Editorial:

Mobile Colistin Resistance (MCR) Gene, Antimicrobial Resistance: A Global Public Health Threat

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Colistin (Polymyxin E) is a novel antibiotic which gains importance in recent years though it was discovered a long time ago in 1947 from a bacteria *Paenibacillus polymyxa* var. colistinus.[1-4] Colistin possess high nephrotoxic and neurotoxic adverse effects; thereafter, it was abandoned in the 1970s and 80s as there was the development of less toxic highly effective newer antimicrobials. [5-7] As the years passed, emergence and widespread distribution of multidrug resistance gram-negative bacteria such as carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), multidrug resistance *Pseudomonas* species, extensively drug-resistant (XDR) *Pseudomonas aeruginos*a, and XDR *Acinetobacter baumannii* were posing a serious threat to human health and safety. [8-9] This paved the way for a reconsideration of colistin as a valuable therapeutic alternative as a last resort used against infections caused by these potentially dangerous gram-negative pathogens. [10, 11] "Colistin is an amphiphilic, complex, multi-component, pentacationic decapeptide antibiotic." [12] Colistin binds electrostatically to the outer membrane of gram-negative bacteria, increasing the permeability of membrane which leads to extravasation of cytoplasmic content, cell lysis and ensues death of pathogens. [13, 14] It is only effective against gram-negative microorganisms, thereafter, designated as a narrow spectrum bactericidal agent. Two forms of colistin are commercially available, colistin methanesulfonate sodium (CMS) used parenterally and colistin sulfate (CS) given oral and topically as powder for skin infections. [1, 15] Nevertheless, alarming news is extensive use of colistin to treat the sturdy bacterial infections especially in ICU setting has led to development of gram-negative colistin-resistant microorganism; such as colistin-resistant *Enterobacteriaceae*, colistin-resistant *Acinetobacter baumannii* (CoRAB), *Pseudomonas* etc. [16-19] Colistin resistance was thought due to chromosomal mutations caused by modifications of Lipopolysaccharide (LPS) at outer cell wall of gram-negative pathogens. Additionally, affinity of colistin towards LPS reduced through amendment of negative charge. [14, 20] These chromosomal mutations among gram-negative organisms towards colistin only vertically transmissible. [21, 22] So it was believed that colistin was one of the last drugs where resistance was not spread from cell to cell. [21, 23, 24] A plasmid-borne transmissible mobile colistin-resistant gene (mcr-1) was identified among gram-negative pathogens *Escherichia coli* SHP45 in Chinese pork meat in 2015. [25] The colistin-

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resistant *E. coli* EC11 strain was identified from dairy farms by 2016 in same city in Shanghai, China.[26] Until now nine different mcr genes were identified. [27] In Belgium mcr-2 was first found in bovine and porcine *E. coli* and rarely found outside European union,[28] mcr-3, [29] mcr-7, [30] mcr-8 [31] in China, mcr-4 found in Italy, Spain and Belgium,[32] mcr-5 in Germany,[33] mcr-6 (formally known as mcr-2.2) in UK.[34] mcr-9 was detected in multidrug-resistant *Salmonella enterica* serotype typhimurium identified isolated from a patient. [27, 35] The presence mcr-1 gene has been evidenced throughout the planet.[36] Additionally, mcr-1 positive *E. coli* widespread presence in environment, food, and animals especially livestock and birds. Nevertheless, human carriers of mcr-1 so far been rare. It has been observed that less than 2% and ≤0.2% among *Enterobacteriaceae* and *E. coli* clinical specimens contain mcr-1 gene in China and Europe, respectively.[25, 37-39] The low human carrier of mcr gene may be due to restricted use of colistin in hospitals than commercial animal and poultry industries.[21] On the other hand, high levels of colistin are utilized in rooster and animal farms, especially to control colibacillosis originated diarrhea diseases,[40] that in-turn promotes a strong selective pressure for colistin resistance animals.[21] So far, to date mcr-1 carrying isolates were recognized from 31 countries. [36] The nations with the highest numbers of mcr-1 positive tested specimens were in China, Vietnam, and Germany. *E. coli* is the main reservoir for mcr-1, but the other gram-negative pathogens were also documented as mcr-1 positive. Those pathogens were *Salmonella enterica*, *Klebsiella pneumoniae*, *Escherichia fergusonii*, *Kluyvera ascorbata*, *Citrobacter braakii*, *Cronobacter sakazakii*, and *Klebsiella aerogenes*. [36]

