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Original Article

A retrospective analysis of adverse events among patients receiving daptomycin versus vancomycin during outpatient parenteral antimicrobial therapy

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Abstract

Objective: Outpatient parenteral antimicrobial therapy (OPAT) is a safe and effective alternative to prolonged inpatient stays for patients requiring long-term intravenous antimicrobials, but antimicrobial-associated adverse events remain a significant challenge. Thus, we sought to measure the association between choice of antimicrobial agent (vancomycin vs daptomycin) and incidence of adverse drug events (ADEs).

Methods: Patients receiving OPAT treatment with vancomycin or daptomycin for skin and soft-tissue infections, bone and joint infections, endocarditis, and bacteremia or endovascular infections during the period from July 1, 2013, through September 30, 2016, were included. Demographic and clinical data were abstracted from the medical record. Logistic regression was used to compare ADEs requiring a change in or early discontinuation of therapy, hospital readmission, and emergency room visits between groups. Time from OPAT enrollment to ADE was compared using the log-rank test.

Results: In total, 417 patients were included: 312 (74.8%) received vancomycin and 105 (25.2%) received daptomycin. After adjusting for age, Charlson comorbidity index, location of OPAT treatment, receipt of combination therapy with either β-lactam or fluoroquinolone, renal function, and availability of safety labs, patients receiving vancomycin had significantly higher incidence of ADEs (adjusted odds ratio [aOR], 3.71; 95% CI, 1.64–8.40). ADEs occurred later in the treatment course for patients treated with daptomycin ($P < .01$). Rates of readmission and emergency room visits were similar.

Conclusions: In the OPAT setting, vancomycin use was associated with higher incidence of ADEs than daptomycin use. This finding is an important policy consideration for programs aiming to optimize outcomes and minimize cost. Careful selection of gram-positive agents for prolonged treatment is necessary to limit toxicity.

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Outpatient parenteral antibiotic therapy (OPAT) is a safe, effective, and cost-saving alternative to prolonged inpatient hospitalization for patients who require long durations of intravenous antimicrobial therapy.[1–6] OPAT enables earlier transitions out of the acute-care setting, reduces the duration of hospitalization, and is associated with high levels of patient satisfaction.[2–4]

Although the benefits of OPAT are well recognized, long-term intravenous antimicrobial treatment carries substantial risk of antimicrobial toxicity and complications of intravenous catheters. Multiple studies report rates of adverse events during a typical OPAT course ranging from 6% to 44%; the most common undesirable outcomes include adverse drug events (ADEs) and vascular access complications.[1,7–13] These complications cause harm to patients, increase healthcare utilization, and diminish the benefits that OPAT programs offer patients and health systems. Minimizing patient risk requires substantial clinical and administrative infrastructure to ensure that treatment is safe and effective.[14–20]

The adverse effects caused by antimicrobial therapy are well established. Among hospitalized patients, antibiotic-associated ADEs are common during treatment and when used for prophylaxis around surgery, with a linear relationship between the duration of therapy and the risk of ADEs.[21,22] Vancomycin is associated with increased rates of ADEs, including nephrotoxicity, when compared to other gram-positive agents.[8,21] Nephrotoxicity risk is compounded when vancomycin is administered in combination with β-lactam antibiotics, which commonly occurs in the OPAT setting if a patient is diagnosed with a polymicrobial infection or if no specific organism is isolated.[22–25] Recent studies suggest that daptomycin may offer a safe and effective alternative

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with reduced need for OPAT staff intervention compared to vancomycin.[12]

Given the well-established concerns regarding antimicrobial toxicity and the challenges of balancing convenience and comfort with safety and effectiveness, we sought to compare the rates and timing of ADEs and healthcare utilization between patients receiving OPAT antibiotic treatment with vancomycin and daptomycin to inform clinical decision making.

Methods

Setting

We performed a single-center, retrospective observational cohort study of patients receiving treatment with either daptomycin or vancomycin in the OPAT program of a large tertiary-care academic medical center. Patients enrolled in the OPAT program require consultation with an infectious disease physician, including the determination of the need for >14 days of parenteral antibiotics following hospital discharge. All enrolled patients have documentation in an integrated inpatient/outpatient electronic health record (EHR) outlining diagnosis, antimicrobial type, dose, anticipated treatment duration, and recommendations for weekly laboratory safety monitoring, based on Infectious Diseases Society of America (IDSA) OPAT Guidelines.[16] Laboratory data, clinic visit notes, and telephone notes are entered into the EHR by OPAT staff. Notes from home visits by external infusion companies and visiting nurse agencies were not available.

