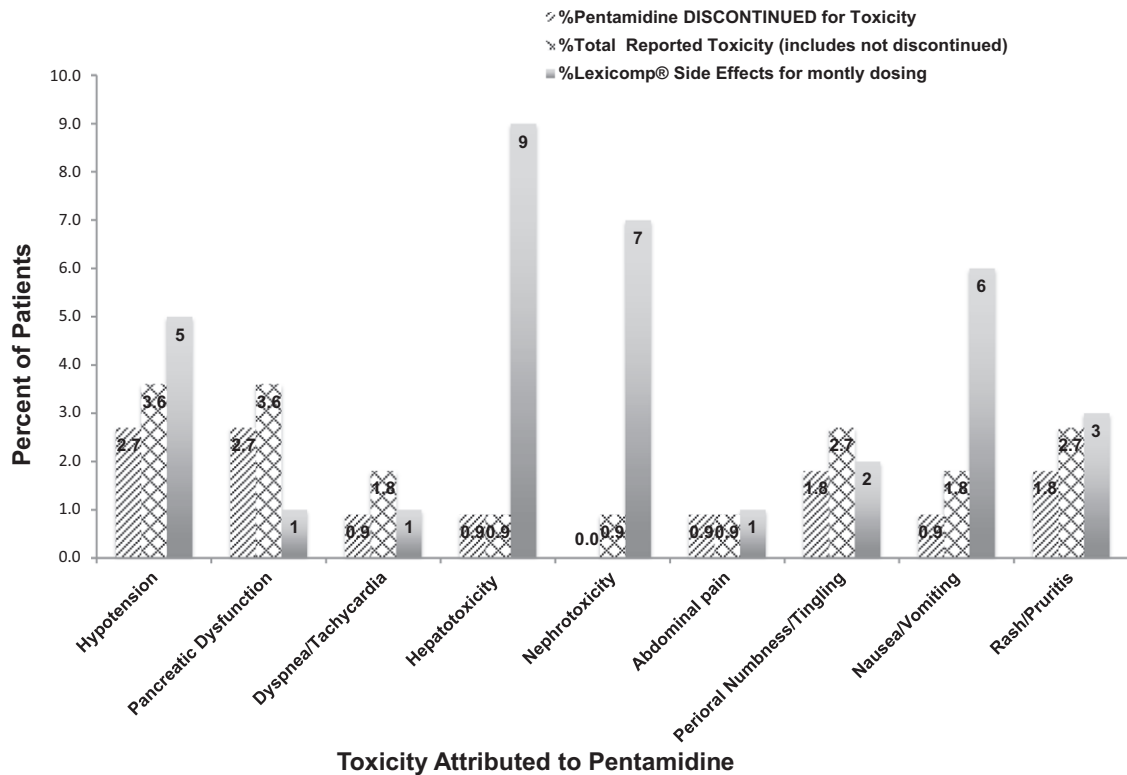


FIGURE 3. Pentamidine toxicity compared with Lexicomp standardized database. This figure compares toxicities that resulted in discontinuation, total toxicities, which were reported or determined because of laboratory values (including those which did not result in discontinuation) and a standardized national database prediction of pentamidine toxicity. Our patients had more pancreatic dysfunction but less than expected hepatotoxicity and nephrotoxicity. Major toxicities like hypotension were similar to expected.

PCP Breakthrough

Our rate of PCP breakthrough was 0% (95% CI: 0–3.2), including 0% in our <2-year-old population (95% CI: 0–11.2). No patients were diagnosed with PCP at any time during or after IV pentamidine. There were 4 patients in the study with respiratory failure for whom clinicians included PCP on the differential diagnosis. Three of these patients underwent bronchoalveolar lavage with resultant negative silver stain. The fourth patient passed away after respiratory failure, and post-mortem lung pathology revealed adenovirus as the source and was negative for PCP.

Using pooling of previous literature reports of efficacy for IV monthly pentamidine prophylaxis in pediatric HCT patients, we created a confidence interval comparison of prior reports for monthly versus every 3–4 weeks versus bimonthly (every 2 weeks) pentamidine PCP breakthrough (Table 3). Sample sizes in all groups were small and were not able to power statistical significance when dealing with such a rare event as breakthrough PCP.

