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IN THIS ISSUE

Need of the Hour: Addressing the Challenges of Multi-Drug-Resistant Health Care-Associated Infections and the Role of the Laboratory in Lowering Infection Rates

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Abstract

Over the past two decades, we have been confronted with an increase in the frequency and diversity of multi-drug-resistant microorganisms, leading in some cases to serious and life-threatening infections. To compound the problem, during the same timeframe, we have seen a significant decrease in the number of new, FDA-approved antimicrobial agents to treat these infections. In order to understand the gravity of the problem, we need to address the reasons behind the dramatic increase in antimicrobial resistance and the consequences facing us, as well as potential solutions to the problem.

Introduction

Over the last two decades, multi-drug-resistant microorganisms (MDROs) have been increasing in frequency and diversity, with few, if any, antibiotics to treat infections caused by these organisms. Development of resistance is inevitable, even prior to the use of drugs for treatment. Resistance can occur in many ways, including DNA mutations in the bacterial chromosome and acquisition of extra-chromosomal DNA, called plasmids; transposons, also known as "jumping genes"; or integron cassettes, which carry multiple resistance genes and can be transferred within or between species. We are faced with a complex problem related to antimicrobial resistance (AR). We need to ask ourselves why the problem is escalating, what are the consequences, how can we solve the issue, and who has the ability to solve the problem.

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Increase in Antimicrobial Resistance

In response to the question of why antimicrobial resistance (AR) is escalating, the Centers for Disease Control and Prevention (CDC) Get Smart program determined that 20 to 50% of all prescribed antibiotics are unnecessary or are used inappropriately [1]. Sixty percent of antibiotic expenditures for humans are in the outpatient setting, where the most common misuse of antibiotics is for upper respiratory tract infections. For example, approximately 20% of children who present to their pediatrician with a cold are prescribed an antibiotic even though antibiotics are ineffective against cold viruses and these infections generally resolve on their own. Not only does overuse of antibiotics contribute to AR, they are also responsible for adverse drug events that necessitate a trip to the emergency department, particularly in pediatric patients [2]. Likewise, patients diagnosed with bronchitis are frequently prescribed an antibiotic even though national guidelines do not recommend them.

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Conversely, patients diagnosed with a bacterial infection, such as strep throat, should be treated with an antibiotic. However, in some cases, either the wrong antibiotic is prescribed or the dose or duration is incorrect. Other reasons for the development of resistance are found in long-term care facilities, where up to 70% of residents receive at least one antibiotic annually [3]; sharing antibiotics; poor compliance in taking antibiotics as prescribed, leading to a subtherapeutic level of the antibiotic; and purchasing over-the-counter antibiotics without a prescription, which is particularly prevalent in some developing countries.

According to the CDC, 80% of antibiotics sold in the United States are used for growth promotion in livestock, leading to development of resistant bacteria in their gastrointestinal tracts. Europe has banned this practice, while the U.S. has recommended voluntary banning. If humans eat uncooked or undercooked meat from these animals, resistant organisms can colonize their gut and potentially cause infection and/or spread to individuals in the community or in health care facilities. Likewise, humans can acquire resistant organisms if they eat crops irrigated with runoff water contaminated with animal feces. The CDC estimates that more than 400,000 individuals in the U.S. develop AR foodborne bacterial illnesses annually [4].

Misuse of antibiotics and inadequate environmental control have led in large part to the development of resistance and global spread, respectively. Epidemiologic evidence suggests health care practitioners are more likely to transmit multi-drug-resistant microorganisms (MDROs) to patients if they do not adhere to approved guidelines for hand hygiene and glove use. That said, health care workers themselves play a limited role in introducing an MDRO into a patient care unit unless they are persistently colonized. Patients transferred between acute or chronic care and long-term care facilities also provide an opportunity for transmission of resistant organisms [5].