Cohort identification

Adult patients receiving their initial OPAT treatment course for management of skin and soft-tissue infections, bone and joint infections (including hardware-associated infections and diabetic ulcer infections), bacterial endocarditis, and bacteremia or endovascular infections who were treated with a regimen containing vancomycin or daptomycin were eligible for inclusion. The study period was July 1, 2013, through September 30, 2016. Patients were excluded for the following reasons: the initial hospital discharge was to hospice care, OPAT enrollment occurred as an outpatient, post-discharge management and follow-up were with a provider outside of the study site's Infectious Disease OPAT clinic, the patient was receiving chronic renal replacement therapy, or if death occurred prior to completion of OPAT treatment (Fig. 1).

Data collection and definitions

Dates of enrollment, hospital discharge, and infection diagnosis were extracted from the OPAT database. The cohort entry date was defined as the date of discharge from the initial hospitalization. Data abstracted from the EHR included demographics, insurance status, baseline clinical and laboratory characteristics (Table 1), microbiology results (site of culture and bacterial organism), other antimicrobials administered during OPAT treatment, location of disposition and receipt of OPAT treatment (home, long-term acute care, or skilled nursing facility), type of vascular access used for infusion, recommended and actual duration of OPAT, frequency of clinic visits and telephone calls with OPAT clinic staff, availability of safety lab testing results, and the occurrence and type of ADEs related to antibiotic therapy.

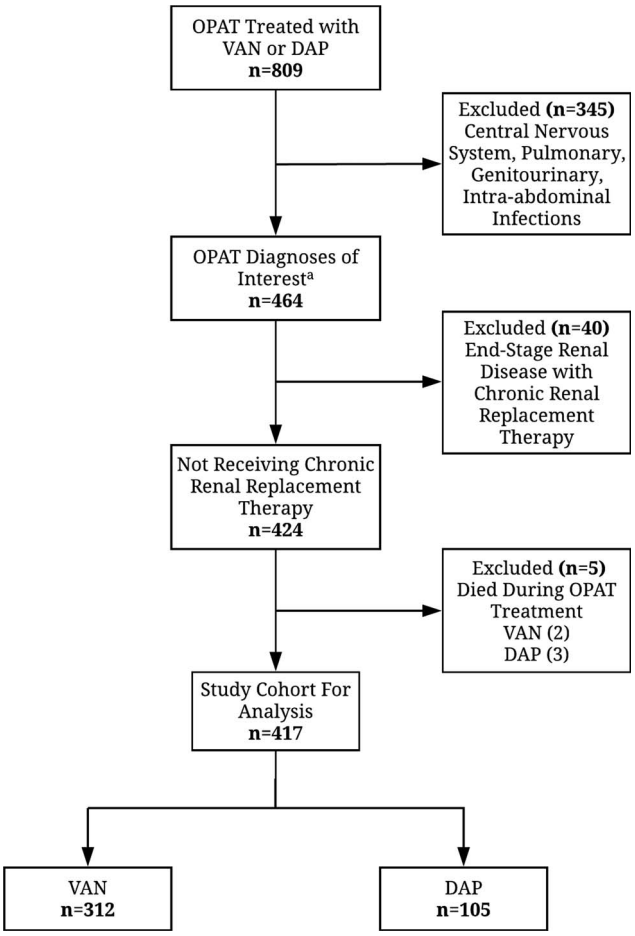

Fig. 1. Patient selection. [a]Skin and soft-tissue infections, bone and joint infections, endocarditis, and bacteremia/endovascular infections. Abbreviations: OPAT, outpatient parenteral antibiotic therapy; VAN, vancomycin; DAP, daptomycin.

Laboratory testing was considered discordant with IDSA OPAT guidelines if recommended labs were unavailable for review by the treating OPAT physician in the EHR for >1 week of the patient's treatment course.[16] Charlson comorbidity index (CCI) was calculated using the *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) or *International Classification of Disease, Tenth Revision* (ICD-10) codes obtained from hospital fiscal databases.[26,27]

Outcomes

The primary outcome was defined as a change or early discontinuation of the antibiotic of interest due to an ADE occurring >7 days prior to the anticipated end date of treatment. An ADE was defined as harm or injury to the individual attributed to the antimicrobial agent according to the treating OPAT physician, as documented in clinic or telephone notes. Secondary outcomes were time from OPAT enrollment to occurrence of ADE, unplanned hospital readmissions and emergency room visits during the 30-day window after completion of OPAT, and change or early discontinuation of the antibiotic of interest due to reason other than ADE occurring >7 days prior to the anticipated end date of treatment. Hospital readmissions and emergency room visits were not independently counted as ADEs, though they may have been related to an ADE.

