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MAJOR ARTICLE

Serious Infections in Patients Receiving Ibrutinib for Treatment of Lymphoid Cancer

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Background. Ibrutinib is a Bruton tyrosine kinase inhibitor that is used for the treatment of lymphoid cancers, including chronic lymphocytic leukemia, Waldenström macroglobulinemia, and mantle cell lymphoma. Several case series have described opportunistic infections among ibrutinib recipients, but the full extent of these infections is unknown. We sought to determine the spectrum of serious infections associated with ibrutinib treatment.

Methods. We reviewed the electronic medical records of patients with lymphoid cancer at Memorial Sloan Kettering Cancer Center who received ibrutinib during a 5-year period from 1 January 2012 to 31 December 2016. Serious infections were identified by review of the relevant microbiology, clinical laboratory, and radiology data. Risk factors for infection were determined by means of univariate and multivariate analyses.

Results. We analyzed findings in 378 patients with lymphoid cancer who received ibrutinib. The most common underlying cancers were chronic lymphocytic leukemia and mantle cell lymphoma. 84% of patients received ibrutinib as monotherapy. Serious infection developed in 43 patients (11.4%), primarily during the first year of ibrutinib treatment. Invasive bacterial infections developed in 23 (53.5%) of these patients, and invasive fungal infections (IFIs) in 16 (37.2%) .The majority of patients with IFIs during ibrutinib therapy (62.5%) lacked classic clinical risk factors for fungal infection (ie, neutropenia, lymphopenia, and receipt of corticosteroids). Infection resulted in death in 6 of the 43 patients (14%).

Conclusions. Patients with lymphoid cancer receiving ibrutinib treatment are at risk for serious infections, including IFIs.

Keywords. infection; ibrutinib; invasive fungal infection.

Ibrutinib is a tyrosine kinase inhibitor that has demonstrated efficacy in the treatment of a variety of lymphoid cancers, including chronic lymphocytic leukemia (CLL), B-cell lymphomas, and Waldenström macroglobulinemia (WM), in which tumor regression or stabilization and improvement in symptoms have been observed in the majority of treated patients [1–7]. Ibrutinib is generally well tolerated. Major adverse effects include fatigue, diarrhea, nausea, increased bleeding risk, atrial fibrillation, neutropenia, and thrombocytopenia [4, 6, 8]. Ibrutinib was approved by the US Food and Drug Administration for the treatment of patients with CLL, previously treated mantle cell lymphoma (MCL) or marginal zone lymphoma, WM, or refractory chronic graft-versus-host disease, and by the European Medicines Agency for the treatment of patients with CLL, WM, or previously treated MCL [1].

The main cellular target of ibrutinib is Bruton tyrosine kinase (BTK), a nonreceptor tyrosine kinase from the Tec family that is critical for B-cell proliferation and survival [9]. BTK and other members of the Tec family also function in other immune cell populations, including macrophages, where they regulate receptor-mediated phagocytosis, including phagocytosis of fungal organisms such as *Candida albicans* [10, 11]. In mice, BTK deficiency is linked to susceptibility to *Aspergillus fumigatus* infection [12]. In humans, loss of BTK expression, as seen in individuals with X-linked agammaglobulinemia (XLA) [13–15], results in the absence of circulating B cells and an increased risk for infections with encapsulated pyogenic bacteria and enteroviruses [16]. However, the infectious risks associated with BTK pharmacologic blockade remain poorly defined.

Recently, there have been several reports of opportunistic infections in patients who received ibrutinib treatment, including in cases of *Pneumocystis jirovecii* pneumonia (PJP), cryptococcosis, and invasive mold infection [12, 17–26]. We sought to comprehensively determine the spectrum of serious infections associated among patients receiving ibrutinib for the treatment of lymphoid cancer and to identify additional risk factors associated with infection in these patients.

METHODS

The study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSKCC), a 473-bed tertiary care cancer center in New York, New York. We reviewed the electronic medical records of all patients ≥18 years of age

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with diagnosed lymphoid cancer, including CLL and non-Hodgkin lymphoma, who were treated with ibrutinib, either as monotherapy or in combination with other drugs, during a 5-year period from 1 January 2012 to 31 December 2016. Patients who were excluded if they did not have ≥30 days of clinical follow-up at MSKCC after initiation of ibrutinib therapy.

