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BRIEF REPORT

# Adverse Events and Healthcare Utilization Associated With Outpatient Parenteral Antimicrobial Therapy Among Older Versus Younger Adults

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Among older (n = 204) versus younger (n = 253) adults, there was no difference in adverse events (adjusted odds ratio [aOR] = 0.98; 95% confidence interval [CI] = 0.6–1.6) or healthcare utilization (incidence rate ratio = 1.09; 95% CI = 0.9–1.3) within 30 days after discontinuing outpatient parenteral antimicrobial therapy. Vancomycin (aOR = 1.92) and oxacillin (aOR = 3.12) were independently associated with adverse events.

**Keywords.** adverse events; healthcare utilization; outpatient parenteral antimicrobial therapy.

Outpatient parenteral antimicrobial therapy (OPAT) is a common method to administer long-term antimicrobial therapy for patients with infection [1]. Approximately 250 000 patients receive OPAT annually in the United States, and 20% of adults receiving OPAT experience an adverse event [2–5]. Although much is known about the types of adverse events associated with OPAT [6], less is known about the time to adverse event and healthcare utilization associated with OPAT [7]. There are also limited data regarding adverse events and healthcare utilization associated with OPAT among older (≥65 years) versus younger (<65 years) adults [8]. We hypothesized that adverse events and healthcare utilization such as OPAT clinic visits may be greater among older adults receiving OPAT due to physiologic changes associated with aging and the higher prevalence of multiple chronic conditions [8–10].

This study evaluated the frequency of adverse events and healthcare utilization associated with OPAT among older versus younger adults. A secondary objective was to evaluate the time interval during which adverse events were most likely in each age group.

## METHODS

We conducted a cohort study of adults who were discharged with OPAT from Yale New Haven Hospital, a 1541-bed tertiary care center in New Haven, Connecticut, from October 1, 2016 through September 30, 2017. Outpatient parenteral antimicrobial therapy was provided across 2 clinics with 10 infectious diseases physicians and 3 mid-level providers. Patients receiving OPAT were informed of abnormal laboratory results and instructed to communicate concerns with their designated OPAT clinic. Patients with a probable OPAT course were identified by the Joint Data Analytics Team, a research team involved in electronic data requests. All patients underwent medical record review to confirm discharge with an intravenous antibiotic or antifungal agent. Outpatient parenteral antimicrobial therapy courses were restricted to the first course for each patient [6]. Outpatient parenteral antimicrobial therapy courses >100 days were excluded due to expected differences in study outcomes. The Yale Human Investigation Committee approved this study. A waiver of consent was granted.

For all patients, we obtained demographics, comorbidities, hospitalization data, microbiological data, infection type, antimicrobial data, and dates of adverse events and healthcare utilization through medical record review. Comorbidities included diabetes, chronic kidney disease, peripheral vascular disease, and dementia based on their association with age, adverse events, and healthcare utilization [11–16]. Adverse events were defined as a missed antimicrobial dose [17], change in antimicrobial agent [6], early discontinuation of an antimicrobial agent [6], or vascular access complications [17–19] (Supplementary Table 1). Healthcare utilization was defined as a visit to the emergency department, planned and unplanned visit to the OPAT clinic, or telephone call or email made by or on behalf of the patient to the OPAT clinic. Follow up for adverse events and healthcare utilization occurred from the time of discharge to 30 days after discontinuation of OPAT. Adverse events and healthcare utilization were identified by a trained reviewer (K.B.) and adjudicated by an infectious diseases physician (R.D., M.M, M.J.-M.).

Patient and OPAT characteristics were compared using $\chi^2$ tests. Adverse events and healthcare utilization data were assessed using incidence rate ratios. The denominator for the incidence rate was the number of OPAT-days at risk for an adverse

