Optimizing Antimicrobial Therapy (OAT): Comparing the Outcomes of Patients Receiving Pre-Prescription Authorization and Post-Prescription Review with Feedback

Introduction

Antimicrobial stewardship programs (ASP) have been shown to reduce antibiotic use, improve patient outcomes, and decrease adverse drug events such as *Clostridium difficile* infections and antimicrobial resistance [1-12]. However, the optimal approach to antimicrobial stewardship has yet to be defined. The 2015 Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines for "Implementing an Antibiotic Stewardship Program" consider both pre-prescription authorization (PPA) and post-prescription review with feedback (PPRF) as A-II recommended approaches for reducing antimicrobial use in the healthcare setting [13]. However, they do not provide additional data on which approach is preferred for optimizing antimicrobial use.

PPA requires that, for certain antimicrobials, the prescriber seek input from the stewardship program prior to the first dose. PPRF allows clinicians to prescribe any empiric antimicrobial regimen but, in the ensuing 48-72 hours, the ASP advises the clinician with recommendations for stopping, discontinuing, or adjusting therapy if the ASP believes the available diagnostic tests or clinical course warrant a change. Both approaches have potential pros and cons [14]. The benefits of PPA include the following: (1) assurance that patients who need antimicrobials get the most appropriate agents when they are particularly vulnerable to negative sequelae from their infections; (2) collection of appropriate culture data prior to antimicrobial initiation; and (3) limiting patient exposure to antimicrobials when no infection warranting anti-infective therapy is present. However, PPA impacts only select agents, allowing prescribers to use unrestricted agents freely; has minimal impact on prescribers decisions about narrowing the spectrum of therapy or duration of therapy after more clinical data are available; and is resource-intensive as it requires someone to be "on-call" to answer requests in real time.

In contrast, PPRF allows for greater flexibility about when the review of antimicrobial use and feedback to prescribers occurs. Additionally, PPRF allows for a more evidence-based discussion with prescribers including microbiological and clinical data that has evolved since antimicrobials were started. However, uptake of PPRF is generally optional as once antimicrobials have been initiated, stewardship teams generally do not have the

authority to discontinue or alter therapy. Additionally, PPRF does not address the large burden of empiric antimicrobials started unnecessarily. We conducted a quasi-experimental, crossover trial of PPA and PPRF in four medical wards at The Johns Hopkins Hospital to determine the optimal strategy for performing antimicrobial stewardship in the acute care setting. We hypothesized that PPRF would be associated with fewer days of antibiotic therapy than PPA.

Methods

Study setting and participants. The Johns Hopkins Hospital (JHH) is a 1059-bed tertiary care facility in Baltimore, Maryland. Adult patients admitted to the general wards at JHH are cared for by one of four medical firms. Each firm admits patients to their own non-ICU specific medicine floor. General medicine patients admitted to non-firm services were excluded from this study. The medical firms are managed by internal medicine housestaff (specific to each firm) who rotate on a two to four week basis. Each firm has an Assistant Chief of Service who oversees the medical care of all patients on the firm for the entire academic year. Patient demographic characteristics, pre-existing medical conditions, and severity of illness are similar between firms.

Amikacin	Cephalexin	Linezolid
Amoxicillin	Ciprofloxacin	Meropenem
Amoxicillin/clavulanate	Clarithromycin	Metronidazole
Amphotericin B	Clindamycin	Micafungin
Ampicillin	Colistin	Moxifloxacin
Ampicillin/sulbactam	Dapsone	Nitrofurantoin
Azithromycin	Daptomycin	Norfloxacin
Aztreonam	Doxycycline	Oxacillin
Cefazolin	Dicloxacillin	Penicillin
Cefepime	Ertapenem	Piperacillin/tazobactam
Cefotetan	Ethambutol	Rifampin
Cefpodoxime	Fluconzaole	Tigecycline
Ceftaroline	Fosfomycin	Trimethoprim/sulfamethoxazole
Ceftazidime	Gentamicin	Tobramycin
Ceftriaxone	Levofloxacin	Vancomycin

Box 1: Antimicrobials reviewed in study

The present study took place from September 2013 to June 2014. Prior to study initiation, clinicians at JHH were required to obtain PPA for 27 restricted antimicrobials by a member of the ASP via a telephone conversation and there was no PPRF on any of the firms. Antimicrobials were selected as "restricted" if they had a broad spectrum of activity, were associated with serious adverse events, or were costly.

