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Safety Of Opat In Older Versus Younger Adults

Kaylen Elizabeth Brzozowski
kaylenbrzozowski@gmail.com

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Master of Public Health, Epidemiology of Microbial Diseases

Yale School of Public Health

Dr. Manisha Juthani-Mehta

Dr. Melinda Pettigrew

Abstract

Introduction Outpatient parenteral antimicrobial therapy (OPAT) is considered practical, safe, and cost-effective, but roughly 20% of all adult patients on OPAT experience an adverse event (AE). Frequency of AEs and healthcare utilization, defined as emergency department visits and infectious disease office visits, phone calls, and emails, may be greatest in the first two weeks of OPAT. Given that older adults (age ≥ 65) have greater cognitive decline, ADL limitations, and comorbidities than younger adults, we sought to evaluate the frequency and timing of AEs in older adults on OPAT. We examine patients on OPAT at Yale New Haven Hospital (YNHH) under the hypotheses that 1) older adults will have a greater frequency of AEs and healthcare utilization than younger adults, and 2) older adults will have AEs earlier than younger adults.

Methods We collected all data from the electronic medical record system, Epic, for YNHH. On 505 probable OPAT courses flagged and abstracted from Epic from October 2016 through September 2017, we reviewed medical records to assess patient, infection, and OPAT characteristics, as well as AEs and healthcare utilization. Data analysis on 457 unique OPAT courses ≤100 days was conducted using SAS, R, and SaTScan.

Results Older and younger adults did not significantly differ in the frequency of OPAT-specific AEs (unadjusted IRR=0.91 [0.60, 1.37], adjusted OR=0.98 [0.61, 1.57]) or frequency of healthcare utilization (IRR=1.09 [0.90, 1.33]). Older adults have the greatest risk of OPAT-specific AEs from days 4-15 after discharge (p=0.01), and younger adults' greatest risk is from days 5-25 (p=0.03).

Conclusion Older adults do not significantly differ in OPAT-specific AEs and healthcare utilization compared to younger adults. Older adults seem to have a more specific risk period, so more attention may be necessary during this time. OPAT remains a safe option for older adults.

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Introduction

Outpatient parenteral antimicrobial therapy, or OPAT, is thought to be a practical, safe, and cost-effective mechanism to administer long-term antimicrobial therapy for patients with severe infections.[1] Previous studies have shown that the home environment leads to quicker psychological and physical recovery, and movement of intravenous (IV) antimicrobial treatment to the outpatient setting can reduce patient care costs by up to 70%.[2]

However, approximately 20% of adult patients undergoing OPAT experience adverse events (AEs), and a significant proportion of these are serious AEs, or AEs which lead to hospital readmission or discontinuation of an antimicrobial course.[2,3,4] Examples of common AEs resulting from IV antimicrobial treatment include skin rash, nausea/vomiting, pain at the catheter insertion site, and fatigue. Predictors for readmission include infection recurrence or progression, central catheter issues,[5] prior hospital admission within the previous 12 months, infection with a resistant organism, use of certain antimicrobials (primarily aminoglycosides, vancomycin, and ß-lactams[6]), and increased age.[7] Also, prior AEs that are less serious, such as renal or vestibular toxicity, leukopenia, and hepatic events, are predictors of the development of more serious AEs.[4,5]

The length of OPAT varies, but averages 20 days after discharge for most infectious diagnoses.[8] Clinical treatment of endocarditis, on the other hand, is typically comprised of 2 weeks of treatment in hospital and 4 weeks of outpatient treatment. Patients are at greatest risk of developing an AE in their first two weeks of OPAT,[9] suggesting that patients receiving OPAT may require increased support at the beginning of the OPAT period. Increased support may be manifested as increased healthcare utilization, defined as number of phone calls, office visits, additional ED visits, and/or additional hospitalizations. More frequent follow-up visits may

reduce patient confusion or the AEs that are causing these utilization events. Few studies have evaluated healthcare utilization in OPAT as a marker for increased patient need, and this information may reveal points in time where increased patient contact is necessary.[9] Due to a lack of recommendations from the Infectious Diseases Society of America (IDSA) for the frequency of OPAT patient follow-up, this judgement is primarily left to the provider.[4] IDSA guidelines do state, however, that patients with life-threatening infections, such as endocarditis and meningitis, may require more frequent follow-up.[4]

AEs of OPAT have been well-classified among adults, but few reports have specifically examined the unique circumstances of older adults (aged ≥65 years) receiving OPAT.[8] It is currently unknown whether certain AEs of OPAT are more common or equivalent in frequency compared to younger adults. Older adults on OPAT may experience a greater frequency of AEs[8] and healthcare utilization than younger adults due to a higher prevalence of cognitive impairment, comorbid conditions such as diabetes or chronic kidney disease, or other functional impairments, rather than from the OPAT course itself. After controlling for relevant comorbidities, a difference in AEs and healthcare utilization between older and younger adults may suggest the necessity of increased support for older patients.

