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Evaluation of Antimicrobial Orders Circumventing an Antimicrobial Stewardship Program: Investigating the Strategy of “Stealth Dosing”

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Abstract

Objective—Prior-approval antimicrobial stewardship programs (ASPs) improve patient outcomes and decrease antimicrobial resistance. These benefits would be limited if physicians circumvent ASP efforts. Our objectives were: 1) to determine if there is an increase in the proportion of orders for restricted (vs. non-restricted) antimicrobials in the first hour when prior-approval is not required compared with the remainder of the day, and 2) to determine if restricted antimicrobials ordered in the first hour when prior-approval is not required are less likely to be continued when the ASP resumes than antimicrobials ordered in the preceding hour.

Design—A cross-sectional study design and a retrospective cohort study design, respectively.

Setting—The study was set in a tertiary care academic medical center with a prior-approval ASP operational from 8 a.m.–10 p.m.

Participants—Inpatients with antimicrobial orders during the study period.

Results—Compared with other hours, a greater proportion of orders during 10–10:59 p.m. were for restricted agents (57.0% vs. 49.9%, $p=0.02$). Surgical patients with orders placed between 10–10:59 p.m. (vs. 9–9:59 p.m.) were less likely to have the ordered antimicrobial continued (60.0% vs. 98.1%, $p<0.001$). Non-surgical patients with orders placed between 10–10:59 p.m. (vs. 9–9:59 p.m.) were also less likely to have the ordered antimicrobial continued (70.8% vs. 84.2%, $p=0.01$).

Conclusion—Physicians avoid prior-approval by waiting until restrictions are no longer in place to order restricted antimicrobials. These antimicrobials are less often continued when the ASP

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becomes operational again, suggesting that they are more likely to be off-guideline or unnecessary.

Keywords

Antimicrobial Stewardship; Patient Safety; Communication

Background

Antimicrobial stewardship programs (ASPs) have become widespread in hospitals.^{1, 2} Many such programs include prior-approval interventions, where an antimicrobial expert approves the use of restricted antimicrobial agents before their use. Prior-approval ASPs decrease antimicrobial usage and resistance, and improve outcomes.^{2–6} In prior-approval systems, the primary care team communicates patient data to the ASP practitioner and requests specific antimicrobials or advice on therapy. The ASP practitioner approves the requested antimicrobial(s), different antimicrobial(s), or no antimicrobials.

Some have suggested that ASPs are viewed as an “inconvenience” that may “...not only waste the physician’s time... but may also generate animosity between these physicians and the individuals controlling antimicrobial utilization.”⁷ A prior study⁸ using interviews and focus groups at our institution noted that housestaff felt dealing with the prior-approval system was stressful and time-consuming (personal communication, R. Koppel, University of Pennsylvania). This may explain why some surgical housestaff participating in the study stated that they engaged in “stealth dosing,” described as waiting until after the prior-approval period ended to prescribe restricted antimicrobials.

The objectives of our study were to determine a) if there is an increase in orders for restricted (compared with unrestricted) systemic antimicrobials in the period immediately after the restriction ends each day, and then b) if restricted antimicrobials ordered in that hour are continued less often than restricted antimicrobials ordered in the preceding hour. We hypothesize that prescribers wait until after the prior-approval period to order off-guideline or unnecessary restricted antimicrobials.

Methods

Setting

The study was at the Hospital of the University of Pennsylvania, a 750-bed tertiary-care academic medical center with an ASP focusing on prior-approval. Requests for restricted antimicrobials are called to a pager carried by an ID-trained pharmacist or ID fellow. Physicians may order any restricted antimicrobial without prior-approval outside of active program hours (10 p.m.–8 a.m.). Approval must be later obtained to continue the restricted agent. Housestaff shift changes are at 6 p.m. (surgery) and 11 p.m. (medicine), and the admissions rate decreases steadily from 5 p.m. through midnight.

