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Peripheral Blood Eosinophilia and Hypersensitivity Reactions among Patients Receiving Outpatient Parenteral Antibiotics

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Abstract

Background—While drug-induced peripheral eosinophilia complicates antimicrobial therapy, little is known about its frequency and implications.

Objective—We aimed to determine the frequency and predictors of antibiotic-induced eosinophilia and subsequent hypersensitivity reactions (HSRs).

Methods—We evaluated a prospective cohort of former inpatients receiving intravenous antibiotic therapy as outpatients with at least one differential blood count. We used multivariate Cox proportional hazards models, with time-varying antibiotic treatment indicators, to assess the impact of demographic data and antibiotic exposures on eosinophilia and subsequent HSR, including documented rash, renal injury, and liver injury. Possible Drug Rash Eosinophilia and Systemic Symptoms (DRESS) syndrome cases were identified and manually validated.

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Results—Of 824 patients (60% male, median age 60 years, median therapy duration 41 days), 210 (25%) developed eosinophilia with median peak absolute eosinophil count of 726/mL [IQR: 594–990/mL]. Use of vancomycin, penicillin, rifampin, and linezolid were associated with a higher hazard of developing eosinophilia. There was subsequent HSR in 64/210 (30%) patients with eosinophilia, including rash (N=32), renal injury (N=31), and liver injury (N=13). Patients with eosinophilia were significantly more likely to develop rash (HR = 4.16 [2.54, 6.83]; p<0.0001) and renal injury (HR = 2.13 [1.36, 3.33]; p=0.0009), but not liver injury (HR = 1.75 [0.92, 3.33]; p=0.09). Possible DRESS syndrome occurred in 7/824 (0.8%) patients; 4 (57%) were on vancomycin.

Conclusions—Drug-induced eosinophilia is common with parenteral antibiotics. While most patients with eosinophilia do not develop an HSR, eosinophilia increases the hazard rate of developing rash and renal injury. DRESS syndrome was more common than previously described.

Keywords

allergy; antibiotic; drug; eosinophilia; hypersensitivity; DRESS syndrome; vancomycin; metronidazole; OPAT

INTRODUCTION

Medications are the most common cause of peripheral blood eosinophilia in developed nations (1). Substantial tissue damage is unlikely to occur with an absolute eosinophil count (AEC) less than 1,500/mL, and expert opinion supports that isolated eosinophilia can be monitored without medication changes. However, drug-induced eosinophilia often prompts clinician concern for an impending hypersensitivity reaction (HSR) (2, 3). The basis of clinical concern is that peripheral blood eosinophilia is associated with many severe HSRs, including organ-specific reactions (e.g. immune-mediated nephritis, hepatitis, and pneumonitis), and Severe Cutaneous Adverse Reactions (SCARs) (e.g. Stevens-Johnson's syndrome (SJS)/toxic epidermal necrolysis (TEN), and Drug Rash Eosinophilia and Systemic Symptoms (DRESS) syndrome) (4–11). However, despite the association of eosinophilia with these HSRs, studies have yet to define whether peripheral blood eosinophilia is truly a risk factor for the development of HSRs.

While almost any drug can be implicated to cause HSRs, the risk is largest with antimicrobial agents (12–15). Today, antibiotic use approaches 60% among inpatients, with many infections requiring extended parenteral antimicrobial therapy (16–19). Inpatients requiring prolonged intravenous treatment may receive continued intravenous antimicrobial treatment at home or in a skilled nursing facility through an Outpatient Parenteral Antimicrobial Therapy (OPAT) program (20). While prior studies of OPAT patients have evaluated tolerability, adverse drug reactions, and some allergic reactions (20), research has not evaluated drug-induced peripheral eosinophilia or captured organ-specific injury that is more likely immune-mediated/allergic (an HSR), rather than toxic, in nature.

Among antimicrobials, asymptomatic eosinophilia has most commonly been described with penicillins, cephalosporins, and flouroquinolones (1, 21). However, these same classes of antibiotics are also implicated in HSRs (10, 22, 23). We aimed to identify the frequency of,

and risk factors for, development of peripheral blood eosinophilia and HSRs among a population of monitored outpatients on antimicrobial therapy.

