ORIGINAL ARTICLE

Unnecessary Antimicrobial Use in Patients with Current or Recent *Clostridium difficile* Infection

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(See the commentary by Pollack et al, on pages 117–118.)

OBJECTIVE. To determine the fraction of unnecessary antimicrobial use among patients with current and/or recent *Clostridium difficile* infection (CDI).

DESIGN. Retrospective review from January 2004 through December 2006.

SETTING. Minneapolis Veterans Affairs Medical Center (MVAMC).

PARTICIPANTS. Patients with new-onset CDI diagnosed at the MVAMC without another CDI diagnosis in the prior 30 days.

METHODS. Pharmacy and medical records were reviewed to identify incident CDI cases, non-CDI antimicrobial use during and up to 30 days after completion of CDI treatment, and patient characteristics. Two infectious disease physicians independently assessed non-CDI antimicrobial use, which was classified as unnecessary if not fully indicated. Factors associated with only unnecessary use were identified through univariable and multivariable analysis.

RESULTS. Of 246 patients with new-onset CDI, 141 (57%) received non-CDI antimicrobials during and/or after their CDI treatment, totaling 2,147 antimicrobial days and 445 antimicrobial courses. The two reviewers agreed regarding the necessity of antimicrobials in more than 99% of antimicrobial courses (85% initially, 14% after discussion). Seventy-seven percent of patients received at least 1 unnecessary antimicrobial dose, 26% of patients received only unnecessary antimicrobials, and 45% of total non-CDI antimicrobial days included unnecessary antimicrobials. The leading indications for unnecessary antimicrobial use were putative urinary tract infection and pneumonia. Drug classes frequently used unnecessarily were fluoroquinolones and β-lactams.

CONCLUSIONS. Twenty-six percent of patients with recent CDI received only unnecessary (and therefore potentially avoidable) antimicrobials. Heightened awareness and caution are needed when antimicrobial therapy is contemplated for patients with recent CDI.

Infect Control Hosp Epidemiol 2013;34(2):109-116

Clostridium difficile infection (CDI), a leading cause of hospital-associated infection, is increasingly frequent and severe.[1] Antimicrobial use is one of the most important CDI risk factors because of the associated alterations of the endogenous fecal microbiota,[2] with receipt of even a single antimicrobial dose capable of initiating disease.[3] Other CDI risk factors include healthcare facility exposure, older age, greater severity of underlying illness, immune suppression, use of antacids (including proton pump inhibitors and H2 receptor blockers), and tube feeding.[4-6]

Recurrence of CDI after successful treatment is also increasingly common and difficult to treat. Up to 20% of CDI patients will have a recurrence, 45% of these will have a second recurrence, and some will experience multiple recurrences.[7] Optimal CDI treatment includes cessation and/or avoidance of non-CDI antimicrobial use whenever possible.[8] Although some antimicrobial use is necessary and unavoidable, a large portion is unnecessary,[9-14] which can be especially detrimental in the setting of a recent CDI episode.

A recent retrospective study at the Minneapolis Veterans Affairs Medical Center (MVAMC) evaluated the frequency of non-CDI antimicrobial use among patients with CDI and its association with recurrent disease.[15] Of 246 patients with new-onset CDI, 141 (57%) received non-CDI antimicrobials during the CDI episode (n = 61; 25%) or within 30 days after completion of CDI therapy (n = 80; 33%). Receipt of non-CDI antimicrobials within 30 days after CDI therapy was significantly associated with the 90-day risk of recurrent CDI (odds ratio, 4.14 [95% confidence interval, 2.00–8.55]) after adjusting for age, disease severity, and recent hospital or in-

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Received July 6, 2012; accepted September 21, 2012; electronically published December 19, 2012.

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https://doi.org/10.1086/669089 Published online by Cambridge University Press

tensive care unit (ICU) stay. Similarly, non-CDI antimicrobial use during CDI treatment showed a trend toward an association with recurrent CDI (odds ratio, 1.77 [95% confidence interval, 0.80–3.93]). Another recent study showed non-CDI antimicrobial use during or shortly after treatment for CDI to be associated with lower cure rates, prolonged time to diarrhea resolution, and (with borderline significance) recurrent CDI.[16]

However, neither of these studies assessed what fraction of the non-CDI antimicrobial use among recent CDI patients was unnecessary. Therefore, we sought to determine the necessity of the non-CDI antimicrobials received in the above MVAMC patient population, using 2 infectious disease physicians to independently assess necessity of therapy. We also evaluated factors associated with and consequences of unnecessary antimicrobial use.

