PROGRAM PROFILE

Vancomycin AUC-Dosing Initiative at a Regional Antibiotic Stewardship Collaborative

Peter Pasek, PharmD, BCPS, BCGP[a]; Joseph Hong, PharmD[a]; Joe Pardo, PharmD, BCIDP[b]; Sidorela Gllava, PharmD[c]; Lauren Bjork, PharmD[d,e]; Linda Cheung, PharmD, BCPS, MBA[e]

Background: Antibiotic stewardship programs (ASPs) are multidisciplinary teams that optimize anti-infective use across health systems. The Veterans Health Administration mandates all facilities to implement ASPs and requires the development of ASP collaboratives in its regional Veterans Integrated Service Networks (VISNs).

Observations: The Veterans Affairs Sunshine Healthcare Network (VISN 8) serves > 1.5 million veterans across Florida, South Georgia, Puerto Rico, and the US Virgin Islands. Established in 2015, the VISN 8 ASP workgroup, serves as a model for ASP VISN collaboratives and includes ASP champions from each Veterans Affairs medical center within VISN 8 and meets monthly to review formulary issues, ongoing initiatives, antimicrobial use metrics, and other related topics. The VISN collaborative structure facilitates multisite quality initiatives, such as the implementation of area under the curve (AUC)-guided vancomycin dosing across 4 health care systems within VISN 8. AUC-guided dosing led to decreased rates of acute kidney injury compared with trough-based dosing (2.4% vs 10.4%) and the quality assurance evaluation identified best practices that could be disseminated across the VISN.

Conclusions: The VISN 8 ASP workgroup exemplifies how ASP champions can work together to solve common issues, complete tasks more efficiently, and impact large veteran populations. ASP collaboratives can leverage their collective size to complete robust multisite quality assurance evaluations. Expansion of the ASP collaborative model further highlights the Veterans Health Administration as a nationwide leader in ASP best practices.

Author affiliations can be found at the end of this article.
Correspondence: Joe Pardo (joseph.pardo@va.gov)

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Antimicrobial resistance is a global threat and burden to health care, with > 2.8 million antibiotic-resistant infections occurring annually in the United States.[1] To combat this issue and improve patient care, the US Department of Veterans Affairs (VA) has implemented antimicrobial stewardship programs (ASPs) across its health care systems. ASPs are multidisciplinary teams that promote evidence-based use of antimicrobials through activities supporting appropriate selection, dosing, route, and duration of antimicrobial therapy. ASP best practices are also included in the Joint Commission and Centers for Medicare and Medicaid Services accreditation standards.[2]

The foundational charge for VA facilities to develop and maintain ASPs was outlined in 2014 and updated in 2023 in the Veterans Health Administration (VHA) Directive 1031 on antimicrobial stewardship programs.[2] This directive outlines specific requirements for all VA ASPs, including personnel, staffing levels, and the roles and responsibilities of all team members. VHA now requires that Veterans Integrated Services Networks (VISNs) establish robust ASP collaboratives. A VISN ASP collaborative consists of stewardship champions from each VA medical center in the VISN and is designed to support, develop, and enhance ASP programs across all facilities within that VISN.[2] Some VISNs may lack an ASP collaborative altogether, and others with existing groups may seek ways to expand their collaboratives in line with the updated directive. Prior to VHA Directive 1031, the VA Sunshine Healthcare Network (VISN 8) established an ASP collaborative. This article describes the structure and activities of the VISN 8 ASP collaborative and highlights a recent VISN 8 quality assurance initiative related to vancomycin area under the curve (AUC) dosing that illustrates how ASP collaboratives can enhance stewardship and clinical care across broad geographic areas.

VISN 8 ASP

The VHA, the largest integrated US health care system, is divided into 18 VISNs that provide regional systems of care to enhance access and meet the local health care needs of veterans.[3] VISN 8 serves > 1.5 million veterans across 165,759 km^2 in Florida, South Georgia, Puerto Rico, and the US Virgin Islands.[4] The network is composed of 7 health systems with 8 medical centers and > 60 outpatient clinics. These facilities provide comprehensive acute, primary, and specialty care, as well as mental health and extended care services in inpatient, outpatient, nursing home, and home care settings.[4]

The 2023 VHA Directive 1031 update recognizes the importance of VISN-level coordination of ASP activities to enhance

the standardization of care and build partnerships in stewardship across all levels of care. The VISN 8 ASP collaborative workgroup (ASPWG) was established in 2015. Consistent with Directive 1031, the ASPWG is guided by clinician and pharmacist VISN leads. These leads serve as subject matter experts, facilitate access to resources, establish VISN-level consensus, and enhance communication among local ASP champions at medical centers within the VISN. All 7 health systems include ≥ 1 ASP champion (clinician or pharmacist) in the ASPWG. Ad hoc members, whose routine duties are not solely focused on antimicrobial stewardship, contribute to specific stewardship projects as needed. For example, the ASPWG has included internal medicine, emergency department, community living center pharmacists, representatives from pharmacy administration, and trainees (pharmacy students and residents, and infectious diseases fellows) in antimicrobial stewardship initiatives. The inclusion of non-ASP champions is not discussed in VHA Directive 1031. However, these members have made valuable contributions to the ASPWG.

