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Antibiotic stewardship implementation and patient-level antibiotic use at hospitals with and without on-site Infectious Disease specialists

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Running title: Antibiotic use and ID specialists

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Summary: Across an integrated healthcare network, patients at hospitals with an on-site ID specialist received fewer total antibiotics, fewer broad-spectrum antibiotics, and more narrow-spectrum antibiotics than patients at hospitals without an ID specialist. ID specialists may be important for antibiotic stewardship.

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Abstract

Objectives: Many US hospitals lack Infectious Disease (ID) specialists, which may hinder antibiotic stewardship efforts. We sought to compare patient-level antibiotic exposure at Veterans Health Administration (VHA) hospitals with and without an on-site ID specialist, defined as an ID physician and/or ID pharmacist.

Methods: This retrospective VHA cohort included all acute-care patient-admissions during 2016. A mandatory survey was used to identify hospitals' antibiotic stewardship processes and their access to an on-site ID specialist. Antibiotic use was quantified as days-of-therapy (DOTs) per days-present and categorized based on National Healthcare Safety Network definitions. A negative binomial regression model with risk adjustment was used to determine the association between presence of an on-site ID specialist and antibiotic use at the level of patient-admissions.

Results: Eighteen of 122 (14.8%) hospitals lacked an on-site ID specialist; there were 525,451 (95.8%) admissions at ID hospitals and 23,007 (4.2%) at non-ID sites. In the adjusted analysis, presence of an ID specialist was associated with lower total inpatient antibacterial use (OR 0.92, 95% CI, 0.85-0.99). Presence of an ID specialist was also associated with lower use of broad-spectrum antibacterials [OR 0.61 (95% CI, 0.54-0.70) and higher narrow-spectrum beta-lactam use [OR 1.43 (95% CI, 1.22-1.67)]. Total antibacterial exposure (inpatient plus post-discharge) was lower among patients at ID versus non-ID sites [OR 0.92 (95% CI, 0.86-0.99).

Conclusions: Patients at hospitals with an ID specialist received antibiotics in a way more consistent with stewardship principles. The presence of an ID specialist may be important to effective antibiotic stewardship.

Introduction

Antibiotic resistance is a public health crisis that is largely driven by the use of antibiotics. Antibiotic stewardship programs (ASPs) improve antibiotic-prescribing while also decreasing inappropriate antibiotic use. ASPs are therefore an important tool to combat the emergence and spread of antibiotic resistant bacteria.

Randomized-controlled trials demonstrating the effectiveness of ASPs have involved interventions led by Infectious Disease (ID) specialists, i.e. an ID physician with or without an ID pharmacist [1-6]. However, approximately a quarter of US hospitals have no access to on-site ID specialists [7, 8]. Hospitals without on-site ID specialists have had success reducing antibiotic use by collaborating with remote ID specialists [6, 9-11], but it is unclear if ID specialists are a prerequisite for effective stewardship.

The Veterans Health Administration (VHA), the largest integrated healthcare system in the United States, has been a leader in advancing antibiotic stewardship. In 2011, the VHA created a national Antimicrobial Stewardship Taskforce (ASTF) to facilitate the implementation of antibiotic stewardship activities [12]. In 2014, the VHA enacted a directive that mandated every VHA hospital to develop and maintain an ASP [13]. This mandate also applied to hospitals where no on-site ID specialist was available.

In this study, we sought to compare the structure, processes and outcomes of ASPs at VHA hospitals with and without on-site ID specialists two years after the VHA directive went into effect. We also aimed to determine whether a patient's

exposure to antibiotics differed whether or not an ID specialist was present at that hospital.

Methods

Ethics

The institutional review board (IRB) of the University of Iowa and Iowa City Veterans Health Care System approved this study. Waiver for informed consent was granted by the IRB for this retrospective cohort.