METHODS

Setting

The MVAMC is a 279-bed, academically affiliated tertiary care hospital. Antimicrobial stewardship activities during the study period included a voluntary computerized decision support system (CDSS) that can assist clinicians with the choice and dose of appropriate antimicrobials, accessed via the Veterans Affairs Computerized Patient Record System (CPRS). Additionally, 55% of formulary antimicrobials are restricted, orderable only through the antimicrobial CDSS or with approval from the infectious disease service either prior to the first dose (eg, daptomycin, tigecycline, linezolid, and quinupristin-dalfopristin) or for continuation beyond 72 hours (vancomycin).

Subjects

Subjects with new-onset CDI at the MVAMC from January 2004 through December 2006 were identified and recorded in a MVAMC pharmacy database as described elsewhere.[15] Briefly, cases of CDI were identified on the basis of a comparison involving pharmacy records for CDI treatment (metronidazole or oral vancomycin), patient symptoms, and laboratory records. Case patients were defined as those who in addition to having a positive *C. difficile* culture or toxin result experienced either (1) at least 4 unformed bowel movements per day or liquid colostomy output of greater than or equal to 1,300 mL/day over 2 days or (2) ileus, unexplained abdominal pain, and leukocytosis. Cases of CDI were excluded if the patients had received another CDI diagnosis in the prior 30 days.

Data Extraction

CPRS was reviewed retrospectively to assess for non-CDI antimicrobial use from the date of CDI diagnosis through 30 days after completing CDI treatment. Antifungal use was included because yeast is commonly part of the fecal microbiota[17] and because antifungal-associated CDI cases have been reported.[18,19] The number of courses and days of non-CDI antimicrobials were calculated. Medication administration data and daily provider notes were used to determine the duration of non-CDI antimicrobials. Repeat courses of CDI treatment during the 30-day period, if present, were not counted.

Patient characteristics collected included age, sex, primary service (medicine, surgery, or rehabilitation), recent hospitalization, recent ICU stay, receipt of antacids or tube feeds during their current hospitalization, and immune suppression. Recent hospital or ICU stay was defined as hospitalization in a general ward or ICU within the previous 12 weeks, respectively. Immune suppression was defined as ongoing chemotherapy, oral corticosteroid use, organ transplantation, and human immunodeficiency virus infection. Each patient was assigned a Horn index score;[20] individual medical conditions were not recorded.

Necessity Determination

Two infectious disease physicians and board-certified internists (M.K.S. and D.M.D.) independently evaluated the necessity of each patient's non-CDI antimicrobial use by reviewing daily provider notes, vital signs, and results of laboratory and imaging studies. An antimicrobial was defined as necessary when antimicrobial therapy was thought to be required for the condition being treated and administered for an appropriate duration, as determined by reviewer opinion and published clinical guidelines when available.[21-24] Empiric antimicrobials were considered necessary if given for suspected septic shock while culture results were pending (up to 72 hours). Necessity determinations were based on whether an antimicrobial was indicated and the selected duration of therapy, not the specific antimicrobial chosen or dose and/or route of administration. All non-CDI antimicrobials administered to a patient on a given day were evaluated for necessity. Non-CDI antimicrobial days were designated as "yes," "no," or "possibly," with a designation of possibly fully necessary used for indications that required clinical examination (such as cellulitis) and complicated scenarios best decided by overall clinical gestalt. For analysis purposes, any antimicrobial considered possibly necessary was regarded as fully necessary (ie, yes) in calculations of unnecessary antimicrobial days. Dates on which unnecessary antimicrobial use started and stopped were recorded. The number of days on which any antimicrobial use was unnecessary and on which all antimicrobial use was unnecessary was calculated for each patient. Calculations of total antimicrobial days per patient were based on overall presence or absence of antimicrobial use on each day, regardless of the number of agents (ie, 5 days of ceftriaxone and azithromycin given concurrently was counted as 5, not 10, days of therapy). In contrast to the

