

An Audit-Based, Infectious Disease Specialist-Guided Antimicrobial Stewardship Program Profoundly Reduced Antibiotic Use Without Negatively Affecting Patient Outcomes

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Background. Antimicrobial stewardship programs are increasingly implemented in hospital care. They aim to simultaneously optimize outcomes for individual patients with infections and reduce financial and health-associated costs of overuse of antibiotics. Few studies have examined the effects of antimicrobial stewardship programs in settings with low proportions of antimicrobial resistance, such as in Sweden.

Methods. An antimicrobial stewardship program was introduced during 5 months of 2013 in a department of internal medicine in southern Sweden. The intervention consisted of audits twice weekly on all patients given antibiotic treatment. The intervention period was compared with a historical control consisting of patients treated with antibiotics in the same wards in 2012. Studied outcome variables included 28-day mortality and readmission, length of hospital stay, and use of antibiotics.

Results. A reduction of 27% in total antibiotic use (2387 days of any antibiotic) was observed in the intervention period compared with the control period. The reduction was due to fewer patients started on antibiotics as well as to significantly shorter durations of antibiotic courses ($P < .001$). An earlier switch to oral therapy and a specific reduction in use of third-generation cephalosporins and fluoroquinolones was also evident. Mortality, total readmissions, and lengths of stay in hospital were unchanged compared with the control period, whereas readmissions due to a nonresolved infection were fewer during the intervention of 2013.

Conclusions. This study demonstrates that an infectious disease specialist-guided antimicrobial stewardship program can profoundly reduce antibiotic use in a low-resistance setting with no negative effect on patient outcome.

Keywords. antimicrobial resistance; antimicrobial stewardship; duration of antibiotic therapy; geriatric.

The emerging antimicrobial resistance of pathogenic bacteria is a major threat to public health worldwide [1, 2]. The lack of novel treatment alternatives is

concerning, and prompt measures are needed to counteract the current development [3]. De novo appearance of resistance during antibiotic treatment is uncommon, but antibiotic treatment readily promotes selection of resistant microorganisms [4]. This selection is linked to the use of antibiotics in the individual patient as well as to the use of antibiotics in a population [5–7]. Other factors that affect resistance levels in a society include antibiotic use in animal husbandry and influx through international travel [8–10].

Antimicrobial stewardship is an umbrella definition of structured programs to promote the rational use of antibiotics, and antimicrobial stewardship programs (ASPs) are becoming increasingly common in hospitals [11]. However, although most ASPs strive to minimize

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collateral damage of antibiotic treatment, such as the selection of resistant organisms and *Clostridium difficile* infections (CDIs), they can include a large variety of strategies and outcome objectives [12, 13]. Antimicrobial stewardship program strategies can be broadly sorted into restrictive and persuasive interventions. Persuasive interventions often consist of audit and feedback systems, whereas restrictive interventions limit the possibility to prescribe certain antibiotics. Restrictive and persuasive interventions can be combined in a variety of measures to optimize antimicrobial use [12–14]. Most ASPs have been introduced in settings with high proportions of multiresistant bacteria or as a countermeasure during outbreaks of resistant bacteria or CDIs. Few programs have been tested in Scandinavian hospitals where, historically, the proportion of antimicrobial resistance has been low [15]. The 2013 Swedish rate of methicillin-resistant *Staphylococcus aureus* (MRSA) was 1%, whereas the rate of extended spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* was 4%, both rates being among the lowest worldwide in countries with surveillance of antimicrobial resistance (http://www.ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/database.aspx). However, recent trends suggest concerning increases of resistance levels in Sweden [16].

The purpose of this study was to investigate, through a historically controlled study design, whether the involvement of infectious disease (ID) specialists in an audit-based ASP leads to improved outcomes for patients treated for infectious diseases. Secondary objectives included whether such an ASP leads to (1) altered or decreased antibiotic use or (2) changes in length-of-stay. Wards that mainly treat multimorbid, often geriatric patients were specifically targeted in the program, because this group of patients is especially vulnerable to collateral damage of nonrational antibiotic use.

MATERIALS AND METHODS

Setting

The study was conducted in the Department of Internal Medicine at Skåne University Hospital in Malmö, Sweden. Skåne University Hospital is one of the largest hospitals in Sweden. It serves as a secondary care unit for an area with a population of 700 000 inhabitants as well as a tertiary care unit for a population above 1.5 million. The hospital has a total of approximately 1100 beds at 2 sites. The Department of Internal Medicine in Malmö is a secondary care unit with 4 wards. The number of available hospital beds as well as total admissions in the included wards varied slightly throughout the study period (Supplementary Table 1), and it was higher in 2013 during the intervention period compared with 2012. In the department of medicine, patients with conditions in internal medicine and/or infections are treated, many of whom are geriatric patients with multiple underlying disorders.

