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Perspectives and Concerns Regarding Antimicrobial Agent Shortages Among Infectious Disease Specialists

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Abstract

Antimicrobial shortages have made treating certain infections more difficult. A webbased survey asking about experience with antimicrobial drug shortages was distributed in 2011 to 1328 infectious diseases physician members of the Emerging Infectious Diseases Network of the Infectious Diseases Society of America. A majority (78%) of 627 respondents reported needing to modify antimicrobial choices because of drug shortages within the past 2 years. Antimicrobials most often reported as not available or available but in short supply were: trimethoprim-sulfamethoxazole injection (by 65% of respondents), amikacin (by 58%), aztreonam (by 31%), and foscarnet (by 22%). Most respondents (55%) reporting a shortage indicated that the shortage adversely affected patient outcomes and that they were forced to use alternative and second line agents which were either less effective, more toxic or more costly. Most (70%) indicated that they learned about the shortage from contact with the pharmacy after trying to prescribe a drug in short supply. More effective means of informing physicians about drug shortages is critical to lessen the impact on patient care.

Introduction

The shortage of prescription medications has the potential to cause significant morbidity and mortality (Jensen and Rappaport, 2010, Steinbrook, 2009). Shortages of antimicrobial agents are of particular concern and have been characterized as a public health emergency (Griffith et al, 2012a) due to the need to start these agents promptly and also because rising

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antimicrobial resistance rates limit therapeutic options for an increasing number of pathogens (Pulcini et al, 2012). Furthermore, for lack of financial and other incentives, there is a shortage of new antimicrobial agents in the pharmaceutical industry pipeline (Freire-Moran et al, 2011, Spellberg et al, 2011).

Shortages of antimicrobials are reported by the Food and Drug Administration (FDA) (US Food and Drug Administration, 2012) and professional organizations such as the American Society of Health System Pharmacists (ASHP) (American Society of Health-Systems Pharmacists, 2012). Although the direct impact of shortages is not easy to measure, the effects on individual patients and public health are considered significant (Hampton, 2007, Harbarth et al, 2003, Pluss-Suard et al, 2012, Steinbrook, 2009). Recent surveys of pharmacists have documented shortages of medications including antimicrobial agents in the US (American Society of Health-Systems Pharmacists, 2011), Canada (Canadian Pharmacists Association, 2010) and Europe (The ESCMID Study Group for Antibiotic Policies ESGAP, 2007). Recently, an analysis and review of recent anti-infective drug shortages from the web site of the AHSP addressed a list of shortages, reasons and time periods (Griffith et al, 2012a). A survey directed exclusively at infectious diseases (ID) physicians was performed a decade ago (Sparling, 2001, Strausbaugh et al, 2001). To capture recent experiences and perspectives of practicing ID physicians on antimicrobial agent shortages, we report results of a 2011 web-based survey that was sent to all registered members of the Infectious Diseases Society of America.

Materials and Methods

A nine-question survey web link was sent by email in May 2011 to all 1328 physician members of the Infectious Diseases Society of America's Emerging Infections Network (IDSA EIN) from the U.S and Puerto Rico. Two reminders were sent to non-responders in the monthlong open period. The EIN is a sentinel network of ID physicians who regularly engage in clinical activity and who volunteer to participate. The network has been funded by the Centers for Disease Control and Prevention (CDC) since 1995 and has been known to be in the forefront of important clinical ID issues (Infectious Diseases Society of America, 2011).

The physicians were asked for their experiences regarding need for modifying management of an infectious disease due to a shortage, availability of antimicrobial agents in their practices within the past 2 years, whether they had encountered any adverse events as a result of shortages, and how they learned of the shortage. Descriptive statistics were used to analyze survey responses.

Results

A total of 627 (47%) of the 1328 active members of the EIN responded. The respondents were from all U.S. Bureau of Census divisions and Puerto Rico. Nearly equal proportions of respondents declared their primary place of practice to be either hospital or clinic, private or group practice, university or medical school, and the US Department of Veterans Affairs facilities (VA) or the military.

Seventy eight percent of the respondents indicated a need to modify their antimicrobial choice for treating or preventing an infectious disease because of a drug shortage within the past 2 years. Physicians in the East North Central U.S. Bureau of Census division reported the highest rate (83%) of shortages and the New England region, the lowest (62%, p= 0.2771). Reported shortages also varied by the type of hospital: ID physicians working in non-university teaching hospitals (82%) and community hospitals (80%) reported shortages significantly more often than those working in the VA or the military (70%, p=0.046). Reported shortages did not vary by hospital size.

Of the medications that were either not available or available but in short supply in the past 2 years, the top 5 were all injectables: trimethoprim/sulfamethoxazole (TMP/SMX), amikacin, aztreonam, foscarnet sodium, and intravenous immune globulin (IVIG) (Table 1). Prominent oral medications reported in shortage included oseltamivir oral suspension and acyclovir tablets. Live zoster vaccine, yellow fever vaccine, and inactivated influenza vaccine were also reported to be in short supply.