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TABLE 1. Characteristics of 141 Veterans with *Clostridium difficile* Infection (CDI) Given Non-CDI Antimicrobials, Overall and Stratified by Unnecessary Use

Category, characteristic	Overall (n = 141)	No unnecessary antimicrobials (n = 33)	Any unnecessary antimicrobials (n = 108)	Only unnecessary antimicrobials (n = 36)	P[a]
Demographics					
Age, mean ± SD, years	70.0 ± 13.4	67.4 ± 13.4	70.8 ± 13.4	69.6 ± 16.8	.56
Male, no. (%)	140 (99)	32 (97)	108 (100)	36 (100)	.29
Primary service, no. (%)					
Medicine	115 (82)	27 (82)	88 (81)	31 (86)	.63
Other[b]	26 (18)	6 (18)	20 (19)	5 (14)	.63
CDI risk factors,[c] no. (%)					
Recent hospital stay	137 (97)	30 (91)	107 (99)	36 (100)	.06
ICU stay	41 (29)	8 (24)	33 (31)	9 (25)	.94
Antacids	117 (83)	30 (91)	87 (81)	30 (83)	.35
Tube feeds	14 (10)	1 (3)	13 (12)	3 (8)	.35
Immune suppression	21 (15)	8 (24)	13 (12)	1 (3)	.008
Horn index,[d] mean ± SD	2.79 ± 0.56	2.64 ± 0.7	2.83 ± 0.5	2.75 ± 0.5	.52
Antimicrobial use					
Days, mean ± SD	15.2 ± 11.8	14.4 ± 12.1	15.5 ± 11.7	6.9 ± 5.3	.001
Courses, mean ± SD	3.2 ± 2.6	2.2 ± 1.9	3.4 ± 2.7	1.6 ± 1.0	.08
≥3 courses, no. (%)	68 (48)	6 (18)	62 (57)	7 (19)	.89
Recurrent CDI, no. (%)	57 (40)	11 (33)	46 (43)	17 (47)	.33

NOTE. ICU, intensive care unit.

[a] P values are for the comparison between no and only unnecessary antimicrobials, determined by the Fisher exact test for recurrent CDI, the χ^2 test for all other categorical variables, the t test for age and Horn index, and the Mann-Whitney U test for antimicrobial days and courses.

[b] Rehabilitation and surgery.

[c] Risk factors were assessed at the time of treatment initiation for the initial CDI episode.

[d] The Horn index is a measure of underlying disease severity at completion of CDI therapy, with 1 = mild, 2 = moderate, 3 = severe, and 4 = extremely severe.

accounting of the number of days of therapy, if more than 1 antimicrobial was given concurrently each antimicrobial was considered a separate course (ie, ceftriaxone and azithromycin given concurrently were counted as 2 separate courses). Additionally, when calculating antimicrobial days for the determination of indications for unnecessary use and frequency of each antimicrobial used unnecessarily (ie, data in Tables 5 and 6), each antimicrobial was counted separately, even if used concurrently.

Any disagreements between the 2 reviewers regarding antimicrobial necessity were discussed, with both reviewers given the option to change their determination. If the initial reviewers could not agree even after discussion, the final necessity determination was made by a third reviewer (J.R.J.), who also is an infectious disease physician and board-certified internist and was blinded to the determinations of the initial reviewers.

Statistical Analysis

Statistical analysis was performed using SPSS software. Categorical variables were compared using either the Fisher exact test (recurrent CDI) or the χ^2 test (all other variables), whereas continuous variables were compared using the t test (for age and Horn index) or the Mann-Whitney U test (for antimicrobial days and courses). Multivariable logistic regression was used to evaluate clinical variables for associations with only unnecessary antimicrobial use, compared with no such use. The MVAMC Institutional Review Board approved the study protocol.