The ASPWG meets monthly. Agendas and priorities are developed by the VISN pharmacist and health care practitioner (HCP) leads. Monthly discussions may include but are not limited to a review of national formulary decisions, VISN goals and metrics, infectious diseases hot topics, pharmacoeconomic initiatives, strong practice presentations, regulatory and accreditation preparation, preparation of tracking reports, as well as the development of both patient-level and HCP-level tools, resources, and education materials. This forum facilitates collaborative learning: members process and synthesize information, share and reframe ideas, and listen to other viewpoints to gain a complete understanding as a group.[5] For example, ASPWG members have leaned on each other to prepare for Joint Commission accreditation surveys and strengthen the VISN 8 COVID-19 program through the rollout of vaccines and treatments. Other collaborative projects completed over the past few years included a penicillin allergy testing initiative and anti-methicillin-resistant *Staphylococcus aureus* (MRSA) and pseudomonal medication use evaluations. This team-centric problem-solving approach is highly effective while also fostering professional and social relationships. However, collaboratives could be perceived to have drawbacks. There may be opportunity costs if ASP time is allocated for issues that have already been addressed locally or concerns that standardization might hinder rapid adoption of practices at individual sites. Therefore, participation in each distinct group initiative is optional. This allows sites to choose projects related to their high priority areas and maintain bandwidth to implement practices not yet adopted by the larger group.

The ASPWG tracks metrics related to antimicrobial use with quarterly data presented by the VISN pharmacist lead. Both inpatient and outpatient metrics are evaluated, such as days of therapy per 1000 days and outpatient antibiotic prescriptions per 1000 unique patients. Facilities are benchmarked against their own historical data and other VISN sites, as well as other VISNs across the country. When outliers are identified, facilities are encouraged to conduct local projects to identify reasons for different antimicrobial use patterns and subsequent initiatives to optimize antimicrobial use. Benchmarking against

TABLE 1 Baseline Characteristics for AUC and Trough Groups

Criteria	AUC (n = 168)	Trough (n = 172)	*P* value
Age, mean (SD), y	66.0	64.7	.30
Sex, No. (%)			.84
Male	160 (95)	163 (95)	
Female	8 (5)	9 (5)	
Total body weight, kg	93.3	92.1	.63
Body mass index	29.2	28.9	.74
Serum creatinine at initiation, mg/dL	0.94	0.98	.24
BUN/creatinine ratio	18.2	18.0	.83
Spinal cord injury, No. (%)	8 (5)	9 (5)	.84
Intensive care unit admission, No. (%)	42 (25)	42 (24)	.90
Gram positive bacteremia, No. (%)	25 (15)	13 (8)	.03
MRSA bacteremia, No. (%)	8 (5)	2 (1)	.05
Vancomycin trough goal, No. (%)			
15-20 mcg/mL	NA	139 (81)	
10-15 mcg/mL	NA	33 (19)	

Abbreviations: AUC, area under the curve; BUN, blood urea nitrogen; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable.

TABLE 2 Pharmacokinetic and Clinical Outcomes

Outcomes	AUC (n = 168)	Trough (n = 172)	*P* value
Loading dose received, No. (%)	128 (76)	82 (48)	.001
Daily vancomycin dose, mg	2402	2605	.02
Initial vancomycin trough, mcg/mL	12.7	13.5	.14
AUC attainment with first dose, No. (%)	80 (48)	-	.46
Any vancomycin trough, No. (%)			
> 15 mcg/mL	61 (36)	85 (49)	.02
> 20 mcg/mL	24 (14)	33 (19)	.23
Duration of vancomycin therapy, d	5.4	6.2	.15
Length of stay, d	13.7	13.6	.93
Acute kidney injury[a]			
≤ 48 h of vancomycin initiation, No. (%)	0 (0)	6 (3)	-
> 48 h of vancomycin initiation, No. (%)	4 (2)	18 (10)	.002
Time to blood culture clearance, d	3.96	2.42	.08
Persistent bacteremia, No. (%)	5 (3)	2 (1)	.24

Abbreviation: AUC, area under the curve; SCr, serum creatinine.
[a]As defined by the Kidney Disease Improving Global Outcomes: increase in SCr by ≥ 0.3 mg/dL within 48 h, or increase in SCr to 1.5x baseline, or urine volume < 0.5 mL/kg/hr over 6 h.