Study Population

All admitted patients (cases) receiving antibiotics, or planned for treatment with antibiotics, whilst admitted to the included wards from April 1 through June 20, 2013 as well as August 26 through October 21, 2013 were eligible for inclusion (Figure 1). The control group consisted of cases that were treated with antibiotics at the corresponding wards in the corresponding time period 2012. If a study patient was discharged, later readmitted to one of the study wards during the study period, and again received antibiotics, this patient was registered as a new case. Thus, the number of individual patients was slightly lower than the number of cases. A database search of the computerized medical records allowed identification of all cases that had received antibiotics, and non-audited cases that did receive antibiotics could be added to the 2013 prospective cohort. Two exclusion criteria were applied. Cases with more than 50% of their hospital stay in a ward outside the study wards were excluded from the study as well as (2) cases receiving antibiotic prophylaxis only.

The Antibiotic Stewardship Program

In 2012, written hospital guidelines of treatment recommendations for infections were accessible to all physicians at the study wards, and an ID consultant was available on demand at all hours.

The antibiotic stewardship program of 2013 consisted of prospective audits twice weekly at the study wards. All hospitalized patients treated with, or planned for, antibiotics were audited by an ID specialist on each visit. In Sweden, an ID specialist is a licensed physician that has at least 5 years of specialist training in the field of infectious diseases postlicensing. Six different ID specialists took turns making audit visits. Individual feedback and treatment recommendations were given for each patient based on discussions with the physicians at the ward. These recommendations were based on results from physical and laboratory tests of the patient as well as x-ray and culture results. When necessary, a renewed physical examination was performed by the auditor. Once a recommendation was given, the final decision on treatment was trusted the physician responsible for the care of the patient. Written guidelines and access to a consultant at all hours was still in place during the intervention.

Data Collection and Definitions

Data on outcome and antibiotic use was collected retrospectively through computerized medical charts. Antibiotic use was defined as full days of therapy, and utilization was based on administered doses as long as the patient was hospitalized and on ordered or prescribed doses after discharge. From the charts, basic parameters including gender, age, type of housing, and information on comorbidities (defined in Table 1) were registered. Parameters relevant for the infection, including maximal value of C-reactive protein (CRP), white blood count (WBC), culture results, primary diagnosis, type and duration of antibiotic

