

Safety of Outpatient Parenteral Antimicrobial Therapy in Nonagenarians

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Background. Although widely accepted for adults, the safety of outpatient parenteral antimicrobial therapy (OPAT) in very old patients has not been examined.

Methods. Nonagenarians (age ≥ 90 years) discharged from the hospital on OPAT over a 5-year period were identified from the Cleveland Clinic OPAT Registry. Three matched controls (< 90 years) were selected for each nonagenarian. Times to OPAT-related emergency department (ED) visit and OPAT-related readmission were compared across the 2 groups in multivariable subdistribution proportional hazards competing risks regression models. Incidence of adverse drug events and vascular access complications were compared using negative binomial regression.

Results. Of 126 nonagenarians and 378 controls, 7 were excluded for various reasons. Among the remaining 497 subjects, 306 (62%) were male, 311 (63%) were treated for cardiovascular or osteoarticular infections, and 363 (73%) were discharged to a residential health care facility. The mean (SD) ages of nonagenarians and controls were 92 (2) and 62 (16) years, respectively. Compared with matched controls, being a nonagenarian was not associated with increased risk of OPAT-related ED visit (hazard ratio [HR], 0.77; 95% CI, 0.33–1.80; $P = .55$), OPAT-related readmission (HR, 0.78; 95% CI, 0.28–2.16; $P = .63$), adverse drug event from OPAT medications (incidence rate ratio [IRR], 1.00; 95% CI, 0.43–2.17; $P = .99$), or vascular access complications (IRR, 0.66; 95% CI, 0.27–1.51; $P = .32$). Nonagenarians had a higher risk of death overall (HR, 2.64; 95% CI, 1.52–4.58; $P < .001$), but deaths were not from OPAT complications.

Conclusions. Compared with younger patients, OPAT in nonagenarians is not associated with higher risk of OPAT-related complications. OPAT can be provided as safely to nonagenarians as to younger patients.

Keywords. aged 80 and over; emergency service, hospital; home infusion therapy; OPAT; patient readmission.

There is a paucity in general of studies that examine treatment outcomes in the elderly, and clinical decisions in the geriatric population are often based upon information gathered from much younger cohorts [1, 2]. This is particularly troublesome as the elderly are more likely to have serious comorbidities, to be taking multiple medications, and to experience adverse events related to therapy [3].

Hospitalization represents a significant risk to the elderly. In addition to complications of therapy, the elderly face additional increased risk of nosocomial events while hospitalized. Outpatient parenteral antimicrobial therapy (OPAT) was introduced in the 1970s and is generally regarded as safe and effective for administering intravenous antimicrobial therapy outside the hospital environment. OPAT therefore provides an alternative to

hospitalization, or allows for shorter hospitalizations, for infections requiring treatment with intravenous antimicrobials if the rate of complications during OPAT is not unacceptably high.

The risk of adverse outcomes during OPAT with increasing age has been examined in a number of studies. By and large, antimicrobial adverse events and vascular access complications have not been found to be associated with older age [4–8]. Readmission while on OPAT has also not been found to be associated with higher age [7, 9–12]. Recent findings have been summarized in the latest OPAT guideline published by the Infectious Diseases Society of America [13]. In almost all the studies that have examined these associations, however, older age was considered to be 60 years or higher. No studies have compared the safety of OPAT in very old patients (> 80 years) with that of younger patients.

The purpose of this study was to evaluate the safety of OPAT in nonagenarians.

METHODS

This was a retrospective cohort study comparing OPAT-related outcomes in nonagenarians and younger patients.

Patient Consent Statement

The study was reviewed by the Cleveland Clinic Institutional Review Board (IRB; No. 18–372) and deemed a minimal

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risk study using data collected for routine clinical practice. A waiver of informed consent and a waiver of HIPAA authorization were approved to allow access to protected health information (PHI) by the research team, with the understanding that sharing or releasing identifiable data to anyone other than the study team was not permitted without additional IRB approval.

Screening, Inclusion, and Exclusion Criteria

All adult patients discharged from the Cleveland Clinic on OPAT are under the supervision of an infectious disease physician. The baseline characteristics of each of these OPAT courses are captured in the Cleveland Clinic OPAT Registry. Adult patients discharged from the Cleveland Clinic Main Campus on OPAT between January 1, 2013, and January 1, 2018, were screened for inclusion in the study. OPAT courses shorter than 1 day in duration were excluded. For those subjects who received >1 course of OPAT, only the first was included.