Eligibility Criteria. Patients were included in the study if they were admitted to one of the four medicine firms and initiated on any study antimicrobial listed in Box 1 during the study period. Prophylactic antimicrobials with no clear stop date were excluded as were antimicrobials used for reasons other than to treat infectious diseases (e.g., rifaximin for hepatic encephalopathy, erythromycin for intestinal motility). Patients prescribed

antimicrobials during their time on a non-study unit and transferred to a study unit were included in the study but only antibiotics received during their time on the study unit were included in the analysis. However, patients admitted to a study unit who were transferred to a non-study unit or discharged within 24 hours of hospital admission were excluded from the study.

Interventions. For the first four months of the study, firms A and B were assigned to PPA and firms C and D were assigned to PPRF and for months 6-9 the firms were assigned to the opposite arm. PPA was conducted in the same manner as before study initiation. There was a one-month wash out period between the two study periods (Figure 1). When a firm was assigned to the PPA arm, housestaff would have to contact a clinical pharmacist (8am-5pm weekdays) or infectious diseases fellow (5pm-10pm weekdays; 8am-10pm weekends; doses dispended overnight required approval the next morning) to request approval for antibiotics listed in Box 1. No PPRF was performed in the PPA after antimicrobials were initiated.

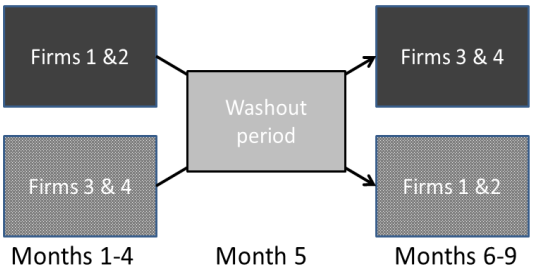

Figure 1: Study Design with gray box indicating pre-prescription authorization and dark box indicating post-prescription review with feedback

When a firm was assigned to PPRF, there was no requirement for seeking approval from the ASP prior to the antimicrobial being dispensed. The ASP made visits at the same time every weekday to housestaff in firms in the PPRF arms to provide feedback on all patients who had been on study antibiotics for at least 48 hours. If results of diagnostic data were not yet available, recommendations were made once this information was known. The requirement for PPA was suspended for teams assigned to the PPRF arm.

Two members of the ASP were involved in adjudicating the appropriateness of antimicrobial use in every case. In cases of disagreement, the third member of the ASP was involved. The ASP members involved in the current study included two infectious diseases physicians (S.EC. or P.D.T) and an infectious diseases pharmacist (E.A). Antimicrobial use was considered appropriate if it was in accordance with the Johns Hopkins Hospital Antibiotic Guideline Handbook [15]. These guidelines are updated on an annual basis and provide detailed recommendations on diagnostic testing, antibiotic selection, and duration of antibiotic therapy for common inpatient infections. Appropriateness of antimicrobial therapy was determined based on the

following criteria: (a) Were antibiotics indicated based on known clinical, microbiological, radiographic, and severity of illness findings of the patient? (b) Was the most appropriate empiric antibiotic regimen selected? (c) Was therapy appropriately adjusted or stopped after a reassessment on day 2-3 of antimicrobials? (d) Was the duration of therapy appropriate for the infection being treated? Known patient-specific adverse drug reactions were accounted for when determining appropriateness.

Data Collection. Demographic data, pre-existing medical conditions, severity of illness measures, detailed antibiotic data, microbiological data, and clinical outcomes data were collected on all eligible patients. Collected data and adjudicated outcomes were entered into data extraction forms and stored in a secure REDCap database. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board, with a waiver of informed consent.