Cross-sectional study

Subjects—We examined patients with orders for systemic antimicrobials between 10/1/04–12/31/04. Orders for antiretrovirals and valganciclovir were excluded since their restriction status could not be defined with available data. Orders coming from the emergency department and neonatal ICU were excluded since these areas are not subject to ASP oversight. It was unnecessary for orders to have been dispensed since we were examining the prescribing behavior of clinicians, not antimicrobial receipt by patients.

Outcome—Restricted antimicrobials were defined based on hospital guidelines,⁹ and may be always restricted or restricted except for use in certain areas or by certain services.

Data collection—Data were obtained from querying the electronic pharmacy database MSMEDS (Version 5.1.0, Cerner Corporation, Kansas City, MO). Queried data included the prescribed antimicrobial name, route, and order time; the prescriber's service (surgical or non-surgical); and if the patient was in the ICU.

Statistical analysis—First, restricted and non-restricted antimicrobials were summated by one-hour intervals in the 24-hour day, and the proportion of restricted antimicrobial orders out of total orders was calculated for each hour. Next, generalized estimating equations (GEE) for binary outcomes were used to compare the rates of restricted antimicrobials ordered between 10–10:59 p.m. vs. the other 23 hours in the day.¹⁰ GEE was used to account for outcome clustering by individual prescribers¹¹ GEE was also used to perform additional bivariable analyses of the effect of other measured independent variables on the proportion of restricted antimicrobials ordered.

Stratified analyses then examined whether the prescribers' service or patient location exerted effect modification or confounding on the relationship between order time and the proportion of orders for restricted agents. The models included main effects for ordering time and the moderator variable (prescriber service or patient location) as well as an interaction term between the two variables. All analyses here and below utilized SAS (NCSS Statistical Software, Kaysville, UT).

Retrospective cohort study

Subjects—We examined the subset of all restricted antimicrobial orders (from the cross-sectional study) that met the following criteria: ordered between 9–10:59 p.m., resulted in antimicrobial dispensing, and the patient remained in the hospital for at least three days after the initial dose. Only the first order for a specific antimicrobial for each individual patient in a seven-day period was included.

Outcome—The outcome was administration of the same antimicrobial as the initial order to the same patient in the period after the initial order from 8 a.m. on day +1 (next day) to 11:59 p.m. on day +2. This subsequent administration must be based on an order that is not a one-time order. This rule avoids the inclusion of repeated one-time orders placed when prior-approval is not required.

A secondary outcome was the continuation of any antimicrobials. Thus, administration of the same antimicrobial, a new antimicrobial (e.g., recommended by the ASP the next day), or continuation of a different antimicrobial (which the patient was already receiving) would all count as continuations whether they were for restricted or non-restricted agents.

Data collection—A selection of the data collected for the cross-sectional study was examined. Medication administration was confirmed using the electronic nursing administration records in the Sunrise Clinical Manager application, version 3.5 (Eclipsys, Boca Raton, FL).

Statistical analysis—GEE was used for bivariable analyses as described above.¹⁰ We examined the difference in continuation rates of antimicrobials ordered between 10–10:59 p.m. (the first hour that the ASP program is inactive each night) and 9–9:59 p.m. (the last hour the program is active each night). GEE was also used to perform bivariable analyses

examining the effect of surgical service prescriber (vs. non-surgical) and ICU patient location (vs. non-ICU) on the outcome.

Stratified analyses then examined whether the prescribers' service or patient location exerted effect modification or confounding on the relationship between order time and the antimicrobial continuation rate. The models included main effects for ordering time and the moderator variable (prescriber service or patient location) as well as an interaction term between the two variables. Finally, the above analyses were repeated using the outcome of the continuation of any antimicrobial. The Institutional Review Board of the University of Pennsylvania approved the study.