METHODS

Outpatient Parenteral Antibiotic Therapy Cohort and Study Sample

Inpatients who were discharged from the Massachusetts General Hospital (Boston, MA) with at least two weeks of remaining parenteral therapy and who were seen by the Infectious Disease Service during their admission were enrolled prospectively in the OPAT program. With the exception of patients on oral linezolid, all OPAT patients' treatment included at least one parenteral antibiotic. OPAT patients had orders for weekly laboratory evaluations. All OPAT patients were logged in the OPAT database, a prospective database maintained by a single administrative assistant (KSM). Data elements collected included demographic information, dates of treatment, site and/or type of infection, culture results, antimicrobials administered (including both intravenous and oral medication and subsequent medications if treatment was changed during therapy), and antimicrobial-induced complications such as rash, renal injury, liver injury, neutropenia, and thrombocytopenia. Antimicrobial therapy changes, including medication and duration changes, were determined by the patient's primary infectious disease physician. At the start and end of a course of therapy for each patient, the OPAT medical director (SBN), reviewed all medical charts and laboratory reports, verified database entries and documented adverse drug reactions.

We retrospectively identified all OPAT patients who began their therapy from September 1, 2012 through December 31, 2013. All OPAT patients who had at least one differential complete blood count (CBC) were included in the analysis. This study was approved by the Partners Human Research Committee.

Definitions of Eosinophilia and Hypersensitivity Reactions

Consistent with literature-reported definitions, we defined eosinophilia as any AEC greater than or equal to 500/mL and hypereosinophilia as any AEC greater than or equal to 1500/mL (20, 24). All rashes were seen by a medical professional and documented as potentially related to antibiotic therapy. Renal injury was defined as a creatinine increase of at least 0.5 mg/dL or 50% above baseline creatinine. Liver injury was defined as a new alanine aminotransferase>100 U/L. We defined onset of eosinophilia as five days before the CBC demonstrating eosinophilia, and considered an HSR to be any documented rash, renal injury, and/or liver injury occurring after defined onset of eosinophilia. This time frame was chosen based on both the infrequency of OPAT laboratory evaluations and the slow, delayed nature of these HSRs. We conducted a sensitivity analysis using two days (rather than five days) before documented date of eosinophilia to determine if our conclusions were sensitive to this definition. To assess whether any patients suffered DRESS syndrome, we identified patients with eosinophilia either before or concurrent with rash and either liver or kidney injury within a three day time period, and subsequently manually reviewed cases using established criteria for "possible DRESS syndrome" and "probable DRESS syndrome" (10, 25).

Statistical Analysis

Descriptive data were displayed as frequencies or median with interquartile range. Exact (Clopper-Pearson) 95% confidence limits for frequencies were calculated from the binomial distribution. Comparisons of variables (e.g. diagnoses; organisms) between groups (with/without eosinophilia or with/without HSR) used the Fisher's exact test or Wilcoxon Rank Sum test, as appropriate.

We considered “initial antibiotics” as those begun during the initial four days of antimicrobial treatment. When applicable, specific antimicrobials were grouped into common drug classes (e.g. penicillins, cephalosporins). For reporting the proportion of patients using an antibiotic, as exposure in the eosinophilia group was only until the detection of eosinophilia, we normalized the follow-up exposure in the non-eosinophilia (control) group to have the same time distribution. To do this, for each patient who developed eosinophilia, we randomly selected patients without eosinophilia and truncated their follow-up time to match that of the case. We randomly selected either two or three controls per eosinophilia patient without replacement, so that each control in the total control population was used exactly once.

For assessing the impact of baseline variables and drug exposures on eosinophilia and HSR onset, we used multivariate Cox proportional hazards models including time-varying antibiotic treatment indicators (and for HSR, a time-varying eosinophilia onset indicator). Because of the large number of antibiotic classes, we used a backward procedure to construct the multivariate proportional hazards model. The model always included age and gender. Drugs used by less than 1% of patients at any time during follow-up and those with univariate p-value less than 0.50 were not considered for the multivariate model. Both univariate and multivariate (adjusted for age, gender, and other antibiotics) hazard ratios (HR) were assessed. Among eosinophilia patients, we assessed the association of hypereosinophilia with HSR using Fisher’s exact test for a 2×2 contingency table. Two-tailed p-values less than 0.05 were considered statistically significant. Statistical analyses were performed in SAS 9.4 (Cary, NC, USA).

