

Antimicrobial Agent Shortages: The New Norm for Infectious Diseases Physicians

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Background. In 2012, the US Food and Drug Administration (FDA) required drug manufacturers to give advance notice of impending drug shortages. A survey of infectious diseases (ID) physicians was undertaken to determine the impact of this requirement and to follow-up on prior perceptions of ID physicians on shortages of antimicrobial agents.

Methods. We used a web-based survey of ID physician members of the Emerging Infections Network in 2016.

Results. Of the 701 of 1597 members (44%) who responded, 70% reported the need to modify their antimicrobial choice because of a shortage in the prior 2 years. A majority (73%) reported the shortages affected patient care or outcomes by the use of broader-spectrum (75%), more costly (58%), less effective second-line (45%), or more toxic agents (37%). The most commonly reported antimicrobials in short supply were piperacillin-tazobactam, ampicillin-sulbactam, meropenem, cefotaxime, and cefepime. Respondents learned of shortages from hospital notification, from a colleague, contact from pharmacy after ordering the agent in short supply, or FDA or other website. The antimicrobial stewardship programs (ASPs) of a majority (83%) of respondents' institutions had developed approaches to deal with shortages. Although 71% indicated that communications were sufficient, most (87%) did not perceive any improvement in communications about shortages since the 2012 FDA requirement.

Conclusions. The persistence of antimicrobial agent shortages reported by ID physicians is disturbing as is the resulting need to use broader-spectrum or more toxic agents. The prominent role of ASPs in helping to deal with shortages, effective communication channels, and the lack of perceived improvement in FDA's communication strategy merit further consideration.

Keywords. antimicrobial agents; patient safety; shortages.

Since early reports of antimicrobial agent shortages [1, 2], many peer-reviewed publications have described continued shortages of a wide range of antimicrobials [3–5]. An important outcome of these early reports has been greater awareness of the problem and the potential threat to patient safety. The greater awareness of shortages in turn led to dedicated drug availability monitoring programs from the US Food and Drug Administration (FDA) [6], professional organizations such as the American Society of Health-System Pharmacists (ASHP), and academic medical centers (such as University of Utah Hospital Drug Information Service) [7]. Recent publications have moved beyond reporting shortages in an attempt to characterize patient safety and harm

and the need to be able to capture data on specific harm [8] and mitigation strategies [5].

In a previous survey, infectious diseases (ID) physicians reported modifying antimicrobial choices on a frequent basis as a result of shortages, and they also reported adverse patient outcomes as a result of using alternative or second-line antimicrobial agents [9]. These ID physicians also reported that communication regarding antimicrobial shortages needed to improve to help mitigate adverse outcomes and difficulties treating infections affected by shortages. At the time of this survey in 2011, pharmaceutical companies were not required to alert the FDA of upcoming drug shortages or to provide any explanation regarding their cause.

In 2012, the FDA required (via The Food and Drug Administration Safety and Innovation Act of 2012) all drug manufacturers to give advance notice of any impending critical drug discontinuations or production interruptions to help prevent drug shortages [10–12]. Thus, to determine the impact of this act on the practice of ID physicians and to follow up on prior perceptions regarding antimicrobial shortages, we again surveyed members of the Infectious Diseases Society of America's Emerging Infections Network (EIN). We specifically asked if and to what extent antimicrobial drug shortages continue to affect the practices of ID physicians, and whether communication about these shortages is effective.

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METHODS

An 11-question survey was sent by an e-mailed web link or by facsimile in March 2016 to all 1597 members of the Infectious Diseases Society of America's EIN. Two reminders were sent to nonresponders. The EIN is a sentinel network of ID physicians who care for adult and/or pediatric patients in North America and who volunteer to participate [13]. Members who had joined the EIN but had not yet responded to any surveys were excluded (N = 150).

The physicians were asked for their experiences regarding need to modify management of an infectious disease due to a shortage, which agents had been in short supply within the past 2 years, whether any adverse effects on patient care or outcomes had resulted, and which communication channels were used to report agents in short supply. Descriptive statistics were used to analyze survey responses.