Results

Cross-sectional study

There were 15,440 eligible orders for systemic antimicrobials, 50% for restricted agents. Visual examination of a smoothed frequency 24-hour graph of ordered antimicrobials (Figure 1) shows that the overall number of prescribed antimicrobials was lowest in the early morning with a midday peak. The ordering patterns for restricted vs. non-restricted agents appear similar, though restricted agents had a higher midday peak and 8 p.m. resurgence. Using the same data, Figure 2 shows that the proportion of ordered restricted (vs. non-restricted) agents was higher in the hour after the ASP approval requirement ended (10–10:59 p.m.) compared with the mean of other hours (57.0% vs. 49.9%, $p=0.02$). Ordering of restricted agents during all hours of the day combined was increased for non-surgical services vs. surgical services (53.7% vs. 44.3%, $p=0.02$) and ICU patients vs. non-ICU patients (70.2% vs. 46.6%, $p<0.001$). Service and patient location did not act as confounders or effect modifiers for the relationship between ordering time and the ordering of restricted agents.

Retrospective cohort study

Inclusion criteria were met by 360 antimicrobial orders. Fifty-seven percent of the orders were placed between 10–10:59 p.m.; the rest were made between 9–9:59 p.m. In bivariable analyses, antimicrobial order time of 10–10:59 p.m. was associated with a lower continuation rate. Continuation rates were not affected by the ordering physician service or whether the patient was located in an ICU (Table 1).

In stratified analyses, ordering service was found to be an effect modifier on the relationship between ordering time and continuation rate (interaction term p -value: 0.012). Patient location did not modify this primary relationship. Since the effect of time differed by ordering service, we evaluated the effect of time in separate models for each service subgroup (Table 2). In both models, the continuation rate of the ordered antimicrobial was lower in orders from 10–10:59 p.m. (vs. 9–9:59 p.m.). However, the effect of time was larger for surgical services (vs. non-surgical services).

We also evaluated the effect of independent variables on the continuation of any antimicrobial. In bivariable analyses, there was a borderline association between order time of 10–10:59 p.m. (vs. 9–9:59 p.m.) with a lower continuation ($p=0.07$). Continuation rates were unaffected by ordering service or ICU patient location (Table 1). Neither ordering service nor patient location acted as confounders or effect modifiers for the relationship between order time and continuation of any antimicrobial. A good example of a 10–10:59 p.m. order was the prescription of vancomycin, levofloxacin, and metronidazole for a patient taken earlier to surgery for an intra-cranial hemorrhage from metastatic melanoma. The patient had not received pre-operative prophylactic antimicrobials, was afebrile, no suspected infection was noted in the chart, and any cultures or chest radiographs performed

were not done that evening. The antimicrobials were changed to 24 hours of cefazolin the next day (a non-restricted agent).

Discussion

We found an increase in the proportion of antimicrobials prescribed for restricted agents in the first hour when prior-approval is no longer required. Patients with orders for restricted antimicrobials placed in the first hour when prior-approval was no longer required were less likely to continue to receive the ordered antimicrobial(s). There was also a borderline significant trend for patients with orders placed during this hour not to have continuation of any antimicrobials.

We found that ordered antimicrobials were less likely to be continued if ordered immediately after the ASP closed (10–10:59 p.m.), vs. the previous hour. We hypothesize that the difference in continuation rates of antimicrobials ordered in the 10–10:59 p.m. window (vs. 9–9:59 p.m.) represent off-target or unnecessary prescribing. In either case, it is unlikely that a subsequent “prior-approval” call would lead to approval of the agent. Alternatively, prescribers may not call for prior-approval, knowing that approval was unlikely. In one example, a patient received broad-spectrum antimicrobials when infection was not suspected and the indication for prophylactic antimicrobials was unclear. This illustrates how unnecessarily antimicrobials may be used when prior-approval is inactive.

We also found a trend toward less continuation of any antimicrobials in patients with orders for restricted antimicrobials placed immediately after cessation of prior-approval. There are instances when antimicrobials are appropriately prescribed but then halted (e.g., fever and infiltrate are later determined to be from a pulmonary embolism). However, the difference in continuation rates between the two periods may represent unnecessary antimicrobial use.