RESULTS

The 141 patients with new-onset CDI who received non-CDI antimicrobials during 2004–2006 were predominately male and had a mean age of 70.0 years (Table 1). Overall, the amount of non-CDI antimicrobials received during and up to 30 days after CDI treatment totaled 2,147 antimicrobial days and 445 antimicrobial courses (Table 2). The majority of antimicrobials were prescribed while patients were in the hospital (data not shown). Of the 141 patients, 108 (77%) received at least 1 dose of an unnecessary antimicrobial, 36 (26%) received exclusively unnecessary antimicrobials, and 33 (23%) received no unnecessary antimicrobials. Of the 2,147 total antimicrobial days, 964 (45%) included at least 1 unnecessary antimicrobial, and 763 (36%) included only unnecessary antimicrobials. Representative examples of anti-

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TABLE 2. Necessity of Non–*Clostridium difficile* Infection (CDI) Antimicrobial Use among 141 Veterans with Current or Recent CDI as Determined by Independent Reviewers

Study finding	Value
Total patients, no.	141
Total antimicrobial days, no.[a]	2,147
Antimicrobial days per patient, range (median)	1–47 (12)
Total antimicrobial courses, no.	445
Antimicrobial courses per patient, range (median)	1–17 (2)
Days including at least 1 unnecessary antimicrobial, no. (% of 2,147)	964 (45)
Days including entirely unnecessary antimicrobials, no. (% of 2,147)	763 (36)
Patients with receipt of any unnecessary antimicrobials, no. (% of 141)	108 (77)
Patients with receipt of only unnecessary antimicrobials, no. (% of 141)	36 (26)
Patients with receipt of no unnecessary antimicrobials, no. (% of 141)	33 (23)

[a] Concurrent antimicrobial use was not counted separately.

microbial use classified as unnecessary are presented in Table 3.

Interreviewer Variability

After their initial review, the 2 primary reviewers agreed as to the necessity of the prescribed antimicrobial days for 85% of the 445 non-CDI antimicrobial courses reviewed. After discussion, they reached agreement for more than 99% of the courses, with only 2 courses requiring adjudication by the third reviewer.

Associations with Unnecessary Antimicrobial Use

Univariable analysis (Table 1) was used to compare the characteristics of the 36 patients receiving only unnecessary antimicrobials with those of the 33 subjects receiving no unnecessary antimicrobials. Immune suppression was significantly associated with receiving no unnecessary antimicrobial use, with 24% of patients receiving no unnecessary antimicrobials being immune suppressed, versus 3% of those receiving only unnecessary antimicrobials ($P = .008$). More subjects having only inappropriate antimicrobial use had a recent hospital stay, but this did not reach statistical significance, and having a recent hospital stay was a common exposure (137/141 [97%]). Duration of antimicrobial use was significantly shorter in patients receiving only inappropriate antimicrobials (6.9 vs 14.4 days; $P = .001$), and a similar trend was observed for the number of antimicrobial courses, with fewer courses prescribed to those receiving only unnecessary antimicrobial use (1.6 vs 2.2; $P = .08$).

Characteristics that in the univariable analysis were significantly or borderline significantly ($P < .10$) associated with only unnecessary antimicrobial use (ie, immune suppression, antimicrobial days, and number of antimicrobial courses) were used in multivariable analysis (Table 4). Recent hospital stay was not included in the final multivariable model because only 3% of patients lacked this exposure, resulting in extremely wide 95% confidence intervals of questionable relevance. In the multivariable model, fewer antimicrobial days alone remained significantly associated with only unnecessary antimicrobial use, whereas the association with immune suppression and antimicrobial courses lost statistical significance.

Indications and Antimicrobials Used

The indications given by the ordering clinicians for the use of non-CDI antimicrobials are listed in Table 5. The common diagnostic categories (by organ system) most frequently associated with unnecessary antimicrobial use were genitourinary (specifically urinary tract infections [UTIs]) and respiratory (specifically pneumonia). Antimicrobials given for empiric therapy (the justifications for which included fever, leukocytosis, and shock) were deemed unnecessary approximately half the time. In contrast, cardiovascular infections (infective endocarditis) and central nervous system infections (meningitis and epidural abscess) had no associated unnecessary antimicrobial use.

Table 6 shows the non-CDI antimicrobials used and the associated percentage of unnecessary use. Antimicrobials with a high percentage of unnecessary use included fluoroquinolones (68% of courses), clindamycin (93%), and nitrofurantoin (100%), although the latter 2 were used infrequently. Overall, β-lactam agents were given most frequently, and approximately one-third of their use was deemed unnecessary. The only antimicrobials without any unnecessary use were linezolid and rifampin.