Of the 490 respondents who reported a shortage, 253 (52%) expressed an opinion that the resulting change in treatment due to the shortage had adversely affected patient care or outcomes. Of the 253 respondents who reported adverse effects, the most common concerns were use of more toxic antimicrobials (62%), more expensive agents (41%), broader-spectrum antimicrobials (38%), long-term morbidity from inadequate treatment of infection (28%) and longer hospitalizations (26%). Use of suboptimal, less-effective or more toxic therapy was the most commonly mentioned additional adverse outcome in an open-text field (7%). Specific examples included use of oral TMP/SMX or pentamidine for *Pneumocystis jiroveci* pneumonia instead of intravenous TMP/SMX, and increased use of colistin for multidrug-resistant Gramnegative bacilli in place of amikacin. Physicians also reported 5 deaths attributed directly to antimicrobial agent shortages. No further information regarding these deaths was provided by the respondents.

A majority of the respondents (70%) indicated that they had learned of the shortage from their pharmacy only after prescribing the drug in short supply. Other common modes of learning about the shortage were from a colleague (59%), and from the FDA or ASHP websites (24%). A majority (70%) indicated that they had never visited the FDA shortages website. Fifty four percent indicated that they were not notified once the shortage was resolved. Suggestions to improve overall communication about drug shortages focused on messages from federal agencies, professional associations such as the IDSA, from pharmaceutical companies, and from the respondents' own institutions and pharmacies. The preferred mode of communication was electronic.

The 137 respondents who did not report experiencing an antimicrobial drug shortage within the past two years were from all 9 U.S. Bureau of Census regions and represented all levels of infectious diseases experience from fellows-in-training to those in practice for more than 25 years. Respondents whose primary employment was with state or local government were somewhat more likely to report not experiencing a shortage (by 55%, p= 0.3212) as compared to military physicians (50%), federal government employees (33%), university or medical school faculty (25%), hospital/clinic-based physicians (19%) and those in private or

group practice (15%). This may reflect less time in providing direct patient care in those settings.

Discussion

We found that 78% of ID physician respondents had experienced an antimicrobial drug shortage within the past 2 years. The agents most often reported as not available or available but in short supply were: trimethoprim-sulfamethoxazole injection, amikacin, aztreonam and foscarnet. Thus, our results indicate that antimicrobial agent shortages are commonly noted in the US. Furthermore, almost half of respondents indicated that, in their opinion, the shortage adversely affected patient care most often by exposing patients to less effective, more toxic or costly medications. Disturbingly, most respondents learned about the shortage from their pharmacy when trying to prescribe that agent for a patient. These reports often came several hours after the prescription had been written, leading to delays in treatment even when an alternative agent was procured.

In the decade since the last EIN survey of ID physicians on the topic of antimicrobial shortages, much has remained the same: shortages continue to occur with only the specific agents changing (Strausbaugh et al., 2001). In 1999 and 2000, the top 5 agents noted to be in short supply were a different group of injectables: penicillin G, meropenem, ticarcillin +/− clavulanate, cephazolin and gentamicin. Similar percentages of respondents in both surveys reported a need to modify treatment regimens due to antimicrobial agent shortage(s) with similar categories of adverse outcomes including greater toxicity, greater expense, wider spectrum of alternative agent, and inadequate treatment of infection. One key difference is that current shortages appear to be no longer “unexpected” (Sparling, 2001). Another difference is that shortages are no longer limited to antimicrobials. In 2011, ID physicians expressed concern about the shortage of IVIG and several vaccines.

Our results suggest several approaches to help minimize problems arising from future shortages. First, more effective ways are needed to alert physicians to an impending or actual shortage. Notifications regarding these shortages need to be readily available without creating information overload for busy clinicians. Second, more information is needed about alternative agents when first-line agents are not available and the alternative agents are considered a ‘distant second’. This information needs to be easily accessible so that busy clinicians are not required to perform literature searches at the point of care after notification regarding a shortage from a pharmacy. Data from clinical trials would be ideal but even aggregating existing relevant experiential data from small and large healthcare systems in the form of guidelines would be helpful. Antimicrobial stewardship programs, with support from professional associations, can play a role collecting and disseminating information and improving messaging to other providers.(Griffith et al, 2012b, Griffith et al, 2012c). Finally, shortages are often localized and are reported by institutions in one area but not in others for unknown reasons. Thus, different approaches will be needed in different settings.

Limitations to this survey are the self-reported nature of the results. The nature and extent of adverse events, the frequency and experience with the use of second-line agents, effects on special populations such as immune-compromised patients and reports of deaths among

patients attributed to antimicrobial agent shortages merit further investigation. Since most prescribers find out about shortages when actually prescribing an antimicrobial agent, those respondents who prescribe some agents less commonly, such as foscarnet or amikacin, might not be aware of existing shortages. Also, members who had experienced a shortage may have been more likely to respond, thus introducing response bias.

