

## A Crucial Role for Antimicrobial Stewardship in the Midst of COVID-19

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As the world deals with a pandemic, there remains another global challenge that cannot be ignored. Use of broad-spectrum antibiotics may be justified as we are trying to treat a novel disease condition, which in turn could lead to an increase in antimicrobial resistance. We can decrease morbidity, mortality, and health care costs by controlling antimicrobial resistance, but it requires antimicrobial stewardship. Major components of effective and timely antimicrobial stewardship are diagnostic stewardship, infection prevention and control, and integration of COVID-19 specific flags into electronic health records, all of which may be integrated into current strategies of COVID-19 mitigation and management. Going through the influenza season of 2020, implementation of antimicrobial stewardship education efforts in the United States can help us contend with influenza in addition to COVID-19 and any bacterial co-infections or secondary infections. Additional solutions include the development of vaccines, alternative therapies such as antibodies, and advanced diagnostics using advances in genomics and computer science.

### INTRODUCTION

Research has shown that medical school students and graduating pharmacy students desire more education on the appropriate use of antimicrobials, a key component of antimicrobial stewardship (AMS) which aims to resolve the patient's infection, minimize antimicrobial resistance, and reduce toxicities associated with antimicrobial use (1, 2). As per the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA), the primary goal of AMS is to optimize clinical outcomes for the patient and minimize consequences of antimicrobial use such as toxicities, selection for opportunistic pathogens such as *Clostridioides difficile*, and antimicrobial resistance (3). An interprofessional curriculum on AMS geared towards preclinical medical and pharmacy students was shown to not only positively influence AMS but also interprofessional

collaboration (4). Significantly more students who participated in this curriculum were able to describe the function of the medical and pharmacy professions in appropriate antimicrobial use, communicate in an interprofessional manner, and find ways to collaborate with each other (4). Even though 65% of medical schools in the United States teach AMS during preclinical years, most of these schools have focused largely on didactic lectures, with only a few offering opportunities for interprofessional education in stewardship (5). There has not been an overt request for AMS inclusion as part of preclinical education. For instance, the 2015 IDSA "Stewardship Commitments for the White House Forum on Antibiotic Stewardship" position statement bypassed AMS education of health professions students as one of its commitments (6). Guidelines by IDSA and SHEA recommend that academic medical centers and teaching hospitals should integrate AMS education into their preclinical and clinical curricula (7). This article highlights the challenges of stewardship in the midst of a fluid and uncertain pandemic. It reiterates the importance of education at all levels so that future healthcare providers have good foundational knowledge of AMS and integrate the principles in their future clinical practice.

The use of broad-spectrum antibiotics as a component of COVID-19 treatment may be justified when you consider

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the overlap of some respiratory symptoms of bacterial community-acquired pneumonia with that of COVID-19, such as cough, fever, and shortness of breath. Compounding this issue is the fact that the risk of COVID-19 severity and hospitalizations increase with age and/or presence of underlying medical conditions, both of which are also risk factors for other infections (8).

Prescribing antibiotics for a viral infection, even one without a U.S. Food and Drug Administration–approved standard of care, has to be considered in the context of antimicrobial resistance. The current pandemic with its urgent need of treating a disease, the progression of which is still being scientifically investigated in real time, has the potential to increase antimicrobial resistance (9). The inappropriate prescription of antibiotics despite the lack of evidence of bacterial co-infections in patients with COVID-19 will inevitably worsen antimicrobial resistance (10). Over 2.8 million antibiotic-resistant infections occur in the United States each year, and over 35,000 people die as a result (11). At last count, which was in 2017, nearly 223,900 people in the United States required hospital care for the opportunistic pathogen *Clostridioides difficile*, and at least 12,800 people died from this preventable infection (11). *C. difficile* infections are caused by the same factors that drive antibiotic resistance: antibiotic use and transmission of infectious agent. The increase in resistant infections in the community not only puts more people in the community at risk of these infections, but also makes transmission harder to identify and contain, thereby threatening the progress made to protect patients in health care (9). Antibiotic resistance disproportionately impacts the young, elderly, and sick, who are the most vulnerable individuals who receive medical care often. However, technically anyone would be at risk of infection with resistant pathogens. Infections with drug resistant pathogens are harder and more expensive to treat, and result in increased morbidity and mortality as well as extended length of hospital stay (12). These resistant pathogens spread from patient to patient within hospitals and across health care facilities through patient transfer, and eventually spill over into communities, becoming much harder to control (11). It may be a few years before we realize the impact of the pandemic on the incidence of antibiotic-resistant infections. What is vital is our continued effort to measure and improve how antimicrobials are prescribed by clinicians and used by patients which, in essence, is AMS.

