

The Impact of Anti-infective Drug Shortages on Hospitals in the United States: Trends and Causes

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(See the Editorial Commentary by Leviton, on pages 692–3.)

Anti-infective shortages pose significant logistical and clinical challenges to hospitals and may be considered a public health emergency. Anti-infectives often represent irreplaceable life-saving treatments. Furthermore, few new agents are available to treat increasingly prevalent multidrug-resistant pathogens. Frequent anti-infective shortages have substantially altered patient care and may lead to inferior patient outcomes. Because many of the shortages stem from problems with manufacturing and distribution, federal legislation has been introduced but not yet enacted to provide oversight for the adequate supply of critical medications. At the local level, hospitals should develop strategies to anticipate the impact and extent of shortages, to identify therapeutic alternatives, and to mitigate potential adverse outcomes. Here we describe the scope of recent anti-infective shortages in the United States and explore the reasons for inadequate drug supply.

A 45-year-old man with a medical history significant for human immunodeficiency virus (HIV)/AIDS was admitted to the medical intensive care unit with acute respiratory failure requiring intubation, after 4 days of shortness of breath, fever, and productive cough. Empiric therapy for community-acquired pneumonia and *Pneumocystis jiroveci* pneumonia was started. Because of the national shortage of intravenous sulfamethoxazole-trimethoprim, the local pharmacy stock was depleted, so the patient began treatment with the oral formulation. When his condition failed to improve, the Antimicrobial Stewardship Program contacted the manufacturer, and, 72 hours after initiation of therapy, an emergency

supply of intravenous sulfamethoxazole-trimethoprim was obtained through a compassionate use program.

Anti-infectives frequently represent irreplaceable life-saving treatments, particularly for hospitalized patients. Access to these medications is jeopardized by the increasing frequency of drug shortages. Anti-infectives represent 13% of the 193 currently unavailable medications as of February 2011 [1]. Compounding this issue is the dramatic reduction in the approval of new anti-infective agents by the United States Food and Drug Administration (FDA) [2, 3]. Meanwhile, anti-infective resistance escalates. These factors have converged to create a public health emergency.

The Center for Drug Evaluation and Research (CDER) Drug Shortage Program of the FDA defines a drug shortage as “a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the user level” [4]. Anti-infectives present significant challenges in the realm of drug shortages. First, lack of drug availability will delay treatment or require the use of nonpreferred therapies

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potentially resulting in worse patient outcomes [5–8]. Second, in a growing proportion of infected patients in acute care hospitals, a single anti-infective agent may represent an irreplaceable therapeutic option [9]. Thus, a tenuous supply of anti-infective agents may result in delays of effective therapy, suboptimal therapeutic selections, and incorrect substitutions [10]. Here we describe the scope and impact of recent anti-infective shortages in the United States and explore the multiple reasons for inadequate drug supply.

SCOPE AND IMPACT OF ANTI-INFECTIVE SHORTAGES

Clinical challenges with drug shortages as illustrated in the former case are unfortunately becoming all too common. According to a survey conducted in 1999 by the Infectious Diseases Society of America Emerging Infections Network, ~82% of respondents reported a need to alter therapy due to a shortage of an anti-infective agent. This survey also identified common disease states for which the therapy alterations occurred, including sepsis, endocarditis, meningitis, and neurosyphilis [11]. In the years that have followed this survey, the difficulties that shortages present remain disturbingly persistent. Drug shortages also have a large economic burden. A 2011 survey conducted by Kaakeh et al found that the labor costs associated with drug shortages in the United States were estimated at \$216 million annually [12].

