Implications of the Growing Antibiotic Resistance in Patient Care

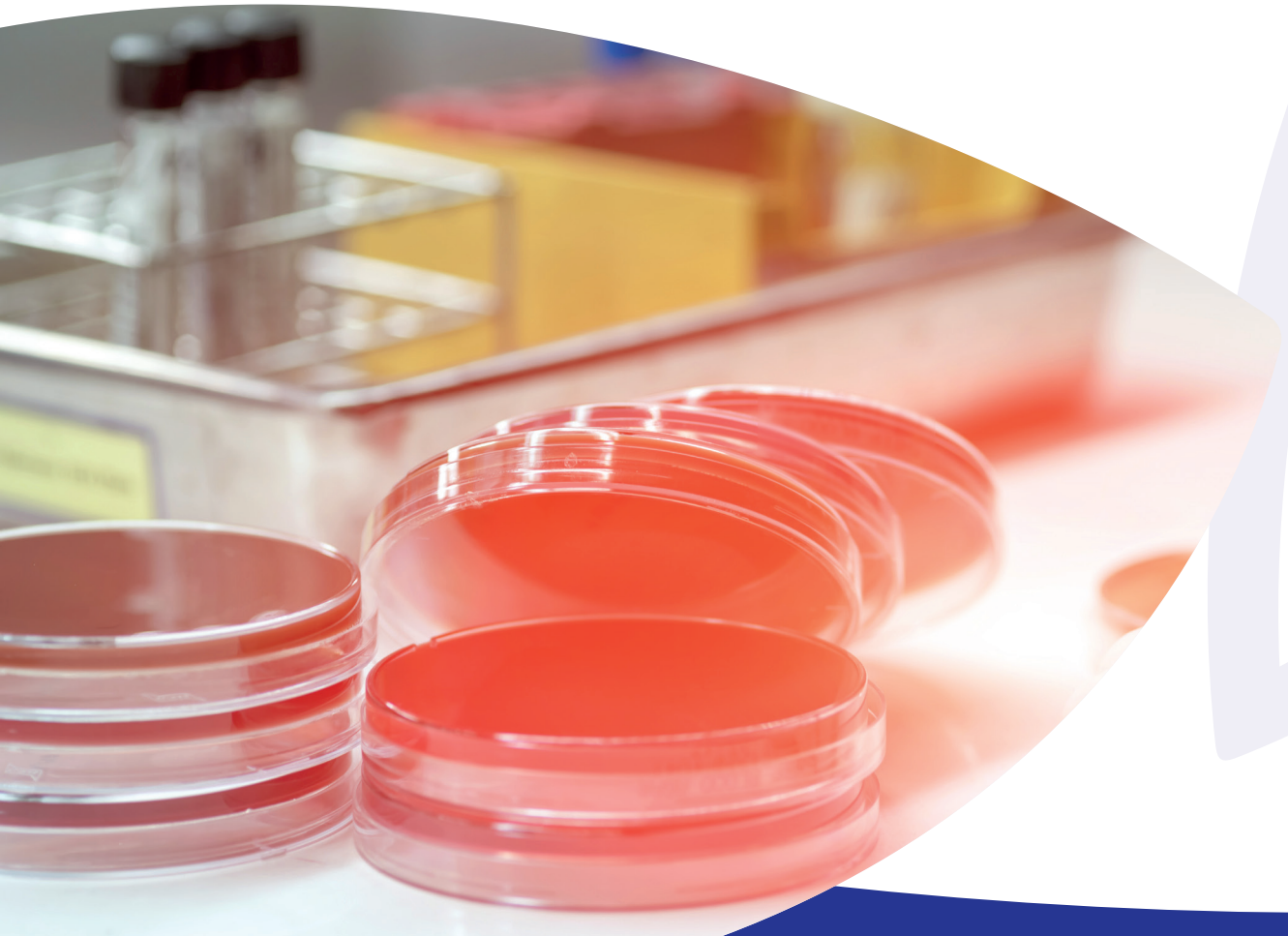
By: Peter Teska, Infection Prevention Application Expert, Diversey
and Jim Gauthier, Senior Clinical Advisor, Diversey

Rev 8 Jun 2016

Introduction

The discovery of penicillin and subsequent generations of antibiotics has been heralded as one of the biggest medical discoveries in history. Yet shortly after his discovery of penicillin in 1928, Dr. Fleming warned of the dangers of resistance and this fear has been proven to be accurate. Within a few years of the introduction of each new class of antibiotics, resistance was detected, helping drive the need for development of the next blockbuster antibiotic.

The pace of introducing new antibiotics has slowed to a crawl, but within the last decade, bacterial resistance to antibiotics appears to have grown at a more rapid pace, leading to concerns about the "end of the antibiotic era" being on the horizon.



Case Report:

A paper accepted for publication in the journal *Antimicrobial Agents and Chemotherapy* (McGann 2016) increased this concern as an organism isolated in a patient in the United States was shown to be resistant to colistin, even though the patient was not receiving colistin. Colistin is rarely used in the US due to side effects and is considered an antibiotic of last resort.