DISCUSSION

We present here the first analysis of efficacy and toxicities for bimonthly IV pentamidine as second-line PCP prophylaxis for

TABLE 3. Efficacy Comparison

	Levy et al (2015)	Clark et al ¹⁴ + Orgel et al ¹⁹	Demasi et al ²⁴ + Kim et al ²⁰ + Prasad et al ²⁵	P Value*
IV pentamidine dosing	Every 2 weeks	Every 3–4 weeks	Every 4 weeks	
Total non-HCT patients	NA	163	138	
HCT patients <2 years old	31	31†	34	
Total HCT patients	111	287	243	
HCT PCP cases <2 years old (95% CI)	0 (0%, CI: 0–11.2)	0 (0%, CI: 0–11.2)	2 (5.9%, CI: 0.7–19.7)	0.33
Total HCT PCP cases (95% CI)	0 (0%, CI: 0–3.2)	1 (0.3%, CI: 0–1.9)	2 (0.8%, CI: 0.1–2.9)	0.77
Total PCP cases (95% CI)	0 (0%, CI: 0–3.2)	3 (0.7%, CI: 0.1–1.9)	5 (1.3%, CI: 0.4–3.1)	0.52

Comparison of previous studies pooled by pentamidine dosing regimen. Compared with those who report monthly dosing, we observed less PCP breakthrough, with a notable, though not statistically significant, difference in the <2-year-old category.

*P value for any difference in 3 groups.

†Total <2 years old (Clark, personal communication, 2015).

pediatric HCT patients. Our review included 111 pediatric HCT patients, with 125 discrete IV pentamidine courses, and 574 pentamidine doses over 8758 patient-days. Our patients had similar total side-effect profiles to the side-effect profile of monthly IV pentamidine, both in the pharmaceutical available databases and to those reported in similar literature, with 8% discontinuation because of allergic reaction. The majority of our patients were in the immediate peritransplant period (51% of courses initiated within 30 days, 81% within 90 days) when T-cell immunity is predicted to be most severely compromised. No patients included in our study contracted PCP.

Although statistical comparison was difficult, side effects that our patient population experienced both in total and the subset prompting discontinuation were generally similar to incidence reported in the standardized pharmacy database Lexicomp (Fig. 3), with perhaps more pancreatic dysfunction, but less hepatotoxicity and nephrotoxicity.²³ Recent groups who have profiled pediatric oncology or HCT patients on monthly IV pentamidine have reported a range of overall adverse event discontinuation from 6.6% to 10%, which is comparable with our overall discontinuation rate of 11.2%, of courses with 8% discontinuation prompted by infusion reactions.^{14,19,24}

Major infusion-related side effects prompting discontinuation (hypotension, anaphylaxis and hemodynamic instability) were seen in 2.7% of all patients, similar when compared with 2% of patients reported by Demasi et al¹⁸ and 1.7% in Orgel et al.^{14,19} Of the 4 patients, who had major reactions (hypotension or anaphylaxis), 3 were very small patients with SCID. We believe that this may have been due to inadequate dilution of the dose, which resulted in the delivery of a small volume via rapid infusion when the line was primed. In January 2012, we changed the pentamidine dilution protocol from 6 to 2 mg/mL for patients less than 40 kg. As this protocol change, there have been no episodes of hypotension during pentamidine infusions.

Our patient population did have a higher percentage of pancreatitis than we expected; an adverse effect which was statistically much more likely in patients with prior diagnosed/treated ALL. Pancreatitis in pediatric HCT patients on IV pentamidine has also been reported by others analyzing adverse events in the HCT population.¹⁴ Patients who are being treated for ALL are likely at higher risk for development of pancreatitis at baseline because of previous asparaginase exposure, and there may be an additive effect from IV pentamidine or other medications known to predispose to pancreatitis. Based on our subgroup analysis of side effects, we suspect that primary oncologic diagnosis and treatment before HCT has significant impact on side-effect predisposition while on pentamidine. For patients with previous diagnoses of ALL, it may be prudent to attempt to avoid concomitant administration of other medications known to contribute or cause pancreatitis while on pentamidine.

