ORIGINAL ARTICLE

Use of a Computer Decision Support System and Antimicrobial Therapy Appropriateness

Gregory A. Filice, MD;[1,2] Dimitri M. Drekonja, MD;[1,2] Joseph R. Thurn, MD;[1,2] Thomas S. Rector, PhD;[3] Galen M. Hamann, RN;[1] Bobbie T. Masoud, PharmD;[1] Anne-Marie Leuck, MD;[2] Curtis L. Nordgaard, MSc;[4] Meredith K. Eilertson, PharmD;[5] James R. Johnson, MD[1,2]

OBJECTIVE. To determine whether antimicrobial (AM) courses ordered with an antimicrobial computer decision support system (CDSS) were more likely to be appropriate than courses ordered without the CDSS.

DESIGN. Retrospective cohort study. Blinded expert reviewers judged whether AM courses were appropriate, considering drug selection, route, dose, and duration.

SETTING. A 279-bed university-affiliated Department of Veterans Affairs (VA) hospital.

PATIENTS. A 500-patient random sample of inpatients who received a therapeutic AM course between October 2007 and September 2008.

INTERVENTION. An optional CDSS, available at the point of order entry in the VA computerized patient record system.

RESULTS. CDSS courses were significantly more likely to be appropriate (111/254, 44%) compared with non-CDSS courses (81/246, 33%, $P = .013$). Courses were more likely to be appropriate when the initial provider diagnosis of the condition being treated was correct (168/273, 62%) than when it was incorrect, uncertain, or a sign or symptom rather than a disease (24/227, 11%, $P < .001$). In multivariable analysis, CDSS-ordered courses were more likely to be appropriate than non-CDSS-ordered courses (odds ratio [OR], 1.83; 95% confidence interval [CI], 1.13–2.98). Courses were also more likely to be judged appropriate when the initial provider diagnosis of the condition being treated was correct than when it was incorrect, uncertain, or a sign or symptom rather than a disease (OR, 3.56; 95% CI, 1.4–9.0).

CONCLUSIONS. Use of the CDSS was associated with more appropriate AM use. To achieve greater improvements, strategies are needed to improve provider diagnoses of syndromes that are infectious or possibly infectious.

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Antimicrobial (AM) therapy has saved millions of lives and averted untold suffering. Exposure of the human microbiota to AMs has also selected for relentless emergence of resistance in a broad array of pathogens.[1-4] Since inappropriate AM use contributes to emergence and persistence of AM resistance, practical means of improving AM use are sorely needed.[2-6]

Improvements in AM therapy would have additional important benefits. Appropriate therapy improves outcomes.[7,8] AMs are responsible for 23% of adverse drug events in hospital inpatients[9] and 19% of all emergency department visits for adverse drug events.[10] The burgeoning *Clostridium difficile* disease epidemic is almost entirely attributable to AM use.[2]

Unfortunately, AM therapy is optimal only about half of the time.[6,11,12] Locally developed guidelines and use of informatics for decision support are recommended to optimize AM use,[6] but comprehensive, practical systems with demonstrated effectiveness are not generally available.[4,6,11,13-15] We developed a computer decision support system (CDSS) embedded within our hospital's electronic medical record system (EMR) to help providers use AMs appropriately for a broad range of conditions. We report here on a retrospective, quasi-experimental evaluation of whether AM courses ordered mainly with the CDSS were appropriate more often than courses ordered mainly without the CDSS.

METHODS

The Minneapolis Veterans Affairs (VA) Medical Center (MVAMC) is a 279-bed academically affiliated hospital. Dur-

Affiliations: 1. Infectious Disease Section, Department of Medicine, Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota; 2. Infectious Disease Section, Department of Medicine, University of Minnesota at Minneapolis, Minneapolis, Minnesota; 3. Center for Chronic Disease Outcomes Research, Department of Medicine, Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota, and Department of Medicine, University of Minnesota, Minneapolis, Minnesota; 4. School of Medicine, University of Minnesota at Minneapolis, Minneapolis, Minnesota; 5. School of Pharmacy, University of Minnesota at Minneapolis, Minneapolis, Minnesota.