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**Table 1. Characteristics of Patients Discharged With Outpatient Parenteral Antimicrobial Therapy From a Tertiary Care Center Between October 2016 and September 2017**

| Characteristics | Older Adults (≥65 Years) n = 204 | Younger Adults (<65 Years) n = 253 | *P* Value |
|---|---|---|---|
| Age, median (IQR) years | 75 (69.0–81.0) | 54 (45.0–59.0) | |
| Male Gender, n (%) | 128 (62.8%) | 149 (58.9%) | .40 |
| Race, n (%) | | | <.01 |
| White | 165 (80.9) | 188 (74.3) | |
| Black | 32 (15.7) | 37 (14.6) | |
| Other | 7 (3.4) | 28 (11.1) | |
| Non-Hispanic ethnicity, n (%) | 198 (97.1) | 224 (88.5) | <.01 |
| Comorbidities, n (%) | | | |
| Diabetes mellitus | 67 (32.8) | 53 (21.0) | <.01 |
| Chronic kidney disease | 62 (30.4) | 42 (16.6) | <.01 |
| Peripheral vascular disease | 44 (21.6) | 29 (11.5) | <.01 |
| Dementia | 10 (4.9) | 0 | |
| Discharge Location, n (%) | | | <.01 |
| Nursing Home | 143 (70.1) | 104 (41.1) | |
| Home | 50 (24.5) | 127 (50.2) | |
| Other | 11 (4.4) | 22 (8.7) | |
| Length on OPAT, median (IQR) days | 31.0 (17.0–38.0) | 33.0 (22.0–38.0) | |
| OPAT course >28 days, n (%) | 111 (54.4) | 151 (59.7) | .26 |
| First Course of Antimicrobial, n (%) | | | .88 |
| Vancomycin | 58 (28.4) | 83 (32.8) | |
| Vancomycin combination | 39 (19.1) | 46 (18.2) | |
| Any ceftriaxone combination[a] | 36 (17.7) | 36 (14.2) | |
| Any ampicillin/sulbactam combination[a] | 13 (6.4) | 15 (5.9) | |
| Any oxacillin combination[a] | 11 (5.4) | 16 (6.3) | |
| Other | 47 (23.0) | 57 (22.5) | |
| Infection Type, n (%)[b] | | | .41 |
| Osteomyelitis | 61 (26.9) | 96 (34.4) | |
| Endovascular infection[c] | 39 (17.2) | 36 (12.9) | |
| Bone and joint infection[d] | 33 (14.5) | 32 (11.5) | |
| Central nervous system infection | 22 (9.7) | 25 (9.0) | |
| Skin and soft tissue infection | 10 (4.4) | 15 (5.5) | |
| Other | 62 (27.3) | 75 (26.9) | |
| Most Common Organism, n (%)[b] | | | <.01 |
| Methicillin-resistant *Staphylococcus aureus* | 32 (8.5) | 65 (14.0) | |
| Methicillin-susceptible *S. aureus* | 36 (9.6) | 49 (10.6) | |
| Hemolytic *Streptococcus* | 21 (5.6) | 29 (6.3) | |
| *Enterococcus faecalis* | 32 (8.5) | 13 (2.8) | |
| Oral *Streptococcus* spp | 24 (6.4) | 22 (4.8) | |
| *Corynebacterium* spp | 15 (4.0) | 27 (5.8) | |
| *Pseudomonas* spp | 17 (4.5) | 24 (5.2) | |
| Other | 200 (53.1) | 234 (50.5) | |
| Healthcare Utilization[e] | | | |
| Total | 189 (92.7) | 231 (91.3) | .60 |
| Emergency department visit | 77 (37.8) | 85 (33.6) | .36 |
| OPAT clinic visit | 140 (68.6) | 191 (75.5) | .10 |

Abbreviations: IQR, interquartile range; OPAT, outpatient parenteral antimicrobial therapy.

[a]All combinations excluded combinations with vancomycin, and there is no overlap between these antimicrobials.

[b]Patients may have had more than 1 infection type or organism.

[c]A total of 17.3% of endovascular infections were primary bacteremia; the remainder were endocarditis.

[d]A total of 67.7% of bone and joint infections were prosthetic joint infections.