RESULTS

A total of 701 (44%) of the 1597 active members of the EIN responded. Respondents practiced adult ID (N = 511), pediatric ID (N = 166), and both adult and pediatric ID (N = 24). Respondents worked in all 9 US Census Bureau regions (N = 691), Puerto Rico (N = 2), and Canada (N = 8). Respondents were significantly more likely than nonrespondents to have at least 15 years of ID experience ($P = .0004$), practice pediatric ID ($P = .03$), and work in US Department of Veterans Affairs (VA) or Department of Defense (DoD) hospitals ($P = .04$).

Four hundred ninety-one respondents (70%) reported a need to modify their antimicrobial choice for treating or preventing an infectious disease because of a drug shortage within the past 2 years. Of the 210 (30%) respondents who had not needed to modify an antimicrobial choice, 205 opted out of responding to the remainder of the survey questions. Respondents who were least likely to report needing to modify their antimicrobial choice because of a drug shortage were employed by the federal government (VA or DoD) or by state/local government ($P = .01$).

Sixty-nine separate antimicrobial agents were identified by respondents as being in short supply within the past 2 years. The top 5 were all injectables: piperacillin-tazobactam (reported by 298 respondents), ampicillin-sulbactam (reported by 103), meropenem (reported by 98), cefotaxime (reported by 77, 70 of whom have pediatric practices), and cefepime (reported by 63). Prominent oral medications reported in shortage included doxycycline (reported by 41) and pyrimethamine (reported by 18). We also specifically asked about shortages of vaccines, and 94 (19%) reported shortages, most often of influenza vaccine (reported by 17, 6 of whom specified the high-dose vaccine and 3 of whom specified nasal/Flumist), yellow fever vaccine (reported by 39), and typhoid vaccine (reported by 15). Thirteen shortages of vaccines were identified by respondents in this open-text field.

Three hundred fifty-eight respondents (73% of 490) reported that the shortage(s) and any resulting change in treatment had, in their opinions, affected patient care or outcomes (see Table 1). The 358 respondents could select from 11 effects that occurred because of the shortage(s) and could also indicate other options in an open-text field. Use of a broader-spectrum antimicrobial than would have been optimal was the most common answer (reported by 268, 75% of 358 respondents). Respondents could select all of the effects of shortages that applied to their practice. The most common response (reported by 57) was use of broader-spectrum agents plus use of more costly agents (which were 2 separate response options).

One hundred seventy-six respondents (36%) reported that price increases for an antimicrobial agent had resulted in their inability to prescribe that agent. In an open-text field, 157 respondents specified 28 agents that had increased in price, including the following: Daraprim/pyrimethamine (reported by 38), doxycycline (reported by 34), linezolid (reported by 16), daptomycin (reported by 8), ribavirin (reported by 7), albendazole (reported by 6), and ceftaroline (reported by 6).

Most (349, 71%) respondents said that current communications about drug shortage issues were sufficient for their practices. Respondents reported most commonly learning about shortages through hospital/system notification, eg, from pharmacy, pharmacy and therapeutics (P&T) committee, and antimicrobial stewardship programs (ASPs) (377, 76%). Other ways of finding out about shortages included the following: communication from a colleague, eg, Doctor of Medicine, PharmD (277, 56%); listserv or social media, eg, EIN, FDA MedWatch Safety Alerts, Twitter (259, 53%); websites, eg, FDA Drug

Table 1. Adverse Effects That Occurred Because of Shortages as Reported by 358 Survey Respondents^a

Concern Expressed by Survey Respondents	N (%)
Use of broader-spectrum antimicrobials than would have been optimal	268 (75%)
Use of more costly agents	209 (58%)
Use of second-line/less-effective therapy	161 (45%)
Use of more toxic antimicrobials than would have been optimal	132 (37%)
Delayed treatment	54 (15%)
Longer hospitalization	43 (12%)
Slower clinical response	37 (10%)
Use of compounded agents	22 (6%)
Long-term morbidity from inadequate treatment of infection	16 (4%)
Transfer patients to other facilities	10 (3%)
Patient contracted disease that agent in short supply should have prevented	8 (2%)
Other ^b	12 (3%)

^aInstructions were to select all that apply; thus, numbers add to more than 100%.