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Table 1. Patient Characteristics

Characteristic	Vancomycin (n = 312), No. (%)	Daptomycin (n = 105), No. (%)	*P* Value[a]
Age[b]	63.1 (14.3)	53.9 (17.8)	**< .01**
Female	129 (41.4)	33 (31.4)	.08
Race			.83
White	236 (75.6)	79 (75.2)	
Black	30 (9.6)	10 (9.5)	
Asian	7 (2.2)	1 (1.0)	
Other	39 (12.5)	15 (14.3)	
Hispanic ethnicity	24 (7.7)	8 (7.6)	.92
Medical insurance			.08
Private insurer	131 (42.0)	51 (48.6)	
Medicare[c]	142 (45.5)	35 (33.3)	
Public, non-Medicare	37 (11.9)	17 (16.2)	
No Insurance	2 (0.6)	2 (1.9)	
Length of stay[b]	9.8 (7.4)	11.1 (9.9)	.15
ICU stay during hospitalization	48 (15.4)	22 (21.0)	.23
Hospitalization in previous 12 months	161 (51.6)	56 (53.3)	.82
Baseline eGFR, mL/min/1.73 m^2			**.02**
>90[c]	138 (44.2)	61 (58.1)	
60–90[c]	103 (33.0)	21 (20.0)	
<60	71 (22.8)	23 (21.9)	
Charlson comorbidity index[b]	1.7 (1.7)	1.4 (1.7)	.09
OPAT diagnosis			.65
Skin and soft tissue	18 (5.8)	5 (4.7)	
Bone/joint	76 (24.3)	32 (30.5)	
Hardware associated	118 (37.8)	32 (30.5)	
Diabetic ulcer	49 (15.7)	15 (14.3)	
Endocarditis	28 (9.0)	11 (10.5)	
Bacteremia/Endovascular	23 (7.4)	10 (9.5)	
Bacteremia during hospitalization	66 (21.2)	34 (32.4)	**.02**
Bacterial pathogen treated in OPAT			**.02**
Methicillin-resistant *Staphylococcus aureus*	92 (29.5)	39 (37.1)	
Vancomycin-resistant *Enterococcus*[c]	0 (0)	10 (9.5)	
Polymicrobial infection			**.02**
No	127 (40.7)	45 (42.9)	
Yes	112 (35.9)	48 (45.7)	
Empiric therapy[c]	73 (23.4)	12 (11.4)	

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Table 1. (*Continued*)

Characteristic	Vancomycin (n = 312), No. (%)	Daptomycin (n = 105), No. (%)	*P* Value[a]
OPAT regimen combination therapy[d]			.50
β-lactam	92 (29.5)	28 (26.7)	
Fluoroquinolone	38 (12.2)	11 (10.5)	
Aminoglycoside	2 (0.6)	0 (0)	
TMP-SMX	1 (0.3)	1 (1.0)	
Location of OPAT treatment			**< .01**
Home	137 (43.9)	73 (69.5)	
Long-term acute care or skilled nursing facility	175 (56.1)	32 (30.5)	
Duration of OPAT course, d[b]	34.5 (12.5)	35.2 (11.6)	.62
Vascular device for OPAT			**.05**
PICC/Midline[c]	311 (99.7)	102 (97.1)	
Tunneled central line	1 (0.3)	2 (0.2)	
Daily peripheral IV catheter	0 (0)	1 (0.1)	
Clinic interactions per week of OPAT, median (IQR)	0.9 (0.6–1.5)	0.7 (0.4–1.1)	**< .01**
Safety labs available weekly[e]	242 (78.0)	71 (67.6)	**.05**

Note. eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; OPAT, outpatient parenteral antibiotic therapy; PICC, peripherally inserted central catheter; TMP-SMX, trimethoprim-sulfamethoxazole; VAN, vancomycin.
[a]Bold values indicate statistical significance.
[b]Data presented as mean (standard deviation).
[c]$P \leq .05$ for univariate comparison of the category.
[d]Only receipt of combination therapy with β-lactam or fluoroquinolone used in multivariate regression model.
[e]Missing data (VAN = 1).

Data analysis

Baseline characteristics of patients receiving vancomycin and daptomycin were compared using the Student *t* test, the Fisher exact test, the Mann-Whitney U test, and the χ^2 test as appropriate. The primary analysis was performed using logistic regression, adjusting for 6 variables chosen a priori based on prior studies: age, CCI, location of OPAT treatment, receipt of combination therapy with either β-lactam or fluoroquinolone, baseline renal function, and availability of weekly safety labs.[1,5,14,23–25,28] To measure the association between antimicrobial choice and hospital readmission and emergency room visits, 3 variables were chosen a priori for inclusion in a logistic regression model: age, CCI, and location of OPAT treatment.[5,14,28] A sensitivity analysis including patients who died during the OPAT treatment course was completed to ensure that our results were robust to inclusion and exclusion criteria.