Conversely, older adults may not differ from younger adults in terms of AEs and healthcare utilization during OPAT, implying that they do not have different care requirements in terms of the OPAT course, and discharge to a nursing facility may be unnecessary. This idea is important because Medicare does not reimburse patients for home-administered OPAT, but they do cover nursing home stays for OPAT. If older adults do not need the increased care provided by a nursing home, Medicare's differential coverage of therapy location may not be beneficial. Because little has been done to evaluate the safety of OPAT in older adults, it is important to

measure differences in older adult populations versus younger adult populations in order to advise best practice in infectious disease clinics.[8]

Gaining age-specific information on OPAT safety and care needs may greatly improve outcomes for patients discharged on OPAT. Optimizing OPAT may reduce the number of patients on multiple or long antimicrobial courses and their likelihood of being readmitted.[7,10] Shortening and simplifying antimicrobial courses may reduce the emergence of multi-drug resistant pathogens, alterations to the gut microbiome, and the incidence of healthcare-associated infections.[10,11]

This longitudinal cohort study seeks to evaluate the frequency of AEs and healthcare utilization in older adult patients (age ≥ 65 years) in comparison with younger adult patients (age < 65 years) undergoing OPAT, as well as to establish a time frame where AEs are most likely to arise in each age group. We hypothesize that 1) older adults will experience a greater frequency of OPAT-specific AEs and healthcare utilization than younger adults, and 2) older adults will have OPAT-specific AEs earlier in the OPAT course than younger adults.

Methods

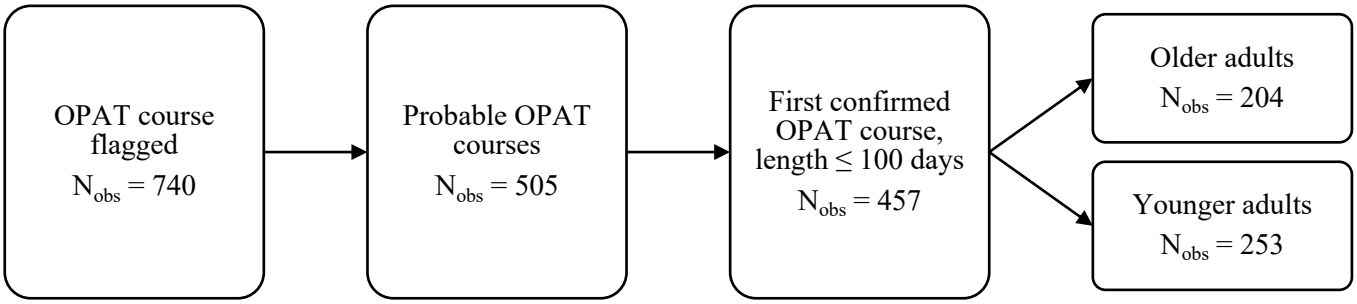
The protocol for this project was reviewed by the Yale Human Investigative Committee and was deemed to be a quality improvement project.

Data collection

Data for this project was obtained from Epic, the electronic medical record system for Yale New Haven Hospital (YNHH), via 1) data abstraction by the Joint Data Analytics Team (JDAT) at YNHH and 2) medical record reviews. Data was obtained for all adults, aged 18 and older, discharged on OPAT from YNHH for a hospital admission beginning October 1, 2016 through September 30, 2017.

Our reference dataset, provided by JDAT, included all patients with an OPAT flag in their medical chart during the given time frame. From this reference dataset, we observed which medications patients were discharged on. Many patients with an OPAT flag were not actually noted to be discharged any IV antiinfective, so we restricted the reference dataset to those that did have an IV antiinfective listed, and we defined these courses as "probable OPAT courses". Based on medical record review of each patient with a probable OPAT course, we confirmed whether patients were truly discharged on intravenous antiinfectives (antimicrobials, antivirals, and antifungals). We limited the dataset to the first course noted for each individual; there were 29 subsequent courses for patients which were removed. We also restricted our patient population to those with OPAT courses lasting ≤ 100 days, as longer courses likely suggest inherent differences in OPAT indication and treatment. See Figure 1 for more detail.

Figure 1. Inclusion criteria flowchart



The reference dataset provided information on patient demographics, insurance coverage (i.e., Medicare vs. private), and comorbidities. We focused on comorbidities that would be most relevant to OPAT (i.e., diabetes mellitus, chronic kidney disease, peripheral vascular disease, and dementia). Chronic kidney disease has been noted to be associated with OPAT AEs,[12] and antimicrobials, such as vancomycin, can be nephrotoxic[13] with effects exacerbated by CKD. Previous studies have associated peripheral vascular disease and diabetes with increased recurrence of osteomyelitis due to an inability to achieve therapeutic antimicrobial

concentrations in infected sites.[14,15] Additionally, peripherally-inserted central catheters have been associated with deep vein thrombosis,[16] and the presence of peripheral vascular disease could precipitate this complication. A certain level of cognitive function is necessary for OPAT[17] because, at a minimum, an individual must be able to live with a central line for an extended period of time. Patients with dementia may be at increased risk of OPAT-specific AEs[18,19] because they are more likely to touch or pull out central lines, causing dislodgement,[19] or be non-compliant with administration. Based on ICD-10 codes in the reference dataset, we noted whether a patient had diabetes, chronic kidney disease, peripheral vascular disease, or dementia.[20,21]