McGann reports that during routine culturing of the urine of a 49 year old female from Pennsylvania with no travel history in the previous 5 months, it was determined that the patient was suffering from an Escherichia coli infection. Per facility policy, the bacterium was tested for resistance to a range on antibiotics. Through this testing, it was determined that the isolate was an Extended Spectrum Beta Lactamase (ESBL) producing phenotype and, consistent with facility policy, it was further tested for colistin susceptibility among other antibiotics. It was shown to be colistin resistant in addition to other antibiotics.

Since the patient has never taken colistin, the authors theorized that a plasmid (small segments of DNA not part of the bacteria's chromosome) containing the resistance gene was shared by another Enterobacteriaceae which enabled this E. coli to develop colistin resistance. This theory suggests that strains of bacteria may trade plasmids, spreading wide antibiotic resistance, which is quite different than previous thinking where the bacteria needed to be exposed to the antibiotic to develop resistance.

CDC Publication on Antibiotic Resistance Threats:

In 2013, the Centers for Disease Control and Prevention (CDC) published a report on antibiotic threats in the United States. The CDC estimates that more than 2 million people acquire a serious infection that is resistant to one or more antibiotics, resulting in at least 23,500 deaths annually in the US. They also estimate that within the United States, at least 50% of the antibiotics prescribed are either not needed or are not optimally effective as prescribed.

The report further discusses how some Gram negative bacteria are becoming increasingly resistant to nearly all drugs that would be used for treatment. Members of the Enterobacteriaceae (along with Pseudomonas species and Acinetobacter species) are specifically called out as they can cause serious infections and are commonly healthcare associated, which is concerning for the Healthcare industry.

The following list from the CDC report summarizes the current concerns with existing classes of antibiotics and Gram negative bacteria.

- **β-lactams:** Gram-negative bacteria have developed several pathways of resistance and ESBL producing bacteria can break down the antibiotics before they can be effective.
- **Penicillin, amino-penicillins, early generation cephalosporins** (a β-lactam subclass): These drugs are rarely used for Gram negative bacteria as resistance is widespread.
- **β-lactamase inhibitor combinations** (a β-lactam subclass): These drugs are important for treating Gram negative infections, but resistance is increasing.
- **Extended spectrum Cephalosporins** (a β-lactam subclass): These drugs have been the cornerstone for treating Gram negative infections for 20 years, but resistance is increasing.
- **Carbapenems** (a β-lactam subclass): Currently the antibiotic of last resort for Gram negative bacterial infections, the rise of carbapenem resistance in the last decade, especially in *Enterobacteriaceae* – Carbapenem Resistant Enterobacteriaceae (CRE) is concerning because once a bacteria becomes resistant to carbapenems, it generally becomes resistant to all β-lactam antibiotics. Other bacteria are Carbapenemase producing organisms (CPO) such as *Acinetobacter* species and some *Pseudomonas* species.
- **Fluoroquinolones:** A broad spectrum antibiotic, but resistant bacteria developed quickly with increased use.
- **Aminoglycosides:** Often used with β-lactam drugs for Gram negative infections, but growing resistance and concerns about side effects makes these less prescribed.
- **Tetracyclines and Glycyclines:** Not considered a first line treatment option, but with increasing resistance in other classes of antibiotics, use is increasing.
- **Polymyxins (includes colistin):** This is an older class of antibiotics, but has toxicity concerns, which reduce its use.

In the same report, the CDC detailed the classes of microorganisms that were of highest concern and assigned a threat level (concerning, serious, or urgent.) After each organism in parenthesis is the number of cases and deaths in the US each year for reference.

Urgent Threats

- Clostridium difficile
  (250,000 cases, 14,000 deaths)
- Carbapenem-resistant Enterobacteriaceae
  (CRE) (9,300 cases/year, 610 deaths)
- Neisseria gonorrhea (246,000 cases, <5 deaths)

Serious Threats

- Multi-drug resistant Acinetobacter
  (7,300 cases, 500 deaths)
- Drug resistant Campylobacter
  (310,000 cases, 28 deaths)
- Fluconazole resistant Candida
  (3,400 cases, 220 deaths)
- Extended Spectrum β-lactamase producing
  Enterobacteriaceae (ESBL)
  (26,000 cases, 1,700 deaths)
- Vancomycin resistant Enterococcus (VRE)
  (20,000 cases, 1,300 deaths)
- Multi-drug resistant Pseudomonas aeruginosa
  (6,700 cases, 440 deaths)
- Drug-resistant Non-Typhoid Salmonella
  (100,000 cases, 40 deaths)
- Drug-resistant Salmonella serotype typhi
  (3,800 cases, <5 deaths)
- Drug-resistant Shigella (27,000 cases, <5 deaths)
- Methicillin-resistant Staphylococcus aureus (MRSA)
  (80,000 cases, 11,000 deaths)
- Drug-resistant Streptococcus pneumoniae
  (1,200,000 cases, 7,000 deaths)
- Drug-resistant Tuberculosis
  (1,042 cases, 50 deaths)