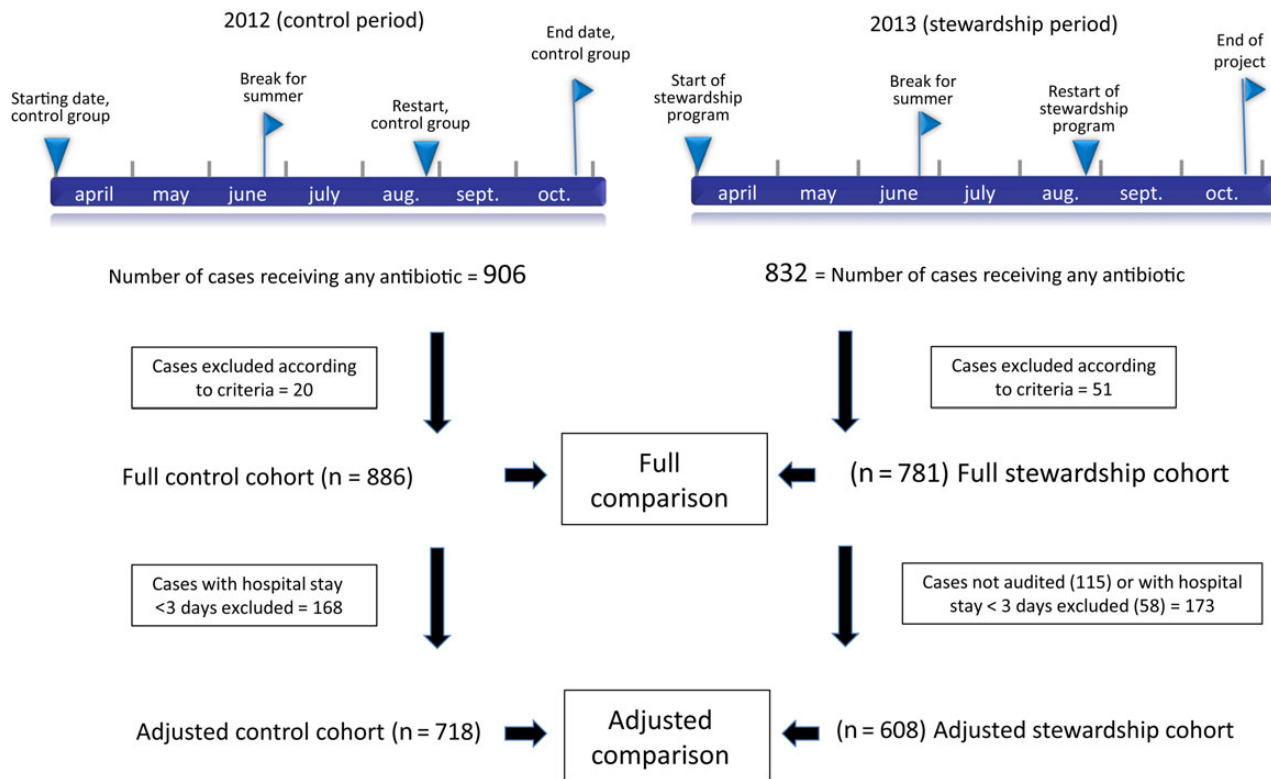


Figure 1. Flow chart of the study outline and creation of study cohorts. The flow chart depicts the creation of the respective study cohorts. The left flow chart depicts the 2012 control group and the creation of the control cohorts after exclusion. The right flow chart depicts the 2013 intervention group and the creation of the stewardship cohorts after exclusions. The full and adjusted comparison of cohorts are illustrated.

therapy, and length-of-stay in hospital, were also collected. Finally, results on patient outcomes were registered, including mortality or readmission within 28 days of discharge from hospital as well as adverse events, such as *C difficile* within 2 months from discharge.

Primary study outcomes were readmission and/or mortality within 28 days of discharge from hospital. The cause of each fatality and readmission was separately assessed for its relation to the prior infection. The definitions applied are described in Table 1. Secondary study outcomes were total antibiotic treatment (including planned treatment at discharge), duration of treatment with intravenous (IV) antibiotics, and a separate assessment of each type of antibiotic. Finally, adverse events and lengths-of-stay in hospital were assessed for all patients.

Data Sorting and Statistical Analysis

Two separate analyses of the collected data were conducted, and this process is outlined in Figure 1. First, the full effect of the stewardship intervention was analyzed. In this analysis, we compared the full 2012 control cohort with the full 2013 stewardship cohort, including patients not audited. Second, adjusted cohorts were created where only audited patients were included in the stewardship cohort. This adjusted prospective cohort was

biased towards longer hospital stays (because many patients with short hospital stays were not audited), and to adjust for this, all patients with a hospital stay of 3 days or less were excluded from both cohorts in an adjusted analysis. A full statistical analysis was performed in the adjusted comparison as well, but results from the adjusted comparison are only presented in the text if they differed substantially from the full comparison.

Comparisons between the groups were performed using χ^2 for nominal data. Continuous data were deemed nonparametric, and comparisons between groups were performed using the Mann-Whitney *U* test. Data were analyzed using IBM SPSS Statistics, Version 22 (SPSS, Inc., Chicago, IL).

Ethical Considerations

The study was approved by the regional ethical Review Board in Lund, Sweden (2013/115).

RESULTS

A total of 832 separate cases/admissions (717 had been audited) received antibiotics during the 2013 intervention period. After applying exclusion criteria, a total of 781 cases were included in the full stewardship cohort (714 individual patients and

Table 1. Definitions Used Throughout the Study

COPD	Registered diagnosis of Chronic Obstructive Pulmonary Disease at the time of the hospital stay.
Cardiovascular disease	A history of acute myocardial infarction, coronary artery bypass surgery, aortic/carotid stenosis, atrial fibrillation, previous surgery for aortic aneurysm, or registered diagnosis of congestive heart failure.
Neoplastic disease	Active neoplasm and/or history of cancer surgery/treatment less than 5 yr prior to hospital stay.
Chronic renal failure	Registered diagnosis of chronic renal failure at the time of the hospital stay, not including patients with elevated P-creatinine alone.
Mortality related to infection	The decision was based on infection severity, clinical parameters, culture results, and information on underlying conditions. If a correlation between the infection and the fatality could not be excluded, mortality was considered related to the infection.
Readmission related to treatment failure or incomplete resolving of the infection	The decision was based on information on symptoms and diagnosis at discharge, on symptoms and diagnosis at readmission as well as on symptoms between discharge and readmission. Two criteria had to be met: (1) the readmission had to be temporally very close to discharge (a finite interval limit of 2 weeks was used) and (2) the patient had to have the same type of infection at readmission as he/she had at discharge, based on clinical symptoms, culture results of the same pathogen, or x-ray findings supporting same location of pneumonia.

7193 patient days). Of the 666 cases/admissions that were audited and not excluded, 58 had a hospital stay of 3 days or less, leaving 608 cases (5989 patient days) in the adjusted stewardship cohort (Figure 1). A total of 906 cases/admissions received antibiotics during the control period of 2012. After exclusions according to criteria, 886 cases (784 individual patients and 7402 patient days) were included in the full control cohort. Among the 886, 168 had a hospital stay of 3 days or less. This left 718 cases (7001 patient days) in the adjusted control cohort (Figure 1).

Patient Characteristics

Basic patient characteristics were similar across all cohorts (Table 2). The median age ranged between 81 and 83 years, reflecting the geriatric nature of patients treated at the medicine wards. There were more women than men in all cohorts, ranging

between 56% and 59%. The prevalence of relevant comorbidities, eg, chronic obstructive pulmonary disease (COPD), chronic renal failure, neoplastic disease, and cardiovascular disease, was very high. The proportions of patients living in a care facility were 16%–17%, whereas the proportions of patients carrying multiresistant bacteria (MRSA and ESBLs) was 3%–4%.