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ing the study period, October 2007 to September 2008, the local formulary included 111 different systemic AMs. Of these, 61 (55%) were restricted, meaning that prescribers were required to either obtain approval from an infectious disease (ID) service physician or order the AM with the CDSS before the AM would be dispensed. Since uncommonly used drugs tend to be restricted, only 29% of inpatient AM orders were for restricted drugs. The MVAMC institutional review board considered analysis of these data for publication exempt under Title 38 Code of Federal Regulations 16.101 (b).

CDSS

The CDSS is available at the point of order entry within the MVAMC computerized patient record system (CPRS). From the CDSS main page, a provider can quickly reach a page with advice about a disease, syndrome, or pathogen. The CDSS provides information about AM adverse effects and dosing and, for selected conditions, limited additional information about diagnosis or management. If the user selects a recommended drug, a "quick order" appears with suggested dose, route, and interval for each disease, syndrome, or pathogen. The CDSS does not use patient-specific information to tailor therapy for individual patients; this remains the responsibility of the prescriber. The user adjusts details as needed and then signs the quick order. CDSS stores information about the order, including that it was made with the CDSS. Recommendations were developed locally by ID physicians and pharmacists on the basis of published reports, national guidelines, local expert opinion, and local AM susceptibility patterns.[16]

Case Selection

All inpatients who received systemic AMs during the study period were identified from CPRS records. A "course" was defined as 1 or more consecutive doses of systemic AM(s) administered to an inpatient. During the study period, 4,476 patients received 9,328 distinct AM courses.

We decided beforehand to exclude courses given for infection prevention. We ignored 4,990 brief (≤24-hour) courses of cefazolin or vancomycin given as the only parenteral AM, since review of 100 randomly selected such courses (see below) showed that all were given for prophylaxis.

There remained 4,338 separate AM courses given to 3,180 patients. We reviewed 1,011 randomly selected medical records to identify 500 cases with at least 1 evaluable AM course. If a patient received AM(s) in 2 or more time intervals separated by at least 5 days, AM(s) given in each period were considered separate courses, and one was selected randomly for evaluation.

Other a priori exclusions were courses started before MVAMC admission, courses in which the patient died before the initial diagnostic evaluation was complete, courses in which AMs were discontinued as a result of comfort care status, and courses with insufficient documentation. AMs ordered in the emergency department and not continued after admission were not considered part of an AM course because such AMs are often ordered quickly without complete evaluation.[17,18]

Data Extraction

Cases were assigned randomly to 1 of 2 trained extractors, a pharmacist and a nurse, who extracted demographic data, reason for admission, and conditions included in the Charlson comorbidity index.[19] They extracted information about the syndrome or disease that led to AM use (index condition), hospital location, service, origin of infection (community, healthcare associated, or hospital acquired), initial provider diagnosis for the index condition, AM(s) given, and outcomes. For each AM given during the period of treatment for an index condition, extractors recorded the drug, dosage, route, and duration and whether the drug was ordered with the CDSS. Extractors determined from provider notes whether each AM was ordered to treat the index condition or an unrelated condition. To verify that clinical information was extracted uniformly and reproducibly, both extractors independently recorded data from each of 42 randomly selected cases.[20] The information was identical between extractors for 97% of major clinical details and 89% of all details, which compares favorably with rates found in similar studies.[20]

AM(s) ordered to treat the index condition constituted the index course. Index courses were classified as CDSS courses if half or more of AM(s) in the course were ordered with the CDSS; the rest were classified as non-CDSS courses. Deaths were identified from VA and Center for Medicare and Medicaid vital status records.[21]