VISN facilities can be useful since VISN facilities may be more similar than facilities in different geographic regions. Each year, the ASPWG reviews the current metrics, makes adjustments to address VISN priorities, and votes for approval of the metrics that will be tracked in the coming year.

Participation in an ASP collaborative streamlines the rollout of ASP and quality improvement initiatives across multiple sites, allowing ASPs to impact a greater number of veterans and evaluate initiatives on a larger scale. In 2019, with the anticipation of revised vancomycin dosing and monitoring guidelines, our ASPWG began to strategize the transition to AUC-based vancomycin monitoring.[6] This multisite initiative showcases the strengths of implementing and evaluating practice changes as part of an ASP collaborative.

Vancomycin Dosing

The antibiotic vancomycin is used primarily for the treatment of MRSA infections.[6] The 2020 consensus guidelines for vancomycin therapeutic monitoring recommend using the AUC to minimum inhibitory concentration (MIC) ratio as the pharmacodynamic target for serious MRSA infections, with an AUC/MIC goal of 400 to 600 mcg*h/mL.[6] Prior guidelines recommended using vancomycin trough concentrations of 15 to 20 mcg/mL as a surrogate for this AUC target. However, subsequent studies have shown that trough-based dosing is associated with higher vancomycin exposures, supratherapeutic AUCs, and increased risk of vancomycin-associated acute kidney injury (AKI).[7,8] Therefore, more direct AUC estimation is now recommended.[6] The preferred approach for AUC calculations is through Bayesian modeling. Due to limited resources and software availability, many facilities use an alternative method involving 2 postdistributive serum vancomycin concentrations and first-order pharmacokinetic equations. This approach can optimize vancomycin dosing but is more mathematically and logistically challenging. Transitioning from trough- to AUC-based vancomycin monitoring requires careful planning and comprehensive staff education.

In 2019, the VISN 8 ASPWG created a comprehensive vancomycin AUC toolkit to facilitate implementation. Components included a pharmacokinetic management policy and procedure, a vancomycin dosing guide, a progress note template, educational materials specific to pharmacy, nursing, laboratory, and medical services, a pharmacist competency examination, and a vancomycin AUC calculator (eAppendix, available at doi:10.12788/fp0520). Each component was developed by a subgroup with the understanding that sites could incorporate variations based on local practices and needs.

The vancomycin AUC calculator was developed to be user-friendly and included safety validation protocols to prevent the entry of erroneous data (eg, unrealistic patient weight or laboratory values). The calculator allowed users to copy data into the electronic health record to avoid manual transcription errors and improve operational efficiency. It offered suggested volume of distribution estimates and 2 methods to estimate elimination constant (K_e) depending on the patient's weight.[9,10] Creatinine clearance could be estimated using serum creatinine or cystatin C and considered amputation history. The default AUC goal in the calculator was 400 to 550 mcg*h/mL.

This range was chosen based on consensus guidelines, data suggesting increased risk of AKI with AUCs > 515 mcg*h/mL, and the preference for conservative empiric dosing in the generally older VA population.[11] The calculator suggested loading doses of about 25 mg/kg with a 2500 mg limit. VHA facilities could make limited modifications to the calculator based on local policies and procedures (eg, adjusting default infusion times or a dosing intervals).

The VISN 8 Pharmacy Pharmacokinetic Dosing Manual was developed as a comprehensive document to guide pharmacy staff with dosing vancomycin across diverse patient populations. This document included recommendations for renal function assessment, patient-specific considerations when choosing an empiric vancomycin dose, methods of ordering vancomycin peak, trough, and surveillance levels, dose determination based on 2 levels, and other clinical insights or frequently asked questions.

ASPWG members presented an accredited continuing education webinar for pharmacists, which reviewed the rationale for AUC-targeted dosing, changes to the current pharmacokinetic dosing program, case-based scenarios across various patient populations, and potential challenges associated with vancomycin AUC-based dosing. A recording of the live training was also made available. A vancomycin AUC dosing competency test was developed with 11 basic pharmacokinetic and case-based questions and comprehensive explanations provided for each answer.

