Infect Dis Ther (2014) 3:349–355
DOI 10.1007/s40121-014-0040-z

BRIEF REPORT

Developing a Method for Reporting Patient Harm Due to Antimicrobial Shortages

Milena M. McLaughlin · Erik Skoglund · Zachary Pentoney · Marc H. Scheetz

To view enhanced content go to www.infectiousdiseases-open.com
Received: June 10, 2014 / Published online: September 19, 2014

ABSTRACT

Introduction: The number of drug shortages in the United States has increased in recent years. While some literature exists on factors that contribute to antimicrobial shortages, the need remains to accurately gage the level of patient harm incurred as a result of realized antimicrobial shortages. Furthermore, current methods of reporting adverse drug events are known to under-report instances of patient harm. We sought to develop an ongoing and accurate method of reporting patient harm due to antimicrobial shortages, which was convenient, anonymous, and allowed clinicians to estimate the causality due to a shortage.

Methods: We distributed a public SurveyMonkey® (SurveyMonkey, Palo Alto, CA, USA) link to gather information regarding institution (for de-duplicating purposes), patient age, sex, antimicrobial product on shortage, type of infection requiring treatment or prophylaxis, adverse event, and patient outcome.

Results: To date complete data were reported on four patients being treated for infections that included *Stenotrophomonas maltophilia* bacteremia, *Pneumocystis jirovecii* pneumonia, neonatal sepsis of unknown etiology, and cytomegalovirus colitis. Antimicrobials that were unavailable to patients included sulfamethoxazole–trimethoprim, gentamicin, and foscarnet. Two adverse events (a delay in treatment and an inability to treat with other antimicrobials due to resistance) were attributed with probable causality due to a shortage, while the remaining adverse events (death and an inability to tolerate high oral doses) were attributed to have unlikely and possible causalities due to a shortage, respectively.

Conclusion: These methods encourage reports of antimicrobial shortage harms.

Electronic supplementary material The online version of this article (doi:10.1007/s40121-014-0040-z) contains supplementary material, which is available to authorized users.

M. M. McLaughlin · E. Skoglund · Z. Pentoney · M. H. Scheetz (✉)
Midwestern University, Chicago College of Pharmacy, Downers Grove, IL, USA
e-mail: mscheetz@nmh.org

M. M. McLaughlin · M. H. Scheetz
Department of Pharmacy, Northwestern Memorial Hospital, Chicago, IL, USA

Keywords: Adverse events; Antimicrobials; Drug reporting; Drug shortages; Infectious diseases; Patient outcomes; Survey

INTRODUCTION

Drug shortages are a persistent and rapidly growing problem in the United States. The annual frequency of drug shortages increased 200% from 2006 to 2010 [1]. Furthermore, in 2012 the Food and Drug Administration (FDA) reported a record number of 251 drugs on shortage [2]. The increasing problem of drug shortages has the potential to adversely affect patient care, delay medical procedures, result in medication errors, and burden the health care system with additional costs [3–5]. Drugs on shortage may be irreplaceable life-saving therapies. When these medications are unavailable, it may lead to significant patient harm when clinicians must resort to second- or third-line agents that may have inferior or less evidence for use. This is especially true for shortages of often non-interchangeable, curative therapies such as antimicrobials and oncologic agents, which comprise the majority of shortages [1]. A 2013 survey of infectious disease physicians found that 78% ($n = 489$) of respondents had to modify their choices of antimicrobial therapy because of a drug shortage in the previous 2 years [6]. Poor patient outcomes due to a shortage were reported by 55% ($n = 345$) of responding physicians who reported having to use alternative agents which were less effective, more toxic, or more costly. The growing magnitude of drug shortages and the risk of patient harm they pose have gained much attention from the government, media, and researchers as strategies are developed to mitigate their effects.

While progress has been made on quantifying the magnitude and causes of drug shortages, a lack of data exists on the causality of shortages on patient outcomes as well as the development of a system for reporting and monitoring patient harm on a real-time basis. There remains a need for appropriate tracking of the relationship between drug shortages and patient outcomes in the long term [1, 4]. Specifically, the need remains for a system where clinicians can report specific instances of patient harm they believe to be due to a drug shortage.