Unnecessary Antimicrobials and Recurrent CDI

Among all patients, a higher proportion of those who received any unnecessary antimicrobials had recurrent CDI (46/108 [43%]) compared with those who received no unnecessary antimicrobials (11/33 [33%]), although this was not significant ($P = .42$; Table 1). The risk of recurrent CDI was similarly high among patients who received only unnecessary antimicrobials (17/36 [47%]), for whom antimicrobial exposure presumably was completely avoidable.

DISCUSSION

Our previous MVAMC-based study[15] found that in the peri-CDI period many patients with current or recent CDI received

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TABLE 3. Examples of Unnecessary Antimicrobial Use within 30 Days of *Clostridium difficile* Infection (CDI) among Male Veterans

Age, years	Underlying condition(s)	Antimicrobial	Details of unnecessary antimicrobial use	Adverse outcome
75	Diabetes, recent amputation	18 days cefazolin	Slow healing of gastrocnemius flap, but no fever, no drainage, and documentation of "no evidence of infection"	None
79	Multiple sclerosis, indwelling catheter	7 days cephalexin	Clearly documented asymptomatic bacteriuria	Recurrent CDI, death
72	Head and neck cancer	4 days ceftazidime, 1 day ciprofloxacin	Positive sputum culture, but no fever or respiratory symptoms and documentation of "no evidence clinical infection"	None
60	Congestive heart failure	5 days ciprofloxacin	Asymptomatic pyuria and bacteriuria while hospitalized	Recurrent CDI
83	Metastatic prostate cancer, seizures	10 days moxifloxacin	"Questionable lung infiltrate," but no fever or respiratory symptoms	Recurrent CDI
62	Rosacea	Oral tetracycline	Mild rosacea	None

non-CDI antimicrobials, which were significantly associated with recurrent CDI. Here, we documented that a sizeable proportion of this antimicrobial use was unnecessary and therefore potentially avoidable. This suggests that a population at high risk for recurrent CDI is being needlessly exposed to antimicrobials.

Patients who received unnecessary antimicrobial therapy actually were somewhat more likely to experience an episode of recurrent CDI than were those whose antimicrobial therapy was deemed necessary. Notably, patients who received only unnecessary antimicrobials had an approximately 3-fold higher rate of CDI (17/36 [47%]) than did patients in our previous study who received no non-CDI antimicrobials (17/105 [16%]),[15] suggesting that some CDI cases are potentially attributable to this unnecessary antimicrobial use, although this estimate does not take potential confounding conditions into account. These data support improved antimicrobial stewardship in the peri-CDI context.

Although our subjects were known to have a recent CDI episode and therefore to be at high risk for recurrent CDI, a large proportion of them still received unnecessary antimicrobials during a high-risk period when clinicians should be exercising increased caution with antimicrobial therapy.

TABLE 4. Multivariable Logistic Regression Assessing Associations with Receiving Only Unnecessary Antimicrobial Use Compared with No Unnecessary Antimicrobial Use among Veterans with Current or Recent *Clostridium difficile* Infection

Variable[a]	Odds ratio (95% CI)	*P*
Immune suppression	0.10 (0.01–1.06)	.056
Antimicrobial days	0.90 (0.83–0.98)	.02
Antimicrobial courses	1.06 (0.63–1.79)	.83

[a] Variables that were significant or borderline significant ($P < .10$) in the univariable analysis (ie, immune suppression, number of antimicrobial days, and number of antimicrobial courses) were included in the model. Recent hospital stay was not included because this exposure was very prevalent (97%), resulting in extremely wide 95% confidence intervals (CIs).

Potential explanations include an absence of awareness of the risk of recurrent CDI with antimicrobial use, unawareness of the patients' previous CDI history, and/or a misunderstanding regarding which conditions require antimicrobial therapy.

Our search for associations with only unnecessary antimicrobial use identified a significant association with a decreased number of antimicrobial days. This may reflect that clinicians eventually recognize that the antimicrobial use is unnecessary and take corrective action by discontinuing the drug. A corresponding trend was seen with number of antimicrobial courses, although this did not reach statistical significance. Similarly, immune suppression was negatively associated with only unnecessary antimicrobial use. This may reflect the immune suppressed patients' greater underlying severity of illness and increased vulnerability, which perhaps led the reviewers to consider empiric antimicrobial therapy and prophylaxis to be necessary, whereas in healthier patients the same therapy might have been considered unnecessary.