By waiting until 10 p.m., physicians can avoid the prior-approval system whether for fear of refusal, spending time on the phone, or simply to avoid a potentially stressful interaction.⁸ Studies have also shown that physicians may attempt to circumvent ASP programs to maintain a freer rein in prescribing restricted antimicrobials.¹² Further, a survey study of medical housestaff found that they might be willing to lie to colleagues, particularly if they believed they were acting in patients’ best interests.¹³

Finally, the effect of ordering time on continuation of the ordered antimicrobials was larger for surgical services than non-surgical services. We hypothesize that the effect of ordering time is due to avoidance of the prior-approval system. This would mean that surgical service prescribers were more likely to avoid the prior-approval system to order antimicrobials that were later changed or stopped. One reason may be the increased power hierarchy in surgical (vs. some non-surgical) physician groups.¹⁵ In this unproven hypothesis, junior surgery trainees may wait until after 10 p.m. to order unnecessary or off-target antimicrobials as directed by their superiors rather than question directions. Alternatively, the medical services may be more familiar with prior-approval staff and less likely to avoid these calls.

Our investigations have several potential limitations. The relationship between ordering time and proportion of orders for restricted agents or continuation of antimicrobials may be confounded by other factors. In this scenario, the other factor would need to both increase the proportion of restricted agents prescribed at 10 p.m. and (for the second aim) decrease the antimicrobial continuation rate. Since the effect of time on continuation of the ordered antimicrobial was stronger for surgery, we do not believe that the relative proximity of the end of prior-approval with the change in medical shift (11 p.m.) is an important factor. In addition, we know that hospital admissions decrease during this time period. While we cannot rule out an effect by other unmeasured factors in our study, it is unlikely that other

factors would lead to an increase in restricted agent prescribing exactly between 10 to 11 p.m.

Information bias could affect the labeling of antimicrobial orders as restricted or unrestricted. However, we used explicit hospital restriction rules. Applying these rules would be non-differential to order timing or antimicrobial were continuation. Information bias could also affect determination of antimicrobial continuation. For example, an antimicrobial may be categorized as discontinued if given less frequently than every 48 hours. Antimicrobial continuations were individually evaluated by examining the computerized physician order entry system. Any misclassification would be non-differential, biasing towards the null, and increase the validity of our positive findings.

We conclude that physicians wait until restrictions are no longer in place to order antimicrobials that are off-guideline and potentially unnecessary. While ASPs have been shown to be beneficial, our findings represent a potential limitation of these programs. Further efforts to identify and correct limitations of existing ASP approaches are needed to optimize their usefulness.

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References

1. Lawton RM, Fridkin SK, Gaynes RP, McGowan JE Jr. Practices to improve antimicrobial use at 47 US hospitals: the status of the 1997 SHEA/IDSA position paper recommendations. Society for Healthcare Epidemiology of America/Infectious Diseases Society of America. *Infect Control Hosp Epidemiol.* Apr; 2000 21(4):256–259. [PubMed: 10782587]
2. John JF Jr, Fishman NO. Programmatic role of the infectious diseases physician in controlling antimicrobial costs in the hospital. *Clin Infect Dis.* Mar; 1997 24(3):471–485. [PubMed: 9114203]
3. Gross R, Morgan AS, Kinky DE, Weiner M, Gibson GA, Fishman NO. Impact of a hospital-based antimicrobial management program on clinical and economic outcomes. *Clin Infect Dis.* Aug 1; 2001 33(3):289–295. [PubMed: 11438891]
4. White AC Jr, Atmar RL, Wilson J, Cate TR, Stager CE, Greenberg SB. Effects of requiring prior authorization for selected antimicrobials: expenditures, susceptibilities, and clinical outcomes. *Clin Infect Dis.* Aug; 1997 25(2):230–239. [PubMed: 9332517]
5. Frank MO, Batteiger BE, Sorensen SJ, et al. Decrease in expenditures and selected nosocomial infections following implementation of an antimicrobial-prescribing improvement program. *Clin Perform Qual Health Care.* Oct–Dec; 1997 5(4):180–188. [PubMed: 10176026]
6. Ruttimann S, Keck B, Hartmeier C, Maetzel A, Bucher HC. Long-term antibiotic cost savings from a comprehensive intervention program in a medical department of a university-affiliated teaching hospital. *Clin Infect Dis.* Feb 1; 2004 38(3):348–356. [PubMed: 14727204]
7. Dunagan WC, Medoff G. Formulary control of antimicrobial usage. What price freedom? *Diagn Microbiol Infect Dis.* Mar–Apr; 1993 16(3):265–274. [PubMed: 8477583]
8. Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. *Jama.* Mar 9; 2005 293(10):1197–1203. [PubMed: 15755942]