Data collected from each patient included demographics, type of underlying cancer, ibrutinib dose and duration, prior and concurrent cancer treatments, use of adjunctive corticosteroids, receipt of antimicrobial prophylaxis, presence of neutropenia or lymphopenia at any time during ibrutinib therapy, and clinical outcomes. Receipt of corticosteroids was defined as receipt of an average daily dose equivalent to ≥20 mg of prednisone for ≥14 days at any time from initiation of ibrutinib treatment to its discontinuation. Neutropenia was defined as an absolute neutrophil count ≤500/μL and lymphopenia as an absolute lymphocyte count ≤400/μL at any time during the course of ibrutinib therapy.

MSKCC guidelines recommend PJP prophylaxis for patients with lymphoid cancer who are receiving chemotherapy with a purine analogue or alemtuzumab or are receiving an average daily dose equivalent to ≥20 mg of prednisone for ≥4 weeks. Antifungal prophylaxis with fluconazole is recommended for patients undergoing chemotherapy with an anticipated absolute neutrophil count <100/μL for >7 days.

Infections were identified by reviewing patient laboratory data and imaging studies and, if available, histopathologic or cytology results. For cases with microbiologic and/or radiologic findings suggestive of infection, we further reviewed the clinical chart to confirm the presence of associated symptoms and ascertain clinical outcomes. Cause of death was determined by consensus agreement among the investigators.

Serious infection was defined as an infection that required hospitalization and/or parenteral antimicrobial therapy that occurred at any time from initiation of ibrutinib until 30 days after its discontinuation. Invasive fungal infections (IFIs) were defined based on the revised 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group guidelines [27].

Statistical Analysis

We used χ^2 or Fisher exact methods for analysis of categorical variables and the Mann-Whitney test to analyze continuous variables. All statistical tests were 2 tailed and were performed using a significance level of .05.

Logistic regression was used to assess for risk factors for infection. First, a univariate analysis of all clinical predictors was performed. All variables significant at $P \leq .15$ in univariate analyses were considered as possible predictor variables for multivariate analysis. Age and ibrutinib dose were coded as continuous variables, and neutropenia and lymphopenia as time-dependent variables. Death was included as a competing event. All statistical analyses were performed using R software, version 3.3 (R Development Core Team).

RESULTS

Patient Characteristics

A total of 459 patients with lymphoid cancer received ibrutinib during the 5-year period. Of these, 81 were excluded for having a clinical follow-up period of <30 days after initiation of ibrutinib. Among the 378 remaining patients in the analysis, the underlying cancer was CLL in 165 (44%), MCL in 61 (16%), diffuse large B-cell lymphoma in 52 (13%), and WM in 34 (9%) (Table 1). Their mean age was 66 years (range, 19–95 years), and 246 patients (66%) were men (Table 2).

The most frequently administered daily ibrutinib doses were 420 mg in 250 patients (66%) and 560 mg in 86 (23%). The mean duration of ibrutinib treatment was 413 days (range, 3–1631 days). The majority of patients (84%) received ibrutinib as monotherapy. For those who received additional agents concurrently with ibrutinib, the most common were rituximab in 18 patients, R-ICE (rituximab plus ifosfomide, carboplatin, and etoposide) in 13 patients, R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) in 5, and nivolumab in 10.

The median number of prior treatment regimens was 2 (range, 0–10). Seventy-one patients (19%) had received ibrutinib as their first-line treatment, and the remainder (307 patients; 81%) had received ≥1 treatment regimen before ibrutinib. Thirty-seven patients (10%) received corticosteroids concurrently with ibrutinib. Nearly three-quarters had received rituximab before ibrutinib. Thirty-seven (10%) had previously received fludarabine, 5 within 2 years before receipt of ibrutinib. Two patients had previously received alemtuzumab, both within a year before receipt of ibrutinib.

Thirty-six patients (10%) had previously undergone autologous and 10 (3%) had previously undergone allogeneic hematopoietic stem cell transplantation (HSCT). Twelve patients (3%) had documented neutropenia, and 28 (7%) had documented lymphopenia more than once during the course of ibrutinib therapy.

