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Emerging trends in antibiotic resistance: Implications for emergency medicine

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ABSTRACT

Background: Many bacteria are demonstrating increasing levels of resistance to commonly used antibiotics. While this has implications for the healthcare system as a whole, many patients infected with these resistant organisms will initially present to the emergency department (ED).
The purpose of this review is to provide a summary of current trends in infections caused by the most clinically relevant resistant organisms encountered in emergency medicine.
Methods: Bacteria were selected based on the Centers for Disease Control and Prevention's National Action Plan for Combating Antibiotic Resistant Bacteria, and PubMed database.
Results: The following bacteria were included: methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci, *Escherichia coli*, carbapenem-resistant Enterobacteriaceae, *Neisseria gonorrhoeae*, and *Pseudomonas aeruginosa*. All have shown increasing rates of resistance to one or more of the antibiotics commonly used to treat them. Increasing rates of antibiotic resistance are associated with worse clinical outcomes and greater healthcare costs.
Conclusions: Antibiotic resistance is increasing and poses significant a risk to both the patient and public health as a whole. Appropriate choice of initial antibiotic is important in improving clinical outcomes, which is often the role of the ED provider. On a broader level, the ED must also take part in institutional efforts such as Antibiotic Stewardship Programs, which have been shown to decrease costs and rates of infection with resistant organisms. Ultimately, a multifaceted approach will be required to curb the threat of antibiotic-resistant bacteria.

1. Introduction

The Centers for Disease Control and Prevention (CDC) estimates that over 2 million people each year are infected with bacteria that are resistant to antibiotics. Of these, approximately 23,000 will die from their infection [1]. Many of these patients will present to emergency departments (EDs). Infections can range in severity from simple cystitis to life threatening septic shock. Emergency physicians must recognize the signs of bacterial infection and initiate appropriate antibiotic treatment in order to reduce patient morbidity and mortality. In the ED setting, culture and susceptibility data are often not immediately available and providers often choose antibiotics based on likely pathogens and local susceptibilities. In cases of sepsis, it is necessary to initiate broad-spectrum antibiotics with the intention of narrowing coverage at a later time. At the same time, inappropriate use of antibiotics when they are not indicated as well as the overuse of broad-spectrum antibiotics has had the unintended effect of creating antibiotic resistance [2].

Antibiotic resistance presents a major and growing challenge to modern healthcare. Multiple mechanisms of resistance have contributed to the emergence and spread of these bacteria, including spontaneous mutations or via plasmid exchange between bacteria. The impact of antibiotic resistance is further magnified by a paucity of new antibiotics in the drug development pipeline and critical shortages of existing antibiotics [2]. Identifying emerging patterns of antibiotic resistance is necessary as it allows providers to tailor antibiotic therapy. This is particularly important for emergency physicians, as they are often the ones who select and administer the initial antibiotics to these patients and inappropriate choice of initial antibiotic has been shown to increase morbidity and mortality [3]. In this review, we discuss common and emerging antibiotic-resistant infectious diseases encountered in the ED and recommended strategies to improve patient safety and combat

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antibiotic resistance. A summary of treatment recommendations is provided in Table 1.

2. Gram positive bacteria

2.1. Methicillin resistant Staphylococcus aureus

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been a public health threat for several decades, and remains a major cause of morbidity and mortality. Originally discovered in 1968, MRSA was initially limited to being a hospital-acquired infection; however, this has changed in recent years. The first case of community-acquired MRSA (CA-MRSA) was reported in 1980 and since then it has been increasing in prevalence [4,5]. CA-MRSA is defined as "MRSA isolates obtained from individuals in the community who have not had recent exposure to the healthcare system, or from patients in healthcare facilities in whom the infection was present or incubating at the time of admission [6]." As of April 2016, the CDC estimates that there are over 16,000 cases of CA-MRSA in the U.S. [7].