## METHODS

In order to establish the significance of what we are proposing, we have reviewed some of the noteworthy papers in antimicrobial resistance and AMS, such as the CDC report on antimicrobial resistance, economist O'Neill's final report to the United Kingdom government on tackling drug-resistant infections globally, as well as the SHEA guidelines for healthcare epidemiologists in U.S. acute-care hospitals.

In addition, we reviewed a few 2020 publications on AMS in the midst of COVID-19 along with select publications on the importance of diagnostic stewardship. Since we would like all medical schools to include teachings on AMS principles, we also reviewed some of the important publications discussing this topic. In addition, we have summarized some of the challenges in upholding principles of stewardship in the midst of seasonal influenza, past influenza pandemics, and also the current pandemic.

## RESULTS

It is time to seriously think of AMS and revisit institutional policies as we head into influenza season. A 2016 research study involving 322 patients hospitalized with influenza revealed that most patients received antibiotics upon admission, with over one-third being inappropriately continued on antibiotics despite a lack of evidence of bacterial infection (13). Traditionally, there have not been any formal recommendations for inclusion of AMS programs in disaster planning or emergency preparedness efforts (14). COVID-19 is underscoring the need to have AMS programs integrated with hospital infection prevention programs (15). A review of scientific literature describing clinical outcomes of the 2009 pandemic influenza virus infection revealed secondary bacterial infection in almost 25% of severe or fatal cases (16). There is a need to prospectively monitor coinfections in patients with COVID-19 to understand whether co-infection affects disease progression and at the same time enables AMS (17).

A major component of effective and timely AMS is diagnostic stewardship, which includes the process of ordering and interpreting diagnostic tests before initiating or continuing treatment (18). Interpretation of sensitive molecular tests that detect multiple targets simultaneously or use of next-generation sequencing tests that detect microbial genomes must also take into account the pretest likelihoods of infection with each target in the test (19). Use of rapid diagnostics enable early diagnosis, leading to use of targeted antimicrobials and bypassing misuse of empiric antimicrobials. However, diagnosis has to be considered in the context of colonization versus an actual infection, with the latter being distinguished by the presence of disease-causing microorganisms on or in the body of a patient, and the former being characterized by microbial presence without disease (20). Hospitals have to continue efforts to distinguish between the two. For instance, laboratory policies may enforce strict conditions of specimen collection and/or handling before specimens are processed, thereby minimizing contamination with colonized microorganisms (19). Tests may also be performed in a stepwise fashion, with subsequent tests dependent on results from the previous tests (19). Some hospitals provide ongoing education to their clinicians about appropriate indications and sampling for tests. A multidisciplinary expert panel of IDSA and

SHEA recommend not relying solely on didactic educational materials for stewardship, and encourages academic medical centers as well as teaching hospitals to integrate AMS education into their preclinical and clinical curricula (7). In order to achieve sustained stewardship, education has to be combined with other AMS efforts, like “Prospective audit and feedback” (PAF), an external, expert review of antibiotic therapy with suggestions to optimize use (7).

It is important to include the role of animals as well in our AMS education efforts. Antimicrobial resistance is compounded by the frequent and heavy use of antimicrobials in our food animals, making animals a crucial player in the spread and evolution of resistant pathogens (21). Even the microbiota of wild animals is being acknowledged as a reservoir of resistance genes (21). Research has also shown that reduction of antibiotic use in food animals is accompanied by a reduction in antibiotic-resistant bacteria in animals as well as in humans directly exposed to these animals (22).

Not surprisingly, timely accurate diagnosis greatly increases the likelihood of improving clinical care and patient health. Proper diagnostic stewardship is a process that involves selecting the correct (or as near-correct as possible) diagnostic test for the appropriate patient with a certain clinical scenario, followed by timely collection of the relevant clinical specimen, its transport and processing, and timely reporting of test results (23). However, ongoing evaluation and careful monitoring of diagnostic stewardship is necessary, as overuse of some rapid tests can increase health care costs without improving patient care, while underuse may delay diagnosis and patient recovery (18). Serving as an example of utilizing existing infrastructure to meet the demands of AMS programs while managing COVID-19, the Mayo Clinic modified its prospective audit system by integrating two COVID-19 specific AMS program flags into their electronic health records (EHRs) (24). The first AMS program flag rule identified in-patients with a negative SARS-CoV-2 reverse transcription-PCR (RT-PCR) test within the last week and who were already on COVID-19 medications as indicated by active therapy, which was hydroxychloroquine in this case. The second AMS program flag rule identified laboratory-confirmed COVID-19 patients and triggered review by an Infectious Diseases team. This second AMS program flag also identified pending patients with an active therapy order, who if RT-PCR negative, reverted to the first flag rule, and if RT-PCR positive, prompted review by the Infectious Diseases team. The flag rules met the goals of providing patients with the benefit of timely and appropriate care within the confines of critical medication resources. It is recommended that the contribution of AMS program flags be considered in relation to the overall EHR flag burden of a facility in order to avoid “alert fatigue,” especially in COVID-19 hotspots with high patient volume (24).