Not only have anti-infective shortages continued to occur with increasing frequency, new anti-infective approvals from the FDA have slowed [2, 3]. To evaluate trends in anti-infective shortages, we performed analysis using available data. Shortages were categorized as either resolved or current and were compiled from national databases (Figure 1) [1, 13]. Each drug formulation was included once from 2005 to 2010, with current shortages receiving priority and resolved shortages classified according to the first year of shortage. If resolution occurred during the time period, the shortage of the drug was classified as resolved. Topical and systemic anti-infectives including antibacterials, antifungals, and antivirals were reviewed. Vaccines were excluded from the analysis because they represent preventative agents rather than direct treatment. New molecular anti-infective entities were determined by searching the FDA drug approvals Web site for new approvals from January 2005 through December 2010 [2]. One limitation of this analysis is that recent shortages were less likely to be resolved when the data were collected. Despite this, shortages increased linearly with 19 anti-infective drugs remaining in outstanding shortage at the time of data collection [1].

The impact of these shortages is probably realized in delays to effective therapy, suboptimal therapeutic selections, and incorrect substitutions. Clearly, both suboptimal therapy and

delay of active anti-infective therapy can lead to worse patient outcomes [5–8, 14].

The potential for anti-infective shortages to lead to suboptimal therapy exists in the setting of multiple therapeutic options, particularly when medical evidence clearly defines a hierarchy of treatment alternatives. This was realized in the treatment of neurosyphilis from 1999 to 2000, during which intravenous penicillin G was voluntarily recalled owing to regulatory concerns from the FDA [15]. Intravenous penicillin G is well established as the drug of choice for neurosyphilis [16]; during the shortage practitioners were forced to use alternative agents that lacked robust efficacy data, such as ceftriaxone [17, 18]. Acyclovir has been recommended as first-line treatment for herpes encephalitis since 1986, when a morbidity and mortality benefit over vidarabine was shown in a randomized trial [19]. During the most recent shortage of the intravenous formulation [13], clinicians may have been forced to use an alternative agent. Sulfamethoxazole-trimethoprim has been the first-line treatment for *P. jiroveci* pneumonia since the 1980s, when a survival benefit over pentamidine was shown in a prospective trial [20, 21]. The current shortage of the intravenous formulation [22] may result in adverse outcomes for patients with severe disease. Two very recent anti-infective shortages include isoniazid [4] and streptomycin [22]. Isoniazid has shown efficacy in placebo-controlled [23] and comparative antitubercular trials against *Mycobacterium tuberculosis* and has been a mainstay of treatment since the 1960s [24]. Owing to the anecdotal nature of second-line therapies, streptomycin has been a keystone in the treatment of gentamicin-resistant enterococcal infections [25, 26]. Given the potential for worse outcomes with second-line therapies, further research regarding the clinical impact of drug shortages on patient outcomes should be conducted.

In the event of a drug shortage, an ineffective alternate agent may be chosen if clinicians with the appropriate expertise are not involved in deciding on the best substitute. Alternatively, time to active therapy may be delayed if therapy is not readily available. Although to date there are limited data regarding patient outcomes specifically in the setting of shortages, the literature does provide insight into the impact of inactive and delayed active therapy in general. Increased mortality has been seen after delays in appropriate anti-infective therapy for patients with bacterial sepsis [27], bloodstream infections [6, 7, 28–30], nosocomial pneumonia [9], ventilator-associated pneumonia [31], and community-acquired pneumonia [32].

Thus, timely and appropriate anti-infective therapy has been demonstrated to be critical for multiple disease states. Complicating the problem is the fact that very few antimicrobial options exist in many cases due to increasing drug resistance. Multiple bacterial pathogens have now earned the status of multidrug resistant (MDR), extremely drug resistant (XDR), or pandrug-resistant (PDR) [9]. Hence, multidrug

