Colistin-Resistant Superbugs and Poultry Politics!

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The ancient Indian scripture *Manusmriti* forbids eating food in which hair or bugs have fallen and food that belongs to a miser, a thief, a cruel man, a liar and a doctor! The list is so long that it mentions almost every food we are expected not to eat, with a notable exception – food that contains colistin-resistant superbugs!

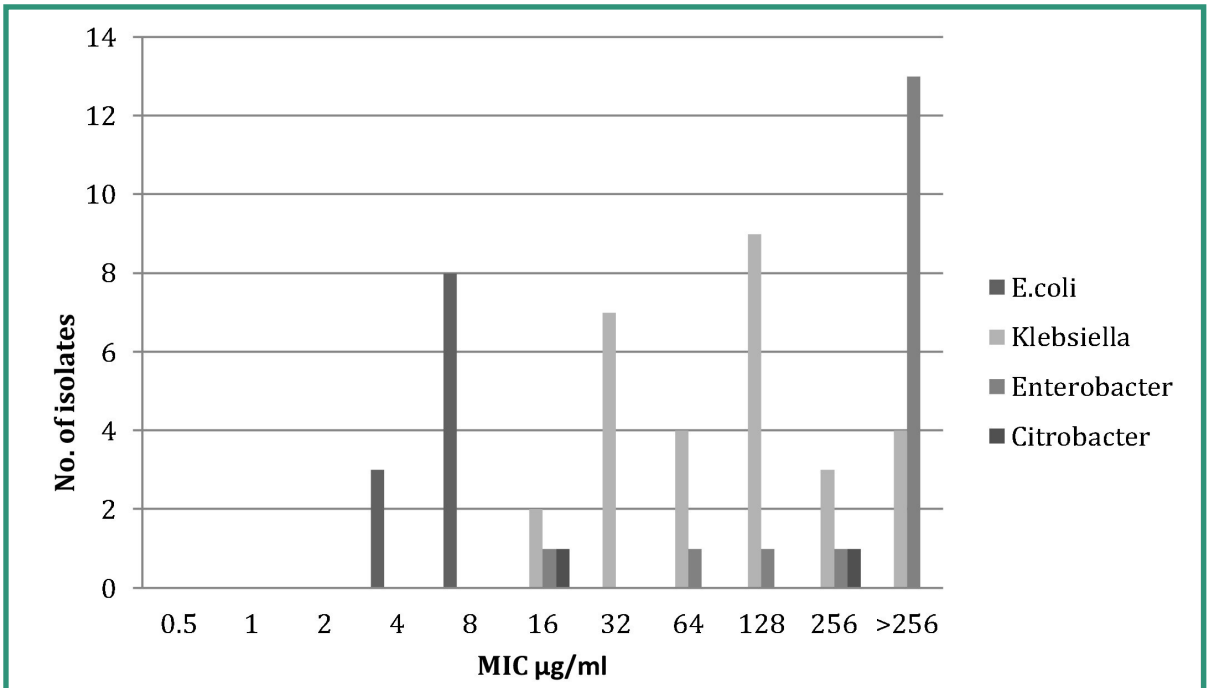
Manusmriti is a compilation of discourses given by Manu, an ancient Indian Guru, 300 BC. Antibiotics are a phenomenon belonging to the current eon, the *Kaliyuga* – where evil and quarrel reign! Colistin is an antibiotic discovered in 1959 which went out of fashion in the 1980s due to the unfriendly attitude of this molecule on human kidneys. Safer antibiotics such as carbapenems replaced colistin and turned out to be the favourite in the armamentarium, fostering extensive usage of this more expensive and more attractive molecule. As expected, extensively drug resistant Gram-negative bacteria (XDR GNB) spread their devilish tentacles across the world, with high mortality rates among the affected patients, especially those undergoing cancer chemotherapy and transplants. The world finally remembered the old sweetheart – colistin. The renewed love and affection towards colistin resulted in worldwide extensive usage of this molecule and hence the spread of colistin-resistant bacteria, with literally no active drug, emerging sensitive on the antibiogram display.