The consequences of AR are significant. In 2013, the National Summary Data published by the CDC estimated at least 2,049,442 illnesses, 23,000 deaths, $20 billion in excess direct health care costs, and $35 billion in lost productivity are caused by AR each year [6]. One of the most significant consequences of AR is the development of hospital-acquired infections (HAIs) that are multi-drug resistant, extensively drug resistant, or pan-drug resistant to available antibiotics. The CDC warns of threats from these infections that lead to increased length of stay, delayed recuperation, long-term disability, higher mortality rates and financial burdens to our health care system. Due to these consequences, the CDC, along with health care and public health partners, are focusing attention on HAIs and their prevention. Examples of HAIs are catheter-associated urinary tract infections (CAUTIs), central line-associated bloodstream infections (CLABSIs), and surgical site infections (SSIs).

HAI data are obtained through the National Healthcare Safety Network (NHSN)

NHSN [https://www.cdc/nhsn] is co-organized by the Centers for Medicare and Medicaid Services (CMS) and the CDC. The NHSN is the most widely used secure Internet-based, health care-associated infection tracking system in the U.S. One of the primary purposes of the NHSN is to reduce HAIs in medical facilities. Data from the laboratories of health care facilities are submitted to state and federal governments, divided by facility type and specialty, and compared to "like" institutions to determine acceptable levels of HAI types, antibiotic use, and drug resistance per institution [6, 7].

The HAI Prevalence Survey, published in 2014, reported an estimated 722,000 HAIs in 2011 in U.S. acute care hospitals, with more than half occurring outside of an intensive care unit (ICU), and approximately 75,000 deaths during hospitalization. More than 17,000 hospitals and other health care facilities report data to the NHSN. Data entered into the NHSN is then sent to the CMS according to the facility CMS certification number. Although a work in progress, the CDC's National and State Health Care-Associated Infections Progress Report highlights the strides made in preventing HAIs. The most recent report (2016) shows a 50% decrease in CLABSIs and a 17% decrease in abdominal hysterectomy SSIs in all settings between 2008 and 2014, progress in overall CAUTIs during 2013 and 2014, and 8% and 13% decreases in hospital-onset *Clostridium difficile* infections and methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, respectively, between 2011 and 2014 [7]. A plethora of clinical care surveillance programs are anticipated that will be rolled out in the next 5 to 10 years, with results available online for the public, health care institutions, and public health, to name a few.

During the past several decades, the prevalence of MDROs in U.S. hospitals has increased. The prevalence of MDROs varies geographically and by health care setting, size of facility, and level of care. The CDC categorizes these MDROs, i.e., urgent, serious, or concerning, based upon their impact on public health. For example, carbapenem-resistant *Enterobacteriaceae* (CRE)/carbapenem-resistant organisms (CRO), *C. difficile*, and resistant *Neisseria gonorrhoeae* are considered urgent threats. A growing number of HAIs are caused by bacteria that are resistant to multiple antibiotics, including the ESCAPE organisms (vancomycin-resistant enterococci [VRE], MRSA, CRE, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.).

Examples of documented increases in AR are described below. What appears to be the first cases of MRSA infection were described in the United Kingdom in 1961 and in the U.S. in 1968. In the 1970s, MRSA was widespread in Europe and in the U.S. by the late 1980s. According to the former National Nosocomial Infections Surveillance (NNIS), by the early to mid-1990s, MRSA accounted for 20 to 25% of *S. aureus* isolates from hospitalized patients, whereas in 1999 and 2003, MRSA accounted for more than 50% and 59.9%, respectively. A similar rise occurred with VRE. Turning to Gram-negative organisms, in 1997, less than 10% of *Klebsiella pneumoniae* isolates were resistant to 3rd-generation cephalosporins based on the SENTRY Antimicrobial Surveillance Program data. By 2003, 20.6% of *K. pneumoniae* isolates from NNIS ICUs were resistant to these drugs. Similar results were seen with *P. aeruginosa* resistance to fluoroquinolones.