CA-MRSA has some major epidemiologic and genetic differences from hospital-acquired MRSA (HA-MRSA). Patients with CA-MRSA may lack the risk factors that are associated with hospital-acquired MRSA including recent hospitalization, dialysis, nursing home residence, or even co-morbid conditions like diabetes and chronic lung diseases [8]. Additionally, HA-MRSA predominantly causes pneumonia while CA-MRSA causes mainly superficial skin infections [9]. CA-MRSA strains tend to be more susceptible to antibiotics as well [10]. Friedman et al. found that a common exposure pathway was contact with a contaminated surface. In their review, they found that populations at risk for acquiring CA-MRSA included emergency response workers, veterinarians, beach-goers, athletes, prison inmates, the homeless, and illicit drug users. In all cases, these populations were found to be at risk due to their interaction with high contact, infected surfaces. Additionally, having an open wound was also found to increase one's risk of acquiring CA-MRSA [11].

There are a variety of treatment options for MRSA. In cases of abscesses suspected to be caused by MRSA, incision and drainage is indicated [12]. For outpatient of treatment of CA-MRSA, clindamycin, sulfamethoxazole-trimethoprim (SMZ-TMP) and doxycycline are recommended [13]. For inpatient therapy, vancomycin has traditionally been used but other options include linezolid, tedizolid, daptomycin, dalbavancin, oritavancin, and telavancin. Vancomycin resistant *S. aureus* has been slow to emerge and is relatively rare [14].

2.2. Vancomycin-resistant Enterococci (VRE)

Enterococci are Gram-positive cocci that commonly cause intra-abdominal infections, urinary tract infections (UTIs), wound infections, and bacteremia. Ampicillin and aminoglycoside resistance has been reported; however, in recent years, VRE has become increasingly common [15]. The incidence of VRE has grown at an alarming rate. In 1990, less than 1% of enterococcal cultures were vancomycin-resistant, while that number is now close to 30%. Vancomycin-resistance is more common with *E. faecium* than with *E. faecalis* [16]. Enterococcus is the second most common bloodstream isolate in the United States. VRE blood stream infections are associated with 10,000–25,000 deaths per year [17].

Enterococcus as a genus has a predilection to developing antibiotic resistance, which in the case of vancomycin, is typically acquired via plasmid transfer. However, improper antibiotic use on the part of clinicians is also contributing to the problem. Interestingly, it is not necessarily the overuse of vancomycin itself that is to blame. McKinnell et al. demonstrated an association between VRE blood stream infection and ceftriaxone use during the preceding month. Their study demonstrated no association between prior vancomycin use and development of VRE infection [15]. Other studies have shown that hospitals that limit their use of cephalosporins have seen a decrease in the number of VRE cases [18].

Treatment options for VRE currently include daptomycin, linezolid, or tigecycline [19]. Daptomycin may have more limited role as a meta-analysis done in 2013 showed that patients treated with daptomycin had significantly higher rates of 30-day mortality. The relapse rate for patients treated with daptomycin was also higher, although the difference was not statistically significant [20]. Stable patients with UTIs caused by VRE can be treated with fosfomycin and nitrofurantoin [21].

Table 1
Treatment options for resistant organisms

Organism	Treatment
ESBL *E. coli*	Inpatient: amikacin, carbapenems, ceftazidime/avibactam, piperacillin/tazobactam Outpatient: fosfomycin, nitrofurantoin
Vancomycin resistant Enterococci	Inpatient: daptomycin, linezolid, tigecycline Outpatient UTI: fosfomycin, nitrofurantoin
Carbapenem-resistant Enterobacteriaceae	Colistin, polymyxin B, tigecycline
Neisseria gonorrhea	Ceftriaxone + azithromycin or doxycycline
Multi-drug resistant *Pseudomonas aeruginosa*	Ticarcillin, piperacillin, imipenem
Methicillin-resistant *Staphylococcus aureus*	Inpatient: vancomycin, linezolid, daptomycin, dalbavancin, oritavancin, telavancin Outpatient: SMZ/TMP, clindamycin, doxycycline

3. Gram negative bacteria

3.1. Escherichia coli (E. coli)

One of the most common reasons for ED visits is urinary tract infection, accounting for at least 2 to 4 million visits per year [22]. *E. coli* accounts for as many as 80% of these cases [23].