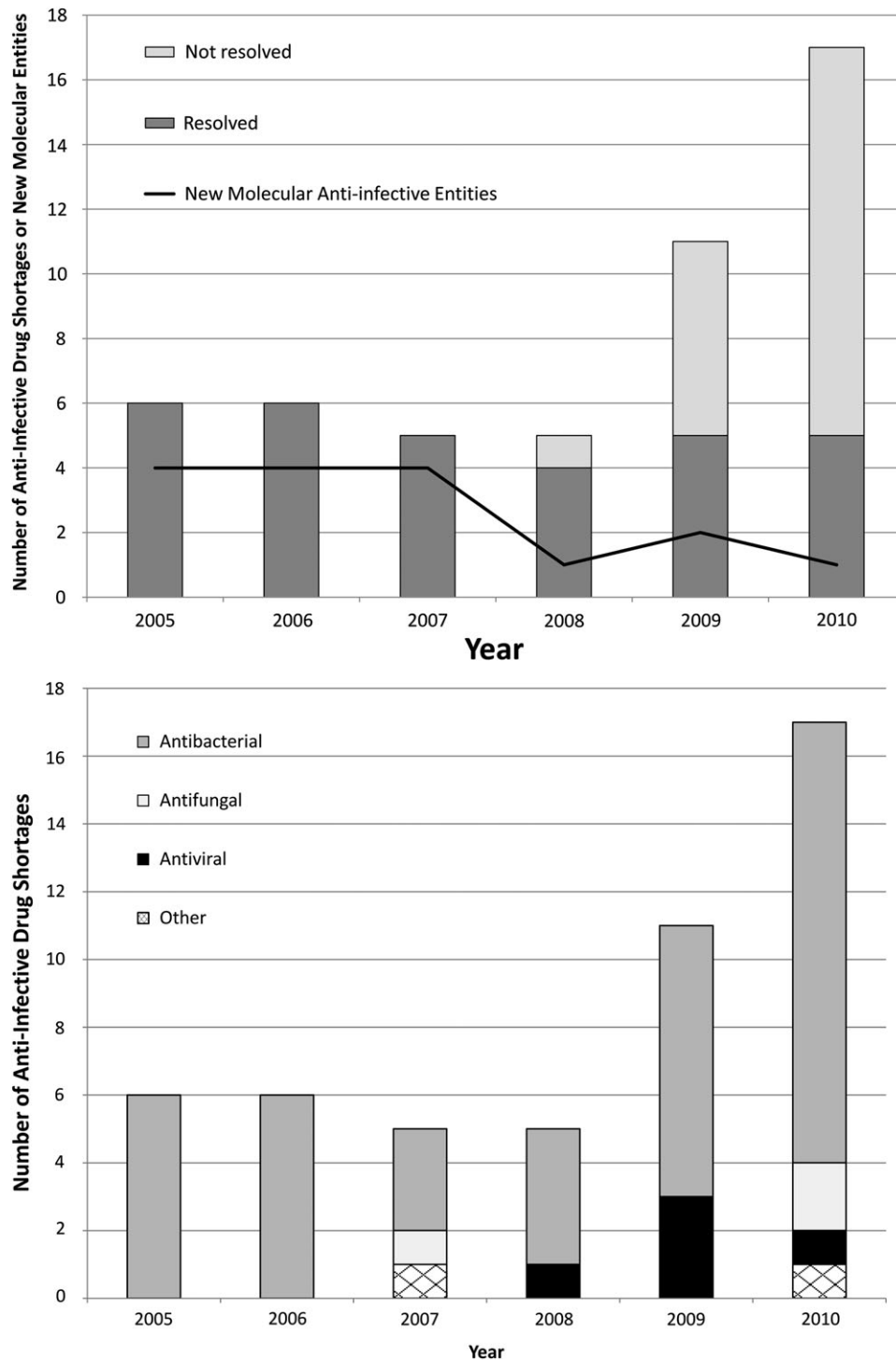


Figure 1. Trends in anti-infective drug shortages and new molecular anti-infective entities. Each drug formulation was included once from 2005 to 2010, with current shortages receiving priority and resolved shortages classified according to the first year of shortage. If resolution occurred during the time period, the drug was classified as resolved. Topical and systemic anti-infectives including antibacterials, antifungals, and antivirals were reviewed. Vaccines were excluded from the analysis. New molecular anti-infective entities were determined by searching the Food and Drug Administration drug approvals Web site.