^bIn open-text field, "other" adverse events listed were as follows: "two drugs instead of one (cefepime/Flagyl)" (by 3 respondents); "actually, has facilitated "time-outs" that we prefer, limiting use of broad-spectrum abx agents; except doxycycline which required alternate agents determined but not necessarily less effective; pyrimethamine COULD affect us but has not to date"; "C diff" (by 1); "changing surgical abx prophylaxis regimen" (by 1); "use of less tested agent in children" (by 1); "readmission to hospital when outpatient/long-term care facility could not provide drug" (by 1).

Shortages or ASHP (115, 23%); or a mobile app, eg, FDA Drug Shortages, RxShortages (26, 5%).

A large majority of respondents (508, 83%) reported that their institution had developed guidelines for prioritizing use of agents in short supply or restrictions on who can get these agents, with an additional 36 (7%) responding “not sure” to this question. Sixty-two percent (N = 307) reported that their institution switches to nonformulary agents when the formulary agent is in short supply, whereas 384 (78%) reported that their institution sought supplies from other hospitals to provide agents in short supply.

Finally, respondents were asked if they had perceived any improvements in FDA’s communication/notification about drug shortages since January 2013. Only 64 (13%) answered yes, whereas 216 (44%) said no and 214 (43%) were not sure. A majority of respondents (298, 60%) thought that shortages for their practices had become more frequent during that time period, whereas 36 (7%) thought shortages were less frequent, 116 (24%) thought there was no change, and 44 (9%) were not sure.

We compared agents that were reported to be in short supply in surveys from 1999 [2] and 2011 [9] to the current survey. Although the rank of individual agents has changed, many commonly used agents continue to be reported over this 17-year period (Table 2), including several antipseudomonal agents (both β -lactamase/ β -lactamase inhibitor combinations, carbapenems), aminoglycosides, and commonly used cephalosporins.

DISCUSSION

Antimicrobial agent shortages have become the norm in the practice of adult and pediatric ID physicians who practice in both private and academic healthcare settings around the United States. Of concern, significantly more physicians reported adverse patient outcomes related to shortages in 2016

compared with a similar survey of the same network in 2011. Respondents frequently reported using broader-spectrum or more expensive antimicrobial agents because of shortages. Our results also show that ASPs frequently assist with the management of shortages. Finally, although fewer physicians learned of shortages after trying to prescribe an affected drug, 87% did not perceive any improvement in the FDA’s communications about shortages since 2011, and 60% believed that shortages for their practices had become more frequent.

At a time when life-threatening infections with susceptible and multidrug-resistant pathogens are increasing and the pipeline of new antimicrobial agents is limited [14], there are critical shortages of existing broad-spectrum and specifically antipseudomonal agents, often with dramatic consequences to patients [3]. Despite the Food and Drug Administration Safety and Innovation Act of 2012 [11], our results clearly show that ID physicians continue to struggle with management issues related to antimicrobial agent shortages. In fact, we found that 70% of respondents reported experiencing a drug shortage within the past 2 years compared with 78% in 2011. The perception by respondents is matched by objective data on shortages as reported by prior publications [4] and tracked by the ASHP on their website [7].

The persistence of shortages, the perception that shortages had become more frequent in the time frame studied, the need to use alternative and second-line agents that were either less effective, more costly, more toxic, or broader spectrum, and the resulting concern for patient harm have been a consistent refrain among ID physicians over the past 17 years [2, 9]. The change in the actual agents in shortage over the years may reflect trends in the indications and use of these agents over time. In addition to antibacterial and antiviral agent shortages in the United States, there are also reports of shortages of anti-mycobacterial agents for management of patients in the United States [15–18].

Table 2. Comparison of Antimicrobial Agents, Vaccines, and Immune Globulin Reported to Be in Shortage in Three Surveys of Infectious Diseases Physicians in 1999 and 2011 With Those Reported in 2016 (in Decreasing Order of Frequency)^a

Shortages Reported in 1999 [2]	Shortages Reported in 2011 [9]	Shortages Reported in 2016 (Current Study)
Penicillin G	Trimethoprim/sulfamethoxazole	Piperacillin-tazobactam
Meropenem	Amikacin	Ampicillin-sulbactam
Ticarcillin-clavulanate	Foscarnet	Meropenem
Cefazolin	Aztreonam	Cefotaxime
Gentamicin	Cefotetan	Doxycycline (tablets or capsules)
Nafcillin-oxacillin	Posaconazole	Imipenem
	Penicillin G	Acyclovir
	Erythromycin	Amikacin
	Acyclovir (tablets or capsules)	Pyrimethamine
	Oseltamivir (oral suspension)	Inactivated influenza vaccine
	Yellow fever vaccine	Yellow fever vaccine
	Intravenous immune globulin	Typhoid vaccine
	Inactivated influenza vaccine	

^aAll antimicrobial agents are injections unless otherwise noted.