RESULTS

Patient characteristics

Among the 827 patients beginning therapy from September 1, 2012 through December 31, 2013, 824 (>99%) had at least one differential complete blood count during their OPAT treatment and were included in the analysis. Patients had a median age of 60 years [IQR: 48–71y], were 60% male, and a median duration of therapy of 41 days [IQR: 31–45d]; the majority of patients (515/824, 63%) initiated therapy on a single antimicrobial agent (Table 1). The most commonly treated infections were orthopedic infections (N=464) and bacteremia (N=161). Most treated organisms were gram positive (N=641). The most commonly used antibiotics at any time during the entire course of OPAT treatment included cephalosporins (46%), vancomycin (40%), and penicillins (27%) (Supplemental Table 1).

Eosinophilia

Eosinophilia was present in 210/824 patients (25%) during their course of treatment with median peak AEC of 726/mL (IQR: 594–990/mL, range: 500–8,610/mL). Median days of therapy until onset of eosinophilia was 15 [IQR: 8–22d]. Patients who developed eosinophilia were more likely to be older (64 years vs 59 years, p=0.0002) and discharged to a skilled nursing facility instead of home (51% vs 39%, p=0.003) (Table 1).

Use of vancomycin, penicillin, rifampin, and linezolid were associated with a significantly higher hazard of developing eosinophilia (Table 2). Cephalosporins and flouroquinolones were not associated with increased risk of eosinophilia. Use of metronidazole was associated with a reduced risk of eosinophilia (HR 0.46 [0.27, 0.77]).

Hypersensitivity Reactions

Among patients with eosinophilia, there were subsequent signs of HSR in 64/210 patients (30%), including rash (N=32, 15%), renal injury (N=31, 15%), and liver injury (N=13, 6%). Among patients without eosinophilia, there were smaller proportions of patients with rash (6%) and renal injury (10%), but a similar proportion of those with liver injury (7%). After adjusting for age, gender, and other antibiotics, patients with eosinophilia were significantly more likely to develop subsequent rash (HR = 4.16 [2.54, 6.83]; p<0.0001) and renal injury (HR = 2.13 [1.36, 3.33]; p=0.0009) compared to those without eosinophilia (Table 3). Although patients with eosinophilia had an increased hazard of developing liver injury, this increase was not statistically significant after adjustment (HR = 1.75 [0.92, 3.33]; p=0.09).

Limiting the analysis to patients with eosinophilia, patients who suffered a subsequent HSR developed eosinophilia earlier in their course (median 11 vs 17 days, p=0.0002) and had a higher peak AEC (median 857 vs 699/mL, p=0.001). Patients with hypereosinophilia were more likely to have rash than eosinophilia patients with lower maximum values (38% vs 13%, p=0.006), but there was no evidence for a significant association with renal injury (19% vs 14%, p=0.52).

Severe Cutaneous Adverse Reactions

Among patients with eosinophilia, 11/210 (5%) had eosinophilia and more than one sign of HSR (rash, liver injury, kidney injury) during their OPAT course. Of these, possible DRESS syndrome was identified in seven patients (0.8% [95% exact CI: 0.3%–1.8%] of OPAT population and 3% of patients with eosinophilia), of whom three met criteria for probable DRESS syndrome (0.4% of OPAT population and 1% of patients with eosinophilia). Possible DRESS culprit antibiotics included vancomycin (4/7, 57%), penicillins (3/7, 43%), metronidazole (2/7, 29%), gentamicin (1/7, 14%), ceftriaxone (1/7, 14%) and cefepime (1/7, 14%). All three probable DRESS syndrome cases were attributed to vancomycin by subspecialist consultants from either Allergy/Immunology or Dermatology. Of all possible DRESS patients, 2/7 (29%) had deaths attributed to DRESS syndrome. No patients developed a rash consistent with other SCARs such as SJS/TEN or Erythema Multiforme.

Sensitivity Analysis on Definition of Hypersensitivity Reactions

When using a two day time-frame for eosinophilia onset before detection date, rather than a five day time-frame, our conclusions remained generally consistent (data not shown). Using a two day time-frame, however, resulted in a weaker relationship between eosinophilia and liver injury (HR 1.11 [0.51, 2.40], p=0.80) and the inclusion of the cephalosporin class of antibiotics in the multivariate model for renal injury.