In addition, a time-to-event analysis was completed. Patients were censored at completion of OPAT treatment, discontinuation of vancomycin or daptomycin, or after loss to follow up and cumulative incidence curves were generated.

Data were collected and analyzed using Microsoft Access 2010 software (Microsoft, Redmond, WA) and SAS version 9.3 software (SAS Institute, Cary, NC).

Ethical considerations

The Institutional Review Board of Beth Israel Deaconess Medical Center approved this study prior to data collection and analysis.

Results

Study population and baseline characteristics

In total, 417 patients met inclusion criteria, including 312 (74.8%) who received vancomycin and 105 (25.2%) who received daptomycin (Fig. 1). We excluded 2 patients from our analysis of the primary outcome due to loss to follow-up.

Baseline characteristics are summarized in Table 1. The most common OPAT diagnoses were bone and joint infections and hardware-associated infections. The mean patient age was 60.8 years, and 38.9% of the patient cohort were female. The distribution of combination regimens was similar among patients receiving daptomycin and vancomycin; the most common additional agents were β-lactams and fluoroquinolones. Patients who received vancomycin were more likely to have mild renal impairment with an estimated glomerular filtration rate (eGFR) of 60–90 mL/min/1.73 m^2 (33.0% vs 20.0%). Patients who received vancomycin were also more likely to have recommended safety laboratory results available to the treating OPAT provider each week (78.0% vs 67.6%). Of 105 patients patients receiving daptomycin, 10 (9.5%) had an infection with vancomycin-resistant *Enterococcus*.

After stratifying by the location of OPAT, (Supplementary Table 1), patients receiving daptomycin therapy at home had the lowest severity of illness (CCI > 1; 26.0%) compared to those receiving daptomycin therapy at a long-term acute-care or skilled nursing facility and those receiving vancomycin at either location. Most patients receiving treatment in a long-term

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Table 2. Unadjusted Rates of Primary and Secondary Outcomes With Vancomycin and Daptomycin

Primary Outcome	Vancomycin (n = 312), No. (%)	Daptomycin (n = 105), No. (%)	*P* Value[a]
ADE leading to a change or early discontinuation of OPAT antibiotic[b]	59 (19.0)	8 (7.6)	**< .01**
Secondary outcomes			
Change or early discontinuation of OPAT antibiotic for other reason[b]	31 (10.0)	3 (2.9)	**.03**
Hospital readmission 30 days following completion of OPAT[c]	94 (30.3)	33 (32.0)	.81
Emergency room visit 30 days following completion of OPAT[d]	105 (34.0)	36 (35.0)	.90

Note. ADE, adverse drug event; DAP, daptomycin; VAN, vancomycin.
[a]Bold values indicate statistical significance.
[b]Missing data (VAN = 2).
[c]Missing data (VAN = 2, DAP = 2).
[d]Missing data (VAN = 3, DAP = 2).

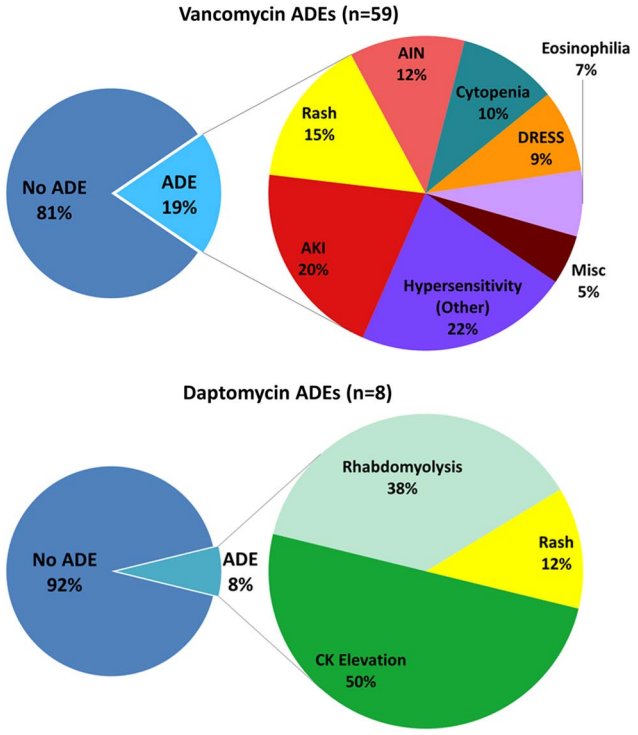

Fig. 2. Rates and categories of ADEs among recipients of vancomycin and daptomycin as part of their OPAT regimen. Abbreviations: ADEs, adverse drug events; AIN, acute interstitial nephritis; AKI, acute kidney injury; CK, creatine kinase; DRESS, drug reaction with eosinophilia and systemic symptoms; OPAT, outpatient parenteral antibiotic therapy.

acute-care or skilled nursing facility had Medicare health insurance , both for daptomycin (56.3%) and vancomycin (52.6%). Patients receiving home infusions of vancomycin had the highest frequency of clinic interactions, with a median of 1.1 per week.