Comparing stewardship structure and processes at sites with and without ID specialists

An ID specialist was defined as a pharmacist or physician who had completed a formal post-graduate residency or fellowship training program in ID. To identify hospitals with an on-site ID specialist, we used data from a mandatory antibiotic stewardship survey of all VHA hospitals. This survey was administered by the VHA's ASTF and the Healthcare Analysis and Information Group between 12/30/2015 and 1/15/2016. The survey was to be completed by an individual at each hospital who was knowledgeable about the hospital's antibiotic stewardship activities.

The presence of an ID-trained physician with formal post-graduate ID fellowship training was determined by a positive response to the following two survey questions:

- Does your facility offer an inpatient ID consultation service?

- Please provide the number of the Infectious Disease physicians who provide clinical services to inpatients at your facility (full-time and part-time).

A pharmacist with formal ID residency training was considered to be present at the facility if, per survey responses, the hospital's designated Antibiotic Stewardship Pharmacy Champion had either 1) completed an American Society of Health-System Pharmacists (ASHP) accredited specialty residency in Infectious Diseases, or 2) had Current Board of Pharmaceutical Specialties (BPS) certification in Pharmacotherapy with added Qualifications in Infectious Diseases BCPS-AQID.

Additional hospital characteristics and antibiotic stewardship processes were also extracted from the survey. We assumed responses to the survey reflected available resources and stewardship processes in 2016.

Measuring antibiotic use

A retrospective cohort was created that included all patient-admissions to an acute-care bed at a VHA hospital during 2016, the year of the above-mentioned survey. Using the Veterans Affairs Informatics and Computing Infrastructure (VINCI), national administrative data was collected from the VHA's Corporate Data Warehouse. This included data on patient demographics, antibiotic use, and comorbidities, as defined by International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes [14]. Inpatient and post-discharge antibiotic use was collected from the bar-coding medication administration record (BCMA) and outpatient medication files, respectively.

Inpatient antibiotics included all antibacterial agents administered via the following routes: intravenous, intramuscular, digestive tract (e.g. oral), or respiratory tract, as defined by the National Healthcare Safety Network (NHSN) [15].

Post-discharge antibiotics included oral outpatient antibacterials dispensed during the last three days of a hospitalization or the day following discharge. We assumed that all outpatient antibacterials dispensed during this time frame were initiated by the patient on the day following discharge and were taken for a duration equal to the days-supply of the dispensed prescription [16]. Post-discharge injectable antibacterials were not included, because most VHA hospitals use contract, non-VHA pharmacies to administer outpatient parenteral antimicrobial therapy (OPAT) [17]. Post-discharge antibacterials administered via the respiratory tract were not included, because these were rarely prescribed. All antibiotic classifications were based on NHSN definitions (supplemental table 1) [15].

For each patient-admission, antibacterial use and time at risk for antibacterial exposure were summarized as days of therapy (DOT) and days-present, respectively. Total antibacterial exposure per admission was defined as inpatient DOT (any route of administration) plus post-discharge oral DOT [18].

Statistical analysis

Continuous variables were compared with the student's t test, and categorical variables were compared with the chi-square test.

Using a patient admission-level analysis, antibacterial use among all patient-admissions at ID sites was compared to antibacterial use among all patient-admissions at non-ID sites. First, unadjusted comparisons were made using negative binominal generalized estimating equations that only adjusted for intra-hospital clustering. Next, adjusted comparisons were made by adjusting for intra-hospital clustering in addition to patient demographics (age, gender, race), obesity, service type (e.g. proportion of total days-present on a medical versus surgical service), intensive care unit (ICU) versus non-ICU (e.g. proportion of total days-

present that were in an ICU), individual comorbidities, immunosuppression status, and severity of illness, as measured by the acute physiology and chronic health evaluation (APACHE) score. Missing values for the APACHE score were assumed to be normal; missing values were uncommon except for albumin and bilirubin (supplemental table 2). In all regression models, DOT was the dependent variable, and the log of days-present was included as an offset variable to account for the time of exposure of each patient-admission.