Outcomes. The primary outcome was days of antimicrobial therapy (DOTs). A single DOT was recorded for each individual antimicrobial administered to a patient on a given day. Antimicrobial use was normalized to days of therapy/1,000 patient-days. Antimicrobials prescribed upon discharge were included in the measurements of antimicrobials used. Length of therapy (LOT) was a secondary outcome. LOT corresponds to each day a patient receives any systemic antimicrobial, regardless of the number of agents or doses. Additional secondary outcomes included the following: (a) Unnecessary DOTs; (b) Incident, symptomatic *Clostridium difficile* infections within 60 days; (c) Length of hospital stay from day 1 of antibiotics until hospital discharge; and (d) In-hospital mortality.

Statistical Approach. Demographic and clinical characteristics of patients, appropriateness of antibiotic use, and outcomes in the two study arms were summarized as percentages for categorical variables and medians and interquartile ranges for continuous variables. Comparisons between the treatment groups were made using the student t-test for continuous variables and the Pearson chi-square test for categorical variables. A time-series analysis was used to assess the changes in DOT per 1,000 patient-days comparing PPA and PPRF across the two study periods. Because antimicrobial consumption in a given time period is likely related to the previous time period, we used an interrupted time-series approach. All included patients were assigned a 10-day period based on antibiotic start date. DOT and LOT for each patient was calculated and totaled for

each 10-day interval, and then standardized to 1,000 patient-days (DOT/1,000 patient-days and LOT/1,000 patient-days), using total patient-days for all admission in that 10-month period to the study firm of interest. To adjust for autocorrelation between the error terms, the generalized least-squares method was applied to estimate the parameters in a linear regression model in which errors are assumed to follow a first-order autoregressive pattern. The models generated included a constant, a baseline slope term to control for secular trends, and terms estimating changes in level and slope of outcome rates. To ensure the validity of the model, a sensitive analysis was also performed based on regression-based time-series methods to evaluate the adequacy of the model and test the error distribution [16]. All analyses were performed in STATA Version 13 (StataCorp, College Station, Texas).

Results

Baseline Characteristics of Patients. There were 2686 and 2693 patients admitted to the PPA and PPRF groups during the study period, respectively. Of these, 778 (30%) patients and 730 (27%) patients were started were started on anti-infective therapy for at least 24 hours in the PPA and PPRF groups, respectively (p=0.90). The PPA and PPRF groups were generally similar with regards to demographic characteristics, preexisting medical conditions, and severity of illness (Table 1). Approximately 13% of patients required ICU care prior to being transferred to a study firm, in both arms. About 1% of patients had surgery in the days preceding study entry. The median McCabe score was similar across both study periods. There were 67 (9%) and 79 (10%) patients in the PPA and PPRF groups, respectively who received infectious diseases consultations during their current hospital admission.

Indications for Antibiotic Therapy. The day 1 indication for antibiotic therapy was determined by the prescribing clinician. The most common indications for initiating therapy on day 1 according to the prescribing team were urinary tract infections (24%), community-acquired pneumonia (16%), and skin and soft tissue infections (13%), with no differences observed between the two study arms. Antimicrobial therapy was adjudicated as suboptimal in 34% of patients in the PPA group and 41% of patients in the PPRF group on day 1; ($p<0.01$), generally because anti-infective therapy was not indicated (Table 2). There were 417 (54%) and 462 (63%) patients who remained on antimicrobial therapy on the third day after therapy was initiated ($p<0.01$).

Indications for therapy on day 3 were determined by the AS team. Approximately 36% of patients in the PPA and 24% of patients in the PPRF group had no indication for continued antimicrobial therapy on day 3, p=0.03 (Table 3). For those requiring anti-infective therapy on day 3, common indications for antimicrobial use included the following: urinary tract infections (15%), skin and soft tissue infections (9%), and community-acquired pneumonia (7%), with no differences noted between the PPA and PPRF groups (Table 4).