Uncomplicated cystitis is typically treated with short courses of either nitrofurantoin or sulfamethoxazole-trimethoprim (SMZ-TMP) [24]. While fluoroquinolones are commonly used for uncomplicated cystitis, recent Food and Drug Administration (FDA) and professional society guidelines recommend avoiding their use when alternatives are available due to serious concerns for adverse events. Specific adverse effects include tendon rupture and central nervous system effects [25]. It is estimated that up to 53% of patients will experience a recurrent UTI within a year of their initial presentation [26]. Patients with recurrent UTIs may be placed on long-term prophylaxis with SMZ-TMP. These patients have been found to develop resistant strains of *E. coli*. One study found that *E. coli* resistance increased from 30% to 90% in patients who had been receiving SMZ-TMP prophylaxis [27]. Extended Spectrum Beta-Lactamase (ESBL) *E. coli* are resistant to most antibiotics, an increasing concern.

One of the biggest threats that ESBL *E. coli* poses to the healthcare field is in the setting of sepsis. Over 750,000 cases occur annually and mortality rates for severe sepsis and septic shock can reach 30% and 50% respectively [28]. In fact, sepsis is the second leading cause of mortality in the non-ICU setting and the most common source of infection in sepsis is UTIs [29]. The most important aspect of managing sepsis is the timely initiation of antibiotics. Kumar et al. demonstrated that initiating appropriate antibiotic therapy within an hour of presentation was the strongest predictor of mortality in sepsis patients. Additionally, they showed that patients who were not given appropriate antibiotics had a fivefold increase in mortality [30]. Capp et al. found that the three most commonly prescribed antibiotics for sepsis in the ED were vancomycin, levofloxacin, and cefepime [7]. Levofloxacin and cefepime both have broad Gram negative coverage; however, these antibiotics do not provide adequate coverage against ESBL *E. coli*.

At the present time, treatment options for ESBL *E. coli* are limited. Fosfomycin, and nitrofurantoin have demonstrated efficacy against *E. coli* and can be used in the outpatient setting [20]. Parenteral

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treatment for ESBL *E. coli* includes carbapenems, doripenem, ceftolozane-tazobactam, and ceftazidime/avibactam, for severe inpatient infections [31]. There may be a role for aminoglycosides such as amikacin as well, although some resistance has been documented [32].

Unfortunately, *E. coli* poses another, far deadlier threat to the healthcare community: colistin Resistance. Colistin was developed in the 1950s for use against Gram-negative organisms; however, its toxicity (primarily nephrotoxicity and neurotoxicity) relegated it to an antibiotic of last resort. While it has been replaced as first line therapy by newer antibiotics, it now serves as the last line of defense against multidrug resistant Gram-negative bacteria. Previously, bacteria had not shown an ability to exchange colistin resistance genes so many felt that the chance of developing major strains of colistin resistant organisms was low. However, in 2015, the first transferable gene for colistin resistance was discovered in China: mcr-1 [33]. In May 2016, the first case of colistin-resistant *E. coli* was confirmed in the United States [34]. Colistin-resistant *E. coli* is a major public health threat as colistin represents the last line of defense against multidrug resistant gram-negative organisms. If colistin fails, there presently are no additional treatment options for these patients [35].

3.2. Carbapenem-resistant Enterobacteriaceae (CRE)

The widespread use of carbapenems has led to the emergence of CRE. The mechanism of resistance is due to production of carbapenemase enzymes. The most clinically relevant Enterobacteriaceae are *E. coli*, *Klebsiella pneumoniae* and Enterobacter species and the most common sources of infection are UTIs and intra-abdominal infections [36]. Using data from the meropenem yearly susceptibility test information collection program, Rhomberg et al. found that the rate of carbepenem resistant *K. pneumoniae* increased from 0.6% in 2004 to 5.6% in 2008 [37].

Patel et al. found that recent organ transplant, mechanical ventilation, and longer hospital lengths of stay all increased the risk of acquiring a CRE. Infection with a CRE also leads to an increase in mortality compared to infections with carbapenem-susceptible Enterobacteriaceae, with mortality reaching over 40% in patients with CRE [38].