Appropriateness and 30-Day All-Cause Mortality

The main outcome was the appropriateness of each AM course.[22] Case summaries were distributed randomly to 2 of 4 physician reviewers, each board certified in internal medicine and ID. The summaries presented a clinical narrative and data for each case without potential biasing information (identifiers, CDSS use, ID consultation, and outcomes). Before enrollment began, extractors and reviewers were trained on methodology and classification of accuracy of initial diagnoses and appropriateness of AM courses. Reviewers independently classified initial provider diagnoses, based on data available to providers at the time and professional judgment, as correct, uncertain, not correct, or a sign or symptom of a potential infectious disease (eg, fever, leukocytosis, infiltrate) rather than a syndrome or disease. They also judged the index course appropriate or not for what reviewers determined to be the correct initial diagnosis, considering drug selection, route, dose, and duration. Criteria for appropriateness, in order of priority, were (1) whether treatment followed CDSS recommendations; (2) alternatives consistent

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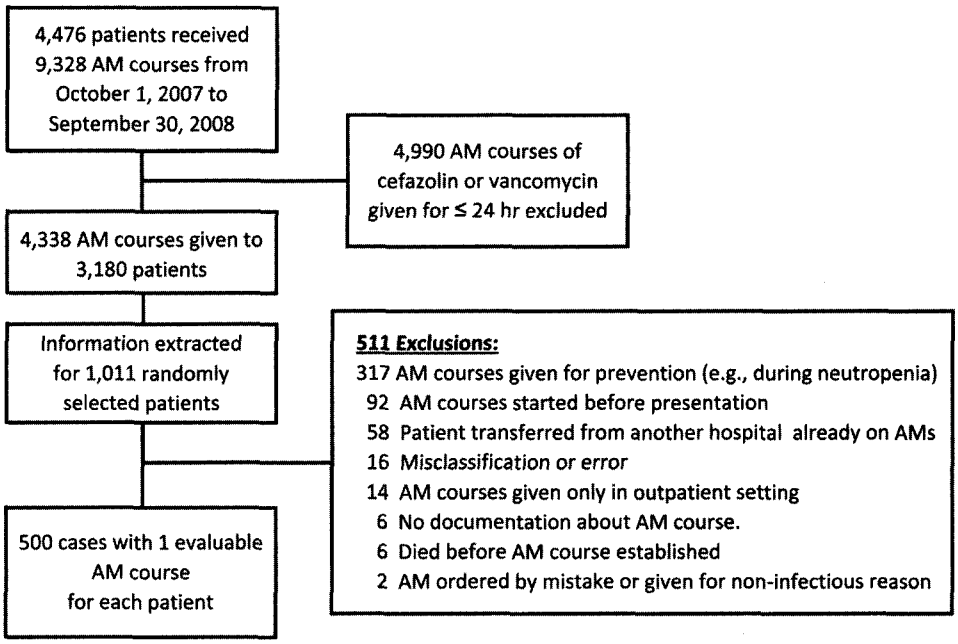


FIGURE 1. Study flow diagram. AM, antimicrobial; AM course, 1 or more consecutive doses of systemic AM(s) administered to an inpatient.

with published guidelines, high-quality evidence, and AM susceptibility patterns; and (3) reasonable alternatives, given specific circumstances. Adjustments to AM therapy based on clinical response and test results were considered. Reviewers ignored trivial errors (eg, 1- or 2-day deviations from recommended durations) that were otherwise clinically appropriate.

On the main question of AM appropriateness, each individual reviewer was compared with the other 3 reviewers combined. Agreement ranged from 69% to 72% in these comparisons, and interrater reliability κ statistics ranged from 0.33 to 0.42. Cases in which the 2 reviewers disagreed on any point were presented to a third reviewer for arbitration, which was necessary for the main outcome in 172 (34%) cases.

We determined whether all-cause mortality within 30 days after the index condition was diagnosed was associated with CDSS use. To adjust for severity of index conditions, we classified the likelihood of death from these conditions as minimal to none, moderate, or high.