Antimicrobial Days of Therapy (DOTs) and Lengths of Therapy (LOTs). Figure 2 displays the results of the time-series analysis. Antimicrobial data during the one-month wash out period was not adjudicated and is represented by the vertical dashed line in Figure 2. During the first four months of the study, DOTs steadily increased in the two firms in the PPA arm (solid line to the left of the vertical line; slope = 1.42, p-value= <0.01).

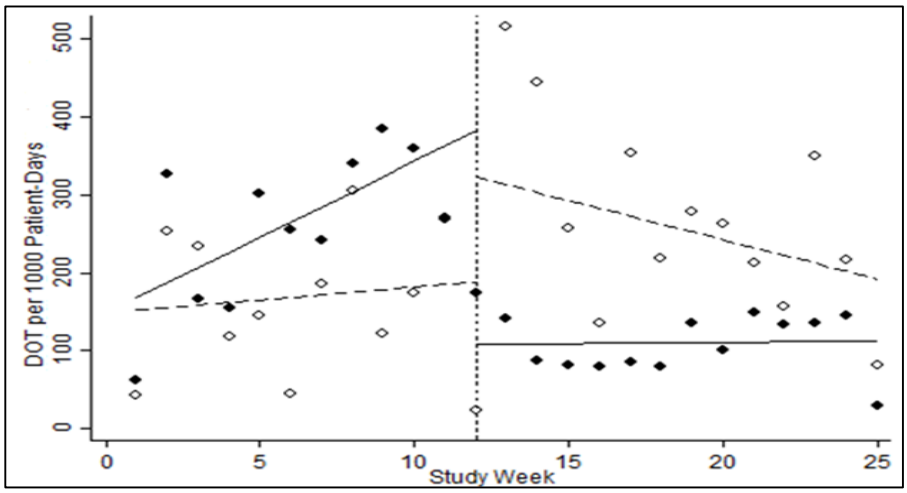

Figure 2: Time-series analyses comparing days of unnecessary antimicrobial therapy during the study period. Solid line indicates pre-approval authorization and dotted line indicates post-prescription review with feedback. Vertical line at 12 weeks indicates the 1-month wash-out period, during which antimicrobial use was not evaluated.

When these firms received PPRF after the washout period, antimicrobial use decreased (dotted line to the right of vertical line; slope=-1.30, p-value = <0.01). In contrast, in the first four months of the study, DOTs remained stable in the PPRF arm (dotted line to the left of the vertical line; slope =1.10, p-value =0.70). For the second four months of the study when these firms were receiving PPA, DOTs were stable (solid line to the right of the vertical line, slope =1.10, p-value = 0.67). The median DOTs in the PPA and PPRF arms were 7 and 6 DOTs per 1,000 patient-days, respectively (p=0.05). The median LOTs in the PPA and PPRF arms were 6 and 5 LOTs per 1,000 patient-days (p<0.01). There was a median of 2 and 1 unnecessary DOTs per 1000 patient-days in the PPA and PPRF arms, respectively. Approximately 48% of antibiotic use in the PPA arm was prescribed in the outpatient setting, compared to 34% in the PPRF arm (p<0.01).

Clinical Outcomes. There were a total of 30 (3.9%) and 22 (3.0%) episodes of incident, clinically significant CDIs in the PPA and PPRF groups, respectively (p=0.40). The median duration of hospital stay from the time

of study enrollment until hospital discharge or death was 3 days (IQR 2-7) in both groups; p=0.99. There was no difference in in-hospital mortality between the two study arms (11% and 14% in PPA and PPRF arms, respectively; p=0.44).