Descriptive Data of the Infection

In all cohorts, the most common primary diagnoses at discharge were cardiovascular disease, respiratory disease (including COPD exacerbations), pneumonia, and urinary tract infections. However, the ratio of pneumonia/urinary tract infection was double in the 2013 cohorts compared with 2012. In both the 2012 and 2013 cohorts, a large proportion of cases had a primary diagnosis that was not an infection.

Table 2. Patient and Infection Characteristics in the Study Cohorts

Characteristic	Full Control Cohort (n = 886)	Adjusted Control Cohort (n = 718)	Full Stewardship Cohort (n = 781)	Adjusted Stewardship Cohort (n = 608)	Significant Difference Between Cohorts
Gender, No. (%) of women	516 (58)	421 (59)	440 (56)	340 (56)	No
Age, mean (range), years	83 (20–100)	83 (20–99)	82 (19–101)	81 (19–101)	No
COPD, ^a No. (%)	262 (30)	208 (29)	217 (28)	154 (25)	No
Cardiovascular disease, No. (%)	501 (57)	419 (58)	443 (57)	350 (58)	No
Neoplastic disease, No. (%)	100 (11)	85 (12)	97 (12)	78 (13)	No
Chronic renal failure, No. (%)	99 (11)	83 (12)	92 (12)	73 (12)	No
Living in care facility, No. (%)	156 (18)	120 (17)	124 (16)	105 (17)	No
Carrier of resistant bacteria, ^c No. (%)	24 (3)	20 (3)	29 (4)	24 (4)	No
Positive blood culture, No. (%)	51 (10)	47 (11)	52 (11)	50 (13)	No
Maximal CRP during hospital stay, mean (range), mg/L	109 (0.6–614)	115 (0.6–614)	116 (0.6–575)	127 (0.6–575)	Yes, P = .02 ^b
Maximal WBC during hospital stay, mean (range), 10 ⁹ /L	12.3 (1.7–21.0)	15 (1.7–21.0)	13.9 (2.2–19.0)	14 (4.0–19.0)	No

^a Chronic Obstructive Pulmonary Disease.

^b Statistically significant difference in the adjusted comparison only.

^c Defined as methicillin-resistant *Staphylococcus aureus* or extended-spectrum β-lactamase producing Gram-negative rod.

Although the maximal WBC was very similar for cases in all cohorts (median of 12.2–12.6 × 10⁹/L), a slightly higher maximal CRP level was observed in the 2013 cohorts (Table 2). In the adjusted comparison, the difference in maximal CRP levels reached statistical significance (*P* = .02), although the difference in absolute levels was small.

Mortality

Mortality within 28 days of hospital admission was high in all cohorts, ranging from 13% to 15%, and no significant difference between cohorts was observed (Table 3). In 36 of 117 fatalities in the full retrospective cohort, the circumstances of the death were unknown, and the corresponding number in the full prospective cohort was 19 of 108 fatalities. The missing data were considered to be missing at random.

Readmissions

The absolute numbers of patients readmitted to hospital within 28 days of discharge were lower in the prospective cohorts, but the proportions of total readmissions did not differ significantly during the stewardship program, and they ranged between 22% and 24% between cohorts (Table 3). The proportion of readmissions related to an unresolved infection (for definitions, see Table 1) was significantly lower during the antibiotic stewardship program (4.9% compared with 7.2%, *P* = .048). A similar trend, but not statistically significant, was observed in the adjusted comparison (5.3% compared with 7.5%, *P* = .072).

Lengths of Stay in Hospital

The median lengths of hospital stay in both cohorts of the full comparison were 7 days (Table 3), whereas the median lengths of hospital stay in both cohorts of the adjusted comparison were 8 days. There were no significant differences between any of the cohorts, but, as suspected due to the nature of the study, a trend towards longer hospital stays was observed in the full stewardship cohort (*P* = .08).

Adverse Events

The number of adverse events, including CDI, due to antibiotic treatment was quite low (ranging from 2.1% to 2.4%) and did not differ between cohorts (Table 3).

Total Antibiotic use

A total of 8851 days of antibiotic therapy was administered/ordered during the study weeks of 2012 (5.0 days of antibiotics per total ward admission), compared with 6464 days of antibiotics during the ASP period of 2013 (3.5 days of antibiotics per total ward admission). This corresponds to an absolute reduction of 27% in absolute antibiotic use (2387 days of any antibiotic). Adjusted for the number of available hospital beds per period, the gross reduction in days of antibiotics/hospital bed was 34%. The number of cases that were given antibiotics was reduced by 12% during the intervention 2013 compared with 2012, explaining less than half of the observed total reduction in antibiotic use. The median duration of antibiotic therapy per patient treated with any antibiotic was shorter during 2013 (from a median of 10 days to a median of 8 days) (Figure 2A and B), explaining the remainder of the observed difference. The difference was highly statistically significant (*P* < .001).