Statistical Analysis

For sample size calculations, we assumed that half of all index courses would be CDSS courses, 40% would be appropriate, and CDSS and non-CDSS courses would differ on appropriateness by 15%. We calculated that 480 courses would yield an estimated power (1-β) of 0.95 with 0.05 probability of α error. For randomizations, items in a list were assigned a random number with RAND() (Excel 2007, Microsoft) and sorted by their random numbers. Group characteristics were described with means, standard deviations, medians, interquartile ranges, and proportions. The Mann-Whitney *U* test and contingency tables with χ^2 or Fisher exact tests were used to compare groups. Logistic regression was used to control for baseline differences between groups defined by CDSS use (Statistical Program for the Social Sciences for Windows, ver 19).

RESULTS

Of the 1,011 records selected randomly for review, 511 AM courses did not qualify for inclusion, leaving 500 cases with 1 evaluable index course each (Figure 1). Subjects' mean age was 67 years, and 97% were male (Table 1). The CDSS and non-CDSS groups differed significantly by age, type of infection, site of acquisition, hospital location, service, and percent of index courses containing at least 1 restricted AM but not by Charlson index, provider experience, whether the initial provider diagnosis for the index condition was correct, or median number of AMs in the index course. The CDSS offered advice for all case index conditions for which AM therapy is recommended.

Index Courses

The 500 index courses included from 1 to 7 (median, 2) AMs. Overall, 254 (51%) qualified as CDSS courses. Of these, 152 (60%) included only CDSS-ordered AMs, while the remaining 102 (40%) included 50%–86% CDSS-ordered AMs. Of the 246 (49%) non-CDSS courses, 175 (71%) included only non-CDSS AMs, while the remaining 71 (29%) included 14%–43% CDSS-ordered AMs.

Index courses were judged appropriate in 192 (38%) of the 500 cases. Reasons AM courses were not appropriate for

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TABLE 1. Baseline Patient Characteristics for Index Cases in Relation to Use of a Computer Decision Support System (CDSS)

	CDSS courses (n = 254)	Non-CDSS courses (n = 246)	P
Median age (IQR), years	68 (19)	64 (20)	.003
Male	247 (97)	238 (97)	.75
Median Charlson index (IQR)	3 (3)	3 (3)	.08
Type of infection			.002
Skin/soft tissue/wound	43 (17)	50 (20)	
Abdominal, intestinal, rectal	26 (10)	23 (9)	
Bone/joint	6 (2.4)	13 (5.3)	
Circulatory	5 (2.0)	6 (2.4)	
Genitourinary	48 (19)	39 (16)	
Head, eyes, ears, nose, throat	4 (1.6)	20 (8.1)	
Lower respiratory	77 (30)	47 (19)	
Sepsis, bacteremia, neutropenic fever	15 (5.9)	9 (3.7)	
Miscellaneous, multiple, sign or symptom	30 (12)	39 (16)	
Site of acquisition			.007
Community associated	127 (50)	99 (40)	
Healthcare associated	78 (31)	70 (29)	
Hospital associated	49 (19)	77 (31)	
Location at start of index course			<.001
Ward	166 (65)	159 (65)	
Step-down	42 (17)	23 (9.3)	
ICU	17 (6.7)	27 (11)	
Observation unit	21 (8.3)	9 (3.7)	
Community living center	8 (3.1)	28 (11.4)	
Provider specialty			<.001
Neurology, physiatry, psychiatry	5 (2.0)	16 (6.5)	
Internal medicine	214 (84.3)	150 (61)	
General surgery	13 (5.1)	25 (10)	
Surgical subspecialties	19 (7.5)	43 (18)	
Community living center	3 (1.2)	12 (4.9)	
Provider experience			.38
Resident	182 (72)	177 (72)	
Staff	35 (14)	33 (13)	
Fellow	24 (9.4)	16 (6.5)	
Nurse practitioner, physician assistant	13 (5.1)	20 (8.1)	
Initial diagnosis			.38
Correct	143 (56)	130 (53)	
Not correct	85 (34)	78 (32)	
Sign or symptom	16 (6.3)	23 (9.3)	
Unsure	10 (3.9)	15 (6.1)	
Median number of AMs per index course (IQR)	2 (2)	3 (2)	.8
≥1 restricted AM in index course	96 (38)	70 (29)	.03