DISCUSSION

We assessed a population on outpatient parenteral antibiotics and found that eosinophilia occurred in one quarter of patients, and that for most patients, the eosinophilia is of no clinical consequence. We found the risk of eosinophilia development was higher with age, discharge to a skilled nursing facility, and specific exposure to vancomycin, penicillins, rifampin and linezolid. We found that a patient on antibiotics who has peripheral eosinophilia is over four times as likely to develop a rash and over twice as likely to develop renal injury than a similar patient without eosinophilia; there was a trend toward eosinophilia-related liver injury as well, though this finding was not statistically significant and results were sensitive to our chosen time-frame for a related event. Development of an HSR after eosinophilia onset was more likely with earlier onset of eosinophilia and higher AEC. Lastly, our data support that antibiotic-associated DRESS syndrome may occur at a higher frequency than previously reported in the DRESS syndrome literature (7, 10, 26).

Our finding that one quarter of patients on OPAT developed drug-induced peripheral eosinophilia supports existing expert opinion regarding its frequency. Although these patients were monitored outpatients, we may find a similar prevalence among inpatients given that the most commonly used antibiotics used for OPAT patients (penicillins, cephalosporins, vancomycin) are similar to those used for inpatients. However, OPAT patients may be more likely to develop eosinophilia given their longer antimicrobial courses, and the median onset of eosinophilia in our cohort was 15 days into the prescribed course.

Eosinophilia development was more common with higher age and discharge to a skilled nursing facility in univariate analysis. Patients who are discharged to a skilled nursing facility may be older, have more medical comorbidities or have poor functional status. Therefore, it is possible that the more chronically ill patients are at highest risk of developing eosinophilia, although we were unable to directly assess this with our cohort.

Use of vancomycin, penicillin, rifampin, or linezolid was associated with an increased risk of eosinophilia. Not only was vancomycin use common and an important risk factor for eosinophilia, it was the only drug associated with renal injury with eosinophilia (HR: 2.53, $p < 0.0001$) and any injury (rash, renal injury or liver injury) with eosinophilia (HR: 1.70, p=0.0002), suggesting its propensity to cause HSRs. Indeed, vancomycin causes many delayed HSRs that may include peripheral blood eosinophilia, such as maculopapular rash, interstitial nephritis, SJS/TEN, DRESS syndrome, and linear IgA bullous dermatosis (22, 23, 27–32). Additionally, vancomycin has not typically been considered a cause of isolated eosinophilia (1, 3, 21). Although SCARs were infrequent among OPAT patients, of seven patients identified with possible DRESS syndrome, four (57%) could have been caused by

vancomycin. Furthermore, the three patients with probable DRESS syndrome had this HSR attributed to vancomycin by subspecialist consultants, prior to our analysis of the data. Vancomycin's potential to cause eosinophilia and HSRs should not be overlooked. With increased vancomycin use due to antimicrobial resistance patterns, we may observe more severe HSRs from vancomycin (22, 23, 27–36). The association we found between linezolid, which typically causes leukopenia, and eosinophilia has not previously been described. This may, however, be a spurious finding because we considered a total of eight drugs/classes for the multivariate model without making adjustments for the multiple statistical tests we performed.

A common and important class of antibiotics, the cephalosporins, were notably not associated with an increased hazard rate of developing eosinophilia. Metronidazole use was associated with a lower risk of developing eosinophilia, something that could be an effect of the drug itself or related to the underlying infection being treated by metronidazole (most often *C. difficile* colitis). Interestingly, while our data suggest that it is uncommon to get eosinophilia on metronidazole, some patients on metronidazole who developed eosinophilia ultimately developed DRESS syndrome. More data are needed to understand if development of eosinophilia while on metronidazole portends a poor outcome.

For most patients, the development of eosinophilia was of no clinical consequence. This finding supports expert opinion that patients do not need medication changes due to eosinophilia alone. Yet patients with eosinophilia are at an increased risk of rash and renal injury, as well as at risk for DRESS syndrome, and possibly liver injury. Although many maculopapular rashes are benign and easy to treat, they can impact patient quality of life (9). While immune-mediated nephritis, hepatitis, and DRESS syndrome can improve with discontinuation of the offending agent and use of corticosteroids, organ failure and death is possible (4, 5, 37). Therefore, results of this cohort could guide clinicians to consider medication changes in patients with earlier onset of eosinophilia or higher AEC because it was these patients who more commonly experienced an HSR. Our data supports that detection of eosinophilia while on parenteral antibiotics warrants increased monitoring for rash and renal injury. Although we did not find a statistically significant increase in liver injury following eosinophilia, there was some evidence that the rate was increased (HR: 1.75, P=0.09) although the strength of this association was dependent on our five day time-frame. However, liver injury was observed less frequently than rash and renal injury, so we may have failed to detect an association because of the small number of events. Thus, more data are needed to determine if eosinophilia detection warrants increased liver monitoring.