Certain variables were not included in the adjusted analysis. First, adjustments were not made for diagnosis-related groups or infection diagnoses, in contrast to prior studies [19, 20]. In one prior study, the infectious syndrome diagnosed upon admission was often incorrect [21]; therefore, adjustment for diagnoses could eliminate important inter-facility differences in antibacterial use. Second, adjustments were not made for VHA hospital complexity, which reflects three categories: 1) patient population, 2) clinical services complexity and 3) education and research. The hospital complexity variable was not entered into the model because it was moderately correlated to the presence of an ID specialist (Pearson's correlation coefficient = −0.53, $p<0.01$). Finally, adjustments were not made for antibiotic stewardship resources or processes, as the acquisition of these resources and implementation of these processes were likely facilitated by the presence of an ID specialist. A proportion of hospitals lacked an on-site microbiology laboratory, which is an important but expensive resource that hospitals may be reluctant to establish, regardless of an ID specialist's recommendations. Therefore, a sensitivity analysis was performed excluding hospitals that lacked an on-site microbiology laboratory.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

There were 18 (14.8%) hospitals without an ID specialist and 104 (85.2%) sites with an ID specialist. Nearly all (99.0%) sites with an ID specialist had at least one ID physician, who was either part-time (n=20) or full-time (n=83); 1 (1.0%) site had an ID pharmacist without any ID physicians. Thirty-nine sites (32.0%) had both an ID physician and ID pharmacist.

All 18 sites without an on-site ID specialist reported seeking advice from another VHA hospital's ID physician via telemedicine or electronic consults. The frequency of consulting with other hospitals' ID physicians was not reported.

Sites without an ID specialist were smaller than sites with an on-site ID specialist (Table 1) . Sites without an ID specialist were also lower complexity facilities and significantly less likely to have an ICU (61.1% vs. 93.3%, p<0.01). An on-site microbiology laboratory was present at 83.3% of non-ID and 96.2% of ID sites (p=0.07).

Antibiotic stewardship resources and processes

An antibiotic stewardship policy existed at 94.4% and 93.3% of non-ID and ID sites, respectively (Table 2). Sites with an on-site ID specialist were significantly more likely to report full-time employment equivalents (FTEE) devoted to antibiotic stewardship (71.8% vs. 33.3%, p<0.01).

An antibiotic stewardship provider champion was more commonly designated at sites with on-site ID specialists (94.2% vs. 77.8%, p=0.04), and the provider champion was usually an ID physician (87.5%). In comparison, hospital without an

on-site ID specialist had designated the following individuals as the provider champion for stewardship: an inpatient internal medicine physician (33.3%), another type of provider (27.8%), nobody (22.2%), or a physician administrator (16.7%) (Table 2).

An antibiotic stewardship pharmacist champion was identified at 94.4% and 96.2% of non-ID and ID sites, respectively. Differences were noted across non-ID and ID sites in the proportion of pharmacist champions who had completed a general residency training program and/or had sought antibiotic stewardship certification (Table 2).

Antibiotic stewardship processes were frequently used across all sites, as shown in Table 3. These processes included prior approval, routine audits, timely review of positive blood cultures, and education. While nearly all sites reported an annual antibiogram, monitoring antibiotic use as defined daily doses or DOT was only performed at 33.3% of non-ID sites and 57.7% of ID sites (p=0.06).

Description of patient-admission cohort

There were 548,458 patient-admissions during 2016, including 23,007 (4.2%) at the 18 non-ID hospitals and 525,451 (95.8%) at the 104 ID hospitals. The median age of all patient-admissions was 68 years (IQR 61-74); 520,287 (94.9%) were male, and 389,588 (71.0%) were white. Differences in patient-admission characteristics between non-ID and ID sites are shown in Table 4.