Traditionally, adverse event reporting is managed through the Adverse Events Reporting System (AERS) of the FDA; however, AERS is known to under-represent actual events due to infrequent clinician reporting [7]. Furthermore, drug shortages that lead to patient harm may not be recognized as adverse events. We have suggested that a novel method for maximizing the reporting of adverse events due to drug shortages would be simple, anonymous, use standardized terminology for easy tabulation, and have a mechanism for attributing causality of the adverse event to a drug shortage [1, 4]. We focused on shortages of antimicrobial drugs as they are often non-interchangeable, curative, and represent a large portion of overall shortages, thus making them particularly sensitive to shortages that result in patient harm. We hypothesized that a novel method for reporting patient harm due to antimicrobial shortages would aid in anonymous and convenient reporting of these cases of patient harm.

METHODS

Clinicians were asked anonymously to report occurrences of patient harm related to antimicrobial drug shortages through an

online survey (SurveyMonkey®; SurveyMonkey, Palo Alto, CA, USA [8]) consisting of 11 questions (Table 1). The survey was distributed through an editorial in *Pharmacotherapy* [4], a letter in the *American Journal of Health-System Pharmacy* [1], and through the American College of Clinical Pharmacy (ACCP) Infectious Diseases Practice and Research Network (ID PRN) email listserv. Reports from the survey were tabulated from August 2012 through October 2013, and three reminder emails were sent to the ACCP ID PRN during this timeframe. This study was approved as exempt by the Midwestern University Institutional Review Board.

Respondents were surveyed regarding: institution (for de-duplication purposes), patient age (if <90 years old), sex, antimicrobial on shortage, type of infection requiring treatment or prophylaxis, adverse event, and patient outcome. Criteria for causality attribution were obtained from the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute [9]. Using these criteria, the reporter assessed the relationship between the adverse event and the antimicrobial shortage as unrelated (clearly not related), unlikely (doubtfully related), possible (may be related), or probable (likely related). The severity of the adverse event was also assessed using standardized AERS criteria, modified for the setting of infectious diseases [10]. Using these criteria, the reporter classified the severity of the adverse event according to the following terminology: death, treatment failure or development of antibiotic resistance, readmission due to treatment failure, increased length of hospital stay, patient transfer to an institution with a supply of antimicrobial, delay of active therapy, canceled care, or other. Survey responses were tabulated and descriptively analyzed as a case series.

RESULTS

Overall, there were seven de-duplicated reports of adverse events related to antimicrobial shortages. Four reports were complete and three were incomplete. The incomplete reports did not provide the level of causality due to a shortage but did report an instance of patient harm. The four complete reports were from unique institutions. All institutions were in urban settings with 500–740 beds ($n = 3$) or 100–249 beds ($n = 1$).

For the complete reports, the antimicrobials on shortage included sulfamethoxazole–trimethoprim, gentamicin, and foscarnet (Table 2). The infections for which these patients were being treated or receiving prophylaxis included *Stenotrophomonas maltophilia* bacteremia, *Pneumocystis jirovecii* pneumonia, neonatal sepsis of unknown etiology, and cytomegalovirus colitis. Final patient outcomes included death, delay of therapy, readmission, and limited access to treatment. Two adverse events (a delay in treatment and an inability to treat with other antimicrobials due to resistance) were attributed to have probable causality due to a shortage, while the remaining adverse events (death and an inability to tolerate high oral doses) were attributed to have unlikely and possible causalities due to a shortage, respectively. The antimicrobials on shortage in the incomplete reports included three cases of a shortage of sulfamethoxazole–trimethoprim. The infections for which these patients were being treated or receiving prophylaxis were *P. jirovecii* pneumonia and *Stenotrophomonas* spp.

Table 1 Survey questions

1	Please list the full name of your institution (for de-duplicating purposes)
2	How many inpatient beds does your institution currently have?
3	Which of the following best describes the location of your institution?
	Urban, Suburban, Rural
4	Was the patient's age under 90 years old? If yes, please list the patient's age
5	Sex: male or female
6	Which antimicrobial was unavailable for your patient?
7	Please list the infection for which treatment or prophylaxis was needed
8	What adverse event did your patient experience?
9	Please attribute the causality of the shortage to the adverse event that occurred in your patient
	Unrelated: the adverse event is clearly not related to the shortage
	Unlikely: the adverse event is doubtfully related to the shortage
	Possible: the adverse event may be related to the shortage
	Probable: the adverse event is likely related to the shortage
10	Please attribute a severity to the adverse event that occurred in your patient
	Death
	Disabling
	Hospitalization
	Life threatening
	Required intervention
	Other (please specify)
11	What was the final patient outcome? Please check all that apply
	Death
	Treatment failure/development of resistance
	Readmission due to treatment failure
	Increased length of hospitalization
	Patient transferred to an institution with a supply of antimicrobial
	Delay of therapy
	Suboptimal treatment
	Other (please specify)