NOTE. Data are no. (%) unless otherwise indicated. AM, antimicrobial; ICU, intensive care unit; IQR, interquartile range; initial diagnosis, initial provider diagnosis of index condition.

the 308 other cases are shown in Table 2. CDSS courses were significantly more likely to be appropriate (111/254, 44%) compared with non-CDSS courses (81/246, 33%, P = .013). Other variables associated with appropriate index courses in univariable analysis included age, type of infection, origin, location, and whether the initial provider diagnosis was correct (not shown). In a separate analysis, index courses with all AMs ordered with CDSS were more likely to be appropriate (65/152, 43%) than courses with no AMs ordered with CDSS (54/175, 31%, P = .026).

Influence of Provider Diagnosis

The initial provider diagnosis was considered correct by reviewers in only 273 (55%) of cases. Overall, AM use was more likely to be appropriate if the initial provider diagnosis was correct (168/273, 62%) than if it was incorrect, uncertain, or a sign or symptom rather than a syndrome or disease (24/227, 11%, P < .001; Table 3). Since the CDSS was designed to assist with AM selection after a correct diagnosis has been made, we analyzed the relationship between CDSS use and

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TABLE 2. Reasons that Antimicrobial (AM) Courses Were Not Appropriate According to Accuracy of Provider Initial Diagnosis

Accuracy of provider initial diagnosis (*n*)	AM course appropriate	Reason AM course not appropriate, *n* (%)			
		Incorrect drug	Incorrect dose	Incorrect duration	Antimicrobial not indicated
Correct (273)	168 (62)	74 (27)	4 (1)	38 (14)	11 (4)
Uncertain (25)	3 (12)	4 (16)	0 (0)	7 (28)	14 (56)
Not correct (163)	13 (8)	23 (14)	1 (1)	7 (4)	132 (81)
Sign or symptom, not syndrome or disease (39)	8 (21)	9 (23)	2 (5)	3 (8)	23 (59)

NOTE. Percentages add up to >100% because some cases had more than 1 error.

appropriateness among cases in which the initial diagnosis was correct. Here, CDSS courses were still significantly more likely to be appropriate (96/143, 67%) compared with non-CDSS courses (72/130, 55%, $P = .046$).

Influence of Restriction Status

Overall, 122/334 (37%) of nonrestricted courses were appropriate compared with 69/166 (42%) of courses with at least 1 restricted AM ($\chi^2 = 0.24$, $P > .05$). CDSS use was significantly more likely if 1 or more of the index course AMs were restricted (96/166, 58%) than if none were restricted (158/334, 47%, $P = .027$). Among the 166 index courses that included restricted AMs, CDSS courses were significantly more likely to be appropriate (49/96, 51%) than non-CDSS courses (21/70, 30%, $P = .007$). In contrast, for nonrestricted drugs, appropriateness did not vary with CDSS use.

Multivariable Analysis

To adjust for potential confounders, we performed multivariable analysis. Here, index courses were significantly more likely to be appropriate if they were CDSS courses (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.1–3.0; Table 4) and when initial provider diagnoses were correct (OR, 3.6; 95% CI, 1.4–9.0). Conversely, they were significantly less likely to be appropriate when the initial provider diagnoses were in the category of miscellaneous, multiple, or sign or symptom rather than a syndrome or disease. There was no evidence of an interaction between CDSS use and correctness of initial provider diagnoses in their relationship to appropriateness. A separate multivariable analysis of the 152 courses in which all AMs were ordered with CDSS and the 175 courses in which no AMs were ordered with CDSS yielded similar results (OR, 2.3; 95% CI, 1.1–4.7).