Treatment options for CRE are very limited. Current therapies include tigecycline, polymyxin B, and colistin [39]. Important strategies to curb morbidity and mortality from CRE are early identification and prevention of spread. CRE appears to be more common in Long-Term Acute Care Hospitals (LTACHs). Perez et al. found that over 50% of patients admitted for CRE came from LTACHs, suggesting that LTACHs may be an important reservoir in the dissemination of the disease [40]. Patients identified to have CRE must be placed on contact precautions to try to limit transmission in the healthcare setting.

3.3. Multi-drug resistant Pseudomonas

Pseudomonas aeruginosa is typically thought of as a hospital acquired infection. Data from the National Nosocomial Infection Surveillance (NNIS) system shows that *P. aeruginosa* is the second most common cause of pneumonia (18.1%) and the third most common cause of UTIs (16.3%) [41]. However, cases have been reported of severe community acquired *P. aeruginosa* infections, especially in immunocompromised patients [42]. Thus, it is important for emergency medicine providers to be aware of the current trends in *Pseudomonas aeruginosa* antibiotic resistance.

Studies have consistently shown that failure to recognize and properly treat *P. aeruginosa* leads to increased morbidity and mortality [43,44]. Antibiotics that can be used as anti-pseudomonals include certain penicillins (ticarcillin, piperacillin), selected cephalosporins, fluoroquinolones, and imipenem. *P. aeruginosa* has shown a troubling trend in terms of resistance to these antimicrobials. While the overall proportion of infections caused by *P. aeruginosa* has remained relatively stable from 1986 to 2003, the proportion of resistant isolates has drastically increased. In the same period, the proportion of isolates resistant to imipenem, fluoroquinolones, and third-generation cephalosporins increased by 15, 9, and 20% respectively [44]. Of these, the highest rates of resistance is to fluoroquinolones. Resistance to ciprofloxacin and levofloxacin ranges from 20 to 35% of all isolates [45]. This increase in resistance has serious implications for patients. Rates of mortality, morbidity, need for surgical intervention, and length of stay have all been shown to increase when a patient is infected with a resistant strain of *P. aeruginosa* [46-48]. With increasing antibiotic resistance rates, selecting the proper antibiotic is growing increasingly difficult. Yet *P. aeruginosa* has a unique property that makes treatment even more difficult: *P. aeruginosa* can actually develop resistance to an antibiotic during treatment. *P. aeruginosa* can do so by either acquiring resistance genes on plasmids or by altering the expression of certain genes in their own genetic code (such as up-regulating the expression of drug efflux pumps on their surface) [48]. When *P. aeruginosa* develops resistance during treatment, it can double the length of stay and cost of treatment [49]. The overall trend of increasing antibiotic resistance combined with *Pseudomonas*' innate ability to develop resistance make the initiation of appropriate antibiotic therapy even more challenging.

3.4. Neisseria gonorrhea

Gonorrhea, caused by *Neisseria gonorrhea*, is the second most prevalent sexually transmitted infection in the U.S. [50]. The CDC actively monitors the susceptibility patterns of gonorrhea through the Gonococcal Isolate Surveillance Project (GISP). Fluoroquinolones used to be the standard of care for patients with gonorrhea. However, in the early 2000s, fluoroquinolone-resistant *N. gonorrhea* strains began to emerge prompting the CDC to no longer recommend fluoroquinolones as first line therapy. However, in 2010 GISP found that 27.2% of all isolates were resistant to penicillin, tetracycline, ciprofloxacin or some combination of the three and 6.9% were resistant to all three [51]. The CDC now recommends dual therapy with ceftriaxone and azithromycin [52].