Table 1. Illustrative Examples of Anti-infective Drug Shortages

Drug	Reason for Shortage(s)	Date of Onset of Most Recent Shortage	Impact
Acyclovir injection	Manufacturing issues	February 2009	Only therapy recommended for HSV/VZV encephalitis [19, 34]
Amikacin injection	Raw material shortage; manufacturing issues	July 2010	Potential aminoglycoside of choice for neutropenic hypotension and pneumonia based on local susceptibilities and patient factors [35, 36]
Aztreonam injection	Raw material shortage	August 2008	Among limited alternatives for atypical mycobacterial infections or multidrug-resistant tuberculosis [37]
Ciprofloxacin injection	Raw material shortage; noncompliance with GMPs	June 2010	Empiric therapy selection in many national guidelines for a variety of infections [35, 36]
Erythromycin ophthalmic ointment	Increased demand; manufacturer halted production	August 2009	Ophthalmia neonatorum prophylaxis; all alternatives have less evidence or higher incidence of adverse effects [16]
Foscarnet injection	Manufacturing issues	July 2010	Recommended alternative for ganciclovir-intolerant patients or ganciclovir-resistant viruses [21]
Ganciclovir capsules	Manufacturing issues	May 2009	Minimal
Mupirocin ointment	Increased demand	January 2005 (personal communication, Michelle Wheeler)	Recommended drug for <i>Staphylococcus aureus</i> decontamination before surgical procedures [38]
Isoniazid tablets	Increased demand; manufacturing issues	September 2011	First-line treatment of active and latent tuberculosis [24]
Penicillin G injection	Single-source manufacturer; noncompliance with GMPs	January 2007	First-line agent for neurosyphilis [16]
Piperacillin-tazobactam injection	Manufacturing issues; formulation change; increased demand; natural disaster	January 2005	First-line anti-infective for many serious nosocomial infections [35, 36]
Polymyxin B injection	Increased demand	January 2008	Often last-line therapy for serious multidrug-resistant gram-negative infections [39]
Streptomycin injection	None given	September 2011	Recommended for gentamicin resistant enterococcal endocarditis [26]
Sulfamethoxazole-trimethoprim injection	Manufacturing issues	May 2010	First-line treatment for <i>Pneumocystis jirovecii</i> pneumonia and <i>Stenotrophomonas maltophilia</i> infections [21]

Table current as of 28 September 2011.

Abbreviations: GMP, good manufacturing practice; HSV, herpes simplex virus; VZV, varicella-zoster virus.

resistance is becoming a frequent occurrence in today's nosocomial setting [33]. The compilation of clinically significant anti-infective shortages presented in Table 1 represents agents that are often the best or the only option to treat these multidrug-resistant pathogens.

Unavailable products broadly affect the treatment and prevention of infectious diseases and are not limited to anti-infective shortages. It is important to note that vaccine shortages have a rich and unfortunate history and have important public health implications. Since the year 2000, there have been shortages for several vaccine-preventable diseases including varicella,

hepatitis B, *Haemophilus influenzae*, meningitis, and influenza [40–42]. Recent examples of vaccine shortages have occurred with the herpes zoster and yellow fever vaccines [43].

REASONS FOR ANTI-INFECTIVE SHORTAGES

As manufacturers are not legally required to supply reasons for drug shortages, discerning causality can be difficult [10, 44]. At their discretion, manufacturers may offer reasons for the shortage. The American Society of Health-System Pharmacists and FDA drug shortage Web sites publish reasons for shortages;

however, these reports originate from voluntary information provided by manufacturers [4, 44].

Contemporary Examples of Anti-infective Shortages

Anti-infective shortages occur for a variety of reasons that can be distilled to problems caused by decreased supply or increased demand (Table 1) [10]. Examples of reasons for decreased supply include issues related to procuring raw materials, processing, distributing, regulatory compliance, and market forces. Increased demand may be due to epidemics, new therapeutic indications, or perceived shortages. A survey of manufacturer reasons for drug shortages conducted in 2000 found that the most common reason was shortage of raw material, followed by regulatory issues and increased production demand [45]. Today shortages are often due to product quality (54%), capacity issues (21%), manufacturers halting production (11%), and other reasons (14%) [46].