Outcomes

Patients receiving vancomycin had higher rates of ADEs resulting in change or early discontinuation of therapy (19.0% vs 7.6%; $P < .01$) (Table 2). In the 59 vancomycin-treated patients with ADEs, the most common were hypersensitivity reactions (22%), acute kidney injury (20%), rash (15%), and acute interstitial nephritis (12%). Among the 8 daptomycin-treated patients with ADEs, the most common were asymptomatic creatine kinase (CK) elevations (50%), rhabdomyolysis (38%), and rash (12%) (Fig. 2). In multivariate logistic regression analysis, vancomycin remained an independent predictor of ADE (adjusted odds ratio [aOR], 3.71; 95% confidence interval [CI], 1.64–8.40) (Table 3). Inclusion of patients who died (N = 5) did not change the association.

Daptomycin-treated patients received longer durations of therapy prior to onset of ADEs ($P < .01$). After 7 and 28 days of therapy, 4.5% and 16.7% of vancomycin patients experienced the primary outcome versus 0% and 6.7% of daptomycin patients (Fig. 3, cumulative incidence curve).

Therapy changes for non-ADE events were higher in vancomycin-treated patients (10.0% vs 2.9%; $P = .03$). Among the 31 vancomycin-treated patients with therapy changes, the reasons included microbiologic results (26%), physician choice (16%), dosing challenges (13%), peripherally inserted central catheter-related issues (13%), and patient preference to discontinue parenteral therapy (13%). For the 3 daptomycin-treated patients with therapy changes, the reasons included OPAT physician concern for clinical failure, readmission for pneumonia, and patient preference to discontinue parenteral therapy. Rates of unplanned hospital readmission (vancomycin 30.3% vs daptomycin 32.0%) and emergency room visitation (vancomycin 34.0% vs daptomycin 35.0%) were similar.

Discussion

This study is one of the largest published cohorts to compare therapy-related outcomes among OPAT patients and provides additional data to inform selection of antimicrobial agents. Patients receiving vancomycin had higher rates of ADEs resulting in change or early discontinuation of treatment and higher rates of healthcare utilization when compared to daptomycin-treated patients (aOR, 3.71; 95% CI, 1.64–8.40). This association persisted throughout the duration of the OPAT treatment course, from week 1 to beyond week 8 of therapy. The incidence of ADEs leading to change or discontinuation of therapy in our cohort (16%) is similar to those reported in other published studies.[1,7–9,12]

The types and severity of ADEs in vancomycin- versus daptomycin-treated patients were substantively different (Fig. 2). The most common reason for therapy change in the daptomycin-treated patients was asymptomatic CK elevation, while

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Table 3. Multivariate Logistic Regression Model of Adverse Drug Events Leading to a Change or Early Discontinuation of Antibiotic Therapy

Covariate	Adjusted OR	95% CI	*P* Value[a]
OPAT antibiotic			
Daptomycin	…	…	…
Vancomycin	3.71	1.64–8.40	**< .01**
Age	1.00	0.98–1.02	.90
Baseline eGFR, mL/min/1.73 m^2			
> 90	…	…	…
60–90	0.75	0.38–1.48	.40
< 60	1.52	0.74–3.13	.25
Charlson comorbidity index	0.81	0.66–0.99	**.04**
Location of OPAT treatment			
Home	…	…	…
Long-term acute-care or skilled nursing facility	0.53	0.29–0.95	**.03**
OPAT combination therapy	1.10	0.48–2.55	.82
Safety labs not available weekly	0.99	0.51–1.92	.97

NOTE. OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; OPAT, outpatient parenteral antibiotic therapy; OR, odds ratio.
[a]Bold values indicate statistical significance.