[e]Defined as any emergency department visit, OPAT clinic visit, phone call or email to the OPAT clinic made by the patient or on behalf of the patient.

event or healthcare utilization, defined as the number of days from the initiation of OPAT to an adverse event or first episode of healthcare utilization. To evaluate the association between age group and adverse events, we performed multivariable logistic regression testing. We used a model adjusted for variables that were associated with an adverse event in univariate testing

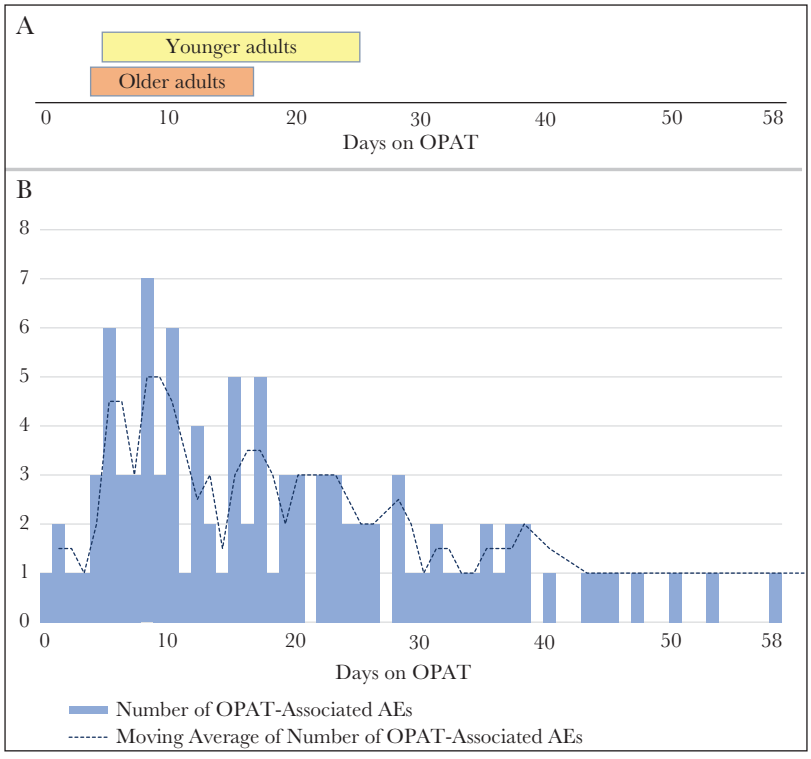


**Figure 1.** Time to adverse event associated with outpatient parenteral antimicrobial therapy (OPAT) among older (n = 204) and younger (n = 253) adults from one institution using SaTScan. (A) SaTScan analysis revealed significant clusters of timing of first OPAT-associated adverse events from days 4 to 17 overall ($P = .01$), days 4 to 15 for older adults ($P = .01$), and days 5 to 25 for younger adults ($P = .03$). (B) Histogram of first OPAT-associated adverse event occurring per day for all adult patients of any age from days 0 through 58.

at $P < .1$ (Supplementary Table 2). All analyses were performed using SAS version 9.4 or R.

To estimate the time interval during which adverse events were most likely in older versus younger adults, we used SaTScan. SaTScan is a public health surveillance software designed to detect clustering of events that does not require predefined cluster periods [20, 21]. In SaTScan analysis, we input a timeline for adverse events, applied Poisson descriptive statistics, and scanned for clusters of adverse events using 1-day increments. After the detection of clusters over a specified time interval, analyses were repeated to refine time intervals associated with clusters of adverse events among older versus younger adults.

## RESULTS

We identified 505 adults with probable OPAT courses. Of these, 48 did not receive an intravenous antibiotic or antifungal or had an OPAT course >100 days and were excluded. Characteristics of the remaining 457 patients are shown (Table 1). During the index hospitalization, median length of stay was 9 days (interquartile range [IQR], 6.0–14.0) among older adults and 10.0 days (IQR, 6.0–17.0) among younger adults. Overall, 20.6% (n = 42) of older adults and 24.9% (n = 63) of younger adults developed an adverse event during follow up. There was no difference in the incidence rate (IR) of adverse events associated with OPAT among older (IR = 77.1 adverse events per 1000 OPAT-days at risk) versus younger (IR = 84.7 adverse events per 1000 OPAT-days at risk) adults (IR ratio = 0.91; 95% confidence interval [CI] = 0.60–1.37).