Selection of Study and Control Subjects

Study subjects were nonagenarians, defined as those aged 90 years or older. For each study subject, 3 control subjects, matched on sex, calendar year, discharge disposition, vascular access, expected OPAT duration, infection site, and antimicrobial class, were selected from those aged 89 years or younger.

Outcomes

Time to first OPAT-related emergency department (ED) visit and time to OPAT-related readmission were the primary outcomes. Secondary outcomes were incidence of adverse drug events, incidence of vascular access complications, and time to death (all-cause mortality). Events were evaluated for up to 90 days from the OPAT start date, which was defined as the date of discharge from the hospital.

Covariates

Covariates considered were patient demographics (age and sex), county of residence, calendar year, select comorbid conditions (diabetes mellitus, end-stage renal disease, liver cirrhosis, chronic obstructive pulmonary disease [COPD], and congestive heart failure), site of infection, baseline white blood cell (WBC) count, baseline platelet count, baseline serum creatinine, *Clostridioides difficile* infection (CDI) while hospitalized, length of hospitalization before OPAT initiation, expected duration of therapy, discharge disposition (home, residential health care facility), vascular access, and antimicrobial class.

Definitions

End-stage renal disease was defined as long-term requirement for renal replacement therapy. Diabetes mellitus, liver cirrhosis, COPD, and congestive heart failure were defined as presence of these diagnoses in the medical record. Counties that share a geographic border with Cuyahoga County (the county where

Cleveland Clinic is located) were considered surrounding counties. Residence locations other than Cuyahoga and surrounding counties were considered distant counties. The last WBC count, platelet count, and serum creatinine, on or before the OPAT start date, were considered baseline levels. OPAT year was defined as the year of the OPAT start date.

Events attributed to worsening of the infection being treated, vascular access complications, and antimicrobial adverse events were considered to be OPAT-related.

Vascular access complications were defined as catheter occlusion, accidental dislodgement, venous thrombosis, and vascular catheter infection. Catheter occlusion was defined as requirement for instillation of tissue plasminogen activator (alteplase; Cathflo) due to inability to infuse medications. Accidental dislodgement was defined as accidental dislodgment of the catheter rendering it useless for administration of OPAT. Venous thrombosis was defined as the finding of superficial or deep venous thrombosis in or immediately proximal or distal to the vein harboring the vascular access device on imaging, or removal of the vascular access device for arm swelling suspected to be from venous thrombosis. Vascular catheter infection was defined as bacteremia or fungemia attributed to a vascular catheter infection or removal of the vascular access device for a suspected vascular catheter infection.

Rash, leukopenia, thrombocytopenia, acute kidney injury, acute liver injury, and other adverse events were considered antimicrobial adverse events. Rash was defined as the reporting of a rash to the OPAT team. Leukopenia was defined as a $\geq 50\%$ reduction in WBC count during the OPAT course. Thrombocytopenia was defined as a $\geq 50\%$ reduction in platelet count during the OPAT course. Acute kidney injury was defined as acute kidney injury according to the RIFLE criteria [14]. Acute liver injury was defined as a ≥ 5 -fold increase above the upper limit of normal in aspartate transaminase or alanine transaminase level. Other events were considered antimicrobial adverse events if they were attributed to an antimicrobial agent at the time by the OPAT team. *C. difficile* infection was defined as a positive *C. difficile* polymerase chain reaction test result during and up to 30 days after completion of the OPAT course.

Data Acquisition

The CoPAT registry contains demographic data (age, sex), infection category, and intravenous antibiotics for each research subject. Baseline comorbid conditions and data regarding complications of therapy were determined by manual review of the electronic medical record (EMR). Mortality was determined by both manual chart review and internet obituary searches. To ensure that the obituary corresponded to the correct patient, the obituary and EMR had to match in at least 3 of the following 4 characteristics: first and last name, age or date of birth, place of residence, and next of kin.

Statistical Analysis

Analyses were performed by N.K.S. using R, version 4.0.0 [15]. Controls for the study were selected by matching on sex, OPAT year, OPAT site, vascular access, expected OPAT duration, diagnosis groups, and antimicrobial groups using the R package *MatchIt* [16] using the nearest neighbor method.