Discussion

Our study compares outcomes related to two commonly used strategies for antimicrobial stewardship: PPA and PPRF. Our results suggest that PPRF may have more of an impact on decreasing both antimicrobial DOTs and LOTs. There was no difference, however, in the clinical outcomes of patients in both groups including incident CDI, length of hospital stay, and in-hospital mortality. Mehta and colleagues also compared PPA and PPRF in a quasi-experimental study at a tertiary care hospital [17]. These investigators found that after introduction of PPRF, antimicrobial DOTs per 1,000 patient-days increased, in contrast to our findings. There are some important differences between the two studies. Mehta *et al*. performed PPRF on three antimicrobials even though their primary outcome included all inpatient antimicrobial use, compared to our study in which PPRF was conducted on all antimicrobials consumed during the study period for patients in the PPRF arm. Additionally, as their study was a quasiexperimental study, the two stewardship interventions occurred at different periods in time and it is unclear if there were other ecologic changes impacting antibiotic prescribing practices (e.g., increased rates of drug-resistant bacteria over time, case-mix data, drug shortages, changes in local or national antibiotic treatment guidelines, etc.). Additionally, the investigators only included inpatient antimicrobial use and did not account for antibiotics prescribed on hospital discharge. As many of their patients had relatively short hospital LOS, durations of therapy were likely artificially shortened for a large number of patients. We found that approximately 40% of all antimicrobial use is prescribed for continuation in the outpatient setting. In fact, there were fewer DOTs of antibiotics prescribed for outpatient completion in the PPRF arm compared with the PPA arm. Without including antibiotics prescribed at the time of hospital discharge, total antimicrobial use would have been significantly underestimated.

In the first four months of the study, DOT in the PPA group steadily increased and in the PPRF group it remained relatively unchanged. In the later four months of the study, DOT decreased in the PPRF group and remained unchanged in the PPA group. We cannot say with certainly that the stewardship interventions led to

any of the changes in antibiotic use. It is possible that as the academic year continued and housestaff became more knowledgeable about antibiotic use, that their antibiotic use would have improved in the second half of the study without any ASP interventions. It is also possible that some of the education provided to the PPRF group lingered when they were assigned to the PPA group in the second half of the study. A fourth possibility is that the study findings we are observing is a result of a Hawthorne effect (18). To be more specific, it is possible that the medicine housestaff modified their antimicrobial prescribing practices because they knew they were part of a study. This might be particularly relevant in the second half of the study where housestaff in the PPRF arm were actively being given feedback and housestaff in the PPA arm had already experienced receiving feedback from the study investigators in the first half of the study so were aware that the study was ongoing. To evaluate these different hypotheses, we will evaluate antibiotic use data from identical time periods in the year before the study when only PPA was occurring and there was no active PPRF. This will help us distinguish between these various hypotheses.

Prior studies of stewardship interventions have found implementation of either PPA or PPRF to be effective strategies for decreasing antimicrobial use [1-12]. However most of these studies compared anti-infective use in the presence of an ASP to anti-infective use in its absence. Cosgrove *et al.* conducted a study involving PPRF across 5 tertiary care medical centers [19]. They found that institutions that overlaid PPRF on already established PPA programs had significant reductions in antimicrobial use, compared with institutions without existing PPA programs which did not have reductions in antimicrobial consumption with implementation of a PPRF intervention.

Interestingly, in both the PPA and PPRF arms, urinary tract infections, community-acquired pneumonia, and skin and soft tissue infections were the most common processes being treated with antibiotics, accounting for almost half of all antibiotic use. This reminds us that although PPA and PPRF are both likely to impact antimicrobial use, if a stewardship program does not have the resources for either of these relatively intensive approaches, a syndrome-specific approach is also reasonable [20, 21]. There are several advantages to a syndrome-specific approach. First it is easier to gather meaningful evidence to develop guidelines and support recommendations for a specific infectious indication. Second, a focused message facilitates provider learning and can lead to sustainable changes. Third, syndrome-specific stewardship allows for a broader impact of

interventions including appropriate laboratory diagnostics, diagnostic imaging, etc. Additionally, with syndrome-specific stewardship, there may be less confounding when measuring the overall impact of the intervention- depending on comprehensive the intervention was.

