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Antimicrobial Agents and Catheter Complications in Outpatient Parenteral Antimicrobial Therapy

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Abstract

Objectives—Debate about whether certain antimicrobial agents traditionally considered vesicants increase the risk of catheter complications has led to uncertainty in venous catheter placement protocols. To understand whether patients requiring home-based outpatient parenteral antimicrobial therapy (OPAT) should receive peripheral catheters (such as midline catheters) versus central venous catheters, and to understand whether certain antimicrobial agents place home-based OPAT patients at higher risk for catheter complications, we investigated associations between antimicrobial agent(s) and catheter complications.

Methods—We performed a prospective cohort study of patients requiring home-based OPAT discharged from two urban tertiary care academic medical centers, including telephone surveys and chart abstractions. Multivariable Poisson regressions were used to evaluate: (1) associations between antimicrobial agents traditionally considered vesicants, based on pH or osmolarity, and catheter complication rates, and (2) associations between antimicrobial agent and rates of catheter complications.

Results—Vesicant antimicrobials defined using pH or osmolarity criteria were not associated with an increased rate of catheter complications (adjusted incidence rate ratio [aIRR]: 1.63, 95% confidence interval [CI]: 0.89–2.96). Vancomycin was associated with an increased rate of catheter complications, as was daptomycin (aIRR: 2.32 [95% CI: 1.20–4.46] and 4.45 [95% CI: 1.02–

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19.41], respectively). *Staphylococcus aureus* infections were also associated with an increased rate of catheter complications (aIRR: 2.13, 95% CI: 1.09–4.19), as were midline catheters (aIRR: 9.44, 95% CI: 2.12–41.97).

Conclusions—Our study supports recent guidance identifying vancomycin as a vesicant, among a subset of antimicrobial agents, and removal of pH criteria for identification of vesicants.

Keywords

Venous catheter; OPAT; antimicrobial therapy; vesicant; parenteral antibiotics; catheter complications

Peripheral midline catheters, peripherally-inserted central catheters (PICCs), and tunneled central venous catheters (CVCs) are common types of catheters placed to facilitate receipt of outpatient parenteral antimicrobial therapy (OPAT) at home.[1] There is debate regarding whether certain OPAT agents should be given only through CVCs. Vesicants are defined as medications capable of causing blistering, tissue sloughing, or necrosis when they escape from the intended vascular pathway into surrounding tissue,[2] and typically are at extremes of pH (≤ 5, ≥ 9) or osmolarity (≥ 900 mosmol/L).[2,3–5] However, it is unclear which of these agents may actually lead to complications such as thrombosis, occlusion, extravasation, or phlebitis in home-based OPAT. The Infusion Nurses Society has recently classified acyclovir, nafcillin (due to reported cases of tissue necrosis from extravasation), pentamidine, and vancomycin as the only antimicrobial agents with enough data to be classified as vesicants.[4,5] However, the data used to make these determinations have been primarily limited to case reports.[4,5] Data on whether particular OPAT agents are more likely to cause catheter complications in OPAT are needed; therefore we analyzed a prospective cohort of OPAT patients to identify whether particular antimicrobials were associated with catheter complications.

Methods

Patient Population and Setting

Eligible patients were at least 18 years of age and discharged from two urban tertiary care academic medical centers (Baltimore, MD) between March 2015 and February 2017 with midline catheters, PICCs, or tunneled-CVCs on OPAT with support from home infusion therapy agencies. The database has been previously described in other studies.[6,7] Patients and their caregivers administered antimicrobial agents and performed day-to-day catheter care, with home health nursing and home infusion nursing support for weekly catheter dressing changes and laboratory monitoring. Consenting patients underwent an electronic health record (EHR) abstraction.

Variables

The Charlson Comorbidity Index (CCI)[8] was dichotomized at ≤ 2 and > 2 based on the median CCI. OPAT days were calculated as the days between hospital discharge and final day of parenteral antibiotics. Antimicrobial agent was coded based on parenteral orders only, and more than one agent could be ordered.