Intravenous Antibiotics

The proportion of patients started on IV antibiotics was similar between cohorts and ranged between 67% and 74%. Although the median duration of IV antibiotic therapy was 4 days in both the full control and the full stewardship cohorts, a statistically significant earlier shift to oral therapy was evident during the 2013 intervention (*P* = .024) (Figure 2C). In the adjusted comparison, the median duration of IV antibiotic therapy was 5 days in the control cohort, compared with 4 days in the stewardship cohort (*P* = .009) (Figure 2D).

Cephalosporins

Approximately 50% of patients in the study received an IV third-generation cephalosporin, and there was no significant

Table 3. Patient Outcomes

Outcome Variable	Full Control Cohort (<i>n</i> = 886)	Full Stewardship Cohort (<i>n</i> = 781)	<i>P</i> Value	Adjusted Control Cohort (<i>n</i> = 718)	Adjusted Stewardship Cohort (<i>n</i> = 608)	<i>P</i> Value
Mortality within 28 d. No. (%)	117 (13)	108 (14)	.71	100 (14)	89 (15)	.71
Mortality related to infection. No. (%)	64 (7)	63 (8)	nc ^a	55 (8)	51 (8)	nc ^a
Readmission within 28 d. No. (%)	203 (23)	180 (22)	.58	166 (23)	138 (23)	.86
Readmission due to incomplete resolving of infection No. (%)	64 (7.2)	38 (4.9)	.048	54 (7.5)	32 (5.3)	.07
Length of stay in hospital Median days (range)	7 (1–44)	7 (1–91)	.08 ^b	8 (4–44)	8 (4–91)	.53
Adverse events. No. (%)	19 (2.1)	16 (2.0)	nc	17 (2.4)	14 (2.3)	nc

^a In a number of cases, the circumstance of the fatality was unknown, and thus this was not calculated.

^b Although the data were clearly skewed towards fewer short stays in the prospective cohort due to the study design, the difference in length of stay in the full comparison did not reach significance.

