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Short report

Assessing an intervention to improve the safety of automatic stop orders for inpatient antimicrobials☆

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SUMMARY

Background: Automatic stop orders (ASOs) for antimicrobials have been recommended as a component of antimicrobial stewardship programs, but may result in unintentional treatment interruption due to failure of providers to re-order an antimicrobial medication. We examined the impact of a multifaceted intervention designed to reduce the potential harms of interrupting antimicrobial treatment due to ASOs.

Methods: An intervention was implemented that included pharmacist review of expiring antimicrobials as well as provider education to encourage use of a long-term antimicrobial order set for commonly used prophylactic antimicrobials. Pharmacist interventions and antimicrobial re-ordering was recorded. Percent of missed doses of a commonly used prophylactic antimicrobial, single strength co-trimoxazole, was compared pre- and post-intervention using a chi-squared test.

☆ **Previous Data Presentations:** Some of the results in this manuscript were previously presented as a poster abstract at the IDWeek Scientific Conference, October 2016, New Orleans, LA.

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Results: From November 1, 2015 to November 30, 2016, there were 401 individual pharmacist interventions for antimicrobial ASOs, resulting in 295 instances of antimicrobial re-ordering. The total percent of presumed missed single strength co-trimoxazole doses was reduced from 8.4% to 6.2% post-intervention ($P<0.001$).
Conclusions: This study found that a targeted intervention was associated with a reduction in unintended antimicrobial treatment interruption related to ASOs.

Introduction

Antimicrobial stewardship programs (ASPs) have been shown to reduce inappropriate antimicrobial use, rates of multi-drug resistant organisms, *Clostridioides difficile* infection, and length of hospitalization [1,2]. Automatic stop orders (ASOs) for antimicrobials have been recommended as a component of ASPs to encourage regular review of medications by providers and prevent unnecessarily prolonged courses of antimicrobials [3]. Furthermore, ASOs have been shown to lead to reduction in antimicrobial use and antimicrobial-related adverse events in several settings [4–6].

Some studies have reported that ASOs may lead to inadvertent interruption or discontinuation of antimicrobials that are still indicated [6–8]. However, the use of safeguards and monitoring for inadvertent antimicrobial discontinuation to reduce the risk of gaps in treatment have not been well studied. This study sought to examine the impact of a multifaceted intervention designed to mitigate the potential harms of interrupting or prematurely discontinuing antimicrobial treatment while still maximizing the benefits of the ASO policy.

Patients and methods

Setting and intervention

This study was conducted at three academic hospitals within the University of Pennsylvania Health System (UPHS): 1) the Hospital of the University of Pennsylvania (776 beds); 2) Penn Presbyterian Medical Center (324 beds); and 3) Pennsylvania Hospital (445 beds). During the study time period, all of these hospitals utilized an electronic health record (EHR) where medication ordering and administration data was documented. These hospitals utilized a 7-day ASO for antimicrobials since June 1, 2009, with the option to order a select group of antimicrobials (typically those used for prophylaxis) under a 90-day ASO order set. On November 1, 2015 two interventions were introduced to reduce the risk of unintended antimicrobial treatment interruptions. The interventions included: 1) provider education regarding use of a pre-existing antimicrobial order set with a 90-day ASO to be used for those antimicrobials being used for prophylaxis and/or longer-term use and 2) implementing a pharmacist-led prospective review of all antimicrobials that expired by ASO.

Prior to the intervention, although providers were able to utilize a 90-day ASO order set for select antimicrobials, including co-trimoxazole, the use of this order set was infrequent. As a part of our intervention, provider education was used to encourage use of this order set for antimicrobials commonly used for longer durations in order to reduce the risk of unintended treatment interruption. This education included email notifications to target prescribing groups and a series of educational sessions for residents and advanced practice providers.