We performed a chart review on each probable course identified in the reference dataset (n=505). We followed each patient from discharge through 30 days after OPAT discontinuation. If a patient had multiple OPAT courses within this time period, follow-up was extended through 30 days past discontinuation of the last course. If a patient had multiple OPAT courses outside of this period, we only included the first course in analysis. Data collected from medical record review include: initial admission/discharge dates, additional admission/discharge dates, physical therapy encounters, discharge location recommendations, specimen data, date of initial infectious disease consult, type of infection, OPAT antimicrobial data, dates of adverse events that could not be determined from laboratory data, and dates of healthcare utilization.

Healthcare utilization was defined as any ED visit, ID office visit, or ID phone call or email made by the patient or on behalf of the patient. ED visits represent both singular encounters and those leading to hospital admission. For this reason, we did not include additional hospitalizations as a variable, as they were already accounted for. OPAT-specific AEs are listed in Supplementary Table 1. We chose to focus on those AEs that could be directly

attributable to the OPAT course in order to produce the most specific conclusions. We chose to exclude non-specific AEs, such as gastrointestinal events, that could be attributable other causes.

When defining first courses of antimicrobial therapy, infection type, and organisms identified (Results, Table 2), many patients had multiple entries. For example, a patient's first course of antimicrobial may have been vancomycin and piperacillin-tazobactam. A patient may have been treated for both osteomyelitis and endocarditis. They may have had both MRSA and *Pseudomonas* species isolated from the infection site. We accounted for multiple antimicrobials prescribed, then described the four most common chosen for all patients. For vancomycin, we separated singular therapy and combination therapy. For ceftriaxone, unasyn, and oxacillin, we listed the number of singular and combination therapies, excluding any with vancomycin (there were no instances where ceftriaxone, unasyn, or oxacillin were used together). We accounted for all infection types, and in this stratification, a patient with both osteomyelitis and endocarditis would have each infection counted separately, so the total number of infection types exceeds the number of unique patients in each age group. Similarly, we listed all organisms identified for all infection types, and the total number of organisms isolated also exceeds the number of unique patients. We determined which antimicrobials were attributable to each AE by whether the AE occurred during or within the 30 days after the final day of administration of that antimicrobial.

Data analysis

Data processing was performed using Excel and SAS 9.4. Descriptive statistics, outcome stratification, and logistic regression modeling were done using SAS. Incidence rate ratios (IRRs) and confidence intervals were calculated using R. The denominator for IRRs was the number of OPAT-days in the patient population, defined as days until the first OPAT-specific

AE or total patient follow-up time for those not experiencing an AE. SaTScan was used to reveal significant periods where patients were at risk for AEs.

We chose to perform multivariable testing to predict the relationship between older age and OPAT-specific AEs in order to accurately control for relevant independent variables. A logistic regression model predicting OPAT-specific AEs was created based on univariate testing of demographic and descriptive OPAT variables at $p < 0.1$ significance (Supplementary Table 2). Significant variables from univariate testing were: OPAT length > 28 days; having ≥ 1 comorbidity (i.e., chronic kidney disease, diabetes, peripheral vascular disease, and dementia); discharge on vancomycin therapy; discharge on oxacillin therapy; indication of bone and joint infection; and indication of skin and soft tissue infection (SSTI). We removed SSTI during model formation because there were only 2 patients with an OPAT-specific AE and an SSTI. These variables were then used in the logistic regression model with the binary variable for older age.

To estimate the timing of patient risk for OPAT-specific AEs, we used SaTScan. SaTScan is a software used primarily in public health surveillance to detect clustering of disease cases in space and/or time. We chose to use SaTScan over a Chi square test because SaTScan does not require pre-defined cluster periods as a Chi square test requires. In other words, a Chi square test would force us to separate the data into increments, and we would test whether each defined increment had a significantly greater number of adverse events than expected. SaTScan examines all possible clustering factors from fifty percent of the provided time period down to the day level, so it should define significant risk periods more specifically. We used the Poisson temporal-only analysis for this data since there is no spatial importance to AE emergence. Temporal analysis in SaTScan searches for higher numbers of cases than expected in all possible

time windows in a given time frame. Prior studies have used the temporal-only analysis in SaTScan to identify clusters of antibiotic-resistant infections in hospitals,[22] as well as to detect abnormal numbers of intussusception cases after the monovalent rotavirus vaccine.[23] SaTScan requires the input of dates, not simply timing to events, so we fabricated an arbitrary timeline for patient AEs from January 1, 2017 to May 21, 2017 (reflecting AEs emerging from Day 0 through Day 140 after discharge) using time to OPAT-specific AE. With this method, an OPAT-specific AE occurring on day 45 after discharge would be equivalent to February 15, 2017. We set time precision to 1 day, chose the retrospective, purely temporal version of analysis, used Poisson descriptive statistics, scanned for areas with high rates, and aggregated by time interval of one day. We scanned for significant clusters from Day 0 to Day 140 for patients of all age groups, then by older and younger age groups. This identified large clusters of varying sizes for each age stratification, so we refined the date range to these large clusters (days 1-38 for all ages, days 1-40 for older adults, and days 2-47 for younger adults), and performed the analysis again to identify a more specific cluster for each group.