DRESS syndrome, also referred to as Drug Induced Hypersensitivity Syndrome (DIHS) or Drug Hypersensitivity Syndrome (DHS) (26, 38), was classically described in response to anticonvulsant agents though DRESS syndrome from antimicrobials is increasingly reported (10, 22, 23). Among antimicrobials, DRESS syndrome can be caused by vancomycin, sulfonamides, tetracyclines, β-lactams, and flouroquinolones (7, 10, 22, 23). We found a higher frequency of DRESS syndrome (approximately 1/100 patients) than previously reported in the DIHS/DRESS literature (1/1000 to 1/10,000 exposures) (7, 10, 26, 38). Reported mortality from DRESS syndrome ranges from 5–40% (10, 26, 38), which is

consistent with our findings that two of seven patients (29%) with possible DRESS died from this HSR.

This study is limited by the lack of detail regarding the diagnosis of eosinophilia and HSRs. Patients were considered to have drug-induced eosinophilia if they developed eosinophilia while on antimicrobial therapy although other causes of eosinophilia were not excluded. However, OPAT patients were being treated for bacterial infections, which are largely associated with eosinopenia (39–41), and developed new eosinophilia while on antimicrobial therapy. Regular home medications were not considered to have caused eosinophilia, and we did not track use of non anti infective medications, such as systemic corticosteroids, that may have interfered with eosinophilia detection. While we identified a number of antibiotics associated with significant HR of developing eosinophilia, we cannot rule-out that antibiotics used infrequently in our cohort (e.g. carbapenems, aminoglycosides, aztreonam) might cause eosinophilia as well. To make a definitive diagnosis of HSRs, additional data such as skin biopsy (rash); renal biopsy, urine eosinophils, or urinary sediment (immune-mediated nephritis/AIN), or liver biopsy (immune-mediated hepatitis) would be necessary. These data were not available since they were not clinically indicated for the management of our OPAT patients. We were also limited in our analysis of hypereosinophilia by having only the maximal AEC value available instead of serial eosinophilia measurements over time. Because laboratory monitoring during OPAT is infrequent, varies by treatment regimen (20), and can be triggered by new clinical signs or symptoms, we created a definition for when rash, kidney or liver injury was related to eosinophilia. While we chose five days for this relative interval, our conclusions were generally unchanged when we reevaluated data with two days. The OPAT cohort consists of patients that have significant infections requiring prolonged parenteral therapy though are well enough to be discharged to home or a skilled nursing facility. Therefore, the results may not be generalizable to other populations of patients on parenteral antibiotics.

As a result of our evaluation of a prospective cohort of former inpatients at a large academic medical center, we found that drug-induced eosinophilia is common; vancomycin, penicillin, rifampin, and linezolid were associated with an increased risk of developing eosinophilia while metronidazole was associated with a reduced risk. Although antibiotic-induced eosinophilia is largely benign, it increases a patient’s risk of rash and renal injury. All patients with drug-induced eosinophilia should be counseled regarding their risk of HSR, and monitored for rash and rising creatinine. Medication changes may be warranted in patients with early onset eosinophilia or a high peak AEC, especially if antimicrobial therapy includes medications, such as vancomycin, that are associated with organ-specific reactions or DRESS syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AEC	absolute eosinophil count
HSR	hypersensitivity reaction
SCAR	Severe Cutaneous Adverse Reaction
SJS	Stevens-Johnson's syndrome
TEN	toxic epidermal necrolysis
DRESS	Drug Rash Eosinophilia and Systemic Symptoms
OPAT	Outpatient Parenteral Antimicrobial Therapy
CBC	complete blood count
HR	hazard ratio
DIHS	Drug Induced Hypersensitivity Syndrome
DHS	Drug Hypersensitivity Syndrome

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Clinical implications

Eosinophilia affects 25% of patients on parenteral antibiotics. Patients with eosinophilia are four times as likely to develop rash and twice as likely to develop renal injury as patients without eosinophilia.