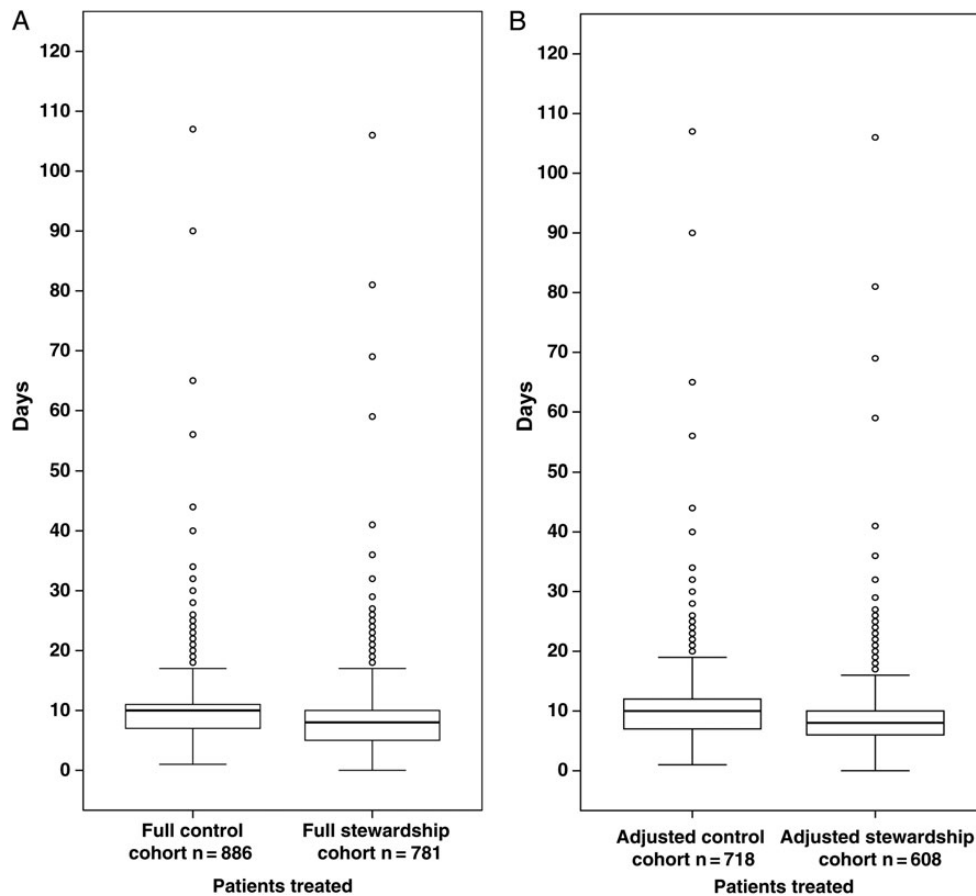


Figure 2. Duration of total and intravenous (IV) antibiotic therapy. A and B, The box plots shows the distributions of antibiotic therapy durations in the cohorts making up the full comparison (full control and stewardship cohorts, plot A) and the adjusted comparison of the study (adjusted control and stewardship cohorts, plot B). The plots demonstrates the lower median of duration during the intervention period, which is also statistically significant in both comparisons ($P < .001$ in both the full and the adjusted comparison). C and D, The box plots shows the distribution of IV antibiotic therapy durations in the cohorts making up the full comparison (full control and stewardship cohorts, plot C) and the adjusted comparison of the study (adjusted control and stewardship cohorts, plot D). Although the box plots in C have equal medians, the stewardship cohort in the adjusted comparison has a lower median. For both comparisons, a statistically significantly shorter duration of IV therapy is evident ($P = .02$ in the full comparison, $P = .009$ in the adjusted comparison).

difference in proportions between cohorts. However, the duration of cephalosporin treatment differed between cohorts. Median treatment duration was 4 days in 2013, compared with 3 days in 2012 ($P < .001$ for both comparisons). The mean use of cephalosporin per patient (Figure 3A) was also lower during the intervention period, a difference that was accentuated when studying gross use/available hospital bed (Figure 3B)

Fluoroquinolones

The use of fluoroquinolones was reduced during the intervention period of 2013 compared with 2012. The proportion of patients receiving fluoroquinolones was 16% in 2012 compared with 12% in 2013. In addition, the median duration of therapy for patients given fluoroquinolones was significantly shorter in 2013. Median treatment duration was 7 days in 2012, compared with 6 days in 2013 ($P = .001$). The mean use per patient was markedly lower in 2013 (Figure 3A), and this difference was

again accentuated when studying gross use/hospital bed (Figure 3B).

Penicillin

The use of penicillin was significantly higher in the stewardship cohorts compared with the control cohorts ($P = .002$). A significantly higher proportion of patients received penicillin in the stewardship cohorts (32% compared with 24% in 2012). However, the median duration of therapy did not differ between 2012 and 2013. Although the mean use per patient was higher in 2013 compared with 2012 (Figure 3A), the use was approximately equal in both years when studying gross use/available hospital bed.

Other Antibiotics

Aside from the specific antibiotics mentioned above, the use of 2 antibiotics used for lower urinary tract infections was significantly reduced during the stewardship intervention; pivmecillinam

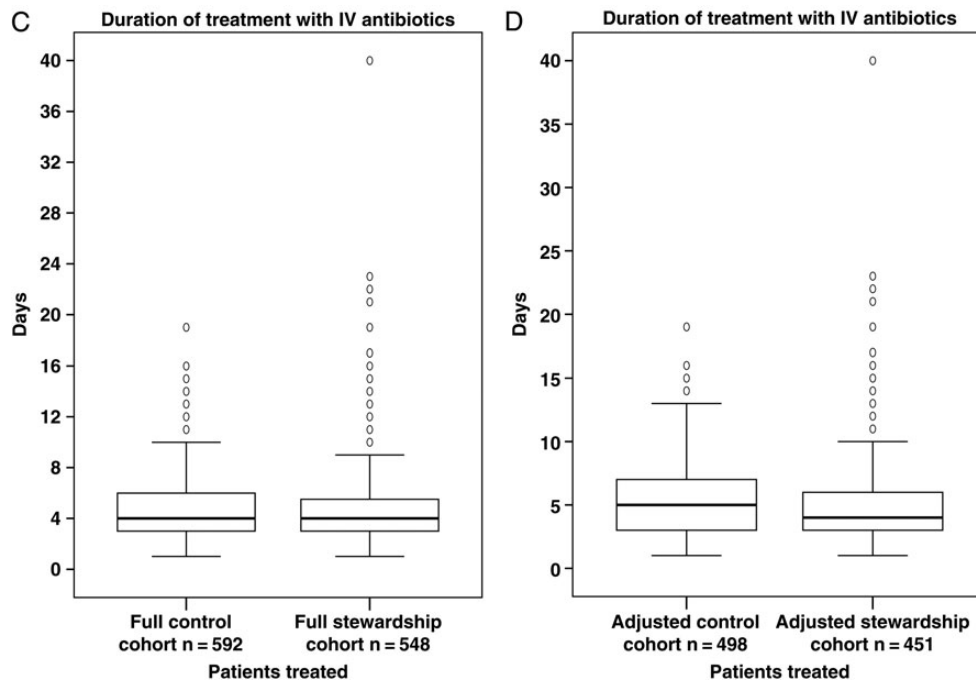


Figure 2 continued

($P = .041$) and nitrofurantoin ($P = .015$). Furthermore, a non-significant reduction in the use of amoxicillin (\pm clavulanate), doxycycline, and clindamycin was observed during the stewardship intervention (Figure 3A). This reduction was accentuated when studying gross use/available hospital bed. The use of piperacillin-tazobactam and trimethoprim-sulfamethoxazole was nonsignificantly increased during the active intervention, and piperacillin-tazobactam was the only antibiotic that had a higher gross use per hospital bed during the intervention period of 2013 (Figure 3B). The use of carbapenems and vancomycin was very low in the study wards during the study period, and the use was not significantly altered during the intervention.