Results

Descriptive Characteristics

Table 1. Descriptive characteristics of patients enrolled in outpatient parenteral antimicrobial therapy following discharge from YNHH between October 2016 and September 2017.

	Older Adults (age ≥ 65 years) n=204	**Younger Adults (age < 65 years)** n=253	p-value [a]
Age, median (IQR)	75.0 (69.0, 81.0)	54.0 (45.0, 59.0)	
Male sex, n (%)	128 (62.75)	149 (58.89)	0.40
Race, n (%)			<0.01
White	165 (80.88)	188 (74.31)	
Black	32 (15.69)	37 (14.62)	
Other	4 (1.96)	25 (9.88)	
Unknown	3 (1.47)	3 (1.19)	
Ethnicity, n (%)			<0.01
Not Hispanic	198 (97.06)	224 (88.54)	
Hispanic	5 (2.45)	26 (10.28)	
Unknown	1 (0.49)	3 (1.19)	
Comorbidities, n (%)			
Diabetes mellitus	67 (32.84)	53 (20.95)	<0.01
Chronic kidney disease	62 (30.39)	42 (16.60)	<0.01
Peripheral vascular disease	44 (21.57)	29 (11.46)	<0.01
Dementia	10 (4.90)	0	<0.01
Discharge disposition, n (%)			<0.01
Nursing home	143 (70.10)	104 (41.11)	
Home, self-care or with services	50 (24.51)	127 (50.20)	
Inpatient rehab/admission	9 (4.41)	15 (5.93)	
Hospice	2 (0.98)	1 (0.40)	
Missing	0	6 (2.37)	
Hospital Length of Stay, median (IQR)	9.0 (6.0, 14.0)	10.0 (6.0, 17.0)	

[a] Chi-square test as appropriate; cells with less than 5 entries were omitted.

The study population was comprised of 204 older adults and 253 younger adults. Median age for older adults was 75 years, and that of younger adults was 54 years. The majority (~60%) of patients were male in both age groups. Most patients in both age groups were white, but

younger adults had a more diverse racial distribution ($p<0.01$). We observed a similar relationship with non-Hispanic ethnicity ($p<0.01$). Older adults were more likely to have chronic kidney disease, diabetes, peripheral vascular disease, and dementia than younger adults ($p<0.01$ for all four). Older adults were most likely to be discharged to a nursing home (70.1%), with a lesser proportion discharged to their homes (24.5%). Younger adults had a more even distribution of discharge location with 41.1% discharged to a nursing home and 50.2% discharged to home. The median initial length of hospital stay was comparable between the two groups at 9-10 days.

OPAT Course

Table 2. Characteristics of outpatient parenteral antimicrobial therapy episodes among patients discharged from YNHH between October 2016 and September 2017.

	Older Adults (age ≥ 65 years) n=204	**Younger Adults (age <65 years)** n=253	p-value [a]
Length on OPAT, median (IQR)	31.0 (17.0, 38.0)	33.0 (22.0, 38.0)	
OPAT course > 28 days, n (%)	111 (54.41)	151 (59.68)	0.26
First course of antimicrobial, n (%)			0.88
Vancomycin	58 (28.43)	83 (32.81)	
Vancomycin combination	39 (19.12)	46 (18.18)	
Any ceftriaxone combination [b]	36 (17.65)	36 (14.23)	
Any unasyn combination [b]	13 (6.37)	15 (5.93)	
Any oxacillin combination [b]	11 (5.39)	16 (6.32)	
Other	47 (23.04)	57 (22.53)	
Infection type, n (%) [c]			0.41
Osteomyelitis	61 (26.87)	96 (34.41)	
Endovascular infection [d]	39 (17.18)	36 (12.90)	
Bone and joint infection [d]	33 (14.54)	32 (11.47)	
Central nervous system infection	22 (9.69)	25 (8.96)	
Skin and soft tissue infection	10 (4.41)	15 (5.48)	
Other	62 (27.31)	75 (26.88)	
Organism, n (%)			<0.01
MRSA	32 (8.49)	65 (14.04)	
MSSA	36 (9.55)	49 (10.58)	
Hemolytic *Streptococcus*	21 (5.57)	29 (6.26)	
Enterococcus faecalis	32 (8.49)	13 (2.81)	
Oral *Strep* spp	24 (6.37)	22 (4.75)	
Corynebacterium spp	15 (3.98)	27 (5.83)	
Pseudomonas spp	17 (4.51)	24 (5.18)	
Other	200 (53.05)	234 (50.54)	

[a] Chi-square test as appropriate; cells with less than 5 entries were omitted.
[b] All combinations excluded combinations with vancomycin.
[c] Patients may have had more than one infection type or organism indicated. These values are the sum of all infection types/organisms isolated in all patients on OPAT, so their total may sum to greater than the number of patients in the study.
[d] 17.33% of endovascular infections were primary bacteremia; the remainder were endocarditis. 67.69% of bone and joint infections were prosthetic joint infections.