Time to first OPAT-related ED visit and time to OPAT-related readmission were compared across the 2 groups in separate multivariable subdistribution proportional hazards competing risks regression models to account for the appropriate competing risks for each outcome, according to the method of Fine and Gray [17], using the R package *cmprsk* [18]. For OPAT-related ED visit, readmission and death were considered competing outcomes. For OPAT-related readmission, non-OPAT-related readmission and death were considered competing outcomes. Overall mortality was examined using Cox proportional hazards regression. For time-to-event analyses, events were censored at 90 days from the date of initiation of OPAT. The initial models included all the nonmatched baseline variables. Variable selection was then done by stepwise backward elimination of the least significant variable until only variables significant at a level of significance of .05 remained in the models, with the county of residence forced into the models. Incidence of antimicrobial adverse events and vascular access complications were compared across the 2 groups in separate negative binomial regression models adjusted for county of residence using the R package *MASS* [19]. Effect sizes for outcomes were expressed as hazard ratios (from the proportional hazards models) or incidence rate ratios (from the negative binomial regression models), with calculated 95% confidence intervals presented as estimates of precision.

RESULTS

During the 5-year study period, 126 nonagenarians received at least 1 OPAT course, out of the 9666 patients who received 13 092 OPAT courses at Cleveland Clinic. With 3 matched control subjects for each nonagenarian, there were a total of 504 subjects in the matched cohort. Seven subjects were excluded, 2 from each group because they were found to have completed their OPAT course while still hospitalized, 1 from each group because the OPAT course was found to have been initiated in the outpatient setting (rather than in the hospital), and 1 subject in the control group because his treatment was a once-weekly intramuscular antibiotic injection. The remaining 497 subjects (123 nonagenarians and 374 controls) were included in the study. The mean (SD) ages of subjects in the nonagenarian and control groups were 92.2 (2.5) and 62.4 (15.6) years, respectively. The baseline characteristics of the included patients are shown in [Table 1](#).

OPAT-Related Emergency Department Visits

[Figure 1](#) shows that the cumulative incidence rates of OPAT-related ED visits were very similar for nonagenarians and matched controls. For this evaluation, death and readmission

were considered competing outcomes, as the occurrence of either would have precluded a subsequent OPAT-related ED visit during that OPAT course. In a subdistribution proportional hazards competing risks regression model, being a nonagenarian was not associated with increased hazard of OPAT-related ED visit (hazard ratio [HR], 0.77; 95% CI, 0.33–1.80; $P = .55$). Residence in a distant county (HR, 0.33; 95% CI, 0.15–0.77; $P = .01$) was associated with decreased hazard of OPAT-related ED visit. Estimates of hazard ratios and 95% confidence intervals for variables in the final model are shown in [Table 2](#).

Results were similar if all ED visits were considered instead of only OPAT-related ED visits. Being a nonagenarian was not associated with increased hazard of ED visit (HR, 0.94; 95% CI, 0.63–1.39; $P = .75$). Estimates of hazard ratios and 95% confidence intervals for the variables in the final model are shown in [Supplementary Table 1](#).

OPAT-Related Readmissions

[Figure 2](#) shows that the cumulative incidence rates of OPAT-related readmissions were very similar for nonagenarians and matched controls. For this evaluation, death and non-OPAT-related readmission were considered competing outcomes, as the occurrence of either would have precluded a subsequent OPAT-related readmission for that OPAT course. In a subdistribution proportional hazards competing risks regression model, being a nonagenarian was not associated with increased hazard of OPAT-related readmission (HR, 0.78; 95% CI, 0.28–2.16; $P = .63$). Residence in a distant county (HR, 0.30; 95% CI, 0.11–0.87; $P = .03$) was associated with decreased hazard of OPAT-related readmission. Estimates of hazard ratios and 95% confidence intervals for variables in the final model are shown in [Table 3](#).

Results were similar if all readmissions were considered instead of only OPAT-related readmissions. Being a nonagenarian was not associated with increased hazard of readmission (HR, 0.73; 95% CI, 0.51–1.03; $P = .07$). Estimates of hazard ratios and 95% confidence intervals for variables in the final model are shown in [Supplementary Table 2](#).

Adverse Drug Events

Adverse drug events occurred in 11 (8.9%) of the nonagenarians vs 30 (8.0%) of the controls at rates of 4.73 vs 4.47 per 1000 OPAT days, respectively. The adverse events noted are tabulated in [Supplementary Table 3](#). Three subjects had *C. difficile* infection, all 3 among the controls. Being a nonagenarian was not associated (incidence rate ratio [IRR], 1.00; 95% CI, 0.43–2.17; $P = .99$) with the incidence of adverse drug events in a negative binomial regression model when adjusted for county of residence ([Supplementary Table 4](#)).

