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Editorial

Combating Antimicrobial Resistance: Going Beyond New Antibiotics

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At the outset of 2020 and prior to coronavirus disease 2019 usurping our attention, the discussion among infectious disease practitioners was focused on the alarming increases in multidrug (antimicrobial)-resistant organisms (MDROs).[1] Antimicrobial resistance had been identified by the Obama administration as a global threat that warranted issuance of a national action plan which outlined needed steps to confront this threat.[2] Although most have looked to new antibiotics as the primary means to combating resistance, this strategy is flawed for many reasons. Given that most antibiotics were originally derived from fungi and other bacteria, bacterial resistance to antibiotics is an evolutionary strategy that has existed since the beginning of time. Market forces do not favor the development of antibiotics, which are used for short periods of time and are often subjected to restricted use to prevent emergent resistance.[3] This means that the profit potential is lower for antibiotics compared with other agents. The Infectious Diseases Society of America has long drawn attention to the dearth of antibiotics in development and has advocated for multiple measures to increase the incentives for antibiotic production.[3–5] For these reasons, efforts to tackle antimicrobial resistance need to go beyond just new antibiotics. Thus, this month's Specialty Update focuses on "Combating Antimicrobial Resistance: Going Beyond New Antibiotics."

When considering the major drivers of antimicrobial resistance, most people tend to focus on the medical uses of antibiotics. The sad truth is that the volumes of medical use of antibiotics are dwarfed by the enormous quantities of antibiotics used in animal food production.[6] Several studies have highlighted the presence of MDROs in meat and poultry found in grocery stores.[7,8] Limiting the use of antibiotics in this realm would go a long way to reducing the emergence of MDROs. Dr. Sameer Patel and co-authors review the current state of antibiotic use in animal food production and highlight strategies to expand antimicrobial stewardship into this arena.[9] They specifically highlight the concept of the "One Health" model and write:

> *"The WHO Action plan is grounded in a 'One Health' model, a 'collaborative, multisectoral, and transdisciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment.' The plan recommends an overall reduction in antibiotics in food-producing animals. Importantly, it recommends a complete restriction of use of all classes of medically important antibiotics in food-producing animals for growth promotion and prevention of infectious diseases that have not yet been clinically diagnosed. In addition, there are recommendations that antibiotics classified as critically important for human medicine should not be used for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals, and that those that are highest priority critically important for human medicine should not be used in food production for any reason, including treatment of food-producing animals with a clinically diagnosed infectious disease."*

The article offers several important ways that physicians and researchers can get involved to advocate for removal of antibiotics from the animal food supply.

Another method used to manage the presence or appearance of MDROs is manipulation of the intestinal microbiome.[10] Because MDROs can be present in a quiescent reservoir within the microbiome, various strategies have attempted to apply pressure against their presence. The most commonly used methods involve administration

of either probiotics, prebiotics, or a combination of the two. Drs. Alexander Newman and Mehreen Arshad review the principles involved and summarize the available literature on this strategy.[11] They write:

> *"As multi-drug resistant (MDR) infections become an increasing burden on global health, the enteric microbiome and resistome offer a target of modification and possible reduction in the burden of these pathogens. In particular, nutritional modification through the use of prebiotics, probiotics, and symbiotics offers a safe and affordable method of reducing the impact of MDR organisms on human health."*

Because patients, families and laypeople frequently use probiotics in some way, this article is relevant to all of us and will help keep us informed about the actual evidence to support their use in preventing MDROs.

As previously mentioned, new antibiotics are not the sole solution to the problems of antimicrobial resistance. Investigators have begun to explore different strategies for treatment that do not require antibiotics. Increasingly, bacteriophage (phage) therapy is emerging as an effective and attractive option. Many of us are most familiar with phage because of introductory biology as the common example of a viral replicative life cycle that may include a lysogenic stage. For selected MDROs for which there are no antibiotic options available, researchers and clinicians have begun to prepare customized phages that are generated to a patient's specific MDRO. A recent example to highlight this approach was phage treatment of a child with cystic fibrosis who had a *Mycobacterium abscessus* infection.[12] This mycobacterial species is a treatment challenge, with very few viable antibiotic options. Tiffany Luong, Ann-Charlotte Salabarria, and Dwayne Roach from San Diego State University review the fundamental concepts of phage therapy and summarize prior experience with treating a variety of different infections using phage.[13] They write:

> *In general, a good phage candidate for therapy is one that infects a wide range of bacterial strains. There is evidence that myoviruses exhibit broader host range. For example, a single phage lysed 17 of 28 S. aureus clinical isolates. In contrast, narrow host range phages may present new therapeutic opportunities. For instance, targeting a prevalent and specific strain of pathogenic bacteria could avoid adverse effects associated with host microbiome dysbiosis.*

In the near future, as production costs decrease and our familiarity with phage technology increases, it is conceivable that large centers in big cities and individual states will have phage production facilities to help treat patients quickly and at relatively low cost.

Because antimicrobial stewardship has long been the primary means of controlling resistance, a critical factor to enable effective and prompt stewardship action is use of a rapid diagnostic method to identify MDROs. In the lone original article of the update, Michelle Lee, Tonya Scardina, Xiaotian Zheng, and Sameer Patel summarize recent experience from the Ann & Robert H. Lurie Children's Hospital of Chicago using a rapid diagnostic and antibiotic susceptibility machine that offers results in ~6 h after culture growth is identified.[14] They write:

> *At our pediatric institution, Accelerate Pheno was highly accurate for both identification and AST of gram-negative BSIs. Accelerate provided rapid susceptibility data approximately 20 h after culture collection, and 40 h before final susceptibility reporting. In the 1-year study period, there were multiple opportunities to modify antibiotic regimens based on rapid susceptibility data, which, when acted upon, led to quicker optimization of therapy. The assay was an important tool to minimize ineffective antibiotic therapy and reduce unnecessary antibiotic use.*

This article offers us insight into what our near future holds in helping treat patients with various infection with a "goldilocks" approach: not too much antibiotic but not too little either.

I want to end with several thoughts. First, I would like to thank all the authors for their contributions to this Specialty Update. They are experts in their respective fields, and we very much appreciate their time to share their

thoughts. Second and as always, I want to thank the team at *Clinical Therapeutics*, including my Co–Editor-in-Chief Jill Maron, and our in-house Elsevier team of Judy Pachella and Stefanie Bronson for helping manage the journal during our evolution into what is now a "new normal." I would also like to acknowledge and thank Terry Materese for his efforts as Executive Publisher at *Clinical Therapeutics*. He was incredibly helpful and supportive of me as I joined this team as a "green" ID topic editor and gave me license to advance many of my ideas in several ways during his tenure. Terry has moved on to other things and we will miss him, but we wish him the best of success in his future endeavors.

Stay safe, everyone, wear a mask, and treasure your family and friends every moment of every day.

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