DISCUSSION

The implementation of IDs specialist-guided, audit-based ASP had profound effects on antibiotic use in our low-resistance setting. An absolute reduction in antibiotic use was evident, and this reduction was mainly seen for broad-spectrum antibiotics known to promote antimicrobial resistance, such as cephalosporins and fluoroquinolones. The reduction in antibiotic use was not accompanied by a negative effect on patient outcome, measured as mortality, readmission, or length-of-stay in hospital. The results even suggested that the proportion of readmissions due to an unresolved infection was lower during the ASP. This is, to our knowledge, the first systematically investigated ASP in Sweden. It is evident that the changes in use of specific antibiotics after an ASP would differ between different

geographical regions due to vast differences in resistance levels. However, we believe that our main finding, that the use of ID specialist physicians to individually assess all in-hospital antibiotic therapy is beneficial to individual patients as well as in reducing antibiotic pressure, is a finding that may be generalizable to different geographical regions.

The strengths of the present study include (1) the detailed characterization of each patient and infection in all cohorts as well as (2) the detailed follow-up of patient outcomes. Another strength of the study design was the elimination of several potential biases [17]. Because the control group was collected from just the year before the intervention, the intervention was independent of changes in diagnostics or treatment guidelines. All outcome variables were objective or addressed blindly. Seasonal bias was eliminated by temporally matching the control period to the active stewardship program. Frequently, stewardship programs are implemented due to outbreaks of *C difficile* or high rates of resistant bacteria, which can result in an overestimation of the effects. The results of this study are representative of the effects that a future ASP would have on antibiotic use.

Limitations of the study include the historical control study design, which has disadvantages compared with an interrupted time series. Although several adjustments for potential biases were made, it cannot be excluded that the difference in antibiotic use in 2013 compared with 2012 could be partly explained by a reduction in the number of bacterial infections in the society. According to official statistics, the numbers of antibiotic prescriptions in primary care were 6% lower during the study

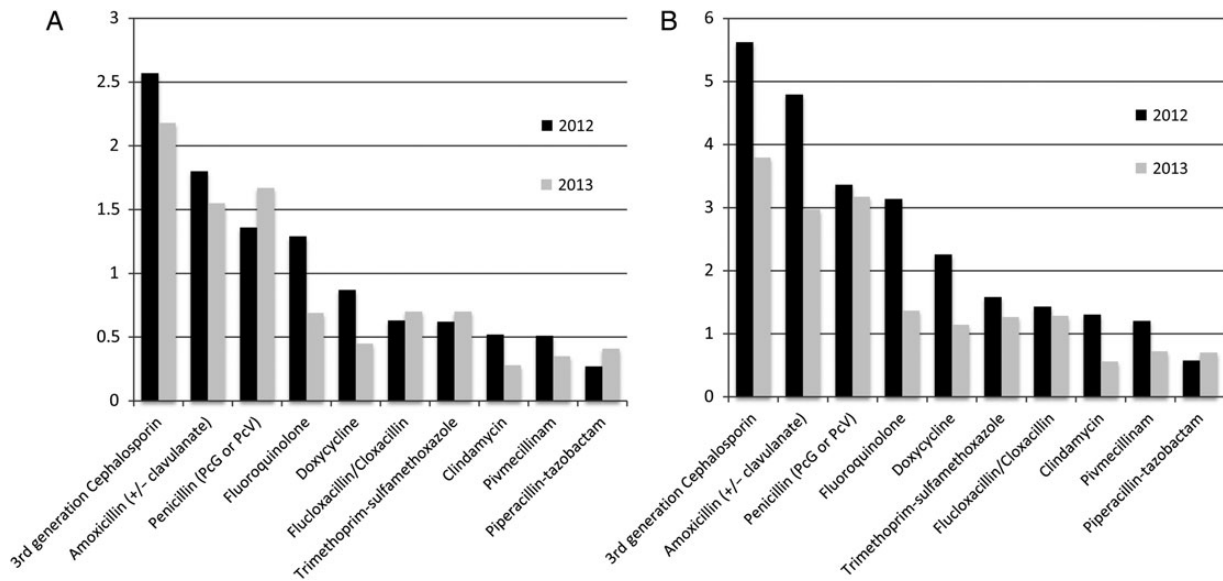


Figure 3. Comparison of use of the 10 most common antibiotics in the study between the antimicrobial stewardship program period of 2013 (black bars) and the control period of 2012 (gray bars). A, The numbers in the graph represent mean days of treatment per all patients in the cohort. The 10 most commonly used antibiotics are shown. The use of all types of antibiotics except penicillin, trimethoprim-sulfamethoxazole, and piperacillin-tazobactam was reduced. According to the Mann-Whitney *U* test, the use of penicillin was significantly increased whereas the use of fluoroquinolones as well as pivmecillinam was significantly reduced during the 2013 antimicrobial stewardship program. B, The numbers in the graph represent total days antibiotic use per available hospital bed and month. The 10 most commonly used antibiotics are shown. When calculated in this way, the use of all types of antibiotics except piperacillin-tazobactam was reduced during the 2013 antimicrobial stewardship program.