Median length of OPAT course was 31 days for older adults and 33 days for younger adults. Over half of both age groups had a course lasting longer than 28 days (p=0.26). The

choice of antimicrobial for the OPAT course was no different between older and younger adults ($p=0.67$). Vancomycin alone or vancomycin given with other antimicrobials was the most common antimicrobial regimen prescribed, followed by ceftriaxone or a ceftriaxone combination, unasyn/unasyn combination, and oxacillin/oxacillin combination, as well as a few other antimicrobials such as piperacillin-tazobactam, cefazolin, daptomycin, and ceftazidime. The most common indication in both age groups was osteomyelitis, followed by endovascular infection, bone and joint infection, central nervous system infection, and skin and soft tissue infection, as well as others including genitourinary tract infection and intraabdominal infection. The most common organisms isolated in this population included methicillin-resistant *Staphylococcus aureus*, methicillin-susceptible *Staphylococcus aureus*, hemolytic *Streptococcus* species, *Enterococcus faecalis*, oral *Streptococcus* species, *Corynebacterium* species, and *Pseudomonas* species. The distribution of organisms isolated differed between older and younger adults ($p<0.01$).

OPAT-Specific Adverse Events

Table 3. OPAT-specific adverse events in patients discharged on outpatient parenteral antimicrobial therapy from YNHH between October 2016 and September 2017.

	Older Adults (age ≥ 65 years) n=204	**Younger Adults (age < 65 years)** n=253	p-value [a]
Percent having at least one OPAT-specific adverse event, n (%)	42 (20.59)	63 (24.90)	0.28
Time in days to OPAT-specific AE, median (IQR)	12.0 (7.0, 28.0)	19.0 (10.0, 32.0)	
Most common antimicrobials attributable to first OPAT-specific AE			0.67
Vancomycin	21 (33.87)	42 (36.84)	
Ceftriaxone	8 (12.90)	13 (11.40)	
Oxacillin	6 (9.68)	7 (6.14)	
Other	27 (43.55)	52 (45.61)	

[a] Chi-square test as appropriate; cells with less than 5 entries were omitted.

20.6% of older adults experienced an OPAT-specific AE during OPAT therapy or within the 30 days after OPAT discontinuation, and 24.9% of younger adults experienced an OPAT-specific AE during this time frame (p=0.26). The median number of days to an OPAT-specific AE was 12 for older adults and 19 for younger adults. The majority of OPAT-specific AEs were attributable to vancomycin, ceftriaxone, or oxacillin, and the distribution of attributable antimicrobials did not differ between older and younger patients (p=0.67). The incidence rate of OPAT-specific AEs was not statistically different between older and younger patients (IRR=0.91, Table 5).

Healthcare Utilization

Table 4. Healthcare utilization in patients discharged on outpatient parenteral antimicrobial therapy from YNHH between October 2016 and September 2017.

	Older Adults (age ≥ 65 years) n=204	**Younger Adults (age < 65 years)** n=253	p-value [a]
Total healthcare utilization			
Percent having at least one healthcare encounter, n (%)	189 (92.65)	231 (91.30)	0.60
ED visits			
Percent having at least one ED visit, n (%)	77 (37.75)	85 (33.60)	0.36
ID office visits			
Percent having at least one ID office visit, n (%)	140 (68.63)	191 (75.49)	0.10
Time to first ID office visit, median (IQR)	32.0 (20.5, 39.0)	34.0 (23.0, 40.0)	

[a] Chi-square test as appropriate; cells with less than 5 entries were omitted.

Over 90% of both age groups had at least one healthcare encounter over their follow-up periods (p=0.60), over 30% had at least one emergency department visit (p=0.36), and approximately 70% had at least one office visit with the infectious disease department at YNHH (p=0.10). The median number of days to their first ID office visit (older=32, younger=34) corresponds with YNHH's general practice of scheduling an office visit at the end of OPAT to ensure treatment effectiveness. There was no difference in the percentage of older and younger adults having at least one instance of healthcare utilization overall, ED visit, or office visit. The rate of overall healthcare utilization between older and younger patients was not significantly different (IRR=1.09, Table 5).

Table 5. Crude incidence rate of OPAT-specific adverse events and healthcare utilization per 1,000 OPAT-days at risk, per age group.

	Older Adults (age ≥ 65 years) n=204	**Younger Adults (age < 65 years)** n=253	**IRR (95% CI)**
OPAT-specific AEs	77.05	84.68	0.91 (0.60, 1.37)
Healthcare utilization	26.07	23.83	1.09 (0.90, 1.33)

Multivariable Analysis

Table 6. Adjusted odds ratios estimated by logistic regression model [a] predicting ≥ 1 OPAT-specific adverse event.