There are a number of limitations to our study. First, as we have had a PPA system in place for several years with detailed antibiotic treatment guidelines, baseline antimicrobial use may have been relatively low in our institution; it is uncertain if our findings are representative of what would be observed at institutions where antimicrobial stewardship programs have not yet been established. Second, it is unclear if we did not observe a decrease in clinically significant CDI infections because we were underpowered to detect such a difference or if there was truly no difference between PPA and PPRF. As CDI is known to occur up to several weeks after antimicrobial exposure, it is possible that we are failed to include some cases of CDI. Additionally, we used 1000 patient-days as the denominator for overall antimicrobial use because a comprehensive denominator that captures both inpatient and outpatient antimicrobial use has not been established. This denominator may be flawed as the numerator of days of outpatient antimicrobial use is not captured in the denominator. Of note, we repeated the time-series analysis of DOTs per 100 patient-admissions and found similar trends (data not shown). These limitations notwithstanding, although both PPA and PPRF have an impact on overall antimicrobial use, a favorable impact on antimicrobial DOTs and LOTs may be more pronounced with PPRF.

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Table 1: Baseline characteristics of patients in the pre-prescription authorization period and post-prescription review with feedback groups

Characteristic	Pre-prescription group (number, percent) N=778	Post-prescription group (number, percent) N=730	P-value
Age in years (median, interquartile range)	59 (48-70)	58 (45-69)	0.10
Female	409 (52.6)	362 (49.7)	0.26
Race			
African American	440 (56.6)	422 (57.9)	0.62
Caucasian	267 (34.4)	239 (32.8)	0.52
Other	70 (9.0)	68 (9.3)	0.83
Preexisting medical conditions			
Diabetes	269 (34.6)	224 (30.7)	0.11
Cardiovascular disease	538 (69.2)	494 (67.7)	0.54
Structural lung disease	314 (40.4)	249 (34.1)	0.01
Human immunodeficiency virus	17 (2.2)	19 (2.6)	0.60
End-stage liver disease	156 (20.1)	117 (16.0)	0.04
End-stage renal disease	259 (33.3)	243 (33.3)	0.99
Chronic corticosteroid use and/or immunomodulator therapy	77 (9.9)	54 (7.4)	0.09
Solid organ transplant	31 (4.0)	32 (4.4)	0.70
Chemotherapy within 6 months	24 (3.1)	23 (3.2)	0.94
Length of stay from hospital admission until study enrollment[1]	0 (0-1)	0 (0-1)	0.71
Intensive care unit admission during current hospitalization prior to study enrollment	102 (13.1)	97 (13.3)	0.92
Surgery during current hospitalization prior to study enrollment	11 (1.4)	16 (2.2)	0.26
McCabe classification (median, IQR)	3 (2-3)	3 (2-3)	0.26
SIRS criteria on day of study enrollment (median, IQR)	2 (1-2)	2 (1-2)	0.32

[1]Study enrollment is defined as day 1 of antibiotic prescription in the study unit

Table 2: Overview of antibiotic therapy on day 1 in the pre-prescription authorization and the post-prescription review with feedback groups[1]

	Pre-prescription group (number, percent) N=778	**Post-prescription group (number, percent)** N=730	**P-value**
Antimicrobial Regimen Inappropriate [2]	**262 (33.7)**	**300 (41.1)**	**<0.01**
Antimicrobial Therapy not Indicated	**138 (18.8)**	**161 (22.1)**	**0.02**
No bacterial infection	122 (16.6)	141 (19.3)	0.07
Treatment course completed	9 (1.2)	11 (1.4)	0.76
Prophylaxis not indicated	7 (1.0)	9 (1.2)	0.71
Antimicrobial Therapy too Broad	**113 (14.5)**	**131 (17.9)**	**0.27**
Unnecessary double-coverage	13 (1.7)	16 (2.2)	0.94
Unnecessary methicillin-resistant *Staphylococcus aureus* coverage	39 (5.0)	36 (4.9)	0.75
Unnecessary broad spectrum gram-negative coverage	33 (4.2)	49 (6.7)	0.14
Unnecessary Gram-negative coverage	14 (1.8)	11 (1.5)	0.66
Unnecessary Gram-positive coverage	5 (0.6)	3 (0.4)	0.54
Unnecessary anaerobic coverage	9 (1.2)	16 (2.2)	0.23
Antimicrobial Therapy too Narrow	**9 (1.2)**	**5 (0.7)**	**0.34**
Equally effective but more cost-effective options existed	**2 (0.3)**	**3 (0.4)**	**0.60**