Patient admission-level analysis of antibacterial use

Table 5 compares antibacterial exposure between patient-admissions (hereafter “patients”) at ID and non-ID hospitals. In unadjusted comparisons, differences in total inpatient antibacterial among patients at ID and non-ID hospitals did not reach statistical significance [OR 0.92 (95% CI, 0.85-1.01)], but in the

adjusted analysis, patients at ID sites received fewer total inpatient antibacterials [OR 0.92 (95% CI, 0.85-0.99)].

In the unadjusted analysis, patients at ID sites received fewer broad-spectrum antibacterial agents predominantly used for community-acquired infections [OR 0.64 (95% CI, 0.56-0.74)), more antibacterial agents predominantly used for resistant gram-positive infections [OR 1.22 (95% CI, 1.05-1.42)] and more narrow-spectrum beta-lactam agents [OR 1.54 (95% CI, 1.31-1.83)]. However, in the adjusted analysis, differences were only noted in two drug categories: patients at ID sites received fewer broad-spectrum antibacterials predominantly used for community-acquired infections [OR 0.61 (95% CI, 0.54-0.70)] and more narrow-spectrum beta-lactam agents [1.43 (95% CI, 1.22-1.67)].

Total antibacterial exposure was lower among patients at ID sites in both the unadjusted and adjusted analyses, but the difference only reached statistical significance in the adjusted analysis [unadjusted: OR 0.97 (95% CI 0.89-1.06); adjusted OR 0.92 (95% CI, 0.86-0.99)].

In a sensitivity analysis that excluded the 7 hospitals without an on-site microbiology laboratory, the findings from the adjusted analysis remained largely unchanged. Total antibacterial exposure no longer significantly differed among patients at ID an non-ID sites, but the OR changed by only 0.02 (0.92 to 0.94, supplemental table 3).

Discussion

In this cross-sectional study of patients admitted to 122 VHA acute-care hospitals, presence of an on-site ID specialist was independently associated with receiving fewer broad-spectrum antibacterials for community-onset infections, more narrow-spectrum antibacterials, and fewer total antibacterials. These differences

were noted in the context of a high degree of antibiotic stewardship implementation across sites with and without ID specialists.

Core principles of antibiotic stewardship include selecting narrow-spectrum agents when feasible, using antibiotics only when necessary, and prescribing antibiotics for the shortest effective duration [22]. Based on our findings, it appears that these stewardship principles were more broadly applied to patients at hospitals with ID specialists.

We speculate that ID specialists, which we defined as ID physicians and ID pharmacists, may mediate these changes in antibiotic-prescribing through a variety of different mechanisms. First, ID physicians who are consulted to see hospitalized patients may recommend the use of more narrow-spectrum antibiotics and the discontinuation of unnecessary antibiotic therapy. ID pharmacists may provide similar feedback through their interactions with prescribers. Second, the presence of an ID specialist may help enhance institutional knowledge about optimal antibiotic-prescribing. For example, having an ID specialist on-site enables a hospital 1) to develop ID training programs for pharmacists and physicians, and 2) to provide trainees the opportunity to rotate on an ID service. Trainees exposed to ID specialists may be more likely to adopt stewardship principles and, in turn, promote these principles to their colleagues. Third, the presence of an ID specialist may facilitate the acquisition of stewardship resources and the effective implementation of other stewardship processes. Hospital administrators may be more willing to provide dedicated FTEEs for stewardship activities if there is a specialist with an ID-specific skill set to take on the role. Clinicians may be more receptive to feedback on their antibiotic-prescribing when the feedback is coming from an ID specialist. Furthermore, ID specialists themselves may help convey the

importance of dedicated salary support and other resources that facilitate stewardship.

In our cohort, there were some key differences in stewardship resources at ID and non-ID sites. We chose not to adjust for these differences, because it was unclear how many of these differences reflected the influence (or lack thereof) of an ID specialist—the primary effect we sought to measure. In a sensitivity analysis, we excluded sites without an on-site microbiology laboratory, and our findings remained largely unchanged. In this sensitivity analysis, the confidence interval for total antibacterial exposure (inpatient plus post-discharge) crossed 1.0—perhaps due to the smaller sample size—but the direction of the effect still favored less use among patients at ID sites.