Recently, there is evidence that *N. gonorrhea* may be developing resistance to cephalosporins as well. In 2009, the first case of ceftriaxone resistant *N. gonorrhea* was isolated from the pharynx of a woman in Japan [53]. While there have not been any reported cases of cephalosporin-resistant gonorrhea in the U.S., GISP has noted an increase in the minimum inhibitory concentration (MIC) for cephalosporins among gonococcal isolates. From 2006 to 2011, the proportion of isolates with an increased ceftriaxone MIC increased from 0.05% to 0.5%. GISP notes that the rates are highest in the western U.S. and among men who have sex with men [54]. If cephalosporin resistant *N. gonorrhea* becomes widespread in this country, the CDC estimates the 10-year health impact to be 75,000 new cases of pelvic inflammatory disease, 15,000 new cases of epididymitis, 222 new human immunodeficiency virus cases and over $235 million in additional healthcare costs [55].

4. Implications/solutions

The examples discussed above highlight the growing problem of bacteria developing resistance to first line therapies. These trends are especially concerning for ED providers, because they are often the first point of contact for individuals presenting with these diseases and must determine which antibiotics to administer. Failure to identify and properly treat these organisms can have a devastating impact on patient outcomes. As such, it is important for ED providers to review previous culture and sensitivity when available, particularly in patients with risk factors for resistant organisms.

While institution specific antibiograms do exist they are not universally available or standard practice. Even if available, antibiograms may not reflect susceptibilities for uncomplicated cases given their bias

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towards resistant pathogens due to the practice of not culturing urine or wound specimens from patients with uncomplicated infections [56,57].

One important strategy to combat antibiotic resistance is the use of institutional Antibiotic Stewardship Programs (ASPs). ASPs are programs that work to promote the appropriate use of antibiotics and to decrease the spread of resistant organisms. They are instituted by the hospital, and they often involve a multidisciplinary team that reviews antibiotic use and advises providers on how to use antibiotics more effectively. ASPs have been shown to be very effective in helping to optimize antibiotic use and reduce healthcare costs. Studies have demonstrated that institutional implementation of ASPs has led to a decrease in patients being infected with both C. diff and even VRE. Additionally, ASPs have led to decreased costs associated with treating patients requiring antibiotics. This is important to consider as the price of many antibiotics has greatly increased. ASPs have shown great promise but implementation is limiting their effect. Currently, 79% of university hospitals have ASPs but only 40% of community hospitals have designated ASPs [58]. ASPs have been shown to make a difference but their effectiveness will be limited until they become more broadly applied. In particular, the inclusion of EDs in ASPs and the development of ED specific stewardship solutions will be critical to supporting emergency providers in improving antibiotic use and patient outcomes [59].

In order to implement successful strategies nationally, significant investment will be required. In the fiscal year 2016, Congress appropriated $160 million to the CDC for the purpose of combating antibiotic resistance [60]. In July 2016, the CDC announced that it was providing $67 million in funding to states to help with antibiotic resistance. According to the CDC, those funds would be divided among the 50 states' health departments, six local health departments (Washington DC, Chicago, Houston, Los Angeles County, Philadelphia, and New York City), and Puerto Rico. This funding became available to states on August 1st with the goal of expanding their ability to detect and track antibiotic resistance trends. Specifically, the CDC's plan allows for every state's health department to have the ability to test for CRE and the ability to perform whole genome sequencing of intestinal bacteria. The CDC will also use these funds to place support teams in nine health departments across the country to rapidly identify antibiotic resistant gonorrhea [61,62].

Finally, emergency providers can impact the development of antibiotic resistance through rational use of antibiotics. The Choosing Wisely campaign in conjunction with the American College of Emergency Physicians has highlighted the importance of avoiding unnecessary use of antibiotics for skin and soft tissue infections as well as viral upper respiratory infections [63]. When available, emergency providers should review previous culture and sensitivity data when making treatment decisions to ensure effective therapy while avoiding the overuse of broad-spectrum antibiotics [64].

5. Conclusion

The growing problem of antibiotic resistance has multiple implications for emergency medicine providers. The potential for negative patient outcomes increases as antibiotic resistance becomes more prevalent. Strategies for addressing the problem of antibiotic resistance include rational prescribing, community-wide antibiograms, as well as expansion and widespread implementation of Antibiotic Stewardship Programs. Further development of these strategies will be pivotal in ensuring the success of EPs in the treatment of antibiotic-resistant infections.

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