For the prospective review of expiring antimicrobials, pharmacists evaluated all inpatient antimicrobial ASOs using Agent (University of Pennsylvania, Philadelphia, PA), a novel electronic dashboard that enabled review of ASO-expired medications. The dashboard was designed to automatically populate with antimicrobials immediately after they expired in the EHR as a result of an ASO. Expired medications were then manually chart reviewed in the EHR by ASP pharmacists to determine if discontinuation was inadvertent based on provider documentation of the antimicrobial treatment plan. All antimicrobials were reviewed for potential intervention. Upon identifying a potential inadvertent discontinuation, the pharmacist notified the covering provider to enable re-ordering if warranted. If the medication may have been inappropriately discontinued, the pharmacist also stratified and recorded whether the indication for the antimicrobial that was inadvertently discontinued was low, medium, or high risk. Low-risk indications included prophylaxis and uncomplicated cystitis; medium-risk indications included bone/joint infections, pyelonephritis/complicated cystitis, gastroenteritis, neutropenic fever without bacteraemia, and skin and soft tissue infections; and high-risk indications included sepsis, bacteraemia, endocarditis, and central nervous system infections. These categories were created by expert opinion of the ASP team based on the presumed risk to the patient if antimicrobial doses were missed, based on the severity of the infection. If pharmacists determined the medication was appropriately discontinued as assessed by chart review, then an intervention was not documented. The ASP of each study site included at least one infectious diseases pharmacist to perform the prospective review.

Outcome assessment

Pharmacist interventions that occurred following implementation of ASO review were described in all patients from November 1, 2015 through November 30, 2016. In order to examine the effect of the intervention on unintended antimicrobial treatment interruptions, an analysis of the proportion of missed doses of co-trimoxazole single-strength (SS) (80 mg trimethoprim − 400 mg sulfamethoxazole) daily was performed pre- and post-intervention. Co-trimoxazole SS daily was selected for analysis because the likelihood is low that it would be stopped intentionally at this dose, which is most often used for infection prophylaxis. Therefore, the assumption was made that the majority of missed doses would be due

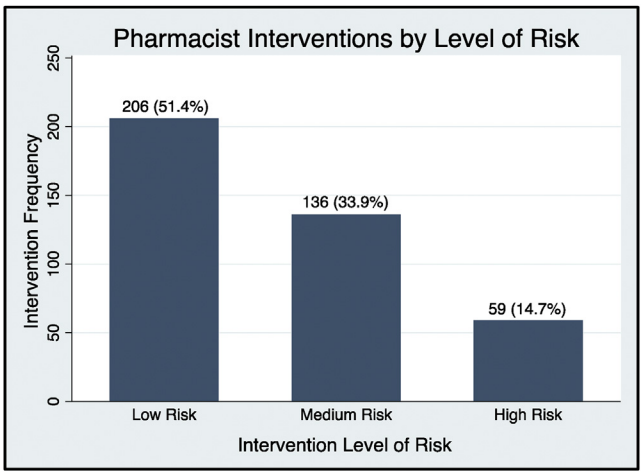

Figure 1. Pharmacist interventions for antimicrobial stop orders (ASOs) November 1, 2015—November 30, 2016 by level of risk of the infection being treated.

to an ASO with unintentional interruption. Additionally, because co-trimoxazole SS was infrequently ordered through the 90-day ASO order set prior to the intervention, assessing a change in proportion of missed doses may reflect the impact of both components of the intervention.

Missed and total administered doses of co-trimoxazole SS were identified for patients who had been hospitalized for at least 7 days to ensure that an ASO could have occurred. A missed dose was defined as no dose administered followed by resumption of the medication. The proportion of missed doses of co-trimoxazole SS was summarized for 2-week intervals pre-intervention (June 26, 2014 through September 30, 2015) and post-intervention (December 1, 2015 through November 28, 2016), excluding a 2-month period during pilot testing and introduction of the intervention (October 1, 2015 through November 30, 2015). Interrupted time series analysis was performed to assess immediate change following the implementation of the intervention and to compare pre- and post-intervention trends in missed doses.