In addition to diagnostic stewardship, another necessary AMS program component is infection prevention and control. By preventing the occurrence as well as the spread

of infections, evidence-based infection prevention and control interventions reduce the demand for antimicrobials, thereby providing an effective antidote to inappropriate and unnecessary antibiotic prescriptions (25). As we confront the hurdles surrounding implementation of universal masking and other measures aimed at preventing SARS-CoV-2 infections, the 2016 report on the global impact of antimicrobial resistance, commissioned by the United Kingdom, shines the spotlight even brighter on this current crisis that needs ongoing, urgent consideration. The report estimated that by 2050, 300 million premature deaths may occur as a result of antimicrobial resistance, with an anticipated loss of between 60 and 100 trillion U.S. dollars in economic output if antimicrobial resistance is not tackled (26). The current pandemic with its unique challenges of diagnosis, uncertainty of the extent of morbidity and mortality, doubts about immunity in recovery, and lack of focused AMS program efforts will only worsen this issue. Now more than ever, we have to incorporate the lessons proposed in economist Jim O’Neill’s 2016 report, including, but not limited to development of vaccines, alternative therapies such as antibodies, advanced diagnostics using advances in genomics and computer science, and continued infection prevention and control efforts (26).

## DISCUSSION

As our frontline providers faced burnout in a health care system overwhelmed by the novelty of the disease, lack of adequate protective equipment, lack of adequate testing (at least initially), delays in receiving laboratory-confirmed results, and uncertainty on how best to manage the illness, it is understandable if there was an initial incorporation of broad-spectrum antibacterial use. As we go through Fall 2020, it is worth remembering that bacterial superinfections in past influenza seasons have presented either as initial co-infections with influenza virus or as secondary bacterial infections in patients hospitalized with influenza (27). One of the complications in COVID-19 is pulmonary distress that results in respiratory failure, acute respiratory distress syndrome, or even ventilator-associated pneumonia, all of which can be fatal (28). Previous influenza pandemics have underscored the importance of treating for secondary bacterial pneumonia, which can be fatal if untreated (16).

To meet the rigors of diagnostic stewardship, EHRs can be designed to provide a more meaningful process for ordering diagnostic tests (15). When implemented thoughtfully, EHRs can facilitate a culture of AMS, disease surveillance (identifying potential disease spread based on monitoring symptoms among a population at risk), and seamless transfers in care that successfully transition management of patients between facilities (29). When health care facilities incorporate AMS program flags, regardless of facility compliance with the AMS program flags, periodic reviews of the flags by the infectious diseases team will provide the health

care community an indication of the nature of COVID-19 AMS program (24). What is most timely and intelligent about this approach is its flexibility in modifying flag rules based on changes in community prevalence of COVID-19 and/or testing recommendations. It would be prudent to adopt this approach to AMS programs in general, adapting rules based on changes in antibiograms and/or availability of diagnostic tests. However, incorporating alert flags into the existing EHR may require appropriate training of personnel serving on the infectious diseases team. In the upcoming influenza season, diagnostic stewardship will be tasked with the urgent need to facilitate timely diagnosis of influenza, COVID-19, and any bacterial pathogens either co-infecting or causing secondary infections. If AMS is not addressed across all health sectors, it could have devastating consequences globally for years to come.

Effective AMS programs can dramatically improve patient care and save more lives. We have to continue to raise awareness and educate our future healthcare providers. Improving antibiotic prescribing and use is a national and international priority (26, 30). It would be prudent for health professions schools and colleges to educate students about AMS before they graduate or before they start their clinical rotations. Knowing about AMS when they learn about early and appropriate diagnoses of infections will help inspire students to understand the relevance of learning about the different antimicrobials, especially as it would mean use of the appropriate antimicrobial instead of indiscriminate use of a broad-spectrum antibiotic. Knowing about AMS when they learn about drugs will help the students comprehend the relevance of side effects and/or black box warnings of certain antimicrobials. How AMS education efforts are undertaken could depend on either guidance from the IDSA or be individualized according to specific medical school curriculum.

The current pandemic is underscoring the need to invest a little time in educating beginner healthcare providers in AMS so they are aware of the challenges, threats as well as solutions. The current crisis brings renewed attention to the need to build a heightened awareness of AMS and we think it is ideal that it start when students enter the health professions.

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