9. Guidelines for Antibiotic Therapy at the Hospital of the University of Pennsylvania: Restricted Antibiotic Manual. http://www.uphs.upenn.edu/bugdrug/antibiotic_manual/restrict.htm
10. Diggle, PJ.; Liang, KY.; Zeger, SL. Analysis of Longitudinal Data. New York: Oxford University Press Inc; 1994.
11. Localio AR, Berlin JA, Ten Have TR, Kimmel SE. Adjustments for center in multicenter studies: an overview. *Ann Intern Med.* Jul 17; 2001 135(2):112–123. [PubMed: 11453711]
12. Calfee DP, Brooks J, Zirk NM, Giannetta ET, Scheld WM, Farr BM. A pseudo-outbreak of nosocomial infections associated with the introduction of an antibiotic management programme. *J Hosp Infect.* Sep; 2003 55(1):26–32. [PubMed: 14505606]
13. Green MJ, Farber NJ, Ubel PA, et al. Lying to each other: when internal medicine residents use deception with their colleagues. *Arch Intern Med.* Aug 14–28; 2000 160(15):2317–2323. [PubMed: 10927729]
14. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest.* Feb; 1999 115(2):462–474. [PubMed: 10027448]
15. Sexton JB, Thomas EJ, Helmreich RL. Error, stress, and teamwork in medicine and aviation: cross sectional surveys. *Bmj.* Mar 18; 2000 320(7237):745–749. [PubMed: 10720356]

Figure 1. Frequency of Restricted and Unrestricted Antimicrobial Orders by Hour

Note: frequency was calculated by hour; the plot lines were smoothed to more easily compare the two ordering patterns.

Figure 2. Proportion of Orders for Restricted Antimicrobials by Hour

Table 1

Rates of continuation of the ordered antimicrobial and of any antimicrobial

	Continuation of ordered antimicrobial		Continuation of any antimicrobial	
	Mean percent of continued orders	P-value*	Mean percent of continued orders	P-value*
Time of initial order		<0.0001		0.07
9–9:59 p.m.	89.0%		98.1%	
10–10:59 p.m.	65.5%		93.2%	
Ordering service		0.61		0.39
Surgery	73.2%		96.7%	
Medicine	77.3%		94.2%	
Patient location		0.32		0.33
Intensive care unit (ICU)	80.0%		97.3%	
Non-ICU location	74.4%		94.7%	

* P-value calculated using generalized estimating equations

Table 2

Rate of Continuation of Prescribed Antimicrobial by Ordering Service and Time

Service	Time	Continuation rate	Odds ratio (95% confidence interval) *	P-value *
Surgical			0.029 (0.0037–0.23)	0.0008
	10–10:59 p.m.	60.0%		
	9–9:59 p.m.	98.1%		
Non-surgical			0.46 (0.25–0.84)	0.01
	10–10:59 p.m.	70.8%		
	9–9:59 p.m.	84.2%		

* Calculations using generalized estimating equations