Vesicants were defined based on the pH at which the antimicrobial agent was typically available, or based on the osmolarity. Low pH (≤ 5) parenteral medications included amikacin, ciprofloxacin, doxycycline, gentamicin, levofloxacin, linezolid, minocycline, pentamidine, quinipristin-dalfopristin, trimethoprim-sulfamethoxazole, tobramycin, and vancomycin.[2,3–5] High pH (≥ 9) parenteral medications included acyclovir and ganciclovir.[2,3–5] No elevated osmolarity (≥ 900 mosmol/L) antimicrobial medications were identified.[2,3–5]

Outcomes were based on chart review. The primary outcome was any catheter complication potentially related to the antimicrobial agent. We defined catheter complications as any catheter occlusion, catheter-associated venous thrombosis (CA-VTE), extravasation, or phlebitis. We excluded bloodstream infection (BSI), central line-associated BSI (CLABSI), dislodgement, coiling, kinking, breaking, or leaking as we did not hypothesize that these would be associated with an antimicrobial agent. Catheter occlusion was defined as a blockage in a catheter lumen necessitating the use of a tissue plasminogen activator agent as documented in the EHR. Phlebitis was defined as redness and swelling around the catheter insertion site or along the vein that was described as phlebitis in the EHR. CA-VTE was defined as a venous thrombosis on imaging in the proximity of the catheter. Catheter complications were measured per 1000 OPAT days.

Data Analysis

Descriptive statistics were used for demographic, clinical, and outcome data (Stata Ver. 14.0, College Station, TX). Multivariable Poisson regressions were used to estimate predictors of overall catheter complications per 1000 OPAT days and are presented as adjusted incidence rate ratios (aIRR); that is, covariates were adjusted for confounders in the entire model. Over-dispersion was absent. Two separate analyses were performed: one including vesicant antimicrobial agents as the independent variable, and one including antimicrobial agents as the independent variables. Individual microorganisms were only included in analyses which included individual antimicrobial agents, as these were thought to not be on the causal pathway of choosing a vesicant agent. Covariates were considered if the association with the outcome of interest was $p \leq 0.20$ (two-sided), and were removed in a stepwise fashion if the association with the outcome was $p > 0.20$ (two-sided). A p-value of <0.05 was considered statistically significant.

This study was approved as expedited with oral consent by the Johns Hopkins University School of Medicine Institutional Review Board.

Results

Of 570 eligible patients, 339 enrolled in the study (59.5%) providing 16,399 home OPAT days. Most patients received OPAT via PICCs (n=241, 71.1%) (Table 1). Patients maintained their catheters for a median of 33 days. Forty-three (12.7%) patients experienced a catheter complication (2.62/1000 OPAT days), which was most commonly from catheter occlusion (n=34, 10%, 2.07/1000 OPAT days). The most common antimicrobial agents prescribed were ceftriaxone (n=41, 12.1%) and vancomycin (n=89, 26.3%) (Table 2). Almost one in

five were on more than one antimicrobial agent (n=66, 19.5%), and almost two in five were on an antimicrobial agent that was defined as a vesicant (n=132, 38.9%).

There was no association between vesicant antimicrobial agent and catheter complications (adjusted incidence rate ratio [aIRR]: 1.63, 95% confidence interval [CI]: 0.89–2.96) (Table 3). However, midline catheters had a higher rate of catheter complications than PICCs (aIRR: 6.45, 95% CI: 1.45–28.0). A second analysis assessing association between specific antibiotics and catheter complications demonstrated that *Staphylococcus aureus* infection, daptomycin, vancomycin, and midlines were each independently associated with catheter complications (aIRR: 2.13, 95% CI: 1.09–4.19; aIRR: 4.45, 95% CI: 1.02–19.41; aIRR: 2.32, 95% CI: 1.20–4.46; aIRR: 9.44, 95% CI: 2.12–41.97; respectively) (Table 4). We did not find a difference between OPAT days per individual antimicrobial agent, focusing on vancomycin, daptomycin, ceftriaxone, and piperacillin-tazobactam.

Discussion

In this study, we found that catheter complications were common. Midline catheters were an independent predictor for catheter complications in OPAT, as was vancomycin. There was no association between vesicant antimicrobial therapy (defined by extremes of pH) and catheter complications.