Mortality

Death within 30 days after diagnosis of the index condition occurred in 31 (6.2%) of the 500 cases. Death occurred in 20/254 (7.9%) cases with CDSS courses compared with 11/246 (4.5%) cases with non-CDSS courses ($P = .12$). Among the 31 cases with death, 9/20 (45%) CDSS courses and 5/11 (46%) non-CDSS courses were appropriate. Immediate cause of death was known for 19/31 cases. Two deaths were definitely and 6 possibly related to infection; these were distributed proportionally among cases with CDSS or non-CDSS courses. In a multivariable analysis, mortality was not significantly associated with CDSS use (OR, 1.5; 95% CI, 0.6–3.5).

DISCUSSION

In this analysis of inpatient AM therapy, we observed a statistically significant improvement in AM appropriateness with use of a CDSS available at the point of order entry. The apparent favorable impact of CDSS use was significant after multivariable adjustment for all identified potential confounders and also when we focused the comparison on courses in which either all AMs or no AMs were ordered through the CDSS. This strongly suggests that use of such a CDSS offers a simple way to improve AM use.

TABLE 3. Correctness of Initial Provider Diagnoses and Appropriateness of Index Courses

Initial diagnosis	CDSS courses		Non-CDSS courses		Overall	
	Appropriate (*n* = 111)	Not appropriate (*n* = 143)	Appropriate (*n* = 81)	Not appropriate (*n* = 165)	Appropriate (*n* = 192)	Not appropriate (*n* = 308)
Correct	96 (67)	47 (33)	72 (55)	58 (45)	168 (62)	105 (39)
Uncertain	1 (10)	9 (90)	2 (13)	13 (87)	3 (12)	22 (88)
Not correct	8 (9)	77 (91)	5 (6)	73 (94)	13 (8)	150 (92)
Sign or symptom, not syndrome or disease	6 (38)	10 (63)	2 (9)	21 (91)	8 (21)	31 (80)
All courses	111 (44)	143 (56)	81 (33)	165 (67)	192 (38)	308 (62)

NOTE. Data are no. (%); χ^2 for the entire distribution, $P < .001$. CDSS, computer decision support system; initial diagnosis, initial provider diagnosis of index condition.

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TABLE 4. Variables Associated with Antimicrobial (AM) Appropriateness in Multivariable Analysis

Variable	Odds ratio	95% CI	*P*
CDSS course	1.83	1.13–2.98	.01
Initial diagnosis[a]			<.001
Correct	3.56	1.40–9.05	.008
Uncertain	0.45	0.09–2.13	.31
Incorrect	0.28	0.09–0.82	.02
Type of infection: miscellaneous, multiple, sign or symptom[b]	0.06	0.01–0.54	.01

NOTE. Variables included age, Charlson Index, diagnostic category, patient gender, origin of infection, location, service, provider experience, correctness of initial provider diagnosis, inclusion of a restricted AM, and whether the index course was a computer decision support system (CDSS) course. Model summary: Nagelkerke, $R^2 = 0.43$; Hosmer and Lemeshow goodness-of-fit test, $P = .68$. CI, confidence interval; initial diagnosis, initial provider diagnosis of index condition.

[a] Reference category was initial provider diagnosis was correct but it was a sign or symptom rather than a disease.

[b] Reference category was skin, soft tissue, or wound infection.

The study confirmed the tremendous impact of diagnostic accuracy on AM appropriateness. Since the CDSS was designed to assist with AM use after a diagnosis has been made, one might expect that AM courses would often be inappropriate if the diagnosis was incorrect.[23] Among cases with a correct initial provider diagnosis, we also observed a significant improvement in AM appropriateness, from 55% for non-CDSS courses to 67% for CDSS courses, which compares favorably with results of other studies in which only cases with correct diagnoses were included.[7,24-26]

