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Alternative measures to address antibiotic resistance

Dr. M. Sonali, Assistant Professor, Department of Veterinary Microbiology, **Dr. E. Kumar**, Assistant Professor, Department of Veterinary public health and epidemiology, College of Veterinary Science, PVNR Telangana Veterinary University, Rajendranagar, Hyderabad
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Antibiotics are a pillar of modern medicine. Their use has reduced childhood mortality, and supported invasive surgery, complex treatments, and robotics-guided surgeries by managing secondary bacterial infections. Several factors, such as incorrect antibiotic use, patient factors, over-prescription by physicians, monotherapy, misuse of antibiotics as a business model by hospitals, prescriptions from the veterinary sector, commercial and marketing promotion, over-the-counter sale of antibiotics, prevailing microbiological testing methods, and the role of globalization in economic growth are combined with the extreme decline in antibiotic research, were only fueled the development of antimicrobial resistance. The increasing use of broad-spectrum antibiotics contributes to the development of MDR organisms. This also adds to the risk of re-emergence of many diseases like the emergence of XDR-TB (extensively drug-resistant tuberculosis) and the development of resistance against tigecycline and colistin, regarded as "salvage" medicines in medical treatment. The World Health Organization (WHO) has identified AMR as one of the three most severe threats to human health. Environmental bacteria may acquire antibiotic resistance by co-existence, evolution, or horizontal gene transfer (HGT), which can significantly impact antimicrobial resistance compared to vertical gene transfer.

Treating MDR organisms with antibiotics is highly complicated, with patients experiencing harmful side effects. There is a risk of developing antibiotic resistance over 10 years with notable antibiotics such as third-generation cephalosporins, vancomycin, imipenem, and intravenous fluoroquinolones. To protect humans and animals from the spread of antibiotic resistance, it is necessary to adopt a substitute non-antibiotic approach that is both significantly safer and free of antibiotics. Alternative measures to address antibiotic resistance are of great interest to drug discovery

researchers worldwide. Alternative mechanisms to treat resistant bacteria like:

1. **Fecal microbiota transplantation and two-component systems (TCS)**: Dietary supplements to boost an individual's immune system area is a healthy method to stop the development of the resistant bacterium, even in critically ill and hospitalized patients. The promising method is fecal microbiome transformation, which involves transferring healthy flora containing fecal matter from a healthy person to a recipient who is ill with enteric infections. Also, the antibiotics related factors disrupt the normal balance of colonic flora and reduce "colonization resistance, by reintroducing normal flora via donor feces, the imbalance can be corrected, the cycle is broken, and normal bowel function is reestablished (Bakken et al., 2011). This technology is also known as fecal transfusion, fecal transplant, fecal enema, human probiotic infusion, and stool transplant, and it is called "transformation" when used to treat cattle.
2. **Antimicrobial Peptides against Resistance**: Mesenchymal stem cells (MSCs) have emerged as a promising remedy for better therapeutic options against various acute and chronic diseases. These stem cells can enhance immunogenic modulation, tissue healing, and inflammation control systems. The AMPs, lipocal, hepcidin, and LL-37 have anti-bacterial properties against common pathogens such as *E. coli*, *S. aureus* and *K. pneumoniae*. They are derived from human bone marrow and umbilical cord MSCs.
3. **Incorporation of hemofiltration machines to combat resistant bacteria**: A severe bacterial infection in a patient leads to organ damage due to the overproduction of cytokines at the site of the infection and subsequent accumulation of immune cells. In those medical situations, hemofiltration machines can be attached to the injury site to remove bacterial accumulation and cytokines. Few recent research reports confirmed that the application of a hemo filter reduces the level of serum with bile acid microbial metabolites containing total bilirubin, direct bilirubin, total bile acids, lactate, and IL-6 in patients with septicemia.
4. **Quorum-sensing mechanism of bacteria:** Quorum sensing and biofilm formation are natural survival mechanisms of bacteria that involve a sequence of intracellular communications under various conditions. According to a study, bacterial species have a wide range of biological compounds with potential quorum-sensing properties. The development of quorum-sensing inhibition technologies, creates an antibiotic-resistant-free, safe situation for patients with complications and serious illness.
5. **Application of CRISPR-Cas in antimicrobial resistance:** Clustered regularly interspaced short palindromic repeats (CRISPR)- cas is a typical natural property inherited by bacteria for their defense, particularly against bacteriophages. This genome-editing technology can kill bacteria in vivo while creating a safe zone of antibiotic-free treatment in patients to prevent

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further spread. The nanosized CRISPR complexes that come under the nano-based CRISP R-editing system are very active against the *mec*-A gene in methicillin-resistant S. aureus.

6. **Phage-based resistance therapies:** Bacteriophage therapy is a practical approach for combating resistant bacterial infections. The study of bacteriophages in these drug-resistant bacteria has gained interest in the research community due to their presence and specificity for species with harmless characteristics. Knowledge of phage application within resistant bacteria is specific to the technical systems and knowledge available for phage selection, as well as the specific target site approach for every attempt, followed by continuous monitoring of the results to limit the side effects during the phage application for antimicrobial-resistant bacteria.
7. **Nanotechnology in the treatment of Resistant Bacteria**: Using nano-syringes medicines can be directly delivered into the cells without interrupting other mechanisms. Such targeted antimicrobial delivery into the cytoplasm of a targeted cell can significantly reduce the growth of AMR, particularly the bacterial type III secretion system (T3SS), which is involved in Gram-negative bacteria pathogenesis mechanisms.

Apart from above said alternatives, probiotics are animal-derived foods used to combat normal and resistant bacteria. Probiotics have a high microbial load and show a high biological activity in the host immune system. This probiotic food system can protect people of all ages from infections while reducing the economic crisis caused by the uncontrolled use of antibiotics. AMR has become a global issue with wide-ranging implications. To reduce the inappropriate use of antibiotics in various disciplines, educational and research communities must create new monitoring systems and proactive methods. In all these critical conditions, antibiotic resistance poses a significant threat to the environment, human life, and animal life. To limit the synthetic manufacturing of antibiotics, it is strongly encouraged to consider traditional forms of natural medicines or alternative technologies such as phage therapy. The epidemiological data must be reviewed regularly for the situational preparation of therapies and technological development. Before reaching the point of a pandemic, the fight against antibiotic resistnce must involve the health, educational, and other sectors.

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