It has been evidenced that the mcr-1 gene and other microbial résistance gene can overlap and exists in the same microbial class. The mcr-1 often presents with ESBLs (CTX-M, SHV, and TEM type) and AmpC cephalosporinase (CMY type), quinolones resistance genes (qnrS and aac (6=)-Ib-cr).[37, 38, 41, 42] Colistin sulfate to be the most commonly used antibiotic in the poultry industry in Bangladesh.[43] Colistin-resistant *E. coli* carrying mcr-1 has not been isolated from hospital settings, and this is the first report of the occurrence of colistin-resistant *E. coli* carrying resistant marker mcr-1 from the environment (city sludge specimens) of Bangladesh.[44] There are several phenotypic and genotypic methods for the detection of mcr-1 producers.[45, 46] Broth microdilution (BMD) is considered the reference test to see the susceptibility profile of polymyxin. [1] The other method to document the mcr-1 gene is Colistin MAC tet (CMT), Combined Disc test (CDT), Colistin MIC reduction (CMR), Modified Rapid Polymyxin NP test (RPNP) and alteration of Zeta potential tests. [46-48] Polymerase Chain Reaction (PCR) and whole-genome Sequence (WGS) is considered the reference tests to identify the mcr gene from cultured bacteria as well as in clinical, fecal, environmental and food samples.[47, 49] The advantage of PCR is to detect known mcr genes and the WGS can identify all known or unknown colistin resistance genes within 2 days.[50] Polymyxin / colistin is an essential therapeutic agent in medicine both for human and food-producing industries; thereafter, it is imperative need to arrest the speedy spread of mcr-1 concealing plasmid.[1, 47, 51] Subsequently to halt such rapid spread of colistin gene utilization this last resort needs to be more rational and minimum in absolute clinical necessity. As irrational imprudent use of antibiotics acts as a promoter of resistance.[52, 53] It is extremely significant to appraise the frequency of human carriers of *E. coli* mcr-1 +.[38] The spread of *E. coli* in the hospital environment by maintaining the proper sanitization protocol, [54] by screening the patients whether they work in food chain.[55] Antimicrobial resistance (AMR) is a global public health threat not only to human life but also for food industries to feed us. Consequently, it is essential to address it on multiple levels. Tourists, vacationers, explorers to those geographic parts with high levels of AMR should have vaccines up-to-date. [56] Resistance to colistin increases potentially problematic for clinicians to choose antimicrobials. As only a few antimicrobials are remaining for Colistin-, Carbapenem-Resistant K*lebsiella pneumonia* (C-C-RKp) infections.[57] The antimicrobial selection procedure should be on strict and appropriate scientific, rational, and prudent basis, such as hospital antibiogram of clinical specimen, the location of infection, pharmacokinetics/ pharmacodynamics (PK/PD) effects and potential adverse drug reactions.[57-59] Researchers suggest recently that the best available treatment options colistin-resistant infection is tigecycline, gentamicin, fosfomycin, and ceftazidime/avibactam.[57, 60] As conclusive statement more research advocated using

the "one health" method to delay/stop antimicrobial resistance and safeguard human life. [61] There is need to aware of the food industry operators along the entire food chain and to reduce colistin as growth promoters. [55, 62] Wide-ranging research should be commenced immediately to discover more novel antimicrobial molecules to fight against the Colistin-Carbapenem resistant pathogens. National and International medicine control agencies must develop stringent policies with regulatory policing activities to control misuse and irrational utilization antimicrobials; and need to develop regular educational intervention programs both for health professionals and consumers to promote prudent use of antibiotics. [63-67]

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