Compared with patients with CLL, those with non-Hodgkin lymphoma received higher daily doses of ibrutinib on average and more commonly received ibrutinib in combination with

Table 1. Underlying Cancers

Cancer	Patients, No. (%)
Chronic lymphocytic leukemia	165 (44)
Non-Hodgkin lymphoma	213 (56)
Mantle cell lymphoma	61 (16)
Diffuse large B-cell lymphoma	52 (13)
Waldenström macroglobulinemia	34 (9)
Follicular lymphoma	23 (6)
Marginal zone lymphoma	15 (4)
Primary central nervous system lymphoma	14 (4)
Other[a]	14 (4)

[a]Other cancers included multiple myeloma (5 patients), mycosis fungoides (4 patients), primary mediastinal large B-cell lymphoma (2 patients), and anaplastic large cell, γδ T-cell, and enteropathy-associated T-cell lymphoma (1 patient each).

Table 2. Patient Characteristics

Patient Characteristics	Patients, No. (%)[a]			
	All Patients (N = 378)	CLL (n = 165)	NHL (n = 213)	*P* Value
Age, mean (SD), y	66 (12)	67 (10)	65.1 (13)	.36
Male sex	246 (66)	115 (70)	131 (62)	.10
Ibrutinib daily dose, mean, mg	485	420	536	<.001
Ibrutinib daily dose				
280 mg	9 (2)	5 (3)	4 (2)	
420 mg	250 (66)	157 (95)	93 (44)	
560 mg	86 (23)	2 (1)	84 (39)	
840 mg	33 (9)	1 (1)	32 (15)	
Prior treatment regimens, mean (range), No.	2.31 (0–10)	1.55 (0–8)	2.90 (0–10)	<.001
Ibrutinib as 1st-line treatment	71 (19)	54 (33)	17 (8)	<.001
Rituximab before ibrutinib	271 (72)	99 (60)	172 (81)	<.001
Fludarabine before ibrutinib	37 (10)	28 (17)	9 (4)	<.001
Alemtuzumab before ibrutinib	2 (0.5)	2 (1)	0 (0)	.19
Prior HSCT[b]	43 (11)	5 (3)	38 (18)	<.001
Autologous	36 (10)	1 (0.6)	35 (16)	<.001
Allogeneic	10 (3)	4 (2)	6 (3)	.99
Ibrutinib monotherapy	316 (84)	157 (95)	159 (75)	<.001
Neutropenia	12 (3)	8 (5)	4 (2)	.14
Lymphopenia	28 (7)	4 (2)	24 (11)	.001
Corticosteroid use	37 (10)	11 (7)	26 (12)	.08
Antimicrobial prophylaxis				
PJP prophylaxis	60 (16)	21 (13)	39 (18)	.16
Antifungal prophylaxis	16 (4)	5 (3)	11 (5)	.44
Infection	43 (11)	20 (12)	23 (11)	.75
Bacterial	23 (6)	9 (5)	14 (7)	.83
Fungal	16 (4)	10 (6)	6 (3)	.13
Viral	4 (1)	1 (0.6)	3 (1)	.64

Abbreviations: CLL, chronic lymphocytic leukemia; HSCT, hematopoietic stem cell transplantation; NHL, non-Hodgkin lymphoma; PJP, *Pneumocystis jirovecii* pneumonia; SD, standard deviation.

[a]Data represent No. (%) of patients unless otherwise specified.

[b]Some patients underwent >1 type of HSCT.

other agents (Table 2). They were more likely to have received other regimens, rituximab, and autologous HSCT before ibrutinib. They were less likely to have previously received fludarabine (Table 2).

Serious Infections

Serious infection developed in 43 patients (11.4%). Infection developed during ibrutinib treatment in 31 patients, and within 30 days after cessation of treatment in 12. The median time from initiation of ibrutinib to development of infection was 136 days (range, 8–1082 days), and 84% of infections occurred during the first year of ibrutinib treatment (Figure 1). Six patients (1.6%) died owing to progression of the infection.