Independent variable	**OR Estimate**	**95% CI**
Older age	0.98	(0.61, 1.57)
OPAT length > 28 days	1.62	(1.00, 2.64)
Presence of ≥ 1 comorbidity	0.46	(0.28, 0.76)
Vancomycin during initial OPAT course	1.92	(1.18, 3.12)
Oxacillin during initial OPAT course	3.32	(1.51, 7.30)
Bone and joint infection	1.51	(0.82, 2.76)

[a] Logistic regression model created based on univariate testing of demographic and OPAT variables' association with OPAT-specific AEs at $p < 0.1$ significance (Supplementary Table 2).

After controlling for variables found to be associated with OPAT-specific AEs with univariate testing (Supplementary Table 2), patients age ≥ 65 years had 0.98 (0.61, 1.57) times the odds of developing an OPAT-specific AE than patients age < 65 years. Based on the 95% confidence interval, this association was not significant. Other control variables were significantly associated with OPAT-specific AEs. Having ≥ 1 comorbidity was associated with having 0.46 times the odds of developing an OPAT-specific AE than that of having no comorbidities. Vancomycin administered during the first course was associated with greater odds of developing an OPAT-specific AE, and we observed a similar association with oxacillin administration.

Physical Therapy

Table 7. Physical therapy (PT) recommendations of older and younger patients with Medicare discharged to SNFs on outpatient parenteral antimicrobial therapy.

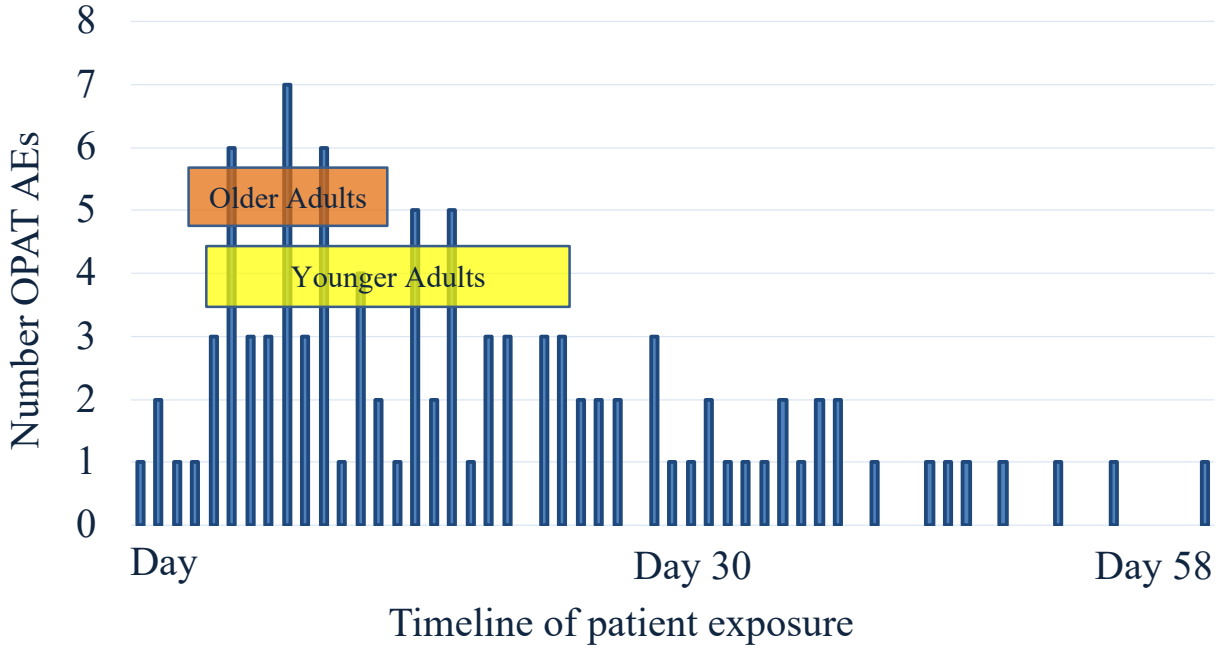
	Older Adults [a] (age ≥ 65 years) n=90 [b]		**Younger Adults [a] (age < 65 years)** n=111 [b]	
	Discharge to SNF	No discharge to SNF	Discharge to SNF	No discharge to SNF
PT recommended SNF, n (% per recommendation)	52 (91.23)	5 (8.77)	13 (92.86)	1 (7.14)
PT did not recommend SNF, n (% per recommendation)	**14 (48.28)**	15 (51.72)	**2 (16.67)**	10 (83.33)

[a] 95.56% of older patients who had a PT encounter were on Medicare; we subsetted older patients to the Medicare population. 23.42% of younger patients who had a PT encounter were on Medicare; we subsetted younger patients to the smaller Medicare population.
[b] Not all patients had a PT encounter during their initial hospitalization. Additionally, the location of PT notes in the Epic system was inconsistent, which may have led to missed PT encounters during medical record reviews. This may have led to an underestimation of the number of patients with PT encounters, but we do not expect that this biased the results presented because discharge recommendation is our outcome of interest, not whether a patient had a PT encounter.

Among older adults for whom physical therapy did not recommend discharge to a nursing facility, 45.2% were still discharged to a nursing facility. Among younger adults, 16.7% were discharged to a nursing facility when physical therapy did not recommend it.