Table 1

Characteristics of patients with and without eosinophilia while undergoing outpatient parenteral antimicrobial therapy (OPAT).

	All (N=824)	Eosinophilia (N=210)	No Eosinophilia (N=614)	P-value†
Age, med [IQR]	60 [48–71]	64 [53–74]	59 [46–70]	0.0002
Male gender, N (%)	494 (60)	121 (58)	373 (61)	0.46
Days of therapy, med [IQR]	41 [31–45]	42 [37–47]	41 [29–44]	<0.0001
Number of initial antimicrobials, med [IQR] ‡	1 [1–2]	1 [1–2]	1 [1–2]	0.38
Discharged to, N (%)				0.003
Home	470 (58)	102 (49)	368 (61)	
Skilled nursing facility	339 (42)	105 (51)	234 (39)	
Infectious Diagnosis, N (%)				
Orthopedic infections§	464 (56)	129 (61)	335 (55)	0.09
Bacteremia	161 (20)	36 (17)	125 (20)	0.36
Skin/soft tissue infections	122 (15)	23(11)	99(16)	0.07
Endocarditis	82 (10)	23 (11)	59 (10)	>0.50
Meningitis or encephalitis	36 (4)	11 (5)	25 (4)	0.44
Pneumonia/empyema	36 (4)	9(4)	27(4)	>0.50
Intraabdominal infections	34 (4)	5 (2)	29 (5)	0.16
Lyme disease	28 (3)	2 (1)	26 (4)	0.03
Epidural abscess	24 (3)	9 (4)	15 (2)	0.23
Urinary tract infections	22 (3)	3(1)	19(3)	0.32
Otitis/sinusitis	18 (2)	4 (2)	14 (2)	>0.50
Vascular graft infection	14 (2)	6 (3)	8 (1)	0.21
Mycobacterial lung infection	8 (1)	3 (1)	5 (<1)	0.43
Organism, N (%)				
Gram positive	641 (78)	167 (80)	474 (77)	>0.50
Gram negative	181 (22)	42 (20)	139 (23)	0.44
Anaerobe	178 (22)	43 (20)	135 (22)	>0.50
Fungal	52 (6)	14 (7)	38 (6)	>0.50
Mycobacterium	9 (1)	3 (1)	6 (1)	>0.50
Other‖	31 (4)	2 (1)	29 (5)	0.01
No organism or not collected	63 (8)	17 (8)	46 (7)	>0.50

†Wilcoxon-Rank Sum test or Fisher's Exact test, as appropriate.

‡Number of antimicrobials begun during the initial four days of antimicrobial treatment

§Orthopedic infections includes osteomyelitis, prosthetic joint infections, septic/arthritis, post-operative spine infections, and infections after fracture/fixation.

‖Other includes *Treponema pallidum*, *Borrelia burgdorferi*, and viral organisms.

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Table 2

Predictors of eosinophilia among patients undergoing outpatient parenteral antimicrobial therapy (OPAT).