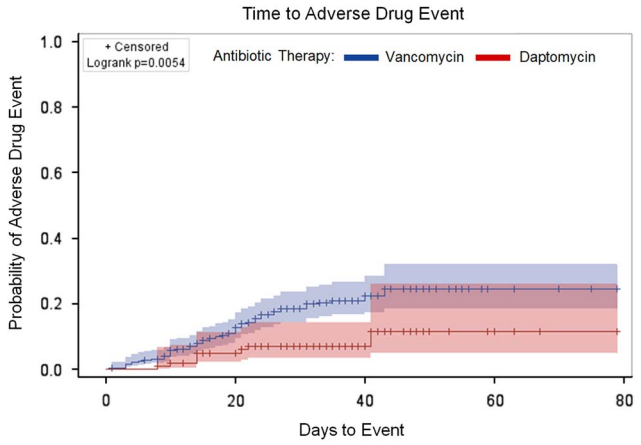

Fig. 3. Cumulative incidence (with 95% confidence intervals) for adverse drug events among recipients of vancomycin and daptomycin as part of their OPAT regimen. Patients were censored at completion of OPAT treatment, discontinuation of vancomycin or daptomycin, or after loss to follow-up.

hypersensitivity syndromes, organ dysfunction, and cytopenias were observed in the vancomycin group. Notably, 3 of 7 daptomycin patients who developed a skeletal muscle ADE were also taking a statin at the time of discharge. Some cases of skeletal muscle toxicity may have been reduced through a robust discharge medication reconciliation process. However, in some high-risk patients, discontinuing the statin may have outweighed any potential benefits. This high-risk population is also at increased risk of kidney injury, further complicating the clinical decision-making process.

The toxicity of intravenous antibiotics, particularly vancomycin, necessitates a careful review of the clinical indication for the expanded-spectrum gram-positive coverage. A significant number of patients in our cohort received vancomycin empirically without a confirmed microbiologic diagnosis of a resistant organism (23.4%). This treatment decision was driven in part by cases in which patients did not have a microbiologic culture obtained in the setting of an infectious process often caused by methicillin-resistant *Staphylococcus aureus* (MRSA) or coagulase-negative *Staphylococci*, such as skin and soft-tissue infections (5.8%), bone and joint infections (24.3%), and hardware-associated infections (37.8%). Careful consideration of MRSA risk is important before committing patients to a prolonged course of vancomycin. If microbiology results are not conclusive, alternative means of MRSA risk stratification, such as MRSA nasal screening, may be useful to tailor decision making. Negative nasal screening has a high negative predictive value and is useful in many instances for narrowing antimicrobial coverage.[29]

The IDSA OPAT guidelines recommend weekly safety laboratory monitoring for patients receiving home infusions of vancomycin and daptomycin. These guidelines were last updated in 2004, however, and logistical challenges result in significant variation in real-world clinical practice.[8,30,31] Availability of OPAT laboratory testing is associated with a lower risk of hospital readmission and higher OPAT success.[1,28] We did not find a significant association between frequency of safety laboratory monitoring and reduced risk of adverse events; however, our study had limited power to detect a difference in this outcome between the 2 exposures groups.

These findings are limited in several ways. First, there is potential for residual confounding present in all observational designs. This may explain our finding that receipt of therapy at a long-term acute-care or skilled nursing facility was associated with a lower risk of medication change due to ADE. A higher burden of comorbidities was noted among patients at facilities (Supplementary Table 1). In a sensitivity analysis including patients who died, the association between receipt of therapy at a long-term acute-care or skilled

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nursing facility and the primary outcome did not persist ($P = .12$), suggesting that unmeasured confounding may be driving this finding. Second, as a single-center analysis, this cohort and the clinical practices in our center may not be reflective of those in other OPAT clinics. In addition, anticipated OPAT duration of at least 14 days was a qualification for enrollment; shorter courses that are at lower risk of ADEs were not included. To ensure that only clinically significant ADEs were reflected in our results, we limited our primary outcome to ADEs that resulted in a therapy change or discontinuation. We also did not consider common adverse events, such as red man syndrome, that may negatively impact a patient's quality of life without resulting in a change in therapy. There was a high rate of hospital readmission in this cohort as compared to other studies, potentially reflecting a sicker patient population, although a long follow up period—extended 30 days beyond the completion of OPAT therapy—may also have impacted this result.[7,8,10,12,14,20]

Our study is one of the few published analyses comparing adverse events and healthcare utilization associated with 2 of the most commonly prescribed gram-positive agents in the OPAT setting, daptomycin and vancomycin. Other strengths include the size of the cohort included, the breadth of infectious diagnoses considered, and the completeness of the data with minimal missing covariates or outcomes. With an organized OPAT program involving physicians, nurses, and administrative staff, pertinent clinical and demographic data for each patient was documented at the time of enrollment and clinical follow up, optimizing data capture.