There has been a debate on whether patients receiving vesicant antimicrobials should preferentially receive these through CVCs. Recent guidelines have broken away from strict pH or osmolarity criteria for defining vesicants based on a lack of data.[4,5] Of the four antimicrobial agents classified as vesicants by the Infusion Nurses Society,[4,5] pentamidine was not used in our population, and nafcillin and acyclovir were only infrequently used. However, vancomycin was commonly used and independently associated with increased complications. In our population, oxacillin was typically used instead of nafcillin. Oxacillin has similar pharmacologic properties, but there have not been case reports of tissue necrosis from extravasation. Meanwhile, updated Infusion Nurses Society guidelines no longer support the pH as a sole consideration for decision making in whether a peripheral intravenous catheter is appropriate.[4,5,9] In our data, vesicants defined solely by extremes of pH were not associated with catheter complications, although many vesicants were infrequently used. Vancomycin and daptomycin were risk factors for catheter complications.

Interestingly, like vancomycin, daptomycin was also associated with catheter complications, even with adjustment for *S. aureus* infection and type of catheter. The pH of daptomycin is typically close to the 5.0 cutoff used here to define vesicant antimicrobial agents.[2,4] This means that patients who may need OPAT for oxacillin-resistant Staphylococcus species, for example, may not have many good options to prevent catheter complications. Clinicians should monitor patients on vancomycin or daptomycin carefully and stop the medication (potentially transitioning to oral antibiotics) as soon as clinically possible.

Few studies have compared vesicant antimicrobial agents by catheter type. A retrospective cohort study of surgical inpatients receiving short peripheral catheters (not midline catheters) found a higher infiltration score with vancomycin than with other antibiotics.[10] In another

trial, Inpatients requiring vancomycin for 6 days or less were randomized to midline catheters or PICCs and no difference was detected in catheter complications.[11] However, patients receiving OPAT frequently maintain catheters for more than 6 days, and data in this setting is still incomplete. In prior studies, the increased risk of catheter complications with midline catheters were typically minor complications, such as catheter occlusion.[11–14] In our study, two of the 10 patients with midline catheters had complications including CA-VTE and catheter occlusion, and none had evidence of phlebitis, infiltration, or extravasation.

S. aureus infection was associated with catheter complications in our study. There could have been collinearity between *S. aureus* infection and two agents commonly used to treat *S. aureus* infection, daptomycin and vancomycin. Alternatively, patients on OPAT for *S. aureus* may receive higher doses of antimicrobial agents. We did not collect data on antimicrobial agent dosing, but it is possible that the higher doses of the medications led to more catheter occlusions.

Our study enhances the OPAT and infusion therapy literature in several ways. We used a prospective cohort where catheter complications could be well defined and evaluated over time. We also used clear definitions of vesicant antimicrobial agents.

Our study has several limitations as well. The population may not represent other OPAT populations as this study was performed at two academically-affiliated hospitals in one urban area. Some antimicrobial agents described as vesicants[2] were used too infrequently to analyze for associations with catheter complications. We may have underestimated catheter complications as we required EHR documentation, and not all home infusion agencies in our study shared an EHR. In addition, it is possible that the longer duration of therapy with certain antimicrobial agents could be a confounder. However, the most frequently used antimicrobial agents in the study and the antimicrobial agents associated with the outcome did not have greater numbers of OPAT days. We were unable to analyze routes of drug administration as home infusion pharmacies in our setting could make modifications to how antimicrobial agents were delivered (for example, continuous infusion dosing modified to continuous intermittent infusion). While it is possible that manipulating the catheter for more frequent OPAT administrations could have led to catheter complications, patients on more than one OPAT agent (who would be accessing their catheter more than once a day) were not at higher risk for catheter complications.

In conclusion, the finding that antimicrobial agents falling into standard definitions of vesicants as extremes of pH are not associated with catheter complications, even when controlling for catheter type, supports recent changes in guidelines removing pH only criteria for determining whether antimicrobial agents should be considered vesicants.[4,5] Our data also supports continuing to classify vancomycin as a vesicant antimicrobial agent, as shown in a recent review,[2] and suggests that daptomycin may be considered a vesicant. Future studies should use controlled trials to investigate the impact of the type of catheter on catheter complications among patients on vancomycin or daptomycin.

