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ANTIBIOTIC RESISTANCE

Stopping superbugs, maintaining the microbiota

THE STEADY AND ALARMING RISE IN ANTIBIOTIC RESISTANCE POSES ONE OF THE greatest challenges to public health. In the United States, the Centers for Disease Control and Prevention estimates that drug-resistant bacteria sicken more than 2 million people annually, causing 23,000 deaths and resulting in \$20 billion in excess health-care costs and an additional \$35 billion in lost productivity (1). The antibiotic resistance crisis is particularly devastating in hospitals and long-term care facilities, where such infections strike the most vulnerable patients with weak immune systems or chronic diseases. High-risk groups include the elderly, cancer patients, diabetics, individuals who have undergone recent surgery, and those who are fighting for their lives in intensive care units. The World Health Organization has recognized that unless we respond forcefully as a global community, we risk entering a post-antibiotic era that would stymie modern medicine.

This spring, the Obama Administration took first action against this imminent threat by releasing the *National Action Plan for Combating Antibiotic-Resistant Bacteria* following recommendations from the President's Council of Advisors on Science and Technology (2). The document articulates a roadmap and goals for enhanced surveillance, diagnosis, control, and research and development. One particular goal of the *National Action Plan* appeals directly to innovative translational scientists: To “intensify research and development of new therapeutics and vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections,” including so-called nontraditional therapeutics.

The roots of our current dilemma are multifactorial. Overzealous use of antibiotics in both clinical and agricultural settings, the departure of many major pharmaceutical companies from antibiotic development (which is viewed as unprofitable), and simple Darwinian evolution of microbes exposed to life-or-death selective pressures each contribute profoundly. Can we, through innovation, lift ourselves out of the hole that we have dug? Changing the very definition of “antibiotic” will be a prerequisite for success.

Seven decades after the introduction of antibiotics to clinics, the pharmacotherapy of acute bacterial infections is effectively defined by a single broad class of agents—chemicals discovered to kill or suppress the growth of bacteria in culture (that is, “direct antibiotics”) and then shown to have pharmacological properties and toxicity profiles acceptable for human administration. The most successful and widely used agents have broad-spectrum activity, a quality equally attractive to physicians prescribing empiric therapy and practicing defensive medicine and pharmaceutical manufacturers seeking the largest market opportunity. However, such agents have the greatest potential to select for resistance genes among the diverse microbes colonizing the patient and severely perturb the normal flora. Beyond risking opportunistic *Clostridium difficile* or fungal infections, collateral damage to the normal microbiota from broad-spectrum antibiotic administration may have lasting immunological and metabolic consequences associated with allergy, chronic inflammatory diseases, or obesity (3).

The scientific basis for current antibiotics centers solely on the bacterium, yet severe infections are more accurately understood in the context of host-pathogen interactions. Most leading agents of human bacterial infection typically colonize the skin or mucosal surfaces of healthy individuals without producing symptoms. By definition, if a bacterium has invaded into the bloodstream or deep tissues to produce acute infection, the innate immune system has failed in its sentinel defense function. A more holistic definition of antibiotic therapy that centers on correcting the dysfunctional host-pathogen interaction can unlock opportunities for therapeutic innovation—including drugs with minimal risk of damage to the normal human microbiome.

One approach garnering attention exploits knowledge of the precise molecular mechanisms used by the pathogen to establish infection, resist clearance by the innate immune system, or otherwise produce harm to our cells, tissues, or physiology. Defining essential bacterial virulence factors or toxins as molecular targets recasts the pharmacological principle of antibiotic therapy: Instead of trying to kill the bacteria, the goal is to disarm the pathogen, rendering it harmless and allowing the body's natural defenses to eliminate the infection. For example,

the surface-expressed FimH pilus lectin of uropathogenic *Escherichia coli* (UPEC) promotes bladder epithelial cell invasion and resistance of intracellular bacteria communities to therapy, leaving patients prone to clinical relapse. Oral treatment with a small-molecule FimH inhibitor that possesses no direct antibacterial activity resolves established UPEC urinary tract infections in mice (4). Likewise, therapeutic monoclonal antibodies are in preclinical or early clinical development to target virulence factors or promote opsonin-driven phagocytic clearance of multidrug-resistant pathogens. In contrast to conventional antibiotics, inhibitors of microbe-specific virulence factors spare the normal flora and its critical functions.

Consider also that numerous drugs in clinical practice down-regulate immune cell activity to alleviate symptoms in inflammatory diseases such as asthma, arthritis, and multiple sclerosis, yet not a single agent has received regulatory approval to augment immune cell bactericidal function in the treatment of acute bacterial infections. Deep-seated infection declares a shortcoming in the host's innate immune defense, and targeted activation of specific phagocytic cell properties might work in concert with antibiotics to promote pathogen clearance. For example, studies on the mechanism of congenital neutrophil immunodeficiency in humans with C/EBPε mutations revealed that nicotinamide (vitamin B3) boosts neutrophil bactericidal activity and provides prophylactic and therapeutic activity against *Staphylococcus aureus* in a mouse model (5). Such host-directed therapeutics can also preserve microbiome integrity, as phagocytic cells are absent on healthy uninflamed mucosa.

The ubiquitous gold standard for antibiotic spectrum and potency, namely, minimum inhibitory concentration (MIC) testing in standard bacteriologic media, is agnostic to immune factors and thus insufficient for evaluation of new therapeutics working at the host-pathogen interface. Azithromycin—the most commonly prescribed antibiotic in the United States—is never recommended for highly drug-resistant Gram-negative bacterial strains (such as carbapenemase-resistant *Acinetobacter baumannii* or *Klebsiella pneumoniae*) because of absent or negligible activity in standard MIC testing. However, this drug shows potent bactericidal synergy with endogenous cathelicidin antimicrobial peptides, leading to substantial reductions in Gram-negative bacterial loads upon azithromycin monotherapy in the mouse model (6). Individualized medical care of the sickest patients with the most complicated antibiotic-resistant pathogen infections will require the analysis of existing and future innovative therapeutic options in the context of human immunity, perhaps in a model in vitro system that contains serum and phagocytic cells or even the patient's own blood.

In the seven decades since their introduction, conventional antibiotics have cured more disease than all other drug classes combined. Unfortunately, this remarkable historical success has bred complacency, while increasingly drug-resistant pathogens are exacting high morbidity and mortality in the face of our monolithic approach to therapy. By contrast, complacency has never taken hold in the field of cancer therapeutics, in which poor prognoses remain for many of the most severe malignancies. Here, recent innovative approaches that rely on mechanistic insights, such as inhibition of the overactive tyrosine kinase BCR-Abl in chronic myelogenous leukemia or PDL-1 checkpoint inhibitors that boost antitumor T cells in melanoma, have improved patient outcomes (7). Because such modalities are fully analogous to virulence factor inhibitors and phagocytic cell boosters in the context of antibacterial therapy, they should provide inspiration for future precision medicine approaches to infectious diseases envisioned by the president's *National Action Plan*.

– Victor Nizet

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