The Post-Antibiotic Era: Colistin Resistant, Carbapenem Resistant Gram Negative Rods

The Story of Colistin Resistance: A Tale of Caution

The story begins in 1947, when Japanese scientists isolated polymyxin E (colistin) from *Bacillus polymyxa*[1]. Doctors frequently used colistin to treat life-threatening gram negative rod (GNR) infections from the 1950s to 1970s. However, colistin was just as toxic to patients as it was to bacteria, so when scientists discovered aminoglycosides, colistin use in humans fell out of favor.

Fast forward to Chinese Hog Farms in the 1980s, when standard practice of adding colistin to hog feed began[2-4]. The gut bacteria in Chinese pigs were exposed to and developed resistance to colistin over time. Hogs and people living in close proximity enabled colistin resistance to cross from pigs to human gastrointestinal flora. This hog-to-human resistance transmission went largely unnoticed because Chinese physicians no longer prescribed colistin to humans. However, the widespread emergence of carbapenem resistance in the early 2000s forced physicians to use colistin again as therapy for carbapenem resistant infections.

As physicians utilized more colistin, sporadic cases of infections with colistin-resistant, carbapenem-resistant gram negative rods began to surface globally. Marchaim et al identified the first American cluster of colistin-resistant, carbapenem-resistant *K. pneumoniae* infections in Detroit, MI in 2011[5]. Similarly, Italian physicians identified clusters of colistin-resistant, carbapenem-resistant *K. pneumoniae* infections in Rome and Sienna[6, 7].

Scientists recognized this shift from sporadic cases of colistin resistance to clusters of resistant cases as a warning sign and began zealously investigating colistin resistance. Kreiswirth and colleague Liu et al discovered the plasmid-mediated resistance mechanism, called MCR-1, as the mechanism of colistin resistance in the majority of colistin-resistant, carbapenem-resistant gram negative rod infections[2, 4]. The MCR-1 plasmid discovery is important and unnerving, as plasmids are “jumping genes.” It is difficult to combat plasmid mediated mechanisms of resistance because these “jumping genes” not only move from one strain to another, but the genes also move from one *species* to another. For example, different species of GNR, such as *E. coli* and *K. pneumoniae*, that are in close proximity of each other (i.e., in the human gut) can exchange the MCR-1 resistance gene in addition to other plasmid mediated resistance genes like NDM genes. NDM genes are one family of plasmids that lead to carbapenem resistance. GNR harboring both the NDM-5 gene and the MCR-1 gene are truly pan resistant[2].

The Scientific Community Responds

The discovery of MCR-1 gene prompted scientists to evaluate historical isolates of *Enterobacteriaceae* for the MCR-1 gene[8]. Now, over 20 countries have identified MCR-1 carrying *Enterobacteriaceae* in humans, food, environmental samples, and animals. Three *E. coli* isolates carrying MCR-1 have been identified in the United States. In May 2016, the microbiology lab at Walter Reed identified the first patient with MCR-1...
mediated colistin resistant *E. coli* infection in the United States. Since then, the Centers for Disease Control (CDC) and the Department of Defense have coordinated efforts to identify the source of the infection. Subsequently, the CDC has developed protocols for testing microorganisms for the MCR-1 gene. Furthermore, the CDC’s Antibiotic Resistance Lab Network will provide lab capacity and additional infrastructure to detect and respond to colistin resistance [9]. The CDC recommends

**Jumping genes, like MCR-1, can move between bacterial strains and species**

further testing for *Enterobacteriaceae* isolates with a minimum inhibitory concentration (MIC) to colistin of 4 mcg/mL or higher. These *Enterobacteriaceae* isolates should be 1) tested for the presence of the mcr-1 gene locally if possible, and 2) sent to the CDC for confirmatory testing.

Unfortunately, no one has a good prevention plan because it is impossible to control the movement of plasmids. Some infectious disease physicians have proposed screening of high risk populations, such as transplant patients, for colistin resistant *Enterobacteriaceae* as a potential management strategy[3]. However, this strategy is both expensive and potentially ineffective. Therefore, we must rely on keen observation, early detection of colistin resistance, and proven infection control practices.

**DICON Responds**

The emergence of colistin resistant, carbapenem resistant gram negative rods is both harrowing and expected. Resistant GNR challenge the best infection control practices because, by nature, GNR are quickly adapting organisms and have polymorphic resistance mechanisms. The CDC needs to rapidly respond with the infrastructure to detect not only colistin resistance, but also resistance to other antibiotics of last resort. In the meantime, we urge all of our DICON members to do the following:

- Continue your commitment to the basic infection control practices of hand hygiene, equipment reprocessing, and safe injection practices
- It is not necessary to test Proteus, Providencia, Morganella, and Serratia spp. for colistin resistance as these bacteria are intrinsically resistant to colistin
- If colistin resistant (MIC>4) GNR are identified, please alert your DICON IP and submit the isolate to CDC for MCR-1 testing. [Click here for CDC submission instructions.]
- If you have a patient with a confirmed colistin resistant infection, contact DICON so we can help you formulate an appropriate infection control plan

**References**