Our finding that antibacterial use was lower among patients at ID versus non-ID sites contributes to the existing literature that has demonstrated the importance of ID specialists in reducing unnecessary antibiotic use [1-6]. A cluster-randomized trial evaluated three strategies for ASP implementation across 15 small hospitals that lacked on-site ID specialists but had telephone access to remote ID specialists [6]. Reductions in total and broad-spectrum antibiotics were only achieved in the cluster of hospitals that had remote ID specialists both pro-actively monitoring microbiologic results and managing antibiotic restrictions. These findings suggest that the active involvement of ID specialists, even if not on-site, can be an effective approach to stewardship. Other smaller non-randomized studies have found that the involvement of remote ID specialists in stewardship activities can reduce antibiotic use [9-11, 23]. All non-ID sites in our study's cohort reported communicating with off-site ID specialists, but only one of the sites identified an off-site ID specialist as their stewardship champion. Based on our personal

communication with this specific site, the off-site ID specialist was not actively engaged in stewardship activities and was instead responding only to ID consult requests.

Our findings do not suggest that hospitals without on-site ID specialists cannot improve antibiotic-prescribing. In fact, a recent crossover trial found that hospitals without ID specialists were able to implement prospective audit-and-feedback and, in turn, reduce antibiotic use [24]. In the VHA cohort we describe, it is possible that the non-ID hospitals were achieving reductions in antibiotic use that could not be detected by our cross-sectional design.

To our knowledge, this is the largest study to evaluate the association between the presence of an on-site ID specialist and patients' antibiotic exposure. It adds to the growing body of literature demonstrating the benefits that ID specialists provide to hospitalized patients [25-30]. It also highlights the importance of developing and maintaining an ID specialist workforce, a need that is even more acute given the recent decline in fellowship applicants to ID physician training programs [31].

Several limitations to our study should be acknowledged. First, all survey responses were self-reported and were not validated. Many hospitals indicated that they were using specific stewardship processes, but we were unable to assess how well these processes had been implemented. Such a validation would have been challenging, as it would have involved in-depth assessments of all 122 sites. Second, it is difficult to measure the isolated effect of having an ID specialist, because the ID specialist may influence antibiotic-prescribing in ways that cannot be quantified. We have proposed some potential explanations for how an ID specialist can have hospital-level effects on antibiotic-prescribing, but these

explanations cannot be verified using our data. Third, our evaluation focused solely on whether an ID physician or ID pharmacist were present on-site, but this does not necessarily indicate their direct involvement in stewardship activities. We were unable to measure the time an ID specialist devoted to local stewardship activities, which would have been a more direct measurement of ID engagement in ASPs. Fourth, given the cross-sectional design of our study, it is unclear whether patterns of antibiotic use reflect the influence of the ID specialist versus unrelated effects, such as institutional norms. Fifth, our model adjusted for several patient-level factors that could be associated with antibiotic use, many of which were included in previously published risk-adjustment models [19, 20]. There is no established approach for risk-adjustment when assessing antibiotic use with patient admission-level data, so we acknowledge other approaches may also be valid. Sixth, because VHA hospital complexity was correlated with the presence of an ID specialist, we were only able to adjust for 2 of its components (i.e. patient population and clinical services). It remains unclear if the third component of hospital complexity (i.e. educational and research programs) influences antibiotic use. Finally, our estimates of total antibiotic exposure did not include post-discharge intravenous antibiotics or post-discharge antibiotic use in patients who were transferred to post-acute care facilities, such as skilled nursing facilities. We suspect that these situations represented a minority of patients who received post-discharge antibiotics.

In conclusion, patients at hospitals with ID specialists received more narrow-spectrum antibacterials, fewer broad-spectrum antibacterials and fewer total antibacterials than patients at hospitals without ID specialists. The wider availability of ID physicians and ID pharmacists may facilitate improvements in antibiotic-prescribing that, in turn, may slow the spread of antibiotic resistant bacteria.