Temporal Trends in Adverse Events

Figure 2. Timing of OPAT-specific AEs in all ages over the course of therapy.



The majority of OPAT-specific AEs appear to occur in the first 45 days of OPAT in all ages. SaTScan analysis revealed significant clusters of timing of first OPAT-specific AEs from days 4-17 overall (p=0.01), days 4-15 for older patients (p=0.01), and days 5-25 for younger patients (p=0.03).

Discussion

These results confirm that OPAT has similar safety implications in older adults as in younger adults. The crude comparison of the percentage of older versus younger adults experiencing OPAT-specific AEs, rate of OPAT-specific AEs per 1,000 OPAT-days, and multivariable analysis of older age's association with OPAT-specific AEs all showed no difference in OPAT-specific AEs in older versus younger patients. We also found that patients discharged on oxacillin or vancomycin had greater odds of developing an OPAT-specific AE

than patients discharged on other antimicrobial regimens, adding to existing data that vancomycin and β-lactam antibiotics may have increased consequences for patients on OPAT.[6,9] Prior studies have also shown similar rates of antimicrobial change, catheter-related complications,[24] and hospital readmissions in older and younger patients.[8] Additionally, previous studies have found insignificant risk ratios for the association between AEs and older age[9] and insignificant multivariable-adjusted odds ratios of older age and AEs.[8]

This study is distinct from prior studies in that it provides a comprehensive analysis of AEs that can be directly attributed to the OPAT course. Previous studies have focused on a more general definition of AEs, and they have not included all of the OPAT-specific AEs that we did in our definition. Our detailed review of the medical record allowed us to provide a specific estimate of risk that we believe is attributable to the OPAT course. These results, in combination with previous conclusions on hospital readmissions and treatment effectiveness in older and younger patients,[8,9] show that risk does not significantly differ for AEs in older compared to younger patients on OPAT. This study also confirms prior estimates that approximately 20% of all patients on OPAT experience at least one AE.[2,3,4]

ID-relevant healthcare utilization did not differ between older and younger patients. Older adults had a higher frequency of comorbidities, but this did not translate into more interaction with the ID team. Patients with comorbidities have been shown to exhibit increased frequencies of general practitioner visits, specialist visits, and hospital admissions,[25] but since patients on OPAT tend to have similar infection types and OPAT characteristics (i.e., length and antimicrobial choice), ID interaction was likely unaffected by age-related comorbidities. Another reason that older adults did not have increased healthcare utilization may be that that older adults were more likely to be discharged to a nursing facility. Any minor events that

occurred would likely have been taken care of by the nursing staff and not reported to the ID team. Other patients that are not in a nursing home may warrant a phone call or office visit.[26]

Interestingly, having at least one comorbidity was associated with fewer odds of OPAT-specific AEs than having no comorbidities. This may also result from greater interaction with the non-ID team and increased likelihood of being discharged to a nursing home, since more minor AEs may have been taken care of and not reported by non-ID physicians/nursing staff, leading to fewer odds of OPAT-specific AEs among this population with more comorbidities.

Our analysis of temporal trends in OPAT-specific AEs using SaTScan revealed significant clustering of patients' first OPAT-specific AEs for both age groups separately and combined. Older adults seemed to have a more specific time period of risk (days 4-15) than younger adults (days 5-25). This suggests that older adults are most at risk of developing an OPAT-specific AE during approximately their first two weeks of therapy, whereas younger adults' risk appears more evenly distributed throughout their therapy. Related to the discussion above, this may be explained by older adults' higher frequency of comorbidities; they are more likely to have regular interaction with overall health services due to other illnesses,[25] and any significant adverse event that occurs (and that is not deterred, see above) can be identified more rapidly. Similarly, because older adults are more likely to be discharged to nursing facilities, significant AEs may be recognized more rapidly. This study revealed SaTScan to be an important tool outside of its typical use in large-scale surveillance activities. Additionally, we were able to use the software's temporal analysis to describe events that did not happen in the same time frame by transposing patient events to an artificial timeline, and this methodology has not yet been described in the literature. One drawback to using SaTScan to evaluate timing of OPAT-specific AEs, however, is that it did not allow us to test whether there was a significant

difference in OPAT-specific AEs between older and younger patients, only identifying significant clusters within each group. Nevertheless, the methods we describe to perform this analysis are remarkably useful in determining the timing of patient events, and SaTScan's utility with clinical data and unique public health data should be explored further.

In cases where physical therapy did not recommend discharge to nursing home among Medicare beneficiaries, older adults seem to be more likely to be discharged to a nursing home than younger adults. Medicare covers nursing home stays regardless of physical therapy recommendation, and a greater frequency of comorbidities among older patients may result in discharge to nursing home against physical therapy recommendation in order to ensure that their conditions are being managed. Additionally, there may be concern for complications with OPAT in older patients if they are discharged to home. However, discharge to a skilled nursing facility was not significantly associated with OPAT-specific adverse events during univariate Chi square testing (Supplementary Table 2), indicating that discharge to a nursing facility to prevent OPAT-related AEs is not necessary. Therefore, if physical therapy determines that a patient does not require post-discharge care at a nursing home, the administration of OPAT should not indicate otherwise.