Vascular Access Complications

Vascular access complications occurred in 7 (5.7%) of the nonagenarians vs 35 (9.4%) of the controls at rates of 3.87 vs 5.39 per 1000 OPAT days, respectively. The vascular access

Table 1. Baseline Characteristics

Characteristic ^a	Nonagenarians	Younger Controls	P Value
	(n = 123)	(n = 374)	
Age, y	92.2 (2.5)	62.4 (15.6)	<.001
Male sex	74 (60.2)	232 (62.0)	.793
County of residence			.013
Cuyahoga	57 (46.3)	120 (32.1)	
Surrounding	21 (17.1)	69 (18.4)	
Distant	45 (36.6)	185 (49.5)	
Discharge to residential health care facility	92 (74.8)	271 (72.5)	.697
Vascular access			.936
PICC	108 (87.8)	328 (87.7)	
Cuffed tunneled catheter	1 (0.8)	5 (1.3)	
Noncuffed tunneled catheter	6 (4.9)	13 (3.5)	
Midline catheter	3 (2.4)	11 (2.9)	
Tunneled dialysis catheter	5 (4.1)	17 (4.5)	
Calendar year			.817
2013	27 (22.0)	67 (17.9)	
2014	23 (18.7)	63 (16.8)	
2015	32 (26.0)	104 (27.8)	
2016	16 (13.0)	57 (15.2)	
2017	25 (20.3)	83 (22.2)	
CDI while hospitalized	6 (4.9)	13 (3.5)	.665
Expected OPAT duration, d	21.1 (13.7)	22.0 (13.7)	.541
Hospital LOS preceding OPAT, d	25.3 (16.6)	22.2 (15.6)	.060
Comorbid conditions			
Diabetes mellitus	26 (21.1)	119 (31.8)	.032
End-stage renal disease	7 (5.7)	24 (6.4)	.941
Liver cirrhosis	0 (0.0)	10 (2.7)	.144
COPD	9 (7.3)	45 (12.0)	.197
Heart failure	38 (30.9)	65 (17.4)	.002
Baseline WBC count, ×1000	8.3 (3.4)	8.5 (3.8)	.693
Baseline platelet count, × 1000	247.5 (92.3)	290.0 (143.8)	.002
Baseline serum creatinine, mg/dL	1.3 (1.1)	1.2 (1.0)	.320
Site of infection			
Abdominal infection	12 (9.8)	42 (11.2)	.773
Cardiovascular infection	42 (34.1)	125 (33.4)	.97
Central nervous system infection	3 (2.4)	6 (1.6)	.832
Genitourinary infection	16 (13.0)	52 (13.9)	.921
Head and neck infection	0 (0.0)	2 (0.5)	1.000
Osteoarticular infection	38 (30.9)	109 (29.1)	.799
Primary disseminated infection	1 (0.8)	2 (0.5)	1.000
Skin and skin structure infection	10 (8.1)	23 (6.1)	.578
Thoracic infection	5 (4.1)	19 (5.1)	.831
Other infection	2 (1.6)	5 (1.3)	1.000
Antimicrobial class			
Antifungal	4 (3.3)	13 (3.5)	1.000
B-lactam/β-lactamase inhibitor combination	16 (13.0)	63 (16.8)	.386
Penicillinase-resistant penicillin derivative	13 (10.6)	28 (7.5)	.374
Other β-lactam antimicrobial	6 (4.9)	14 (3.7)	.771
Carbapenem	21 (17.1)	70 (18.7)	.784
Cephalosporin	23 (18.7)	56 (15.0)	.402
Cycline	0 (0.0)	1 (0.3)	1.000
Daptomycin	5 (4.1)	20 (5.3)	.744
Quinolone	2 (1.6)	6 (1.6)	1.000
Vancomycin	46 (37.4)	151 (40.4)	.632
Other antibiotic	1 (0.8)	2 (0.5)	1.000

Abbreviations: CDI, *Clostridioides difficile* infection; COPD, chronic obstructive pulmonary disease; LOS, length of stay; OPAT, outpatient parenteral antimicrobial therapy; PICC, percutaneously implanted central catheter.

^aExpressed as No. (%) unless a unit is given, in which case data are expressed as mean (SD).