The indications most commonly associated with unnecessary antimicrobial use—UTI and pneumonia—have been documented in multiple studies as frequent indications for unnecessary antimicrobials.[9-14,25,26] For these and several other indications that prompted unnecessary therapy (including surgical prophylaxis, asymptomatic bacteriuria, UTI, and pneumonia), treatment guidelines are readily available that could have facilitated appropriate prescribing.[21-24] These conditions appear to be promising candidates for antimicrobial stewardship efforts, since 60%–80% of the associated antimicrobial use was judged as unnecessary. Unnecessary antimicrobial use for prophylaxis was most often due to continuation of surgical prophylaxis for longer than necessary (data not shown), which has been reported previously, with 80% of surgeons surveyed acknowledging regular use of prophylaxis for greater than 24 hours.[27] It is also concerning that the antimicrobials commonly used unnecessarily were previously demonstrated to be high risk for inducing CDI, including fluoroquinolones, clindamycin, and β-lactams.[28] Fluoroquinolone use in particular has been linked to CDI caused

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TABLE 5. Indications Given by Prescribing Team for Non–*Clostridium difficile* Infection (CDI) Antimicrobial Use among Veterans with Current or Recent CDI

Indication	Total antimicrobial days, no. (% of 2,974)[a]	Unnecessary antimicrobial days, no. (row %)
No reason given	7 (0.2)	7 (100)
Genitourinary[b]	403 (14)	329 (82)
Urinary tract infection	379 (13)	307 (81)
Respiratory[c]	537 (18)	327 (61)
Pneumonia	482 (16)	306 (63)
Empiric therapy[d]	271 (9)	143 (53)
Miscellaneous[e]	122 (4)	56 (46)
Skin/soft tissue[f]	309 (10)	98 (32)
Gastrointestinal[g]	238 (8)	6 (21)
Neutropenic fever	92 (3)	16 (17)
Prophylaxis[h]	229 (8)	40 (17)
Bloodstream infections[i]	336 (11)	22 (7)
Bone/joint[j]	234 (8)	2 (0.8)
Cardiovascular[k]	72 (2)	0 (0)
Central nervous system[l]	124 (4)	0 (0)

[a] Individual percentage values do not sum to 100 because of rounding; total number of antimicrobial days differs from that in Table 2 because concurrent antimicrobials given to a patient each day were counted separately.
[b] Includes urinary tract infection, hematuria, urosepsis, nephrocalcinosis, and pyelonephritis.
[c] Includes pneumonia, bronchitis, lung abscess, and empyema.
[d] Includes shock, fever, and leukocytosis.
[e] Includes candidiasis, rosacea, motility treatment, paronychia, ocular rosacea, and otorrhea.
[f] Includes cellulitis, abscess, and surgical wound infections.
[g] Includes diverticulitis, peritonitis, intra-abdominal abscess, cholangitis, ischemic colitis, liver abscess, bacterial overgrowth, *Helicobacter pylori* infection, abdominal perforation, and diarrhea.
[h] Includes surgical and immunocompromised patients (chemotherapy, human immunodeficiency virus infection, and splenectomy).
[i] Both catheter related and not catheter related.
[j] Includes osteomyelitis, septic joint, and prosthetic joint infection.
[k] Includes endocarditis.
[l] Includes meningitis and epidural abscess.

by the epidemic and hypervirulent North American pulsotype 1 strain.[28,29]

In contrast, complicated infectious diseases (ie, central nervous system infections, bone/joint infections, and endocarditis) and more specialized and/or restricted antimicrobials (ie, rifampin and linezolid) were associated with minimal to no unnecessary use in our study. This likely was due to consistent involvement of the infectious disease service in patients with these clinical scenarios at our institution (unpublished data), which may not be the case at other institutions. Additionally, antimicrobials typically are considered necessary for conditions such as neutropenic fever and bloodstream infections. However, even these entities encountered some unnecessary use in our study because of inappropriate duration of antimicrobial therapy or incorrect diagnosis as determined by the reviewers (eg, antimicrobials were continued when the patient was no longer febrile and neutropenic or a blood culture contaminant was treated as true bacteremia).

