The Supply and Demand for Antibiotics:

Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteremia as an Example

Barry Eisenstein, MD, FACP, FIDSA

Senior VP, Scientific Affairs
Cubist Pharmaceuticals
Clinical Professor of Medicine
Harvard Medical School
Boston, Massachusetts

The initiation of the antibiotic era 7 decades ago led to extraordinary progress in the treatment of serious and often fatal bacterial infections. In the early part of that era, however, there was a lack of appreciation for mutation, genetic transfer, and Darwinian selection of resistant bacteria by the use (and overuse) of antibiotics. As a result, for decades, physicians were relatively indiscriminate in routinely using antibiotics for even trivial infections (many caused by viruses), which led to inappropriate expectations of their use by patients. We now know better, with, for example, the resurgence of infections caused by *Staphylococcus aureus*, and with organisms resistant to β-lactams now being the norm rather than the exception. As a rational response to this upsurge in resistant bacteria, caregivers, epidemiologists, and microbiologists trained in infection management began embracing "antibiotic stewardship," the approach of prolonging the effectiveness of currently available antibiotics through their prudent use.[1] The stewardship approach is an acknowledgment that antimicrobials are unique among the therapeutic classes; as they are the sole agents whose efficacy will depreciate with use. The closest analogous class is oncology, where eliminating "bad cells" and occasionally selecting resistant ones mirrors antibiotic use. However, whereas drug-resistant cancer cells die with the patient, thereby preserving the effectiveness of the drug for the next patient, resistant bacteria spread horizontally to other patients.

In analyzing such wasting of limited and shared assets, economists speak of the "tragedy of the commons," where common pastures are overgrazed or oceans are overfished for the asymmetric benefit of the individual. In such situations, the communal response is to control the depletion of such assets for the common good. Antibiotic stewardship likewise balances individual and community needs by uniquely adding selection for resistance to the cost side of the usual cost–benefit analysis used for all drugs. Upsetting the normal flora and selecting more resistant bacteria can be a negative event both for the individual and the community (eg, enterocolitis caused by *Clostridium difficile*, whose spores then spread to others in the health care facility). At the care provider level, stewardship can lead to "reserving" newer agents in order to preserve them for later community needs. Unfortunately, routine use of older antibiotics, such as vancomycin for methicillin-resistant *S. aureus* (MRSA), occasionally creates risk for seriously ill patients,[2] as discussed in the article by Lodise and Butterfield in this issue.[2-4] Clearly, the balance between the needs of the individual and the community is a dynamic one reflecting changes in disease presentation and resistance to specific drugs, leading to constant updating of treatment guidelines, as has been seen recently for vancomycin use.[4]

Hidden from the typical practitioner, however, is a perverse consequence of antibiotic stewardship: decreased return on investment in new antibiotics. Numerous economic disincentives—such as short-course treatment for acute conditions, high regulatory hurdles, and risk aversion for new drug approval—can discourage investment in antibiotic development. The recent problems with Ketek[5] highlight the risks posed by new agents, whereas cheaper generic competitors with outdated package inserts often deter investment in agents with similar indications (eg, vancomycin was approved by the FDA in 1958 before the statutory requirement for proof of efficacy was enacted[6]). Yet the expectation still exists that new antibiotics specifically designed for the most resistant bacteria will be held in reserve for rescue therapy. Thus, antibiotic stewardship, although an appropriate approach for controlling the "demand" side, is indirectly hurting the "supply" side.

Is there an answer to this dilemma? Just as communal control of antibiotic use has become a rational way to balance individual and public health needs, I believe that, to balance the unique commercialization hurdles caused by antibiotic stewardship, government should provide some unique incentives to encourage their development. In the "Extending the Cure" monograph prepared

by Resources for the Future[7] and in the series of "Bad Bugs, No Drugs" position and public policy papers by the Infectious Diseases Society of America (IDSA),[8,9] both "push" and "pull" incentives are discussed. One example is as follows: If antibiotics were to be treated in a manner analogous to drugs for "orphan diseases" (that are subject to unique commercial incentives), they too would be given an extension of data or market exclusivity. The consequent delay in generic entry would provide an increase in the expected return on investment in innovative antibiotic development, particularly those focused on otherwise resistant pathogens. Such a position would recognize the typical practice of keeping newer antibiotics in reserve, acknowledging the need to manage appropriately the demand side, while simultaneously supporting the supply side for these lifesaving products.

When we recognize that in the United States more deaths per year occur in patients with MRSA infections than in those with AIDS[10] and that an old drug (vancomycin) still viewed as standard of care for MRSA is losing effectiveness,[2,4] it is obvious that, in addition to antibiotic stewardship, we also need new antibiotics. I believe it is time for practicing physicians (and their patients) to not only pay attention to the demand side, but also to get more involved with the efforts of the IDSA and Resources for the Future to urge Congress to provide the needed commercial incentives required for the supply side.

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