Concerning Threats

- Vancomycin-resistant Staphylococcus aureus (VRSA)
  (<5 cases, <5 deaths)
- Erythromycin-resistant Group A Streptococcus
  (1,300 cases, 160 deaths)
- Clindamycin-resistant Group B Streptococcus
  (7,600 cases, 440 deaths)

Potential Actions:

The range of bacteria causing infections and the large number of infections across these bacteria presents treatment challenges for physicians. When fighting a problem as complex as antibiotic resistance, it is appropriate to consider a multi-factor approach as multiple actions will likely be required to have a significant impact on this issue. The list that follows was generated from multiple sources in an attempt to identify some potential levers to impact antibiotic resistance. Many of these actions would require prolonged efforts with the involvement of a number of different parties, yet broad strategy with numerous actions is the only strategy likely to have significant impact.

1. **Antibiotic stewardship:** An antibiotic stewardship program can help limit resistance developing within healthcare by ensuring patients receive the right antibiotic, for the right indication, using the proper route for the ideal length of time. Once an organism is identified as causing an infection, and tested for antibiotic susceptibility, it is prudent to switch to a less broad-spectrum antibiotic if possible so normal flora organisms are not damaged. In the community, many of the antibiotics currently being prescribed for people have little clinical value for a range of reasons including giving antibiotics to people that have viral infections or using antibiotics that are ineffective against the bacteria causing the infection. Strategies and tactics should be considered to prevent additional resistance from developing in the community, and monitoring people to ensure they take all their doses would help limit the development of antibiotic resistant strains.

2. **Reduce use in animals.** Reduce and/or eliminate the routine use of antibiotics in animals. The CDC report discusses that many of the antibiotics given to animals are prophylactic or growth promoting, rather than in response to an actual illness. These antibiotics can potentially contribute to bacteria developing resistance. If the antibiotic remains in the animal meat after slaughter, low levels of the antibiotic can provide time for organisms to evolve resistance.

3. **Prevention of infections**. Vaccinations, hand hygiene, effective environmental cleaning and disinfection, and the use of barriers (gloves, gowns, and masks) can all have a significant impact on how bacteria are transmitted between people. If fewer people become sick, fewer antibiotics will be prescribed, giving the bacteria fewer chances to develop resistance. Better education around the use of hand hygiene, cleaning and disinfection, and using gloves, gowns, and masks, can help protect those around someone who is sick.

4. **Tracking and better testing.** Test patients with infections to determine the antibiotic resistance of the organisms causing their infections. Share this information on highly resistant organisms with CDC and other authorities to determine the prevalence of antibiotic resistance. Rapid tests may be needed to determine whether people have true bacterial infections which can lead to faster treatment and proper use of antibiotics. Rapid tests should also be developed to identify the resistance of the bacteria to current antibiotics, making treatment easier for physicians.

5. **Healthcare staff decolonization**. Many healthcare workers are colonized with antibiotic resistant bacteria. Routine testing would allow for identification and decolonization for these workers, reducing the spread of resistant bacteria. This could also lead to more resistance, however, depending on how decolonization is carried out.

6. **Develop new antibiotics**. There are a number of challenges with this strategy. First, the discovery of the current library of antibiotics may mean that there are only a few drugs yet to be discovered. New antibiotic producing organisms are being investigated by looking to new sources such as our oceans. Second, developing any new drug is expensive and time consuming. This would be no exception. Third, drug companies look at the potential for use to decide whether to spend money developing a drug. A drug that is used daily for the rest of a person's life, such as a cholesterol lowering medicine is attractive to develop. A new antibiotic would only be used for infections, which hopefully clear up. Also, a new antibiotic is unlikely to be widely used because of concerns about bacteria developing resistance. Thus developing antibiotics is not financially attractive for drug companies. Governments may need to provide a significant financial incentive to offset the small revenue likely to be associated with a new antibiotic.

References:

McGann P, Snesrud E, Maybank R, et all. Escherichia coli harboring mcr-1 and blaCTX-M on a novel IncF plasmid: First report of mcr-1 in the USA. Antimicrob Agents Chemother, 2016. Published on-line. doi:10.1128/AAC.01103-16. Downloaded May 31, 2016 from http://aac.asm.org/content/early/2016/05/25/AAC.01103-16.full.pdf+html

CDC, Antibiotic resistant threats in the United States, 2013 (2013). Downloaded from http://www.cdc.gov/drugresistance/threat-report-2013/index.html. Accessed 1 Jun 2016.

Diversey has been, and always will be, pioneers and facilitators for life. We constantly deliver revolutionary cleaning and hygiene technologies that provide total confidence to our customers across all of our global sectors. Led by Dr. Ilham Kadri, President & CEO, and headquartered in Charlotte, North Carolina, USA, Diversey employs approximately 9,000 people globally, generating net sales of approximately $2.6 billion in 2016.

For more information, visit www.diversey.com or follow us on social media.

www.diversey.com