Of the 43 patients in whom serious infection developed, 16 (37.2%) had fungal infections, including proved or probable invasive aspergillosis (IA) in 8 patients, PJP in 3, concurrent probable IA and PJP in 1, pulmonary cryptococcal infection in 3, and *C. albicans* bloodstream infection in 1. Of the 8 cases of aspergillosis, 2 involved the brain in addition to the lungs and 1 involved the pleura; the remaining cases were limited to the lungs. Clinical characteristics of patients with fungal infection are detailed in Supplementary Table 1. None of these patients had undergone prior HSCT. One had received fludarabine and 1 alemtuzumab in the 2 years before ibrutinib initiation. One patient in whom IFI developed had received prophylaxis with

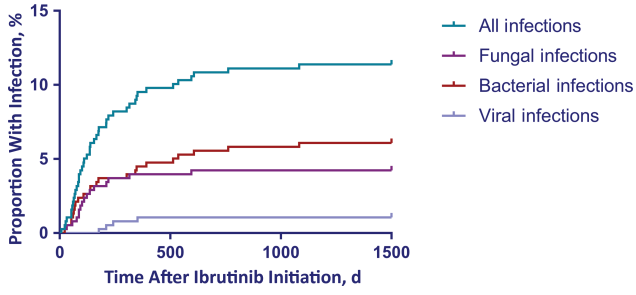

Figure 1. Serious infection after ibrutinib initiation. A Kaplan-Meier graph shows the probability of developing any serious infection, bacterial infection, fungal infection or viral infection after initiation of ibrutinib therapy. The y-axis represents the cumulative incidence of infection.

Table 3. Infection Risk Analysis: Patients With All Serious Infections Versus Those with No Infection

Parameter	Univariate Comparison		Multivariate Comparison	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	1.01 (.98–1.04)	.49	…	…
Female sex	1.09 (.59–2.01)	.79	…	…
CLL as underlying cancer	0.87 (.48–1.57)	.64		
Ibrutinib daily dose	1.001 (.999–1.003)	.42	…	…
≥3 Prior treatment regimens	1.98 (1.09–3.61)	.02	2.03 (1.17–3.52)	.01
Concurrent antitumor agents other than ibrutinib	1.23 (.52–2.93)	.64	…	…
Prior fludarabine	0.66 (.21–2.15)	.66	…	…
Neutropenia	3.35 (1.67–6.75)	.001	2.78 (1.34–5.76)	.006
Lymphopenia	2.08 (.81–5.34)	.13	2.02 (.84–4.86)	.11
Corticosteroid use	1.72 (.65–4.50)	.27	…	…
Antimicrobial prophylaxis				
PJP prophylaxis	1.95 (.94–4.05)	.074	1.30 (.61–2.77)	.49
Antifungal prophylaxis	1.73 (.42–7.04)	.45	…	…

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; OR, odds ratio; PJP, *Pneumocystis jirovecii* pneumonia.

fluconazole, and 3 had received prophylaxis against PJP for a period of time while taking ibrutinib. No patient was receiving prophylactic regimen at the time of IFI.

Bacterial infection developed in 23 patients (53.5%), with *Staphylococcus aureus* the most common bacterial pathogen identified. Among the cases of bacterial infection were 10 cases of pulmonary or pleural space infections and 7 of bloodstream infection. Clinical characteristics of patients with bacterial infection are shown in Supplementary Table 2.

Viral infections developed in the remaining 4 patients (9.3%), including 3 cases of pneumonia due to respiratory viruses and 1 of hepatitis B reactivation. The clinical characteristics of patients with viral infection are shown in Supplementary Table 3.

Risk Factors Associated With Development of Serious Infection

Table 3 shows a comparison between patients in whom any serious infection developed and those in whom it did not. In univariate analysis, risk factors associated with development of serious infection included receipt of ≥3 prior antitumor regimens and the presence of neutropenia at any time during the course of ibrutinib. In multivariate analysis, both factors remained statistically significant. The daily dose of ibrutinib was not associated with infection risk, nor was the cumulative ibrutinib dose (164 953 vs 191 775 mg for infected and uninfected patients, respectively; $P = .24$).

