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BRIEF REPORT

First-Dose Antimicrobial Infusion Reactions in Patients Enrolled in Outpatient Parenteral Antimicrobial Therapy Services

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After receiving a monitored first-dose antimicrobial infusion at an infusion center, 6 of 93 (6%) patients enrolled in outpatient parenteral antimicrobial therapy services experienced an immediate reaction, none of which were consistent with immunoglobulin E-mediated reactions. These findings suggest it would be reasonable to forgo monitoring for most patients receiving first-dose intravenous antimicrobials outpatient.

Keywords. first-dose intravenous infusions; hypersensitivity reactions; outpatient parenteral antimicrobial therapy (OPAT).

Outpatient parenteral antimicrobial therapy (OPAT) programs have grown rapidly over the last few decades, with approximately 250 000 patients treated each year in the United States [1]. For patients requiring extended treatment with intravenous (IV) antimicrobial therapy, outpatient administration allows patients to safely complete treatment from home while limiting time of hospitalization, reducing healthcare costs, and avoiding exposure to additional nosocomial complications [2–6].

Although most inpatients who continue IV antimicrobials outpatient will demonstrate tolerability before hospital discharge, some outpatients may require a change in antimicrobial therapy during OPAT care, or they are newly initiated on antimicrobial therapy without hospital admission. The 2018 Infectious Diseases Society of America (IDSA) OPAT guidelines recommend that in patients with no prior history of allergy to antimicrobials in the same class, the first dose of a new IV antimicrobial may be administered at home under the supervision of healthcare personnel who are qualified and equipped to respond to anaphylactic reactions [2]. This may involve a home health nurse, but if resources are limited, home health agencies' protocols may require a first dose of an antimicrobial infusion to be completed in a monitored healthcare setting to assure that immediate hypersensitivity reactions can be managed appropriately if they arise. Although the IDSA OPAT guidelines note that this a weak recommendation, it is primarily supported by the relatively rare reports of anaphylaxis (less than 1%) in patients receiving OPAT services [7, 8]. The objective of this study is to assess the incidence of immediate reactions in patients enrolled in OPAT services at our institution who received a supervised outpatient first-dose infusion as part of care for long-term antimicrobial management.

METHODS

In this single-center, retrospective case series, we evaluated adult patients enrolled in the OPAT program at University of Virginia (UVA) Health who received a first-dose outpatient antimicrobial infusion between January 1, 2019 and October 31, 2021. First-dose was defined as a 1-time dose of an antimicrobial provided in a UVA-affiliated outpatient infusion center per UVA protocol. At UVA, a patient receives a 1-time dose of an antimicrobial outpatient when they have not received that same antimicrobial within the last 90 days. Reasons for 1-time doses include newly initiating an antimicrobial in the outpatient setting or changing an antimicrobial that was prescribed on hospital discharge. The UVA OPAT service coordinates these first-dose infusions with the infusion center and patient. The patient is monitored by a registered nurse who documents details of the visit within the patient's electronic health record (EHR), including vitals before infusion, antimicrobial received, and tolerability. A physician is available at the infusion center for notification and management of allergic or infusion-related reactions.

Patients enrolled in the UVA OPAT program who received dalbavancin or daily antimicrobial infusions at a UVA-affiliated infusion center were excluded. The research protocol was exempt from review by the Institutional Review Board for Health Sciences Research at UVA.

The primary endpoint is the percentage of patients enrolled in UVA OPAT services who experienced an immediate reaction after receiving a supervised first-dose infusion at an infusion center. Immediate reaction was defined as symptoms or signs of allergy, infusion-related reaction, or intolerance that

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occurred within 60 minutes of exposure to the antimicrobial [9]. Potential clinical manifestations included, but were not limited to, urticaria, flushing, pruritis, gastrointestinal symptoms, angioedema, bronchospasm, chest pain, and anaphylaxis. Progress notes and other pertinent history in the patient's EHR were retrospectively reviewed to collect patient demographics, allergy history, infection characteristics, and first-dose infusion characteristics. A descriptive analysis was performed using Excel (Microsoft Corporation).