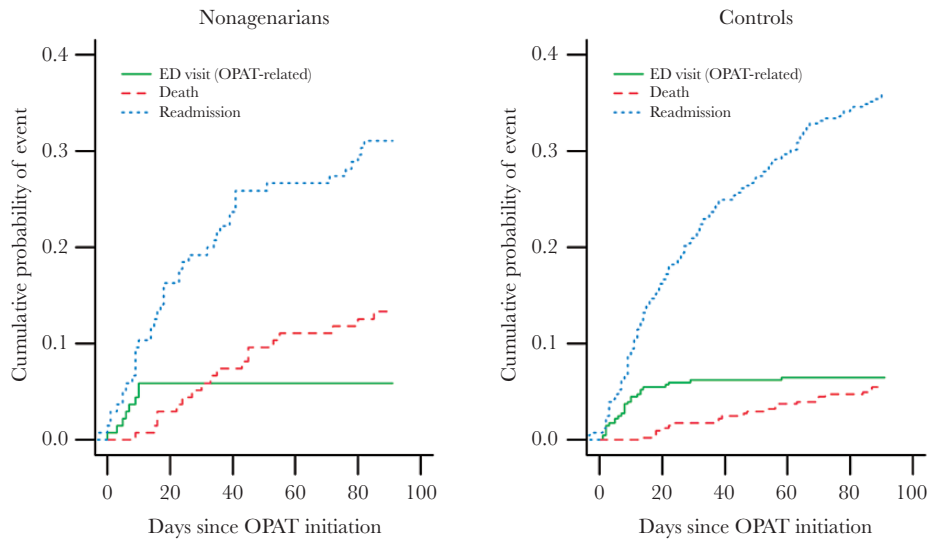


Figure 1. Cumulative incidence of OPAT-related ED visits (solid green line) and competing outcomes of death (dashed red line) and readmission (dotted blue line) for nonagenarians (left panel) and matched controls (right panel). Abbreviations: ED, emergency department; OPAT, outpatient parenteral antimicrobial therapy.

complications noted are tabulated in [Supplementary Table 5](#). Being a nonagenarian was not associated (IRR, 0.66; 95% CI, 0.27–1.51; $P = .32$) with the incidence of vascular access complications in a negative binomial regression model when adjusted for county of residence ([Supplementary Table 6](#)).

Mortality

Nonagenarians had a higher hazard of death overall (HR, 2.64; 95% CI, 1.52–4.58; $P < .001$) compared with matched controls younger than 90 years of age. Other variables associated with increased mortality were CDI during the hospitalization, higher baseline WBC count, and lower baseline platelet count ([Supplementary Table 7](#)). Only 1 death among the nonagenarians occurred while the patient was still on OPAT, but it was not clear if the death was from a complication of OPAT. None of the other deaths among the nonagenarians appeared to be a consequence of complications of OPAT.

DISCUSSION

Nonagenarians make up a very small fraction of patients in any population (1.3% of all patients who were treated with OPAT in

our institution), but given their advanced age and frailty there is genuine concern for causing unintentional harm with any treatment. This study provides reassurance that nonagenarians receiving OPAT are not at increased risk of OPAT-related ED visits, OPAT-related readmission, adverse drug events, or vascular access complications, compared with younger patients. Nonagenarians had a significantly higher risk of death than controls overall, but this mortality was not related to OPAT. Hospitalized nonagenarians have been shown to have a very high risk of death over the subsequent 5 years, with 55% dead within a year [20].

The main strength of the study is the sample size. The large number of OPAT courses in our institution allowed for a large enough number of nonagenarians to make a meaningful study possible. Because of the organization of our electronic health records, ED visits and readmissions were captured not only at Cleveland Clinic Main Campus, but in the entire Cleveland Clinic Health System, which at the time included 7 hospitals in the Northeast Ohio region.

A limitation of our study is that outcomes were evaluated retrospectively. A substantial number of relevant events were probably not recorded. However, there is little reason to suspect that nonrecording of events would be distributed differently across the groups. If different, it would be more likely that nonagenarians would have had a greater intensity of nursing support (more frequent home visits by visiting nurses), and therefore nonrecording of significant events would have been less likely for nonagenarians than for younger patients. Also ED visits and readmissions outside the Cleveland Clinic Health System would have been missed. Patients who lived at greater distances from Cleveland Clinic might have been less likely to visit one of the Cleveland Clinic EDs or hospitals when complications

Table 2. Associations With Time to First OPAT-Related ED Visit in the Final Subdistribution Proportional Hazards Competing Risks Regression Model

Variable	Hazard Ratio	95% CI	PValue
Nonagenarian	0.77	0.33–1.80	.55
Residence in a surrounding county ^a	0.66	0.26–1.66	.37
Residence in a distant county ^a	0.33	0.15–0.77	.01

Abbreviations: ED, emergency department; OPAT, outpatient parenteral antimicrobial therapy.