Table 4 shows risk factors associated with the development of IFIs. In univariate analysis, IFIs were associated with receipt of corticosteroids at any time during ibrutinib therapy, and with receipt of ≥3 prior antitumor regimens. Table 5 shows an analysis of factors associated with development of bacterial infection. The only factor associated with development of bacterial infection was the presence of neutropenia. Seventy-one patients had received ibrutinib as first-line treatment; of these, serious infection developed in 7 (10%), including 3 (4.2%) with IFI.

DISCUSSION

We found an 11.4% incidence of serious infections among patients with lymphoid cancer who received ibrutinib therapy. Serious bacterial infections were observed in 6.1% of ibrutinib recipients, and IFI developed in 4.2%, including pulmonary and disseminated IA, pulmonary cryptococcosis, and PJP.

Risk factors for IFI among patients who received ibrutinib included receipt of ≥3 prior antitumor regimens and receipt of corticosteroids at any time during the course of ibrutinib. These factors define a population of patients at increased risk for IFI in which increased monitoring and antifungal prophylaxis should be studied as potential preventive strategies.

Given our study design, we are unable to conclude whether ibrutinib directly contributed to the risk of IFI or other

Table 4. Infection Risk Analysis: Patients With Versus Patients Without Invasive Fungal Infection

Parameter	Univariate Comparison	
	OR (95% CI)	*P* Value
Age	1.002 (.96–1.05)	.94
Female sex	0.46 (.13–1.58)	.21
CLL as underlying cancer	1.78 (.66–4.83)	.26
Ibrutinib daily dose	1.00 (.996–1.004)	.92
≥3 Prior treatment regimens	3.35 (1.22–9.21)	.02
Concurrent antitumor agents other than ibrutinib	2.33 (.74 – 7.31)	.15
Prior fludarabine	1.34 (.29–5.41)	.66
Neutropenia	2.92 (.71–12.09)	.14
Lymphopenia	3.36 (.98–11.55)	.054
Corticosteroid use	4.29 (1.40–13.18)	.01
Antimicrobial prophylaxis		
PJP prophylaxis	1.63 (.47–5.66)	.44
Antifungal prophylaxis	2.12 (.28–15.91)	.46

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; OR, odds ratio; PJP, *Pneumocystis jirovecii* pneumonia.

Table 5. Infection Risk Analysis: Patients With Versus Those Without Bacterial Infections

Parameter	Univariate Comparison	
	OR (95% CI)	*P* Value
Age	1.02 (.99–1.05)	.26
Female sex	1.33 (.58–3.02)	.50
CLL as underlying cancer	0.64 (.28–1.43)	.27
Ibrutinib daily dose	1.002 (.999–1.004)	.25
≥3 Prior treatment regimens	1.611 (.70–3.74)	.27
Concurrent antitumor agents other than ibrutinib	0.74 (.18–3.11)	.68
Prior fludarabine	0.40 (.04–2.36)	.71
Neutropenia	4.24 (1.78–10.11)	.001
Lymphopenia	1.47 (.34–6.34)	.60
Corticosteroid use	0.60 (.08–4.46)	.61
Antimicrobial prophylaxis		
PJP prophylaxis	2.08 (.76–5.66)	.15
Antifungal prophylaxis	1.68 (.23–12.41)	.61

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; OR, odds ratio; PJP, *Pneumocystis jirovecii* pneumonia.

infections. It is important to stress, however, that most of the patients with IFI in our study lacked the established risk factors for IFI. Notably, none of them were HSCT recipients, and 10 (62.5%) had not received corticosteroids, exhibited neutropenia or lymphopenia in the 4 weeks before development of IFI, or received agents associated with long-term immune dysfunction, such as alemtuzumab and fludarabine, in the 2 years before receipt of ibrutinib (Figure 2 and Supplementary Table 1). In addition, the frequencies of IFI among those who received ibrutinib as first-line treatment and those who had received ≥1 prior treatment were identical (4.2%), suggesting that ibrutinib itself may be a direct driver of infection risk rather than prior treatment. Strengthening this conclusion is the fact that the incidence of IFI in our study was higher than what was seen in similar patient populations before the advent of ibrutinib [28, 29]. However, it remains possible that other factors contributed to the risk of IFI in these patients.