DISCUSSION

Our study found specific instances of patient harm due to antimicrobial shortages. The methodology demonstrated in this study illustrates a successful system capable of capturing real-time instances of patient harm and attributing the causality of that harm to antimicrobial shortages. By maintaining a database where the specialists most likely to manage shortages can continuously report

Table 2 Patient vignettes of complete reports detailing adverse drug events due to antimicrobial shortages

Patient	Age (sex)	Antimicrobial on shortage	Infection being treated	ADE experienced	Causality due to shortage	Severity of ADE	Final patient outcome
1	<90 (F)	Sulfamethoxazole–trimethoprim IV	*Stenotrophomonas maltophilia* bacteremia	Death	Unlikely	Death	Death
2	45 (F)	Sulfamethoxazole-trimethoprim IV	PCP pneumonia	Nausea/vomiting/diarrhea when given high oral dose	Possible	Required intervention	Delay of therapy
3	<90 (F)	Gentamicin	Empiric neonatal sepsis	1 h delay of treatment	Probable	Required intervention	Readmission
4	25 (M)	Foscarnet	CMV colitis	Untreatable due to resistance	Probable	Other: disease still present	Other: obtained foscarnet outside the United States

ADE Adverse drug event, *CMV* cytomegalovirus, *F* female, *IV* intravenous, *M* male, *PCP Pneumocystis jirovecii* pneumonia

instances of patient harm anonymously and conveniently, we believe our methodology offers an ability to capture harmful effects of antimicrobial drug shortages on patient outcomes. Clinicians wishing to report on future harms due to antimicrobial shortages can do so at: http://www.surveymonkey.com/s/antimicrobialshortages.

The instances of patient harm reported in this study further underline the harmful effects of drug shortages reported elsewhere in the literature. These effects include utilization of less effective or more toxic alternative medications, medical errors, delays in procedures, and higher healthcare costs [3–5]. For example, two of the drugs on shortage reported in our survey are first-line agents for their respective indications (i.e., sulfamethoxazole–trimethoprim for *P. jirovecii* pneumonia prophylaxis, and foscarnet for cytomegalovirus colitis). It is worth noting that two of the three antimicrobials reported to be on shortage in our survey required clinicians to follow special instructions to obtain a supply. For example, sulfamethoxazole–trimethoprim was available through drop shipments from the manufacturer only after the need for therapy was documented to the manufacturer. Foscarnet was available from the United Kingdom via importation from a single manufacturer. As there may be significant time lags associated with obtaining such products, special measures are required to ensure ready access to the product at the time of need.

Of further note, the number of full-time equivalents allocated to shortage management has increased in many healthcare institutions; this has not seemed to curb the inability of some institutions to procure drugs on shortage [11]. One potential solution may be increased education about procuring drugs on shortage

and how best to mitigate their harmful effects, which antimicrobial stewardship programs could potentially provide [12].

This survey methodology, a quick and anonymous online survey, offers an advantageous alternative over conventional surveys which may only provide a snapshot of the incidence of patient harm and not specific patient characteristics [4]. The benefits of the FDA AERS system include that it is a publically available system for reporting adverse events and it provides a form that prompts reporters for pertinent information. However, due to issues such as prescriber disinclination to report for fear of identification and litigation, lack of time to submit reports, and lack of knowledge of the reporting structure, most adverse drug events are never reported. It has been estimated that under-reporting exists over 90% of the time [13]. Specifically in regards to the AERS system, an original study found that only 57% of prescribers were aware of AERS, likely leading to reporting rates ranging from 1% to 5% [14]. We have written about the need for standardization of assessing the impact of antimicrobial shortages on patient outcomes and suggested that the traditional method of reporting adverse events is likely under-reporting the true impact due to the time required for submissions, the complexity of the system, and the personally identifying nature of the report [1, 4]. A 2009 review of the determinants of under-reporting of adverse events found under-reporting to be influenced in part by a lack of suitable means to report the event in 75% ($n = 45$) of all studies, and that the available system was considered to be too bureaucratic or not easy enough in 25% ($n = 45$) of all studies [7]. The methodology presented here may also be useful in assessing patient harm due to shortages in other drug classes.