Problems with supply can occur at many steps throughout the manufacturing process. Unavailable raw materials or bulk items have been the suggested reason behind the shortages for gentamicin, vancomycin, amikacin, aztreonam, and ciprofloxacin [44, 47]. Noncompliance with current good manufacturing practices or other regulations may result in FDA enforcement actions and temporary halting of manufacturing. The FDA has cited regulation infraction or noncompliance with current good manufacturing practices as the cause of shortages of penicillin G sodium and potassium injections, ticarcillin-clavulanate, and ciprofloxacin [44, 47]. Product contamination due to impurities or manufacturing delays has also led to shortages. Many anti-infectives are sterile injectable products, which are at a higher risk of contamination than oral medications and thus more likely to become unavailable owing to sterility concerns. In addition, manufacturing equipment issues or lack of excipients may lead to production delays. Contamination or manufacturer delay has resulted in shortages for piperacillin-tazobactam, foscarnet, amikacin, acyclovir, and sulfamethoxazole-trimethoprim [44, 47]. Changes in product formulation may delay production, resulting in a shortage, as in the case of piperacillin-tazobactam. The product was reformulated to contain edetate disodium dihydrate and sodium citrate, which allowed for increased compatibility with other concomitantly administered intravenous agents while leaving dosing and administration unchanged [44, 47].

Corporate business decisions may contribute to drug shortages by decreasing or limiting supply of a drug. Manufacturers may cease production of a drug due to availability of therapeutic alternatives, reallocation of their resources, or other financial reasons [48]. A recent example may be the case of injectable minocycline in 2005; the same year tigecycline, a competing tetracycline, was approved for use. The company (then Wyeth Pharmaceuticals) halted the production of injectable minocycline [49], presumably to preferentially market tigecycline. This decision is concerning as minocycline may represent the most active

compound in the tetracycline class for some clones of multidrug-resistant *Acinetobacter baumannii* [50, 51], an emerging nosocomial threat [3]. Triax Pharmaceuticals has risen to the challenge of providing injectable minocycline but unfortunately has priced it similarly to tigecycline and notably higher than the previously available injectable minocycline product.

There are further examples of manufacturer decisions to halt production of medications that have affected the supply on the market and decreased the number of manufacturers producing a product. Examples of manufacturers voluntarily ending production of medications include ticarcillin, kanamycin, cefoxitin, loracarbef, cefotetan, spectinomycin, and erythromycin ophthalmic ointment [44, 47]. The impact of any shortage may be compounded if the product is only available from a single source, such as with sulfamethoxazole-trimethoprim [22]. Although all name-brand medications will have a single-source manufacturer when they are under patent protection, generics may also be produced only by a single manufacturer because of profit motives. Single-source manufacturers negatively affect consumers when they increase the price of a generic product when few alternatives are available. Examples of agents affected by these price increases include ritonavir [52], oxacillin [53], and penicillin G [53].

Stockpiling and poor inventory practices may result in an artificial shortage [54, 55]. Artificial shortages, or the maldistribution of product, decrease available supply for purchase and may occur when institutions buy in excess of their needed inventory in response to speculation of impending shortage [54, 55]. A shortage of ciprofloxacin, for example, was attributed to consumer hoarding after the *Bacillus anthracis* exposures in 2001 [56].

Changes in therapeutic indications may increase product demand, resulting in a shortage. Higher demand for a medication may have many causes, such as an epidemic, an emerging infectious disease, a new FDA-approved indication, a new unlabeled use, or market factors. Increased demand has caused shortages of ganciclovir, mupirocin, streptomycin, erythromycin ophthalmic ointment, vancomycin, polymyxin B, and piperacillin-tazobactam [44, 47].

Shortages are often due to a myriad of reasons, and manufacturers often offer no explanation. Because manufacturers declined to provide reasons for shortages in the case of cefotaxime, rifabutin, minocycline, cefazolin, cefepime, and tobramycin [44, 47], the reasons for shortages of these products remain unknown.