Our reports of shortages in the United States are similar to antimicrobial shortages reported in other developed countries [19, 20].

Differences from the last 2 ID physician surveys [2, 9] include the perception of improved communication about shortages and the development of guidelines to address shortages. Although a majority did not perceive any difference in official communication from the FDA regarding shortages, it is encouraging to note that ID physicians indicated that specific communication with regard to shortages where they practiced was sufficient. Over 75% indicated that they received communications from their pharmacy, P&T committee, and/or ASPs. Personal communications from colleagues and other channels such as social media likely reflect the changing demographic of the ID physicians and mode of professional and personal communication over the years.

An important development since the last survey of ID physicians seems to be the increasing role of ASPs in communicating information on shortages to providers and also, possibly, assisting with guidance on how to manage patients when a specific agent is unavailable. The role of ASPs in this area is likely an extension of the communication channels that are already in place between ASPs and providers at their institutions. When a shortage was noted, ASPs were in an ideal position to first communicate and then advise on alternative therapies in the setting of the shortage and the conditions being managed. Although stewardship programs seem to have helped ID physicians learn about shortages and deal with the consequences of shortages, the frequent occurrence of shortages and even the threat of shortages undoubtedly place additional burdens on ASPs.

New approaches for dealing with shortages are clearly needed. Our results suggest that physicians may be learning about the presence or absence of shortages sooner. However, these shortages remain disruptive. Although the 2012 FDA act requires manufacturers to report potential shortages, what is needed is the dissemination of information regarding the clinical impact, especially because many of the agents in shortage are reserved for complex hospital-associated infections due to multidrug-resistant organisms. Furthermore, many of these shortages depend on current supplies, usage patterns, and may be regional. In fact, the announcement of a shortage may exacerbate a shortage if, for example, hospital pharmacies place larger orders in anticipation. Thus, new ways to aggregate information, about not only shortages but also the extent of the shortages and impact on practices, could help coordinate responses. Given the increased role that antimicrobial stewardship teams are playing, networks of stewardship teams could work together to aggregate information about shortages and, more importantly, ways to deal with these shortages.

We acknowledge several limitations associated with this investigation. First, there is a potential for bias in our sample. The EIN is not a random sample of ID physicians, and the

experience of members may not reflect the experiences of non-members. In addition, ID physicians who had directly experienced a shortage may have been more likely to respond to our query. Second, our results are based on self-report, and we do not have a mechanism for independently validating responses of ID physicians via chart review or pharmacy interviews and audits. Finally, this query was not designed to determine the reasons that shortages exist. Thus, our results do not provide any insight into why these shortages exist or why they seem to affect different types of ID practices in a nonuniform fashion. A recent US government report suggests that shortages may be triggered by supply disruptions [21]. In analyzing shortages of sterile, injectable, anti-infective and cardiovascular drugs during the years 2012–2014, they found that (1) a decline in the number of suppliers and (2) the failure of at least one establishment to make a drug that complied with manufacturing standards—resulting in a warning letter—were strongly associated with the shortages.

CONCLUSIONS

In conclusion, ID physicians are learning about antimicrobial agent shortages earlier, but shortages are still occurring and frequently result in the use of second-line or more broad-spectrum agents than necessary. Accordingly, further work is needed to increase awareness of potential consequences of drug shortages and to implement communication strategies to meet the needs of prescribing physicians. In addition, robust data are needed to determine potential adverse outcomes related to substitution of antimicrobials and why some practices are affected more than others. However, with shortages of antimicrobial agents becoming the norm in ID practice in the United States, it may be time to move beyond reporting the shortages to mitigation strategies such as national consensus guidelines on use of second-line agents in the event of shortage of the first-line agents and a greater role for ASPs in managing stocks of available agents.

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