^aCompared with residence in Cuyahoga County (where the Cleveland Clinic is located).

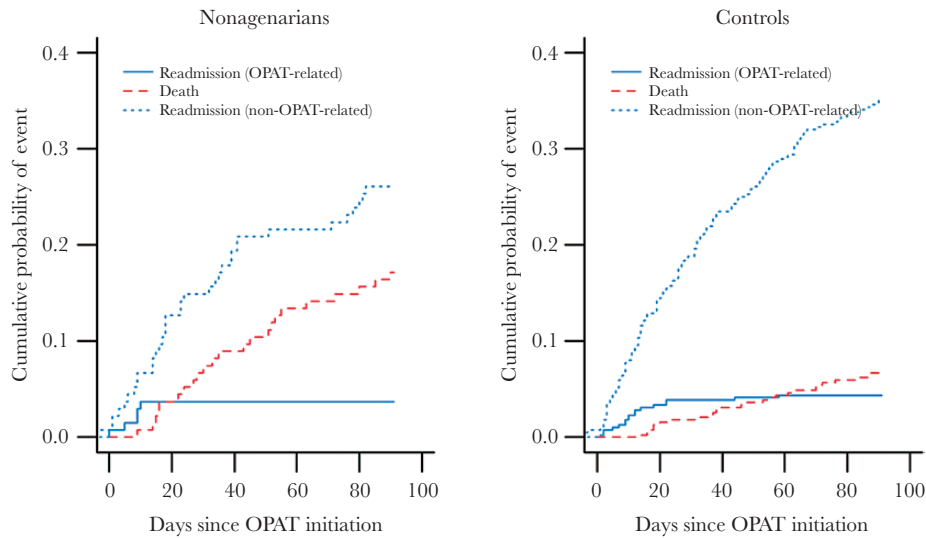


Figure 2. Cumulative incidence of OPAT-related readmissions (solid blue line) and competing outcomes of death (dashed red line) and non-OPAT-related readmission (dotted blue line) for nonagenarians (left panel) and matched controls (right panel). Abbreviation: OPAT, outpatient parenteral antimicrobial therapy.

occurred. Adjusting for county of residence in our models should have mitigated against missed ED visits and readmissions due to possible differences in the 2 groups by place of residence.

Although this study did not find harm related to OPAT for nonagenarians compared with younger patients, one cannot be complacent about treating the very elderly. Successful outcomes with OPAT require systems that are designed to identify problems early and processes to address problems that arise. Our OPAT program has been operational for over 4 decades and systems in place here contribute to successful treatment courses in our health system. Every patient discharged on OPAT is under the supervision of the same ID physician who saw the patient in the hospital; this physician remains in charge for the entire OPAT course [21]. This minimizes complications that might arise from lack of familiarity with the patient. Extra caution is advisable in places where monitoring and response systems are less robust.

In conclusion, being a nonagenarian is not associated with an increased risk of adverse outcomes during OPAT in the presence of a robust OPAT infrastructure. The wisdom of treating a nonagenarian with OPAT should always be an important

consideration, but when necessary, this study shows that treatment of nonagenarians with OPAT can be accomplished as safely as in younger patients.

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.

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Author contributions. N.K.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. N.K.S. conceived and designed the study, analyzed the data, and wrote and revised the manuscript. C.B. designed the study and collected the data. A.E. collected the data. S.M.G. and S.J.R. designed the study and critically reviewed the manuscript.

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Table 3. Associations With Time to OPAT-Related Readmission in the Final Subdistribution Proportional Hazards Competing Risks Regression Model

Variable	Hazard Ratio	95% CI	PValue
Nonagenarian	0.78	0.28–2.16	.63
Residence in a surrounding county ^a	0.79	0.28–2.23	.66
Residence in a distant county ^a	0.30	0.11–0.87	.03

Abbreviation: OPAT, outpatient parenteral antimicrobial therapy.

^aCompared to residence in Cuyahoga County (where Cleveland Clinic is located).

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