Immuno-VIP and Immuno-CIP: a support in the effort to treat the urinary tract infections with bacteria and superbugs resistant to antibiotics

The "superbug" Escherichia coli, multiply resistant, including to the last-resort antibiotic colistin, showed up in China in 2015. The drug resistance gene known as mcr-1 – which has the capacity to move from one bacterium to another – was found in about 1% of *E.coli* bacteria and 1% of a bacteria known as *Klebsiella pneumoniae*, that can cause pneumonia, bloodstream infections, and wound infections. The mcr-1 gene confers transferable colistin resistance. Mcr-1-positive Enterobacteriaceae (MCRPE) have attracted substantial medical attention; the focus has been on the clinical aspects of mcr-1-positive *Escherichia coli* (MCRPEC) infection, and on the risk factors for MCRPEC carriage. Of 17,498 isolates associated with infection, mcr-1 was detected in 76 (~1%) of 5,332 *E.coli* isolates, 13 (<1%) of 348 *Klebsiella pneumoniae*, one (<1%) of 890 *Enterobacter cloacae*, and one (1%) of 162 *Enterobacter aerogenes*. Due to resistance to better antibiotics on the rise, Colistin had taken on increasing importance in medicine as a reserve antibiotic [1].

Acquired resistance due to chromosomal mutation and selection is termed vertical evolution, since the advantage will be conferred to a bacterial line. Bacteria also develop resistance through the acquisition of new genetic material from other resistant organisms through horizontal transfer; this may occur between strains of the same species or between different bacterial species or genera sharing a same ecological niche. Mechanisms of genetic exchange include conjugation, transduction, and transformation. For each of these processes, transposons facilitate the transfer and incorporation of the new resistance genes into the genome of the bacterial host or into plasmids [2].

Superbugs are present in Europe. Colistin-resistant *E. coli* was identified in the pork meat [3]; Colistin-resistant *Klebsiella pneumoniae* strains were isolated from 18 patients in Romania, being included in the bacterial collection of the Faculty of Biology in Bucharest and in the germs collection of Activeimmunity.

Colistin resistance has been seen before, but not in this form. What makes this situation unique – and unsettling – is that the gene that makes the bacteria Colistin-resistant is contained in a plasmid, a mobile piece of DNA. Plasmids can easily move from one bacterium to another, both within a family of bacteria and to other families, as well. That means *E.coli* carrying mcr-1 can share it with other E.coli, as well as pass it to bacteria like Klebsiella pneumoniae [5].

Bacteria found in humans, animals and food continue to show resistance to widely used antimicrobials, says the latest report on anti-microbial resistance (AMR) in bacteria by the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC). The findings underline that AMR poses a serious threat to public and animal health. Infections caused by bacteria that are resistant to antimicrobials lead to about 25,000 deaths in the EU every year [6]. "Antimicrobial resistance is an alarming threat putting human and animal health in danger," said Vytenis Andriukaitis, the EU's health and food safety commissioner. "We have put substantial efforts to stop its rise, but this is not enough. We must be quicker, stronger and act on several fronts." [7].

The emergence of multidrug resistant bacteria in urinary tract infections (UTIs) is a challenge to medical professionals. According to ECDC (2018), more than a third of *K. pneumoniae* and half of *E. coli* strains reported were resistant to at least one of the antibiotics under surveillance. Moreover, the emergence of Colistin resistance among Enterobacteriaceae leave few therapeutic options against these ”superbugs”. Thus, immunological active proteins (IAP) have emerged as a potential supporting agent.

Chicken immunologically active proteins (CIAP) (egg proteins: IgY, holo-ovotransferrin, ovomucin, ovalbumin and lysozyme) were obtained from chickens immunized with antigens from *Escherichia coli, Klebsiella pneumoniae, Enterococcus spp, Pseudomonas spp, Proteus spp, Candida spp,* and MRSA strains. Immuno-CIP efficiency was demonstrated in vitro by: quantitative assay for Chicken IgY (ELISA Kit - ABCAM), rapid and slow agglutination test and bacterial growth inhibition test (HB&L ALIFAX, CIAP + live bacterial cultures).

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