This study has several strengths. These include the high-risk population, the inclusion of cases from both medical and surgical services, the use of multiple independent infectious disease physician reviewers for the determination of necessity, and the presumed limited loss to follow-up due to the tendency of veterans to remain within the Veterans Affairs healthcare system.

This study also has limitations. First, the single-center design and predominately male population limit generalizability. Second, although we assumed that the prescribing clinician was aware of the patient's CDI history, this was not always clearly documented and may not have been true, despite all CDI diagnoses having been made at the MVAMC and thus being readily available to all providers via the electronic medical record. Third, not all risk factors for CDI recurrence reported previously in the literature were evaluated (eg, hypoalbuminemia, individual medical conditions, and hospital length of stay).

Finally, there are inherent limitations to accurate retrospective determination of the necessity of antimicrobials.

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TABLE 6. Non–*Clostridium difficile* Infection (CDI) Antimicrobials Used in 141 Veterans with Current or Recent CDI

Antimicrobial	Total antimicrobial days, no. (% of 2,974)[a]	Unnecessary antimicrobial days, no. (row %)
Nitrofurantoin	3 (0.1)	3 (100)
Clindamycin	27 (1)	25 (93)
Fluoroquinolones	560 (19)	379 (68)
Tetracyclines	147 (5)	71 (48)
Metronidazole	68 (2)	27 (40)
Macrolides	55 (2)	21 (38)
β-lactams[b]	1,047 (35)	362 (35)
Antifungals[c]	225 (8)	65 (29)
Trimethoprim-sulfamethoxazole	288 (10)	54 (19)
Aminoglycosides	28 (1)	5 (18)
Vancomycin, intravenous	445 (15)	77 (17)
Linezolid	40 (1)	0 (0)
Rifampin	41 (1)	0 (0)

[a] Individual percentage values do not sum to 100 because of rounding; total number of antimicrobial days differs from that in Table 2 because concurrent antimicrobials given to a patient each day were counted separately.

[b] Includes penicillin, aminopenicillins, dicloxacillin, cephalosporins, extended spectrum (piperacillin-tazobactam, ticarcillin-clavulanate, ampicillin-sulbactam), and carbapenems.

[c] Includes fluconazole, amphoterocin, caspofungin, and voriconazole.

These include the inability to examine the patient and make direct clinical judgments, possibly incomplete and/or inaccurate documentation of pertinent clinical findings and provider thought processes, and the benefit of hindsight, which precludes a valid, "real-time" perspective on the case as it unfolded to the providers. We attempted to correct for these limitations by (1) designating antimicrobial use as "possibly" fully necessary, (2) analyzing possibly fully necessary antimicrobial use leniently as fully necessary, and (3) using multiple reviewers. The reviewers also consistently reviewed each patient's record in chronological order, considering only the information available to the prescribing clinician at the time of antimicrobial administration. Despite these attempts, the retrospective nature of the study may have led to some overestimation of unnecessary use, since without the benefit of hindsight even seasoned clinicians may disagree regarding antimicrobial management of patients. However, notwithstanding the difficulty of retrospective determination of the necessity of antimicrobial use, in many instances (eg, Table 3) it was abundantly clear that antimicrobials were not indicated.

In conclusion, at our institution non-CDI antimicrobials are often used unnecessarily in patients with a current or recent history of CDI. This suggests that during this window of heightened risk of CDI recurrence a large portion of non-CDI antimicrobial use could be avoided, thereby presumably mitigating some of the associated recurrence risk. Providers contemplating antimicrobial therapy need to be more aware of (1) the risk for recurrent CDI that accompanies antimicrobial use, (2) the patient's medical history (especially prior CDI episodes), and (3) which clinical scenarios actually require antimicrobial therapy, and they should be especially cautious when treating patients with a recent CDI episode.

ACKNOWLEDGMENTS

Financial support. This study was supported by the resources of the Minneapolis Veterans Affairs Health Care System, including the Center for Epidemiological and Clinical Research.

Potential conflicts of interest. J.R.J. reports receiving research support from Merck, Rochester Medical Group, and Syntiron. All other authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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