Table 1. Patient Demographics and First-Dose Infusion Characteristics

Patient Demographics	
Characteristic	N = 93
Median age, years	60 [51–67]
Female, n (%)	37 (40)
Median documented number of allergies	2 [1–3]
History of hypersensitivity	
Any antimicrobial	28 (30)
Same antimicrobial class	0
Type of infection[a]	
Bone/joint	63 (68)
Central Nervous System	4 (4)
Endovascular	5 (5)
Pulmonary	5 (5)
Skin and Soft Tissue	24 (26)
Other	5 (5)
Total number of first-dose infusions	115
Amphotericin B	3 (3)
Ceftriaxone	24 (21)
Daptomycin	30 (26)
Ertapenem	11 (10)
Meropenem	3 (3)
Micafungin	3 (3)
Penicillin	8 (7)
Piperacillin/tazobactam	4 (4)
Vancomycin	20 (17)
Other[b]	9 (8)
Reason for first dose	
New OPAT start	69 (60)
Change in therapy[c]	46 (40)
Culture data	5 (11)
Lab abnormality	13 (28)
Symptomatic drug reaction/intolerance	21 (46)
Other	7 (15)
Antimicrobial warranting change[d]	
Cefepime	4 (9)
Ceftriaxone	5 (11)
Metronidazole PO	5 (11)
Piperacillin/tazobactam	4 (9)
Vancomycin	25 (54)
Other	7 (15)

Abbreviations: OPAT, outpatient parenteral antimicrobial therapy; PO, oral.

NOTE: Values are presented as median [interquartile range] and number (percentage), as appropriate.

[a]Patients could have multiple types of infection. Other includes: bloodstream (2), genitourinary (1), intraabdominal (1), rhinosinusitis (1).

[b]Other includes: amikacin (1), ampicillin (2), ampicillin/sulbactam (2), cefazolin (1), ceftaroline (1), tigecycline (2).

[c]Symptomatic drug reaction/intolerance: rash (13), nausea/vomiting (4), drug fever (1), hot flashes (1), itching (1), ototoxicity (1); Other includes: unknown (3), adherence (2), access to care (1), imaging results (1).

[d]Patients could have received multiple antimicrobials. Other includes: amikacin (1), clindamycin (1), daptomycin (2), micafungin (1), nafcillin (2).

RESULTS

Ninety-five patients enrolled in UVA OPAT services were identified during the study time frame, 2 of whom were excluded for receiving dalbavancin or daily infusions at an infusion center. Therefore, 93 patients who received 115 first-dose infusions were included (Table 1). The median age was 60 years and 40% were female. The most common types of infections treated were bone and joint (63, 68%) and skin and soft tissue (24, 26%).

Among the 115 first-dose infusions, 69 (60%) were for new OPAT initiations whereas 46 (40%) were due to a change in therapy. A change in therapy was most often a result of a symptomatic drug reaction (n = 21 of 46, 46%) (which was most commonly a rash [n = 13 of 21, 62%]), followed by laboratory abnormality (n = 13 of 46, 28%). None of those who required a change in therapy due to rash experienced an immediate reaction with the first-dose infusion. Reactions to vancomycin (54%), ceftriaxone (11%), and oral metronidazole (11%) most commonly prompted a change to alternative therapy, leading to 33 of 46 (72%) of the aforementioned first-dose infusions. Daptomycin (26%), ceftriaxone (21%), vancomycin (17%), and ertapenem (10%) were the most common first-dose infusions.

Six patients (6%) receiving an outpatient first-dose of an antimicrobial experienced an immediate reaction, which included itching, erythema, and nausea (Table 2). Four of these patients reacted to an infusion of vancomycin, 2 of whom had received the same antimicrobial more than 12 months prior. All patients (1) received symptomatic treatment for the reaction, (2) were able to complete their first-dose infusions, and (3) continued to receive the antimicrobial safely as planned. Of the 87 patients who did not experience an immediate reaction, 18 (21%) had previously received the same antimicrobial.