There are a number of limitations to this study. We relied on data from medical charts at all stages of the project. Medical records tend to give an incomplete picture of a clinical course due to patients' lack of interaction with healthcare providers in the outpatient setting, incomplete recording of relevant information by providers, other shifts in information storage, or changing tendencies of those interacting with the medical record system. Also, there is a potential for observation bias in this study; since we reviewed medical records retrospectively on all observations to obtain the majority of relevant information, we could not be blinded to patient

age, and it is possible that we searched for characteristics and outcomes differentially between older and younger patients. We likely underestimated the risk of AEs due to OPAT because we focused our analyses on those AEs that could be specifically related to OPAT. We did not evaluate events such as gastrointestinal issues, allergic reactions, or laboratory-confirmed toxicities because these were highly non-specific to OPAT, and it would be inaccurate to assume that any instance of these AEs during OPAT through the 30 days after OPAT discontinuation was due to the OPAT course. Most providers did not conclusively state the indication of such AEs, and their occurrence may be due to the prevalence of comorbidities, non-OPAT medications, and other health events in the population. Finally, this is an epidemiologic study, and our findings alone are associations.

Conclusion

Older and younger adults discharged on OPAT experience similar frequencies of AEs, but older adults should be monitored more carefully in the first two weeks of OPAT. Healthcare utilization is a simple method to describe patient interaction with a healthcare system and identify follow-up needs in a patient population, and the utility of SaTScan's temporal-only analysis to evaluate clinical events should be studied further. Older adults do not experience a greater frequency of AEs in the home versus nursing home setting, so discharge to a nursing home is unnecessary if physical therapy recommends the home setting.

OPAT is a safe option for older adults requiring IV antimicrobial therapy in comparison with younger adults. It may be optimized further by focusing on issues of AE timing and discharge discrepancies discussed in this study. As general OPAT practice continues to improve, we should continue to take AE incidence, timing of AEs, and patient support needs into account. Additionally, older adults may have the same safety considerations as younger adults on OPAT,

but over 20% of both groups experienced at least one OPAT-specific AE. Many of these AEs are preventable, so there are still improvements to be made in OPAT safety overall.

Supplementary Tables

Supplementary Table 1. List and definitions/justifications of collected OPAT-specific AEs.

OPAT-Specific AEs	**Definition**
Antimicrobial indications	
Missed antimicrobial dose [27]	As documented in medical record. Represents difficulty with therapy and/or lack of attention by patient/caregiver.
Change in antimicrobial agent [9]	As documented in medical record. Telling of any AE serious enough to change therapy, or lack of efficacy of chosen antimicrobial
Early discontinuation of antimicrobial agent [9]	As documented in medical record. Telling of any AE serious enough end therapy early. Excludes cases where antimicrobial was ended early due to infection resolution.
Vascular access complications	
Dressing problem [27]	As documented in medical record. Line, not wound, dressing.
Occlusion [28]	As documented in medical record.
Dislodgement [28]	As documented in medical record. Either accidental dislodgement, or patient altering the line or pulling line out.
Thrombosis [28]	As documented in medical record. Only thrombosis in the same extremity as the line insertion site.
Broken extension	As documented in medical record. No citation to previous use of this AE, but observed during chart reviews and clearly related to OPAT line access.
Pain or swelling (without thrombosis) [28]	As documented in medical record. Only at line insertion site or in same extremity as insertions site.
Leaking [28]	As documented in medical record. From insertion site.
Bleeding [28]	As documented in medical record. From insertion site.
Site infection [28]	As documented in medical record.
Site itching	As documented in medical record. No citation to previous use of this AE, but observed during chart reviews and clearly related to OPAT line complications.
Change in line [24]	As documented in medical record. Represents issues with original line.

Supplementary Table 2. Univariate Chi square analysis of variables' relationship with OPAT-specific AEs [a] to create multivariable logistic regression model (Results Table 6).

Relevant Variables	**p-value** [b]
Patient characteristics	
≥ 1 comorbidity	**0.001**
Hispanic ethnicity	0.348
White race	0.812
Male gender	0.708
Discharge to SNF	0.200
Initial LOS > 8 days	0.745
Infection characteristics	
Osteomyelitis	0.155
Endocarditis/primary bacteremia	0.712
Bone and joint infection	**0.054**
CNS infection	0.941
Skin and soft tissue infection [c]	0.067
Other infection type	0.540
Infection with MRSA	0.364
OPAT characteristics	
OPAT length > 28 days	**0.008**
Treatment with vancomycin	**0.025**
Treatment with oxacillin	**0.004**

[a] Binary variables' relationship with binary OPAT-specific AEs (at least one AE=1; no AE=0)
[b] Variables chosen at $p < 0.1$ significance.
[c] SSTI has a significant association with the occurrence of an OPAT-specific AE, but there were only two individuals with an SSTI and who developed an AE, so we removed this variable from the multivariable analysis.

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