This survey was not designed to elucidate reasons for the shortages. In general, shortages of medications occur due to a combination of factors along the supply chain; most often cited reasons include bulk and raw material availability, manufacturing and quality problems, delays and discontinuations, voluntary recalls, economics of manufacturing, shifts in clinical practice and unexpected increase in demand(American Society of Health-Systems Pharmacists, 2012, Griffith et al, 2012b, US Food and Drug Administration, 2012). The reasons leading to shortages of IVIG and vaccines may be different to those associated with antimicrobials. Hospitals and pharmacies manage shortages in different ways(American Society of Health-Systems Pharmacists, 2012, Kaakeh et al, 2011). Management usually occurs in three phases: identification and assessment phase, preparation and contingency. Strategies include conducting a shortage analysis to assess impact, stewardship of existing supplies and arranging collaborations with other local healthcare systems for sharing existing supplies. At the government level, the FDA is active in pursuing both prevention and response strategies (US Food and Drug Administration, 2011). These include working with manufacturers to review practices, exercising regulatory discretion and asking other manufacturers to increase production.

The majority of ID physicians reported shortages of antimicrobial and biologic agents. The Institute for Healthcare Improvement has labeled the shortage “a crisis that has real consequences” (Institutes for Healthcare Improvement, 2011). The U.S. Government Accountability Office (GAO) has recently conducted a study to better understand drug shortages and to identify the steps the FDA could take to better identify and resolve drug shortages (http://www.gao.gov/products/GAO-12-315T). The GAO report reinforced widely held views that drug shortages were increasing and that the FDA was constrained by its lack of authority to require manufacturers to report potential or current shortages. The report did conclude that the FDA was able to prevent the majority of shortages if they had advance knowledge of those shortages.

In our opinion, mechanisms for addressing shortages in other fields, e.g., organ sharing programs for scarce organs, could potentially inform efforts to alleviate effects of antimicrobial shortages. Intense lobbying efforts by various professional organizations combined with an increased awareness of shortages has led to the enactment of a new law that requires pharmaceutical manufacturers to inform the FDA of temporary and permanent shortages and also provides incentives for developing new antibiotics. (One Hundred Twelfth Congress of the United States Of America, 2012) Given the limited number of new antimicrobial agents in the pharmaceutical industry pipeline (Freire-Moran et al, 2011, Spellberg et al, 2011) and the likelihood that shortages will continue to occur, better and up-to-date ways must be found to address this longstanding unmet need. In understanding and addressing shortages, our goals must be to better understand the human aspect of the

shortage in terms of adverse events and how this affects the care, outcomes and quality of life of our patients.

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Table 1

Antimicrobial agents, biologicals and vaccines and reported to be in short supply by infectious disease physicians, May 2011 (N=number of ID physicians reporting a shortage, %=percent of 627 respondents)

	Not available N (%)	**Available but short supply N (%)**
TMP/SMX injection	198 (32)	209 (33)
Amikacin injection	120 (19)	242 (39)
Foscarnet sodium injection	66 (11)	72 (11)
Aztreonam injection	54 (9)	143 (23)
Cefotetan injection	50 (8)	34 (5)
Zoster vaccine live	39 (6)	64 (10)
Posaconazole	25 (4)	61 (10)
Penicillin G (aqueous or benzathine)	24 (4)	86 (14)
Erythromycin lactobionate injection	25 (4)	24 (4)
Acyclovir tablets and capsules	22 (4)	54 (9)
Oseltamivir oral suspension	19 (3)	77 (12)
Yellow fever vaccine	13 (2)	65 (10)
Intravenous Immune Globulin IVIG (Human)	12 (2)	105 (17)
Inactivated influenza vaccine	10 (2)	60 (10)
	Not available N (%)	**Available but short supply** N (%)
TMP/SMX injection	198 (31)	210 (33)
Amikacin injection	120 (19)	242 (38)
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Yellow fever vaccine	13 (2)	65 (10)
Intravenous Immune Globulin IVIG (Human)	12 (2)	105 (16)
Inactivated influenza vaccine	10 (2)	60 (9)

Other shortages reported by at least one physician (typed into ‘Other’ field): **Anti-bacterial agents**: amoxicillin/clavulanate, ampicillin-sulbactam, azithromycin, capreomycin, cefazolin, ceftazidime, chloramphenicol, ciprofloxacin oral, clarithromycin tabs, clindamycin injection, clofazimine, dapsone, doxycycline (IV or not specified), erythromycin ophthalmic ointment, gentamicin (including preservative free), isoniazid intravenous, kanamycin, meropenem, metronidazole injection, metronidazole oral, nafcillin injectable, piperacillin injection, piperacillin-tazobactam injection, pyrimethamine, quinupristin-dalfopristin, rifampin injection, streptomycin, ticarcillin/clavulanate; **Anti-viral agents**: acyclovir injection, ganciclovir capsules; **Anti-parasitic agents, anti-fungal agents, immune globulins, vaccines and others**: albendazole, amphotericin – liposomal, ethanol for central venous catheter locks, Hemophilus influenza B vaccine, Itraconazole, Japanese encephalitis virus vaccine, measles/rubella vaccine, rabies immune globulin, rabies vaccine, Varicella zoster immune globulin