DISCUSSION

National guidelines and many home health and home infusion protocols require that the first dose of an IV antimicrobial be monitored, whether that is supervised by a healthcare professional in the home or administered in a healthcare setting [2]. Studies of the risk of adverse events in patients enrolled in OPAT services have indicated that the risk is very low, but the majority of patients in these studies have received first doses in the inpatient setting with monitoring [8, 10]. There are limited data evaluating the safety of first doses of antimicrobials in the outpatient setting [7, 10]. The study presented here addresses first doses provided in outpatient infusion centers due to the

Table 2. Description of Patients Who Experienced an Immediate Reaction After Receiving a Supervised First-Dose Antimicrobial Infusion

Patient	First-Dose Antimicrobial	Previously Received Same Antimicrobial	History of Antimicrobial Hypersensitivity	Immediate Reaction Experienced	Infusion Paused or Slowed	Treatment of Reaction
1	Vancomycin	>12 months	Yes	Itching and erythema	Slowed	Diphenhydramine
2	Vancomycin	>12 months	No	Erythema	Paused	Diphenhydramine
3	Vancomycin	No	No	Itching	Paused	Diphenhydramine
4	Vancomycin	No	No	Itching and erythema	Paused, slowed	Diphenhydramine Famotidine
5	Ertapenem	No	No	Nausea	N/A	Ondansetron
6	Ceftriaxone	No	No	Itching	Paused	Diphenhydramine

requirement of many home health and home infusion companies. Not surprisingly, very few patients (6%) experienced a non-life-threatening immediate reaction, and all of these patients continued to receive the antimicrobial for their course of therapy.

Prior studies evaluating the safety of OPAT infusions have focused primarily on the rate and timing of adverse drug reactions at any point during the outpatient treatment course [11, 12]. One study reported a 6% incidence of rash or hives and 3% incidence of infusion reactions; however, the authors did not describe the details and timing of these specific reactions [12]. Most patients who plan to receive prolonged parenteral antimicrobial therapy as outpatients have received the first dose as an inpatient and demonstrated tolerability before discharge [8, 10]. Studies describing the safety of first-dose infusions under medical supervision have observed a less than 0.5% incidence of anaphylaxis in patients enrolled in OPAT services [7, 8]. Our results further corroborate these findings that a first-dose infusion in the outpatient setting is also safe.

Although national guidelines recommend that a first dose of a new IV antimicrobial be monitored in patients without a history of allergy to antimicrobials in the same class, no recommendation is provided on whether a monitored 1-time dose is necessary in patients who have previously demonstrated tolerability of the same antimicrobial [2]. Some home infusion or home health companies may require prior tolerability within a certain time frame to forgo a 1-time monitored dose. However, our data support that this requirement may not be necessary because approximately 95% (69 of 73) of patients who did not demonstrate prior tolerability did not experience an immediate reaction; in addition, the 4 patients who exhibited an immediate reaction despite no prior exposure to the antibiotic were able to continue the same antibiotic safely.

We found that the majority of first-dose infusion reactions were in response to vancomycin, with 20% of all vancomycin infusions leading to an infusion-related reaction (4 of 20). This incidence of vancomycin infusion-related reactions aligns with what has been previously described in patients enrolled in OPAT services [13, 14]. Vancomycin infusion-related reactions are most commonly mediated by histamine release rather than IgE, which can be influenced by the infusion rate [15, 16]. It is recommended to infuse vancomycin at a rate of 10 to 15 mg/minute to minimize infusion-related reactions; however, an infusion rate of 10 mg/minute or less is associated with fewer infusion-related events [17]. Our findings could be explained by a defaulted infusion rate between 12 and 17 mg/minute at our institution, with instructions to reduce the rate to less than 10 mg/minute if an infusion reaction is suspected.

This study has several limitations. Given its retrospective design, the study was reliant on accurate documentation within the electronic medical record. In addition, our sample size was small and limited to a select population at a single center. As such, we may not have been able to detect anaphylaxis in our study because the universal incidence of anaphylaxis is low.

CONCLUSIONS

In conclusion, our case series of outpatient first-dose antimicrobial infusions in patients enrolled in OPAT services support the rare incidence of serious adverse reactions. Combined with the understanding that first-dose oral antibiotics are provided to outpatients routinely, these data suggest that it would be a reasonable consideration to forgo monitoring for a majority of patients who receive first-dose IV antimicrobials as an outpatient. Larger studies are needed to determine generalizability of presented data.

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