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Table 1

Demographic and Clinical Data Among 339 Patients Discharged on Outpatient Parenteral Antimicrobial Therapy (OPAT)

Demographic	**N (% of 339)**
Age (mean, median, IQR)	52.0, 55, 41–63
Female gender	159 (46.9)
Race/ethnicity—white non-Hispanic	238 (70.2)
Black non-Hispanic	78 (23.0)
Other	23 (6.8)
Insurance: private (missing=2 self-pay, % of 337)	215 (63.8)
Medicaid	40 (11.9)
Medicare	82 (24.3)
Type of catheter: PICC	241 (71.1)
Tunneled central venous catheter	88 (26.0)
Midline	10 (3.0)
CCI > 2	207 (61.1)
Renal diagnosis	81 (23.9)
Bacteremia	71 (20.9)
Abdominal	30 (8.9)
Osteomyelitis	102 (30.1)
Septic arthritis	25 (7.4)
Coagulase-negative *Staphylococcus*	37 (10.9)
Any gram-negative rod: *Acinetobacter* n=1, *Burkholderia* n=1, *Escherichia coli* n=18, *Enterobacter* n=5, *Klebsiella* n=15, *Proteus* n=7, *Pseudomonas* n=39, *Salmonella* n=1, *Serratia* n=4	85 (25.1)
Staphylococcus aureus	75 (22.1)
Other gram-positive cocci (*Streptococcus* n=49, Enterococcus n=20, other n=19)	88 (26.0)
Empiric treatment	64 (18.9)
Polymicrobial infection	22 (6.5)
Days on OPAT (mean, median, interquartile range)	64.5, 29, 15–44
Catheter days (mean, median, interquartile range)	48.6, 33, 17–56
Readmission within 30 days of discharge	71 (20.9)
Catheter occlusion requiring a tissue plasminogen activator agent	34 (10.0)
Rate per 1000 OPAT-days (95% confidence interval)	2.07 (1.5–2.9)
Venous thromboembolism	12 (3.5)
Rate per 1000 OPAT-days (95% confidence interval)	0.73 (0.42–1.29)
Any catheter complication[a]	43 (12.7)
Rate per 1000 OPAT-days (95% confidence interval)	2.62 (1.94–3.53)

CCI = Charlson Comorbidity Index; IQR = interquartile range; PICC = peripherally-inserted central catheter.

[a]Including phlebitis, catheter occlusion, and catheter-associated venous thromboembolism. Three patients had both a catheter occlusion and a catheter-associated venous thromboembolism.

Table 2

Antimicrobial Agents Prescribed Among 339 Patients Discharged on Outpatient Parenteral Antimicrobial Therapy (OPAT)

Antibiotic Prescribed for OPAT[a]	**Number (% of 339)**
Acyclovir	10 (3.0)
Aminoglycoside (amikacin n=4, tobramycin n=21, gentamicin N=3)	28 (8.3)
Antifungal (liposomal amphotericin n=6, fluconazole n=1, micafungin n=5)	12 (3.5)
Penicillins (ampicillin n=6, ampicillin-sulbactam n=21, penicillin n=18)	45 (13.3)
Anti-staphylococcal penicillin (nafcillin n=3, oxacillin n=22)	25 (7.4)
Piperacillin-tazobactam	30 (8.8)
Cefazolin	15 (4.4)
Ceftriaxone	41 (12.1)
Cefepime	26 (7.7)
Daptomycin	8 (2.4)
Ertapenem	26 (7.7)
Meropenem	23 (6.8)
Vancomycin	89 (26.3)
Ganciclovir	11 (3.2)
More than one antimicrobial agent	66 (19.5)
Vesicant antimicrobial[b]	132 (38.9)

[a] Other antibiotics included ceftaroline (n=2), parenteral ciprofloxacin (n=2), parenteral clindamycin (n=1), imipenem (n=4), parenteral azithromycin (n=2), aztreonam (n=1), colistin (n=1), and tigecycline (n=1).

[b] Vesicant antimicrobial defined as pH < 5 or > 9, or osmolality > 600 mosmol/L, including acyclovir, amikacin, ciprofloxacin, doxycycline, ganciclovir, gentamicin, levofloxacin, linezolid, trimethoprim-sulfamethoxazole, tobramycin, and vancomycin.