The spectrum of infections seen in our study is distinct from that seen in individuals with XLA, who lack BTK expression. In particular, our patients had a relative abundance of IFIs, including invasive mold infections, which have rarely been reported in patients with XLA [30]. This difference may be due to ibrutinib off-target effects on non-BTK Tec family proteins [31]. Another possible explanation is that immune suppression from the underlying lymphoid cancer or from prior lines of chemotherapy acted in conjunction with the ensuing ibrutinib therapy to predispose to IFI.

Primary central nervous system lymphoma (PCNSL) was the underlying diagnosis in only 14 patients in our study, and IFI developed in only 1 of them (7%). In a 2017 study, 7 of 18 (39%) patients with PCNSL who received ibrutinib developed possible, probable, or proved IA [12]. The much higher incidence of IFI in patients with PCNSL in our study may be due to the fact that most patients were receiving cytotoxic chemotherapy and corticosteroids in addition to high-dose ibrutinib (840 mg/d) [12].

An important limitation of our study is that our methods did not allow for identification of infections diagnosed outside MSKCC. Our study may therefore have underestimated the

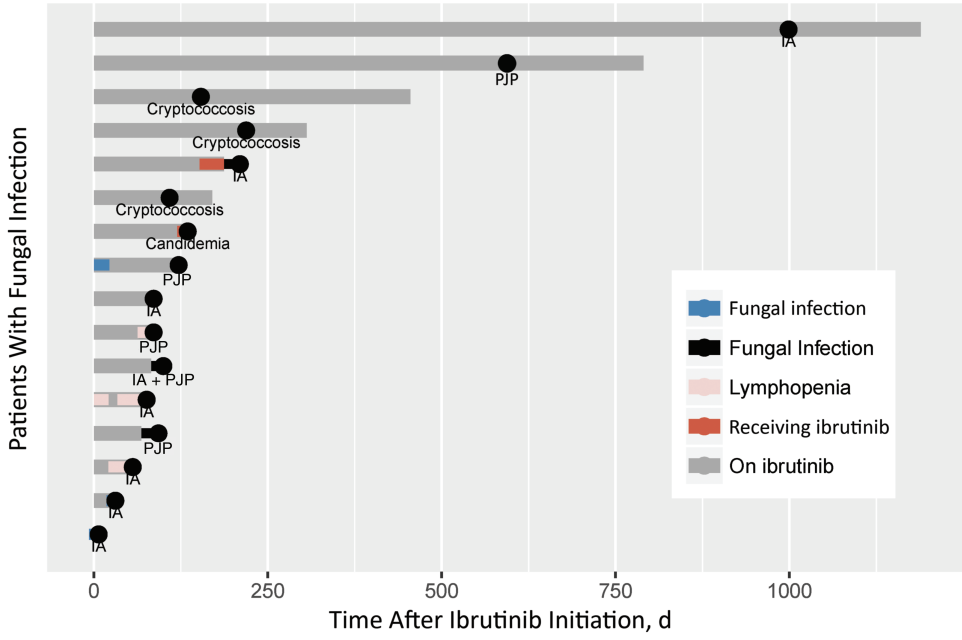

Figure 2. Swimmer plots of patients in whom fungal infections developed. Each bar represents a single patient. Abbreviations: IA, invasive aspergillosis; PJP, *Pneumocystis jirovecii* pneumonia.

incidence of infection if patients sought treatment at alternate facilities. An additional limitation is the relatively few patients with IFI and bacterial infections, which may have affected the validity of our subgroup analyses.

In conclusion, patients with lymphoid cancer receiving ibrutinib are at risk for a variety of serious infections, including IFI. Although ibrutinib was initially approved by the Food and Drug Administration for the treatment of MCL, CLL, and WM [32], recent approvals have expanded its use to include patients with marginal zone lymphoma and chronic graft-vs-host disease [33, 34]. In addition, ibrutinib is currently being evaluated for the treatment of solid tumors, where it is thought to promote a tumor-targeted immune response [35]. As the indications for ibrutinib use continue to expand, it is likely that more patient groups may be at risk for serious infections associated with its use, highlighting the need to for further study to define those most likely to benefit from close clinical monitoring for infectious complications and from targeted prophylaxis strategies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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