VHA facilities implemented AUC dosing in a staggered manner, allowing for lessons learned at earlier adopters to be addressed proactively at later sites. The dosing calculator and education documents were updated iteratively as opportunities for improvement were discovered. ASPWG members held local office hours to address questions or concerns from staff at their facilities. Sharing standardized materials across the VISN reduced individual site workload and complications in rolling out this complex new process.

VISN-WIDE QUALITY ASSURANCE

At the time of project conception, 4 of 7 VISN 8 health systems had transitioned to AUC-based dosing. A quality assurance protocol to compare patient outcomes before and after changing to AUC dosing was developed. Each site followed local protocols for project approval and data were deidentified, collected, and aggregated for analysis.

The primary objectives were to compare the incidence of AKI and persistent bacteremia and assess rates of AUC target attainment (400-600 mcg*h/mL) in the AUC-based and trough-based dosing groups.[6] Data for both groups included anthropomorphic measurements, serum creatinine, amputation status, vancomycin dosing, and infection characteristics. The χ^2 test was used for categorical data and the *t* test was used for continuous data. A 2-tailed α of 0.05 was used to determine significance. Each site sequentially reviewed all patients receiving ≥ 48 hours of intravenous vancomycin over a 3-month period and contributed up to 50 patients for each group. Due to staggered implementation, the study periods for sites spanned 2018 to 2023. A minimum 6-month washout period was observed between the trough and AUC groups at each site. Patients were excluded if pregnant, receiving renal replacement therapy, or presenting with AKI at the time of vancomycin initiation.

There were 168 patients in the AUC group and 172 patients in the trough group (Table 1). The rate of AUC target attainment with the initial dosing regimen varied across sites from 18% to 69% (mean, 48%). Total daily vancomycin exposure was lower in the AUC group compared with the trough group (2402 mg vs 2605 mg, respectively), with AUC-dosed patients being less likely to experience troughs level ≥ 15 or 20 mcg/mL (Table 2). There was a statistically significant lower rate of AKI in the AUC group: 2.4% in the AUC group (range, 2%-3%) vs 10.4% (range 7%-12%) in the trough group (P = .002). Rates of AKI were comparable to those observed in previous interventions.[6] There was no statistical difference in length of stay, time to blood culture clearance, or rate of persistent bacteremia in the 2 groups, but these assessments were limited by sample size.

We did not anticipate such variability in initial target attainment across sites. The multisite quality assurance design allowed for qualitative evaluation of variability in dos-

ing practices, which likely arose from sites and individual pharmacists having some flexibility in adjusting dosing tool parameters. Further analysis revealed that the facility with low initial target attainment was not routinely utilizing vancomycin loading doses. Sites routinely use robust loading doses achieved earlier and more consistent target attainment. Some sites used a narrower AUC target range in certain clinical scenarios (eg, > 500 mcg*h/mL for septic patients and < 500 mcg*h/mL for patients with less severe infections) rather than the 400 to 550 mcg*h/mL range for all patients. Sites targeting broader AUC ranges for all patients had higher rates of target attainment. Reviewing differences among sites allowed the ASPWG to identify best practices to optimize future care.

CONCLUSIONS

VHA ASPs must meet the standards outlined in VHA Directive 1031, including the new requirement for each VISN to develop an ASP collaborative. The VISN 8 ASPWG demonstrates how ASP champions can collaborate to solve common issues, complete tasks, explore new infectious diseases concepts, and impact large veteran populations. Furthermore, ASP collaboratives can harness their collective size to complete robust quality assurance evaluations that might otherwise be underpowered if completed at a single center. A limitation of the collaborative model is that a site with a robust ASP may already have specific practices in place. Expanding the ASP collaborative model further highlights the VHA role as a nationwide leader in ASP best practices.

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Judith Garcia, PharmD; Kayla Bartel, PharmD; Tasmiah Rahman, PharmD; Joyce Hernandez-Maldonado, PharmD; Robert Ross, PharmD.

Author affiliations

[a]Bay Pines Veterans Affairs Healthcare System, Florida
[b]Veterans Affairs North Florida/South Georgia Veterans Health System, Gainesville
[c]James A. Haley Veterans Hospital, Tampa, Florida
[d]Bruce W. Carter Veterans Affairs Medical Center, Miami, Florida
[e]VISN 8 Pharmacy Benefits Management, Tampa, Florida
[e]Enanta Pharmaceuticals, Miami, Florida

Author disclosures

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Ethics and consent

The data presented in this article was deemed nonresearch and exempt from Institutional Review Board review. Participating sites obtained an initial determination of quality assurance vs research using the VA Electronic Determination Aid Portal and subsequently followed local policy to document formal quality assurance designation. Formal ethics approval was not required.

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