Table 3

Association of Vesicant Antimicrobial Exposures with Rate of Venous Catheter Complications per 1000 Home Outpatient Parenteral Antimicrobial Therapy (OPAT) Days Among 339 Patients Discharged on OPAT

Characteristic	IRR for Catheter Complications/1000 OPAT Days (95% CI)	aIRR for Catheter Complications/1000 OPAT Days (95% CI)
Vesicant antimicrobial	1.36 (0.76–2.42)	1.63 (0.89–2.96)
Age >/65	0.58 (0.26–1.29)	--
Female	1.08 (0.61–1.93)	--
Race/ethnicity: Caucasian non-Hispanic	--	--
African American non-Hispanic	0.90 (0.45–1.79)	--
Other race	0.30 (0.041–2.19)	--
Insurance: private	--	--
Medicaid	2.29 (1.04–5.05)	2.18 (0.98–4.84)
Medicare	0.91 (0.45–1.83)	0.37 (0.049–2.73)
Venous catheter: PICC	--	--
Tunneled central venous catheter	0.80 (0.43–1.49)	0.80 (0.43–1.51)
Midline	6.03 (1.43–25.29)	6.45 (1.49–28.0)
CCI >2	1.20 (0.62–2.32)	--
More than one antimicrobial agent	1.39 (0.74–2.60)	--

aIRR = adjusted incidence rate ratio; CCI = Charlson Comorbidity Index; CI = confidence interval; IRR = incidence rate ratio; PICC = peripherally-inserted central catheter.

Table 4

Association of Exposures Among all Antibiotics with Rate of Venous Catheter Complications per 1000 Home Outpatient Parenteral Antimicrobial Therapy (OPAT) Days Among 339 Patients Discharged on OPAT

Characteristic	IRR for Catheter Complications/1000 OPAT Days (95% CI)	aIRR for Catheter Complications/1000 OPAT Days (95% CI)
Age >/65	0.58 (0.26–1.29)	--
Female	1.08 (0.61–1.93)	--
Race/ethnicity: Caucasian non-Hispanic	--	--
African American non-Hispanic	0.90 (0.45–1.79)	--
Other race	0.30 (0.041–2.19)	--
Insurance: private	--	--
Medicaid	2.29 (1.04–5.05)	2.12 (0.89–5.03)
Medicare	0.91 (0.45–1.83)	1.08 (0.53–2.22)
Venous catheter: PICC	--	--
Tunneled central venous catheter	0.80 (0.43–1.49)	0.66 (0.34–1.28)
Midline	6.03 (1.43–25.29)	9.44 (2.12–41.97)
CCI ≥2	1.20 (0.62–2.32)	--
Renal diagnosis	0.71 (0.36–1.39)	--
Bacteremia	0.97 (0.48–1.94)	--
Abdominal	1.09 (0.43–2.76)	--
Osteomyelitis	1.30 (0.70–2.41)	--
Septic arthritis	1.63 (0.64–4.12)	--
Coagulase-negative *Staphylococcus*	0.77 (0.30–1.95)	--
Any gram-negative rod	0.70 (0.32–1.49)	--
Staphylococcus aureus	2.45 (1.30–4.64)	2.13 (1.09–4.19)
Other gram-positive cocci	0.81 (0.34–1.91)	--
Empiric treatment	0.97 (0.48–1.94)	--
Polymicrobial infection	0.26 (0.036–1.91)	0.17 (0.023–1.28)
Acyclovir	1.28 (0.18–9.28)	--
Cefazolin	1.28 (0.31–5.28)	--
Cefepime	1.20 (0.51–2.84)	--
Ceftriaxone	0.16 (0.023–1.19)	0.23 (0.031–1.72)
Daptomycin	3.37 (0.82–13.92)	4.45 (1.02–19.41)
Ertapenem	1.73 (0.68–4.37)	--
Meropenem	0.61 (0.15–2.52)	--
Oxacillin	1.31 (0.41–4.23)	--
Vancomycin	1.68 (0.93–3.04)	2.32 (1.20–4.46)
More than one antimicrobial agent	1.39 (0.74–2.60)	--

aIRR = adjusted incidence rate ratio; CCI = Charlson Comorbidity Index; CI = confidence interval; IRR = incidence rate ratio; PICC = peripherally-inserted central catheter.