Pre-enrollment evaluation of patients with an infectious disease consultation and sufficient clinical support to ensure a complete care transition reduces adverse events and overall OPAT costs.[17,19,20] Careful consideration is necessary when selecting an antibiotic agent for long-term therapy, including the risk of selection for antibiotic resistance, costs, ease of administration, need for monitoring, and the known risk of complications, including ADEs. By defining the primary outcome as ADEs that required a change or discontinuation of therapy, the results of this study are more directly related to the choice of antimicrobial agent used for treatment, a programmatic decision for an OPAT clinic, rather than outcomes related to healthcare delivery, nursing care, or patient preferences. Our study informs inpatient clinicians and infectious disease OPAT providers regarding the risks of ADEs among recipients of vancomycin versus daptomycin.

The perceived drawbacks of daptomycin—primarily cost and broader spectrum of activity—must be weighed against the apparent challenges of long-term vancomycin: high rates of clinically significant ADEs and utilization of OPAT clinic resources. While our study did not include an economic analysis, our results suggest that vancomycin, although less expensive on a per-dose basis, is associated with complications that may render it more expensive when used for prolonged therapy in the outpatient setting. Notably, Medicare recipients (42.4% of this study's cohort) without supplemental insurance are often restricted in their long-term antibiotic options with regard to type of antimicrobial agent and site of therapy. As our analysis demonstrates, daptomycin is a safer alternative to vancomycin for gram-positive therapy in OPAT. Therefore, a Medicare recipient with a low burden of comorbidities and the ability to self-administer a once-daily medication may be better served receiving daptomycin home infusions. In addition to the direct medical costs associated with complications, vancomycin is also associated with other societal costs attributable to lost time and work productivity. For example, vancomycin infusions last for 1–2 hours, typically multiple times per day, compared to <30 minutes once daily for daptomycin. Prospective analysis to compare the rates of clinical success and ADEs would alleviate some of the confounding challenges present in this study, and further cost-effectiveness analyses of these 2 medications would greatly inform the decisions of health systems beyond the wholesale price of the medication.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2018.107

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

References

1. Ruh CA, Parameswaran GI, Wojciechowski AL, Mergenhagen KA. Outcomes and pharmacoeconomic analysis of a home intravenous antibiotic infusion program in veterans. *Clin Therapeut* 2015;37:2527–2535.
2. Durojaiye OC, Bell H, Andrews D, Ntziora F, Cartwright K. Clinical efficacy, cost analysis and patient acceptability of outpatient parenteral antibiotic therapy (OPAT): a decade of sheffield (UK) OPAT service. *Int J Antimicrob Agents* 2018;51:26–32.
3. Chapman AL, Dixon S, Andrews D, Lillie PJ, Bazaz R, Patchett JD. Clinical efficacy and cost-effectiveness of outpatient parenteral antibiotic therapy (OPAT): a UK perspective. *J Antimicrob Chemother* 2009;64:1316–1324.
4. Saillen L, Arensdorff L, Moulin E, *et al*. Patient satisfaction in an outpatient parenteral antimicrobial therapy (OPAT) unit practising predominantly self-administration of antibiotics with elastomeric pumps. *Eur J Clin Microbiol Infect Dis* 2017;36:1387–1392.
5. Bhavan KP, Brown LS, Haley RW. Self-administered outpatient antimicrobial infusion by uninsured patients discharged from a safety-net hospital: a propensity-score-balanced retrospective cohort study. *PLoS Med* 2015;12:e1001922.
6. Vargas-Palacios A, Meads DM, Twiddy M, *et al*. Cost-effectiveness of outpatient parenteral antibiotic therapy: a simulation modelling approach. *J Antimicrob Chemother* 2017;72:2392–2400.
7. Suleyman G, Kenney R, Zervos MJ, Weinmann A. Safety and efficacy of outpatient parenteral antibiotic therapy in an academic infectious disease clinic. *J Clin Pharm Therapeut* 2017;42:39–43.
8. Keller SC, Williams D, Gavgani M, Hirsch D, Adamovich J, Hohl D, Gurses AP, Cosgrove SE. Rates of and risk factors for adverse drug events in outpatient parenteral antimicrobial therapy. *Clin Infect Dis* 2018;66:11–19.
9. Lee B, Tam I, Weigel Bt, *et al*. Comparative outcomes of beta-lactam antibiotics in outpatient parenteral antibiotic therapy: treatment success, readmissions and antibiotic switches. *J Antimicrob Chemother* 2015;70:2389–2396.
10. Means L, Bleasdale S, Sikka M, Gross AE. Predictors of hospital readmission in patients receiving outpatient parenteral antimicrobial therapy. *Pharmacotherapy* 2016;36:934–939.
11. Hale CM, Steele JM, Seabury RW, Miller CD. Characterization of drug-related problems occurring in patients receiving outpatient antimicrobial therapy. *J Pharm Pract* 2017;30:600–605.
12. Shrestha NK, Mason P, Gordon SM, *et al*. Adverse events, healthcare interventions and healthcare utilization during home infusion therapy with daptomycin and vancomycin: a propensity score-matched cohort study. *J Antimicrob Chemother* 2014;69:1407–1415.