A recent meta-analysis of 46 heterogeneous studies found that providers with decision support were 1.6 (95% CI, 1.4–1.8) times more likely to order recommended treatments than providers without decision support.[27] One of the first decision support systems for AM use offered patient-specific recommendations to clinicians and generated alerts when it detected potentially suboptimal AM use.[28] That system was associated with improved prescribing and decreased AM costs.[16,24,28] Other decision support systems for AM therapy have been described.[25,26,29-32] Despite this, AM decision support has not been available in EMRs in most medical care settings.[15,31,33] Some decision support systems have been designed for a narrow group of conditions, and others have been designed for unique EMRs, making them difficult to translate into other EMRs.[34]

The MVAMC CDSS provides recommendations for a broad array of infectious or potentially infectious conditions. CPRS has excellent archival and retrieval capacity but lacks the capacity to provide sophisticated, nuanced patient-specific advice. In this way, CPRS is similar to most EMRs. Since it does not provide patient-specific advice, CDSS is a technologically simple and relatively affordable "knowledge-driven" decision support system,[35,36] and similar advice systems should be feasible within many different EMRs.

Providers' ability to order restricted AMs through the CDSS provided an alternative motivation for CDSS use that might have diluted its effect on appropriateness.[37] We hypothesized that if some providers used the CDSS primarily to order restricted drugs without ID approval, the association between CDSS use and appropriateness should be weaker for restricted drugs than for others. On the contrary, with restricted drugs, CDSS courses were more likely to be appropriate than non-CDSS courses, and in multivariable analysis, restriction status was not significantly associated with appropriateness. Thus, restriction status and providers' ability to order restricted AMs with the CDSS did not negate the CDSS impact on appropriateness.

Two other CDSS characteristics might have diluted our ability to accurately estimate its full impact. First, although the CDSS offers advice, it is also a convenient way to order AMs. In some cases, providers might have decided which AM(s) to use and then ordered them with the CDSS for convenience. Second, formative evaluations (G. Filice, unpublished data; 2007, 2010) have indicated that the CDSS has influenced MVAMC prescribing practices generally. Some providers reported that after using CDSS several times for conditions they encounter frequently, they preferred to order recommended AMs without the CDSS. Some also reported using the CDSS as a reference or teaching tool, which would be expected to affect prescribing habits more broadly.

This study has several strengths. First, comprehensive VA electronic record systems enabled us to identify a random sample representative of inpatient AM use. Second, cases were reviewed by at least 2 of 4 blinded ID physician reviewers. Expert judgments about AM appropriateness are known to be variable.[20,22] Judgments in this study were especially difficult because cases were diverse and judgments were complex, involving appropriateness of initial and subsequent AM choices, dose, route, and duration. Despite these challenges, the degree of agreement and interrater reliability between reviewers was similar to that observed in previous studies on AM appropriateness.[20,22] Lack of precision in our ability to judge appropriateness would tend to blur the distinction between groups, bias toward the null, and make a true difference more difficult to detect, yet the study still demonstrated a substantial significant advantage favoring the CDSS.

This study also had limitations. First, because of practical and logistical barriers common among studies of AM stewardship strategies, it was not randomized.[31] As would be expected, there were baseline differences between CDSS and non-CDSS cases. Second, important information about index courses may not have been recorded in CPRS, and we cannot exclude the possibility that omission of undocumented characteristics biased results in favor of CDSS use. Third, since the study was conducted in a VA hospital, the findings may not be directly applicable to other settings. Fourth, as anticipated since death occurred within 30 days in only 6.2% of

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cases, the study was not large enough to detect a small association between CDSS use and mortality.

This study demonstrated that a conceptually and technically simple system that provides quick, accessible information on optimal AM use will be used and may substantially improve prescribing. It also emphasized starkly the need for better approaches to the diagnostic evaluation of syndromes that are infectious or likely to be infectious.

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Address correspondence to Gregory A. Filice, MD, Minneapolis Veterans Affairs Health Care System, 1 Veterans Drive, Minneapolis, MN 55417 (filic001@umn.edu).

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