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Table 1. Characteristics of 122 VHA hospitals, stratified by the presence of an on-site ID specialist

	On-site ID specialists N=104	No on-site ID specialists N=18	p-value
Admissions per month, mean (SD)	424.4 (244.0)	107.2 (57.6)	<0.01
Hospital location, n (%)			
Urban	99 (95.2)	10 (55.6)	<0.01
Rural	5 (4.8)	8 (44.4)	
Hospital complexity, n (%)[1,2]			
1a, 1b, or 1c	82 (78.8)	0	<0.01
2	15 (14.4)	9 (50.0)	
3	7 (6.7)	9 (50.0)	
Intensive care unit, n (%)	97 (93.3)	11 (61.1)	<0.01
Microbiology laboratory on-site, n (%)	100 (96.2)	15 (83.3)	0.07

1. The Veterans Health Administration classifies its medical facilities at the following levels of complexity: 1a, 1b, 1c, 2, or 3. A hospital's complexity level is based on its patient population, clinical services, education and research. The most complex hospitals are level 1a, and the least complex are level 3.
2. For this category, a comparison was made between the number of level 1 facilities versus the number of level 2/3 facilities.

Table 2. Antibiotic stewardship resources at 122 VHA hospitals, stratified by the presence of an on-site ID specialist

Antibiotic stewardship resources	On-site ID specialists N=104	No on-site ID specialists N=18	p-value
Leadership commitment, n (%)			
ASP policy exists	97 (93.3%)	17 (94.4%)	1.00
Any FTEEs dedicated to stewardship	74 (71.8%)	6 (33.3%)	<0.01
Accountability and drug expertise, n (%)			
Stewardship provider champion	98 (94.2%)	14 (77.8%)	0.04
Training of stewardship provider champion			
Infectious Diseases	91 (87.5%)	0	<0.01
Inpatient IM physician	6 (5.8%)	6 (33.3%)	<0.01
Physician administrator	0	3 (16.7%)	<0.01
Other type of provider[1]	1 (1.0%)	5 (27.8%)	<0.01
Stewardship pharmacist champion	100 (96.2%)	17 (94.4%)	0.56
Training of stewardship pharmacist champion[2]			
• General residency[3]	80 (76.9%)	9 (50%)	0.02
• ID training[4]	40 (38.5%)	0	<0.01
• Stewardship certification[5]	42 (40.4%)	13 (72.2%)	0.01

ASP=antibiotic stewardship program; FTEEs = full-time employment equivalent; ID=Infectious Disease; IM=Internal Medicine; OPAT= outpatient parenteral antibiotic therapy

1. Other type of provider includes an off-site ID physician (n=1), advanced practice nurse (n=1), a nursing home provider (n=1), an outpatient physician (n=1), and a pulmonologist (n=1).
2. The categories listed are not mutually exclusive. For example, a pharmacist may have had general residency training while also earning stewardship certification.
3. Completed an accredited general residency accredited by the American Society of Health-System Pharmacists or holds a current Board of Pharmacy Specialties (BPS)-certification in Pharmacotherapy.
4. Current BPS certification with added qualification in ID and/or completed an American Society of Health-System Pharmacists accredited ID-specialty residency.
5. Obtained certification in antibiotic stewardship from the Society for Infectious Diseases Pharmacists (SIDP) or Making a Difference in Infectious Diseases Pharmacotherapy (MAD-ID).