Table 1 shows healthcare utilization findings. The median number of days to the first OPAT clinic visit was 32 days (IQR, 20.5–39.0) for older adults and 34 days (IQR, 23.0–40.0) for younger adults. There was no difference in the rate of healthcare utilization among older (IR = 26.1 episodes per 1000 OPAT-days at risk) versus younger (IR = 23.8 episodes per 1000 OPAT-days at risk) adults (IR ratio = 1.09; 95% CI = 0.90–1.33).

The median number of days to an adverse event was 12 (IQR, 7.0–28.0) for older adults and 19 (IQR, 10.0–32.0) for younger adults. Temporal analysis of adverse events using SaTScan revealed significant differences in clusters of adverse events associated OPAT among older (days 4–15, $P = .01$) versus younger (days 5–25, $P = .03$) adults (Figure 1).

In multivariable testing, older age was not associated with the development of an adverse event (adjusted odds ratio [aOR] = 0.98; 95% CI = 0.5–1.6), whereas vancomycin

(aOR = 1.9; 95% CI = 1.2–3.1) and oxacillin (aOR = 3.3; 95% CI = 1.5–7.3) were predictive of an adverse event.

## DISCUSSION

Few studies have evaluated adverse events and healthcare utilization among older adults treated with OPAT compared with younger adults. Our study included over 200 older adults, making it one of the largest observational studies of older adults receiving OPAT. After controlling for the greater prevalence of comorbid conditions among older adults and other clinically significant factors, we found no difference in the odds of an adverse event or rate of healthcare utilization associated with OPAT among older versus younger adults. Combined with prior data [6, 8], our findings support the safety of OPAT in older adults.

Our work confirms that approximately 20% of patients treated with OPAT experience at least 1 adverse event [3–5], and vancomycin and beta-lactam antibiotics increase the risk for adverse events [6, 9]. However, our work expands upon prior research by providing a comprehensive analysis of adverse events that are directly attributable to OPAT. These adverse events have been established through earlier investigations (Supplementary Table 1) and exclude nonspecific drug reactions. Using these validated measures, the adjusted odds of an adverse event associated with OPAT was 1.9-fold greater among patients receiving vancomycin and 3.3-fold greater among patients receiving oxacillin. These data suggest that patients receiving vancomycin or oxacillin should be monitored closely during OPAT.

Visits to general practitioners and specialists have been shown to occur more frequently among patients with greater comorbid conditions [22]. However, healthcare utilization in this study may have been unaffected by age-related comorbid conditions because 70% of older adults were discharged to a skilled nursing facility. At the study site, discharge to a skilled nursing facility occurred at the discretion of the clinical team in consultation with physical therapy and rehabilitation medicine. It is possible that the clinical care in skilled nursing facilities reduced the need for emergency room visits and telephone calls to the OPAT clinic among patients receiving OPAT [23].

This study is novel for its application of SaTScan to identify temporal trends in adverse events associated with OPAT. Our analysis revealed significant clustering of adverse events for older adults at days 4–15 of treatment and for younger adults at days 5–25 of treatment. These findings support the need for close follow up [24], particularly during the first weeks of OPAT when older adults incur the greatest risk of an adverse event.

Our work has limitations. First, we relied on 1 year of data from an academic center, and follow up was limited to 30 days after OPAT discontinuation. Thus, our findings may lack generalizability. Second, the risk of adverse events associated with OPAT was likely underestimated because we excluded nonspecific events such as gastrointestinal disturbances. Third, vascular access type was not evaluated. In addition, although vascular access-associated infections were examined, we did not specifically assess for central line-associated bloodstream infections using standardized criteria [25].

## CONCLUSIONS

In conclusion, we found no difference in the occurrence of adverse events or healthcare utilization associated with OPAT among older versus younger adults. Patients receiving vancomycin and oxacillin were found to be at increased risk for adverse events. We further showed that the greatest risk period for an adverse event was during the first 2 weeks of OPAT among older adults in contrast to younger adults whose risk appears more evenly distributed throughout treatment. Future studies should consider applying public health surveillance software, such as SaTScan, to improve follow up for patients receiving OPAT.

### Supplementary Data

Supplementary materials are available at *Open Forum 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.

**Supplementary Table 1.** Definition and justification of adverse events associated with outpatient parenteral antimicrobial therapy.

**Supplementary Table 2.** Univariate $\chi^2$ analysis of variables associated with an adverse event.


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