Limitations to our survey must be considered. Reports may have been limited as respondents may have not wished to disclose medication errors or adverse events which occurred at their institutions. Accuracy of self-reporting is an inherent liability to which all surveys, including the FDA AERS database, are subject. The results from our survey were driven by large institutions in urban settings; however, results from elsewhere in the literature clearly demonstrate that institutions of all sizes and settings are affected by shortages [6, 11]. Despite these limitations, the results of this survey provide valuable information regarding patient harm due to antimicrobial drug shortages.

CONCLUSIONS

Our study demonstrated a novel method for encouraging providers to report patient harm due to antimicrobial shortages. This method is standardized, anonymous, convenient, and capable of de-duplicating responses. This pilot study has revealed unique instances of patient harm with assessed causality attributed to antimicrobial shortages. Such studies may help gage the true impact of shortages and may help guide policies aimed at allocating appropriate resources to control and prevent patient harm caused by future shortages.

ACKNOWLEDGMENTS

No funding or sponsorship was received for this study or publication of this article. Portions of this paper were presented as a poster at the American Society of Heath-System Pharmacists Midyear Clinical Meeting, Las Vegas, NV, USA, December 2–6th, 2012. All named authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the

integrity of the work as a whole, and have given final approval to the version to be published.

Conflict of interest. Milena M. McLaughlin, Erik Skoglund, Zachary Pentoney, and Marc H. Scheetz have no conflicts of interest to disclose pertaining to the subject matter of this manuscript. This study was unfunded.

Compliance with ethics guidelines. This study was approved as exempt by the Institutional Review Board of Midwestern University.

REFERENCES

1. McLaughlin MM, Pentoney Z, Scheetz MH. Need for standardization in assessing impact of antibiotic shortages on patient outcomes. Am J Health Syst Pharm. 2012;69:2129–30.

2. United States Food and Drug Administration. Drug shortages frequently asked questions. http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050796.Htm. Accessed Sep 8, 2014.

3. Griffith MM, Gross AE, Sutton SH, et al. The impact of anti-infective drug shortages on hospitals in the united states: trends and causes. Clin Infect Dis. 2012;54:684–91.

4. Griffith MM, Pentoney Z, Scheetz MH. Antimicrobial drug shortages: a crisis amidst the epidemic and the need for antimicrobial stewardship efforts to lessen the effects. Pharmacotherapy. 2012;32:665–7.

5. McLaughlin M, Kotis D, Thomson K, et al. Effects on patient care caused by drug shortages: a survey. J Manag Care Pharm. 2013;19:783–8.

6. Gundlapalli AV, Beekmann SE, Graham DR, et al. Perspectives and concerns regarding antimicrobial agent shortages among infectious disease specialists. Diagn Microbiol Infect Dis. 2013;75:256–9.

7. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2009;32:19–31.

8. SurveyMonkey®. http://www.surveymonkey.com. Accessed 31 Oct 2013.

9. National Cancer Institute. NCI guidelines for investigators: adverse event reporting requirements for DCTD (CTEP and CIP) and DCP, INDS and IDES. http://ctep.Cancer.Gov/protocoldevelopment/electronic_applications/docs/aeguidelines.Pdf. Accessed 11 Dec 2013.

10. United States Food and Drug Administration. FDA adverse event reporting system (AERS). http://www.Fda.Gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/default.Htm. Accessed 11 Dec 2013.

11. Kaakeh R, Sweet BV, Reilly C, et al. Impact of drug shortages on U.S. Health systems. Am J Health Syst Pharm. 2011;68:1811–9.

12. Griffith MM, Patel JA, Sutton SH, et al. Prospective approach to managing antimicrobial drug shortages. Infect Control Hosp Epidemiol. 2012;33:745–52.

13. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29:385–96.

14. Goldman SA, Kennedy DL. Medwatch: FDA's medical products reporting program. Postgrad Med. 1998;103:13–6.