Table 3. Antibiotic stewardship processes at 122 VHA hospitals, stratified by the presence of an on-site ID specialist

	On-site ID specialists N=104	No on-site ID specialists N=18	p-value
Antibiotic stewardship interventions, n (%)			
Prior approval for targeted antibiotics	94 (90.4%)	15 (83.3%)	0.41
Routine audits of targeted antibiotics at day 1-2[1]	80 (76.9%)	12 (66.7%)	0.38
Routine audits of targeted antibiotics at discharge[1]	49 (47.1%)	8 (44.4%)	0.83
Blood culture review[2]	69 (66.4%)	9 (50%)	0.18
Automatic stop orders	80 (76.9%)	15 (83.3%)	0.76
Clinical pathways or guidelines for specific inpatient conditions	89 (85.6%)	15 (83.3%)	0.73
Monitoring, education and feedback, n (%)			
Monitor antibiotic use[3]	60 (57.7%)	6 (33.3%)	0.06
Submit data to NHSN AU option	37 (35.6%)	2 (11.1%)	0.04
Annual antibiogram	102 (98.1%)	18 (100%)	1.00
Education[4]	75 (72.1%)	11 (61.1%)	0.34
Feedback to groups of providers	41 (35.3%)	4 (26.7%)	0.51

ID=Infectious Disease; MRSA=methicillin-resistant *Staphylococcus aureus*; NHSN AU option=National Healthcare Safety Network's Antimicrobial Use and Resistance option

1. Routine audits refer to systematic reviews of patient-level use of targeted antibiotics at least 3-4 times per week
2. Antibiotic stewardship team reviews positive blood cultures in a timely fashion
3. Hospital-level antibiotic use is monitored as DDDs (defined daily doses) and/or DOTs (days of therapy).
4. Face-to-face group presentations to educate providers on prudent antibiotic prescribing

Table 4. Characteristics of patient-admissions in VHA acute-care hospitals during 2016, stratified by the presence of an on-site ID specialists

	Total N=548,458	On-site ID specialists N=525,451	No on-site ID specialists N=23,007
Age, median (IQR)	68 (61-74)	68 (61-74)	68 (60-76)
Male gender, n (%)[1]	520,287 (94.9)	498,400 (94.9)	21,887 (95.1)
Race, n (%)			
White	389,588 (71.0)	370,321 (70.5)	19,267 (83.7)
Black	114,208 (20.8)	112,121 (21.3)	2,087 (9.1)
Other/missing	44,662 (8.1)	43,009 (8.2)	1,653 (7.2)
Obesity, n (%)	187,372 (34.1)	179,343 (34.1)	8,029 (34.9)
Modified APACHE score, median (IQR)[2]	24 (16-33)	24 (16-33)	24 (16-33)
Comorbidities			
Alcohol abuse	107,371 (19.6)	102,009 (19.4)	5,362 (23.3)
CHF	159,188 (29.0)	153,082 (29.1)	6,106 (26.5)
COPD	210,395 (38.4)	199,268 (37.9)	11,127 (48.4)
Dementia	54,406 (9.9)	52,013 (9.9)	2,393 (10.4)
Diabetes	239,125 (43.6)	229,100 (43.6)	10,025 (43.6)
Drug abuse	78,010 (14.2)	74,748 (14.2)	3,262 (14.2)
Liver disease, severe	18,875 (3.4)	18,181 (3.5)	694 (3.0)
Neurological disorders, other	72,343 (13.2)	69,565 (13.2)	2,778 (12.1)
Paralysis	16,559 (3.0)	16,044 (3.1)	515 (2.2)
PVD	114,745 (21.0)	110,296 (21.0)	4,449 (19.3)
Renal failure	145,916 (26.6)	140,265 (26.7)	5,651 (24.6)
Immunosuppressed[3]	33,737 (6.2)	32,809 (6.2)	928 (4.0)
Admitting service, n (%)			
Medicine	434,291 (79.2)	412,461 (78.5)	21,830 (94.9)
Surgery	114,167 (20.8)	112,990 (21.5)	1,177 (5.1)
ICU stay, n (%)	85,990 (15.7)	83,874 (16.0)	2,116 (9.2)
Days-present per admission, median (IQR)	4 (2-6)	4 (2-6)	4 (2-6)
Infectious Diagnoses			