Statistical analysis

The proportion of pre- and post-intervention missed co-trimoxazole SS doses was compared using a chi-squared test. Interrupted time series analysis was performed using the Prais-Winsten model, in order to accommodate the first-order serial correlation (autocorrelation) potentially present in the outcome. This calculation is based on a standard linear model Prais-Winsten transformed parameter estimates to adjust for the autocorrelation [9,10]. Univariate logistic regression was also used to assess the association between the intervention (exposure) and missed co-trimoxazole SS doses (binary outcome). For all calculations, a two-tailed *P*-value of 0.05 was considered statistically significant. All calculations were performed using STATA v14.2 (Stata Corp, College Station TX). This study was approved by the Institutional Review Board at the University of Pennsylvania.

Results

There were 401 pharmacist interventions for ASOs from November 1, 2015 to November 30, 2016. The number of interventions was 206 for low-risk indications (51.4%), 136 for medium-risk indications (33.9%), and 59 for high-risk indications (14.7%) (Figure 1). Within the low-risk group, 73 (35.4%) were associated with co-trimoxazole, of which 33 (15.9%) interventions were associated with co-trimoxazole SS specifically. The top five most common antimicrobials for which interventions were performed were: co-trimoxazole (all doses) (78 interventions, 19.5%), valacyclovir (42 interventions,

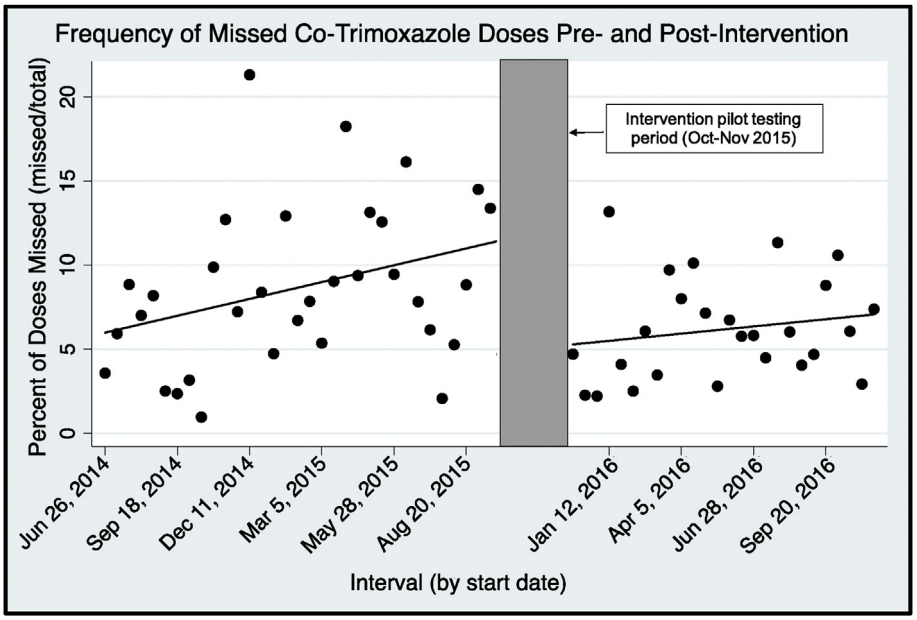

Figure 2. Interrupted time series analysis of missed doses of co-trimoxazole SS daily before and after a multifaceted intervention to reduce inadvertent missed doses due to antimicrobial stop orders (ASOs).

10.5%), fluconazole (33 interventions, 8.2%), levofloxacin (24 interventions, 6.0%), and metronidazole (23 interventions, 5.7%). Of all 401 interventions, 295 (73.6%) were associated with subsequent re-ordering of the same antimicrobial. Within the low-risk group, 140 (70.0%) were associated with antimicrobial re-ordering, followed by 103 (75.7%) and 52 (88.1%) in the medium- and high-risk groups, respectively. Each completed pharmacist intervention (resulting in provider notification) was estimated to require 5—10 minutes of time, for a total of 33.4—66.8 pharmacist hours over the course of 13 months.