An unfortunate by-product of the frequency and financial impact of drug shortages has been the creation of the “gray market.” Although little documentation of the gray market exists in medical literature, it is a well-known entity to those involved in purchasing pharmaceuticals, with many institutions reporting daily solicitations from gray market vendors [57, 58]. In the gray market, intermediary distribution companies

purchase large quantities of medications at discounted prices and resell the product at inflated prices during a shortage. Of concern, little regulation exists, and these drugs may have been improperly handled, counterfeited, or recalled [59]. During a shortage, these medications are offered by gray market wholesalers to pharmacies for the purpose of procuring a large profit. In some cases, medications have been purchased and then resold at up to 5 times the normal price [60]. Medications that are bought from the gray market owing to shortage are not guaranteed to be unadulterated. Counterfeit anti-infectives that may be sold in the gray market pose a threat to public health and may result in poor patient outcomes [61]. Unfortunately this process continues despite increased scrutiny from the FDA [60].

Role of Federal Oversight

The FDA lacks authority to require companies to manufacture a product or to produce a certain amount of a product. Instead, this agency passively monitors drug shortages and relies on information provided by manufacturers and reports of shortages [62]. Under the Food, Drug, and Cosmetic Act, 21 USC Section 506(c), a company is required to notify the FDA 6 months before ending production of a “medically necessary” drug if it is the only manufacturer of that product [62].

An important function of the FDA is to provide notification if FDA-approved medications exist as foreign-marketed products. These preparations may be available for importation into the United States. Notification of this possibility may occur via electronic communication from the FDA Current Drug Shortages Web page [4]. Fosfarnet is an example of an anti-infective approved for importation from the United Kingdom [63].

Because of the currently constrained role of federal oversight, an enhanced role for the FDA was proposed in November 2010 at a meeting of several national associations, including the American Society of Anesthesiologists, the American Society of Clinical Oncology, American Society of Health-System Pharmacists, and the Institute for Safe Medication Practices. A plan intended to reduce patient harm and minimize interruptions in patient care was devised to address the growing number of drug shortages [64]. The panel recommended expanding the role of the FDA, requiring manufacturers to provide between 9 and 12 months of notification for market withdrawals. The proposed plan broadens the definition of “medically necessary” to include any medication for which interruptions in manufacturing would decrease the current supply to the point that it would not be able to meet demand. Other suggestions from this group included improving distribution options for drugs in limited supply and requiring manufacturing redundancies as part of the FDA approval process in order to limit single-source products [64].

As a first step to address these suggestions, a US Senate bill (S 296, Preserving Access to Life-Saving Medications Act) was introduced in February 2011 and was referred to the Committee

on Health, Education, Labor, and Pensions. This bill would amend the Food, Drug, and Cosmetic Act by requiring manufacturers of prescription drugs to notify the FDA 6 months before halting or interrupting production or any manufacturing changes that could potentially lead to a shortage [64–66]. Unplanned interruptions would require manufacturers to notify the FDA immediately. If a manufacturer failed an inspection, a reinspection would be conducted within 90 days with a priority placed on inspections that are likely to result in a drug shortage. The FDA would penalize noncompliance and partner with manufacturers to prevent drug shortages [65]. Furthermore, the FDA would identify drugs susceptible to shortage by assessing the following factors: the number of manufacturers, the sources of raw material or active pharmaceutical ingredients, the supply chain characteristics, and the availability of therapeutic alternatives. Any actions taken to address drug shortages would be reported by the Secretary of Health and Human Services to Congress on an annual basis [65]. At the end of June 2011, a similar House of Representatives bill (HR 2245, Preserving Access to Life-Saving Medications Act of 2011), was introduced and referred to the House Committee on Energy and Commerce, Health Subcommittee [67]. We support such efforts to amend the Federal Food, Drug, and Cosmetic Act.

CONCLUSIONS

Anti-infective drug shortages continue to pose significant problems for clinicians and are a rapidly evolving public health emergency. Multiple examples exist to substantiate potential harm to patients unable to receive specific anti-infectives. Enhanced oversight by governmental agencies may be necessary to identify and correct shortages of these life-saving anti-infectives. Bills such as the Preserving Access to Life-Saving Medications Act could provide the FDA with the appropriate authority to minimize the impact of drug shortages.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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