	All (N=824)	Eosinophilia (N=210)	No Eosinophilia (N=614)	Univariate Hazard Ratio† [95% CI]	Multivariate Hazard Ratio† [95% CI]	Multivariate P-value†
Age, med[IQR]	60 [48–71]	64 [53–74]	59 [46–70]	1.01 [1.00, 1.03]**	1.02 [1.00, 1.03]	0.0007
Male gender, N (%)	494 (60)	121 (58)	373 (61)	0.89 [0.67, 1.17]	0.95 [0.72, 1.26]	>0.50
Antibiotic‡, N (%)						
Vancomycin	314 (38)	95 (45)	219 (36)	1.41 [1.07, 1.86]*	1.66 [1.22, 2.26]	0.001
Penicillins	207 (25)	58 (28)	149 (24)	1.18 [0.86, 1.61]	1.45 [1.02, 2.06]	0.03
Metronidazole	123 (15)	19 (9)	104 (17)	0.46 [0.27, 0.77]**	0.46 [0.27, 0.77]	0.003
Rifampin	107 (13)	40 (19)	67 (11)	1.61 [1.13, 2.29]**	1.47 [1.03, 2.11]	0.03
Linezolid	31 (4)	10 (5)	21 (3)	1.55 [0.82, 2.94]	2.09 [1.07, 4.06]	0.03
Cephalosporins§	347 (42)	75 (36)	272 (44)	0.78 [0.58, 1.04]		
Flouroquinolones§	110 (13)	23 (11)	87 (14)	0.61 [0.37, 1.01]		
Carbapenems§	58 (7)	17 (8)	41 (7)	1.22 [0.73, 2.04]		
Daptomycin	54 (7)	14 (7)	40 (7)	0.92 [0.51, 1.66]		
Fluconazole	42 (5)	10 (5)	32 (5)	0.91 [0.48, 1.72]		
Aminoglycosides	27 (3)	6 (3)	21 (3)	0.80 [0.32, 1.94]		
Tetracyclines	14 (2)	3 (1)	11 (2)	0.90 [0.28, 2.84]		
Voriconazole	7 (<1)	2 (1)	5 (<1)	1.17 [0.29, 4.72]		
Aztreonam	6 (<1)	2 (1)	4 (<1)	2.01 [0.49, 8.08]		
Clindamycin	6 (<1)	2 (1)	4 (<1)	1.17 [0.16, 8.36]		
Amphotericin B	5 (<1)	2 (1)	3 (<1)	1.86 [0.46, 7.51]		
Macrolides	5 (<1)	1 (<1)	4 (<1)	0.75 [0.10, 5.32]		

† Based on Cox proportional hazards model. Antibiotics were considered for multivariate model if univariate p-value < 0.50 and if any-use was greater than 1% during OPAT follow-up. Antibiotic inclusion in final multivariate model was based on backwards elimination. Antibiotics not tabulated (<5 patients exposed) include micafungin, trimethoprim/sulfamethoxazole, flucytosine, ganciclovir, foscarnet, and posaconazole.

‡ Proportion of patients using antibiotics anytime during "eosinophilia-normalized" follow-up, see methods for details.

§ Antibiotic was considered in the backward elimiation process, but was not included in the final model.

* <0.05,
** <0.01,
*** <0.001,
**** <0.0001

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Table 3

Eosinophilia as a predictor of subsequent hypersensitivity reactions among patients undergoing outpatient parenteral antimicrobial therapy (OPAT).

	Eosinophilia[†] (N=210)	**Never Eosinophilia (N=614)**	**Univariate Hazard Ratio[‡] [95% CI]**	**Multivariate Hazard Ratio[‡§] [95% CI]**	**Multivariate P-value[‡§]**
Potential exposure time in person months (p-m)	203.8[†]	870.1			
Rash, N	32	36	4.16 [2.54, 6.81]****	4.16 [2.54, 6.83]	<0.0001
Proportion	15%	6%			
Rate per p-m	0.157	0.041			
Renal injury, N	31	62	2.38 [1.52, 3.70]***	2.13 [1.36, 3.33]	0.0009
Proportion	15%	10%			
Rate per p-m	0.152	0.071			
Liver injury, N	13	41	1.57 [0.82, 2.96]	1.75 [0.92, 3.33]	0.09
Proportion	6%	7%			
Rate per p-m	0.064	0.047			
Any Injury[//], N	64	127	2.68 [1.97, 3.65]****	2.65 [1.94, 3.62]	<0.0001
Proportion	30%	21%			
Rate per p-m	0.314	0.146			

Abbreviations: p-m: person-months

[†]Period after onset of eosinophilia.

[‡]Cox model also incorporates the time and events in the eosinophilia group prior to onset of eosinophilia (109.0 person-months, 14 injuries, 2 rashes, 5 renal injuries, 7 liver injuries) with the never eosinophilia data.

[§]Based on Cox proportional hazards model adjusted for age, gender, and antibiotics. Antibiotics were considered for multivariate model if univariate p-value < 0.50 and greater than 1% any-use during OPAT follow-up. Antibiotic inclusion in final multivariate model was based on backwards elimination. Vancomycin was included in multivariate model for renal injury (HR=2.53 [1.69, 3.80], p<0.0001) and for any HSR (HR=1.70 [1.29, 2.25], p=0.0002). No other antibiotics were included in multivariate models for HSR.

[//]Rash,, renal injury or liver injury.

*<0.05,

**<0.01,

***<0.001,

****<0.0001