> ***"Usage of colistin as a growth promoter must be banned urgently."***

Pan drug resistance, or possible pan drug resistance is indeed the result of extensive colistin usage in the human world. Genes coding for colistin resistance (alterations in *mgrB , phoP/Q, pmr A/B*) are situated in the chromosomal part of the bacteria and as such, are less transmissible. Colistin-resistant bacteria were sporadic and we anticipated them to remain sporadic forever. Until a few years ago, a cluster of patients with colistin-resistant bacterial infections could easily be contained with very good infection control practices. The appearance of the plasmid mediated *mcr-1* gene and its variations dramatically changed the scenario. More than thirty countries reported the presence of *mcr* positive bacteria in human, food and environmental samples in just three years. Though the *mcr* gene is a well-reported cause of colistin resistance in human *Enterobacteriaceae* isolates, especially in *E.coli*, the gene does not explain the rapid dissemination of colistin resistance in *Klebsiella spp* in humans. *mcr* and its variants are rare in *Klebsiella* of human origin. Then how could *Klebsiella* change their behaviour from sporadicity to clonality and unleash havoc across the world? The answer… insertion sequences!

Insertion sequences (IS) help the alterations in *mgrB* or other similar genes to lose their celibacy and turn into highly promiscuous elements, moving out of the chromosome to plasmids and then to other bacteria. Plenty of publications are now available on the role of IS in the dissemination of colistin-resistant *Klebsiella spp* in healthcare institutions.[1-3]

mcr and its variants are less significant in clinical practice. Most colistin-resistant infections in hospitals across the world are due to *Klebsiella* (without mcr) and not *E. coli* with *mcr.* If the *mcr* gene in colistin-resistant *Enterobacteriaceae* could be of poultry origin, then why couldn't the *mgrB* mutations in *Klebsiella* have an indirect poultry connection? If *mgr B* mutations and IS are present in human *Klebisella*, naturally these elements should be present in *Klebisella* of food origin. If so, consumption of food containing *Klebsiella* with colistin resistance due to *mgrB* mutation could transmit these gene alterations to human *Klebsiella*. The first step in proving the hypothesis is to look for *mgrB* mutations in food *Klebsiella*. For the first time in global literature, our team of researchers from Chennai and Vellore, India, reported the presence of insertional inactivation of *mgrB* gene coding for colistin resistance in *Klebsiella* of food origin.[4] The paper has inspired scientists across the world to search for chromosomal mutations and insertional inactivation in food *Klebsiella* and, of late, at least one more publication has enriched the literature.[5] We have also identified human intestinal carriage of food born *Klebsiella* with *mgrB* mutations and insertional inactivation (unpublished data), further corroborating the food hypothesis. Can the human intestinal coexistence of carbapenem-resistant colistin sensitive bacteria of human origin and the colistin-resistant carbapenem sensitive *Klebsiella* of food origin, result in transmission of *mgrB* mutations and colistin resistance, generating possible pan drug resistance? This is quite possible – but we do need further evidence to prove the hypothesis.



Colistin minimum inhibitory concentration (MIC) distribution of bacterial isolates from food samples in Chennai, India.

Our paper, quite incidentally, is also the first Indian paper on the presence of colistin-resistant bacteria in raw food samples. We could also detect the presence of *E.coli* with *mcr* genes, though we were more excited about the *Klebsiella* with *mgrB* mutations and insertional inactivation!

The paper inspired widespread discussion on the growth promotional use of colistin in the poultry industry and its implications on the healthcare system.[6-8] Colistin is extensively used in poultry and aqua farming in India, though the exact magnitude of the usage is not yet available. India imports at least 200 tonnes of colistin, worth $1,648,612 every year, to be used as growth promoter.[9] More than 95% of the import is from China. The Chinese Government has already banned the use of colistin in animal feed since November 2016. China still exports and India still imports colistin for growth promotional use. Though there is a rule specifying withdrawal period of antibiotics before processing food-producing animals, currently India has no regulations to prevent antibiotic usage as a growth promoter.

Considering the public health impact of the extensive spread of colistin-resistant bacteria in food samples, with subsequent potential gut colonisation and clinical infection; usage of colistin as a growth promoter must be banned urgently.[4] The Chennai Declaration of Medical Societies in India and India's AMR National Action plan have made clear cut recommendations to ban the usage of antibiotics as growth promoters in livestock and aqua farming.[4,10]

Since publication of our paper, the Indian Ministry of Health and other relevant ministries have fast tracked efforts to ban growth promotion use of colistin and a rule regarding this is in its final stage. Indian data inspires Indian action!

Manusmriti certainly advised against eating food offered or touched by doctors! The text was unequivocally right and eminently futuristic in this regard. Hand hygiene compliance rate among doctors was not considerably better in 300BC than in 2019 AD!

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