13. Shrestha NK, Shrestha J, Everett A, *et al*. Vascular access complications during outpatient parenteral antimicrobial therapy at home: a retrospective cohort study. *J Antimicrob Chemother* 2016;71: 506–512.
14. Schmidt M, Hearn B, Gabriel M, Spencer MD, McCurdy L. Predictors of unplanned hospitalization in patients receiving outpatient parenteral antimicrobial therapy across a large integrated healthcare network. *Open Forum Infect Dis* 2017;4:ofx086.
15. Allison GM, Muldoon EG, Kent DM, *et al*. Prediction model for 30-day hospital readmissions among patients discharged receiving outpatient parenteral antibiotic therapy. *Clin Infect Dis* 2014;58:812–819.
16. Tice AD, Rehm SJ, Dalovisio JR, *et al*. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. *Clin Infect Dis* 2004;38:1651–1672.
17. Conant MM, Erdman SM, Osterholzer D. Mandatory infectious diseases approval of outpatient parenteral antimicrobial therapy (OPAT): clinical and economic outcomes of averted cases. *J Antimicrob Chemother* 2014;69:1695–1700.
18. Gilchrist M, Seaton RA. Outpatient parenteral antimicrobial therapy and antimicrobial stewardship: challenges and checklists. *J Antimicrob Chemother* 2015;70:965–970.
19. Muldoon EG, Snydman DR, Penland EC, Allison GM. Are we ready for an outpatient parenteral antimicrobial therapy bundle? A critical appraisal of the evidence. *Clin Infect Dis* 2013;57:419–424.
20. Madaline T, Nori P, Mowrey W, *et al*. Bundle in the Bronx: impact of a transition-of-care outpatient parenteral antibiotic therapy bundle on all-cause 30-day hospital readmissions. *Open Forum Infect Dis* 2017;4:ofx097.
21. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med* 2017;177:1308–1315.
22. Branch-Elliman W, Ripollone JE, O'Brien WJ, *et al*. Risk of surgical site infection, acute kidney injury, and *Clostridium difficile* infection following antibiotic prophylaxis with vancomycin plus a beta-lactam versus either drug alone: a national propensity-score-adjusted retrospective cohort study. *PLoS Med* 2017;14:e1002340.
23. Karino S, Kaye KS, Navalkele B, *et al*. Epidemiology of acute kidney injury among patients receiving concomitant vancomycin and piperacillin-tazobactam: opportunities for antimicrobial stewardship. *Antimicrob Agent Chemother* 2016;60:3743–3750.
24. Kim T, Kandiah S, Patel M, *et al*. Risk factors for kidney injury during vancomycin and piperacillin/tazobactam administration, including increased odds of injury with combination therapy. *BMC Res Note* 2015;8:579.
25. Moenster RP, Linneman TW, Finnegan PM, Hand S, Thomas Z, McDonald JR. Acute renal failure associated with vancomycin and beta-lactams for the treatment of osteomyelitis in diabetics: piperacillin-tazobactam as compared with cefepime. *Clin Microbiol Infect* 2014;20:O384–O389.
26. Quan H, Sundararajan V, Halfon P, *et al*. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care* 2005;43:1130–1139.
27. Li B, Evans D, Faris P, Dean S, Quan H. Risk adjustment performance of Charlson and Elixhauser comorbidities in ICD-9 and ICD-10 administrative databases. *BMC Health Serv Res* 2008;8:12.
28. Huck D, Ginsberg JP, Gordon SM, Nowacki AS, Rehm SJ, Shrestha NK. Association of laboratory test result availability and rehospitalizations in an outpatient parenteral antimicrobial therapy programme. *J Antimicrob Chemother* 2014;69:228–233.
29. Acuna-Villaorduna C, Branch-Elliman W, Strymish J, Gupta K. Active identification of patients who are methicillin-resistant *Staphylococcus aureus* colonized is not associated with longer duration of vancomycin therapy. *Am J Infect Control* 2017;45:1081–1085.
30. Keller SC, Ciuffetelli D, Bilker W, *et al*. The impact of an infectious diseases transition service on the care of outpatients on parenteral antimicrobial therapy. *J Pharm Technol* 2013;29:205–214.
31. Lane MA, Marschall J, Beekmann SE, *et al*. Outpatient parenteral antimicrobial therapy practices among adult infectious disease physicians. *Infect Control Hosp Epidemiol* 2014;35:839–844.

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