months 2013 than in the corresponding months of 2012 [18], but this lowering coincided with a campaign in primary care to reduce unnecessary antibiotic use. It is important to note that the reduction in numbers of individuals started on antibiotics explained less than half of the intervention effect, which amounted to a reduction of >25%. Finally, the final treatment decision was always discussed with the physician at the ward, in most cases fully agreed on, and the change was generally made during the audit. However, the adherence of the ward physician to the given treatment recommendation was not objectively investigated, although it was likely very high. This is a limitation, because the effect of audit and feedback on behavior of professionals varies considerably across studies [19].

There is a strong body of evidence showing that ASPs can reduce antibiotic consumption [12, 20, 21]. This is consistent with the results of our study. In our study, a transition from the use of the broad-spectrum agents in favor of narrow-spectrum variants was apparent, which is also in line with prior studies [22]. The 2013 intervention, due to its design, had differential effects depending on how the antibiotic normally is used. The same proportion of patients in 2013 received initial empirical therapy with a third-generation cephalosporin, but courses were more often discontinued, shortened, or changed at audits compared with the control group of 2012. For fluoroquinolones, which are rarely used for empirical treatment in Sweden, the intervention affected both the duration of therapy and the

proportion of patients started on treatment. Reducing the use of cephalosporins and fluoroquinolones has been linked to the reduction of collateral damage of antibiotic treatment [7, 23]. Intravenous therapy was also shortened during the intervention, which has also been seen in prior stewardship interventions [24]. This is generally a positive change, because oral therapy is cheaper and associated with fewer adverse events than IV therapy. Although we did not identify a decrease in lengths of stay in hospital, this has been linked to early conversion from IV to oral therapy in other studies [24].

The reduction in antibiotic use was reached without a negative effect on mortality or readmissions. It is interesting to note that readmissions related to treatment failure of the previous infection (defined in Table 1) were fewer during the 2013 intervention, even though less antibiotics were used. As concluded in the review by Ohl et al [20], positive effects of ASPs on patient outcomes have been more difficult to show than effects on antibiotic prescribing. According to the meta-analysis by Davey et al [13], interventions intending to decrease excessive prescribing of antibiotics are often associated with decreased rates of resistant bacteria and CDIs. Our lack of effect in these parameters may be attributed to a brief study period and by international comparison, a low incidence of *C difficile*.

Our intervention specifically targeted wards where geriatric, multimorbid patients dominate, and quite a few patients were very frail or terminally ill. This likely explains the observed

high rates of 28-day mortality and readmissions. A substantial proportion of patients had a noninfection primary diagnosis at discharge, which may explain the lack of effect on lengths of stay in hospital, because hospitalization lengths were mainly dependent on other factors than the infection. Elderly individuals are especially vulnerable to collateral damage from antibiotic treatment, because the risk of both CDIs and carriage of resistant bacteria increases with age and frailty [25–27]. Another issue in elderly patients is the overinterpretation of positive urine dip slides [28, 29]. It is interesting to note that the use of both antibiotics recommended for cystitis treatment in Sweden, piv-mecillinam and nitrofurantoin, were significantly reduced during the 2013 stewardship intervention.

Restrictive stewardships are suggested to have greater impact on short-term prescribing outcomes than persuasive interventions, but this difference is not seen long term [13]. Restrictive measures generally require fewer resources compared with persuasive interventions and may be more cost effective. However, the long-term effect of restrictive measures on antimicrobial resistance is not clear and may lead to unchanged or increased resistance [12, 30]. It is clear that fewer patients were started on antibiotics during the intervention program. It is possible that a part of this effect was due to a threat of being audited, which is a possibility that is difficult to interpret. We firmly believe that a focus on reducing antibiotics or cutting costs is not enough when conducting an antimicrobial stewardship. A well designed stewardship should focus on optimizing the treatment for the individual patient, while simultaneously minimizing collateral damage of antibiotic use to the individual and the society. We also believe that this can be best attained by an individual assessment of each patient by an ID specialist.

CONCLUSIONS

In conclusion, the present study shows that an ASP by an ID specialist profoundly reduced the use of antibiotics with no negative effect on patient outcome. Our objective is to implement our stewardship model on a permanent basis and to expand it to other wards and hospitals in Sweden.

Supplementary Material

Supplementary material is available online at *Open Forum Infectious Diseases* (<http://OpenForumInfectiousDiseases.oxfordjournals.org/>).

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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