Biliary tract infection	4,137 (0.8)	4,025 (0.8)	112 (0.5)
COPD, acute exacerbation	29,065 (5.3)	26,667 (5.1)	2,398 (10.4)
Intra-abdominal infection	7,797 (1.4)	7,506 (1.4)	291 (1.3)
Osteo-articular infection	9,813 (1.8)	9,476 (1.8)	337 (1.5)
Pneumonia	34,694 (6.3)	32,359 (6.2)	2,335 (10.2)
Skin and soft tissue infection	26,098 (4.8)	24,637 (4.7)	1,461 (6.4)
Urinary tract infection	35,312 (6.4)	33,690 (6.4)	1,622 (7.1)

Abbreviations: APACHE=Acute Physiology and Chronic Health Evaluation; COPD=chronic obstructive pulmonary disease; CHF=congestive heart failure; ID=infectious diseases; ICU=intensive care unit; IQR=interquartile range; PVD=peripheral vascular disease

1. If the gender value was missing, it was classified as male.
2. The modified APACHE score does not include comorbidities, as these were adjusted for separately.
3. The immunosuppressed category includes either having a diagnosis of lymphoma, leukemia, HIV/AIDs, or organ transplantation during the 12 months prior to admissions OR receipt of an immunosuppressive medication, which was defined as follows: prednisone or steroid equivalent at a dose ≥20 mg/day during the 30 days prior to admission, chemotherapy within the 30 days prior to admission, or an anti-rejection medication, biologic agent or a disease-modifying anti-rheumatic drug (DMARD) within the 3 month prior to admission

Table 5. Patient admission-level antibiotic use in VHA acute-care hospitals during 2016, stratified by the presence of an on-site ID specialist

National Healthcare Safety Network (NHSN) antibacterial categories	On-site ID specialists N=525,451	No on-site ID specialists N=23,007	Unadjusted comparison[2,3] RR (95% CI)	Adjusted comparison[2,4] RR (95% CI)
Inpatient antibacterial exposure, mean (SE) DOT per 1000 days-present				
Broad-spectrum antibacterial agents predominantly used for community-acquired infections	112.9 (2.9)	175.9 (11.6)	0.64 (0.56-0.74)	0.61 (0.54-0.70)
Broad-spectrum antibacterial agents predominantly used for hospital-onset infections	104.2 (2.5)	93.1 (5.5)	1.12 (0.99-1.27)	1.01 (0.89-1.13)
Antibacterial agents predominantly used for resistant gram-positive infections	73.8 (2.1)	60.5 (4.3)	1.22 (1.05-1.42)	1.09 (0.95-1.26)
Narrow-spectrum beta-lactam agents	77.5 (2.4)	50.2 (3.9)	1.54 (1.31-1.83)	1.43 (1.22-1.67)
Total antibacterials[1]	464.2 (7.1)	502.9 (19.3)	0.92 (0.85-1.01)	0.92 (0.85-0.99)
Inpatient + post-discharge antibacterial exposure, mean (SE) DOT per 100 admissions				
Total antibacterial exposure	380.7 (6.3)	391.1 (15.9)	0.97 (0.89-1.06)	0.92 (0.86-0.99)

Abbreviations: SE = standard error, DOT = days of therapy, RR = rate ratio, CI = confidence interval.

1. Total antibacterials include the 4 NHSN antibacterial categories listed plus all other antibacterial agents (supplemental table 1).
2. DOT was the dependent variable, and the log of days-present was included as an offset variable to account for the time of exposure of each patient-admission.
3. Unadjusted comparisons were made using negative binominal generalized estimating equations that adjusted for intra-hospital clustering.

4. Adjusted comparisons were made by adjusting for intra-hospital clustering, patient demographics (age, gender, race), obesity, service type (e.g. proportion of total days-present on a medical versus surgical service), intensive care unit (ICU) versus non-ICU (e.g. proportion of total days-present that were in an ICU), individual comorbidities, immunosuppression status, and severity of illness, as measured by the acute physiology and chronic health evaluation (APACHE) score.