In the pre-intervention period, the total percent of missed co-trimoxazole SS doses was 8.4%, compared to 6.2% in the post-intervention period ($P<0.001$). The intervention was associated with an odds ratio for missed doses of 0.71 (95% CI 0.61 to 0.82, $P<0.001$). Utilizing interrupted time series analysis, the baseline proportion of missed doses of co-trimoxazole SS was 6.0% at the beginning of the pre-intervention period, and missed doses were increasing at a rate of 0.17% per 2-week interval (95% CI, 0.004%—0.33%; $P=0.045$) (Figure 2). Immediately after implementation, there was a drop in the rate of missed co-trimoxazole SS doses by 6.2% (95% CI, -10.8% to -1.6%, $P=0.009$). This drop was followed by an increase in the rate of missed doses of 0.07% per 2-week interval (95% CI, -0.16%—0.30%, $P=0.54$). There was a non-significant 0.10% decrease in the slope of the proportion of missed doses over time from the pre-intervention to the post-intervention period (95% CI, -0.38%—0.19%, $P=0.51$).

Discussion

Though ASOs have potential benefits, they also have the potential to lead to interruption or discontinuation of indicated medications. Cleary *et al.* reported six cases in one year of inadvertent antimicrobial discontinuations due to their ASO policy, leading to prolonged length of stay for four patients and possible contribution to one patient death [8]. However, in an era of ASPs and electronic health records, ASOs may be able to be more safely implemented. This study demonstrates that, while treatment interruption does occur as a result of ASOs, interventions can reduce missed antimicrobial doses in the presence of ASOs. In particular, there was a decrease in missed doses of co-trimoxazole SS, which was likely due both to prospective pharmacist intervention as well as increased usage of an order set allowing for 90 days of continuous use prior to discontinuation.

However, our study does have several limitations. This study assumed that all gaps in co-trimoxazole SS represented unintended interruptions in treatment, likely causing an overestimate in the true proportion of unintentionally missed doses in both pre- and post-intervention groups. However, the reduction in missed doses does suggest an impact of our intervention. In addition, because our alert was triggered by the discontinuation of orders rather than actual missed doses, the number of interventions made likely overestimates the number of missed doses that would have occurred in the absence of any intervention. Furthermore, we did not evaluate the impact of the pharmacist-led intervention on missed doses of used for treatment rather than prophylaxis; future studies to examine the clinical impact of interventions on reduction in interruptions in critical treatment therapy are warranted. Additionally, by examining co-trimoxazole only, we assessed the impact of both aspects of the intervention (education regarding the 90-day ASO order set and pharmacist alerts), rather than isolating the impact of pharmacist alerts alone or examining antimicrobials used primarily for treatment rather than prophylaxis. Finally, we acknowledge that as a quasi-experimental study, the lack of randomization with a control arm precludes definitively concluding that this intervention caused the improvement in missed antimicrobial doses. While it is certainly possible that other factors also influenced this effect, there were no other concurrent interventions to improve antimicrobial ASO safety during this period.

Overall, this study demonstrated that, while ASOs alone have the potential to result in inadvertent discontinuation of antimicrobial therapy, there are effective strategies to reduce the risk that ASOs present, particularly through ASPs. Unintentional gaps in antimicrobial therapy have the potential to cause significant harm to patients, and reducing their occurrence through an intervention such as the one utilized here could significantly improve patient safety for health systems that utilize ASOs. However, is important to consider the pros and cons of the approach described in this study, given that our intervention utilized review of expiring orders, which requires dedicated pharmacist time that could potentially be devoted to other ASP tasks. Furthermore, the alert dashboard was created internally at no cost for the ASP teams, which may not be feasible elsewhere. While the overall pharmacist time for the interventions was not especially high in this academic setting and spread over the course of 13 months, it has the potential to be more burdensome in other settings. However, given that missed antimicrobial doses is a significant safety concern, the benefit may outweigh the cost. Future studies should systematically examine optimal means of utilizing ASOs while mitigating risk of harm to patients.

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Declaration of interests

S.M. is employed by Tetraphase Pharmaceuticals, Inc. All other authors report no conflicts of interest relevant to this article.

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