There have been multiple retrospective studies reviewing the efficacy of monthly IV pentamidine prophylaxis in pediatric patients. Although concerns had been raised in the past regarding reduced lung penetration of IV pentamidine, many of these studies demonstrated clinically equivalent efficacy compared with the aerosolized route, and thus, IV pentamidine is often preferred in the very young because of ease of delivery.^{3,7,20,22,29,30} Weintrub et al³¹ reported breakthrough of 14% in a small national survey about monthly IV pentamidine in pediatric HIV, and Gupta et al³² reported 6% PCP breakthrough for q3–q4 weeks dosing in 30 children with HIV; both groups concluded IV pentamidine was acceptable as second-line prophylaxis for their populations with comparable breakthrough rates to other available options.

More recently, there have been numerous studies describing IV pentamidine prophylaxis in pediatric oncology and HCT populations. Two single-center studies reviewed monthly IV

pentamidine prophylaxis in pediatric oncology patients; Orgel et al¹⁹ found 1.8% PCP breakthrough (95% CI: 0.2–6.0) and Prasad et al²⁵ found 16.7% PCP breakthrough (95% CI: 2.1–48.4). Kim et al²⁰ described their institutional experience of monthly IV pentamidine for prophylaxis in oncologic and HCT patients, with an overall breakthrough in HCT patients of 1.9% (95% CI: 0.2–6.6). Kim et al²⁰ suggested that, in particular, young HCT patients (<2 years old) were at higher risk for PCP breakthrough based on this subgroup infection rates of 9.1% (95% CI: 1.1–29.25). Demasi et al²⁴ published a retrospective analysis of monthly IV pentamidine in their pediatric HCT population; they reported no PCP incidence [all included 0% (95% CI: 0–4.3), <2-year-old population 0% (95% CI: 0–26.5)] and hypothesized that IV pentamidine may be as effective as TMP–SMZ for prophylaxis.¹⁸ Notably, the Demasi et al¹⁸ study included only 12 patients in the <2-year-old subgroup, a population that has been hypothesized to be at higher risk for PCP breakthrough.^{19,20} Most recently, Clark et al¹⁴ conducted a similar retrospective review of q3–q4 weeks IV pentamidine in all transplant patients in their institution, including pediatric HCT patients; their group reported 0.3% PCP breakthrough [95% CI: 0–1.9]. Interestingly, Clark et al¹⁴ reported less breakthrough than Kim et al²⁰ in a comparably sized HCT retrospective study, but Clark et al¹⁴ also reported a range of dosing frequency (21–28 days) based on provider preference and did not analyze how many HCT patients were in the <2-year-old group.

Our rate of PCP breakthrough was 0% (95% CI: 0–3.2), with a rate of 0% (95% CI: 0–11.2) in the <2 population.^{19,20} Our population demographics were broadly representative of national pediatric HCT populations. One notable demographic difference from previously published studies is that our population included a larger percentage of patients in the <2-year-old HCT subgroup, with 31 patients total; this enrichment was in part because of our larger population of primary immunodeficiency patients. In comparison with pooled numbers for all IV monthly pentamidine prophylaxis in pediatric HCT patients, our dosing regimen demonstrates high efficacy, although sample sizes were not able to power statistical significant comparison among the groups.

This retrospective study had multiple limitations, including a relatively small sample size as limited by our pediatric HCT population. As we were focused on dosing, we had to exclude several patients who did receive IV pentamidine, but not the correct dosing profile. Additionally, this study took place at a single center, with a very high concentration of pediatric HCT in patients with primary immunodeficiencies, which also translated to a population enriched with the very young. We were not able to compare safety or efficacy of different dosing frequencies within a similar population, but instead compared with previous studies done at other single centers. It was difficult to ascertain a trend in the total population when combining multiple heterogeneous groups. Thus, further multicenter studies are needed for final conclusions about secondary prophylaxis comparisons.

In summary, our data supports the use of IV pentamidine as a safe and effective second-line PCP prophylaxis in pediatric HCT patients and suggests that bimonthly dosing should be considered, particularly in very young patients who might be at higher risk for PCP breakthrough with monthly dosing. We found that bimonthly IV pentamidine for PCP prophylaxis has comparable safety in the pediatric HCT population to previous reports of monthly IV pentamidine, without an appreciable increase in major adverse events.

ACKNOWLEDGMENTS

We thank University of California San Francisco, Clinical and Translational Science Institute (CTSI) for biostatistical consulting.

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