[1]For antimicrobial therapy considered inappropriate, a single reason was selected whenever possible;
[2]Inappropriate regimens are inclusive of any reason in table

Table 3: Overview of antibiotic therapy on day 3 in the pre-prescription authorization and the post-prescription review with feedback groups[1]

	Pre-prescription group (number, percent) N=417	**Post-prescription group (number, percent)** N=462	**P-value**
Antimicrobial Regimen Inappropriate [2]	**239 (57.3)**	**168 (36.4)**	**<0.01**
Antimicrobial Therapy not Indicated	**148 (35.5)**	**109 (23.6)**	**0.03**
No bacterial infection	128 (30.7)	74 (16.0)	<0.01
Treatment course completed	12 (2.9)	27 (5.8)	<0.01
Prophylaxis not indicated	8 (1.9)	8 (1.7)	0.84
Antimicrobial Therapy too Broad	**87 (20.9)**	**57 (12.3)**	**<0.01**
Unnecessary double-coverage	9 (2.2)	5 (1.1)	0.21
Unnecessary methicillin-resistant *Staphylococcus aureus* coverage	27 (6.2)	17 (3.7)	0.25
Unnecessary broad spectrum gram-negative coverage	26 (5.6)	19 (4.1)	0.83
Unnecessary Gram-negative coverage	16 (3.8)	8 (1.7)	0.16
Unnecessary Gram-positive coverage	4 (0.9)	0	--
Unnecessary anaerobic coverage	5 (1.2)	8 (1.7)	0.31
Antimicrobial Therapy too Narrow	**3 (0.7)**	**0**	**--**
Equally effective but more cost-effective options existed	**1 (0.2)**	**2 (0.4)**	**0.50**

[1]For antimicrobial therapy considered inappropriate, a single reason was selected whenever possible;
[2]Inappropriate regimens are inclusive of any reason in table

Table 4: Overview of the indication for antibiotic therapy in the pre-prescription authorization and the post-prescription review with feedback groups according to the antimicrobial stewardship team on day 3 of therapy, if antimicrobial therapy was considered indicated[1]

	Pre-prescription group (number, percent)	**Post-prescription group (number, percent)**	**P-value**
	N=473	N=447	
Meningitis	4 (0.9)	2 (0.5)	0.45
Endocarditis	6 (1.3)	9 (2.0)	0.37
Community-acquired pneumonia	32 (6.8)	35 (7.8)	0.54
Healthcare-associated pneumonia	17 (3.6)	12 (2.7)	0.43
Aspiration pneumonia	7 (1.5)	10 (2.2)	0.39
Chronic obstructive pulmonary disease exacerbation	20 (4.2)	13 (2.9)	0.28
Biliary tract infection	6 (1.3)	1 (0.2)	0.07
Intra-abdominal infection	18 (3.8)	21 (4.7)	0.50
Infectious diarrhea	1 (0.2)	3 (0.7)	0.29
Clostridium difficile infection	21 (4.4)	30 (6.7)	0.13
Osteoarticular infection	27 (5.7)	25 (5.6)	0.94
Urinary tract infection	67 (14.2)	73 (16.3)	0.36
Cystitis	32 (6.8)	20 (4.5)	0.13
Pyelonephritis	15 (3.2)	9 (2.0)	0.27
Urosepsis	12 (2.5)	19 (4.3)	0.15
Catheter-associated UTI	15 (3.2)	19 (4.3)	0.49
Nephrostomy-tube associated infection	3 (0.6)	5 (1.1)	0.43
Skin and soft tissue infection	45 (9.5)	37 (8.3)	0.51
Sepsis not otherwise specified	7 (1.5)	5 (1.1)	0.63
Prophylaxis	6 (1.3)	8 (1.8)	0.52

[1]Only including patients who were still receiving inpatient antibiotics on day 3