Superbug, an Emerging Global Threat in Current Scenario: A Review

Arpita Padhy[1], Amit Ranjan Sahu[2], Siddharth Ranabijuli[3] and Subha Ganguly[4]*

[1]Additional Veterinary Assistant Surgeon, Department of Animal Husbandry and Veterinary Services, Government of Odisha, India.
[2]Ph.D Scholar, Division of Veterinary Biotechnology, Indian Veterinary Research Institute, Izatnagar, Bareilly, U.P, India.
[3]Subject Matter Specialist (Veterinary Science), Krishi Vigyan Kendra, Puri, OUAT
[4]Associate Professor, Department of Veterinary Microbiology, Arawali Veterinary College (Affiliated with Rajasthan University of Veterinary and Animal Sciences, Bikaner), N.H. – 52 Jaipur Road, V.P.O. Bajor, Sikar, Rajasthan, India
ganguly38@gmail.com

Abstract*: Antibiotics have been used for chemotherapeutic purpose from the early part of the 19th century. The development of antibiotics decreased the mortality among the human and animals leading to a better life expectancy. But the injudicious use of antimicrobials and selection pressure the microbes have developed resistance which became more prominent during last few decades. With the evolution of Methicilin-resistant Staphylococcus aureus (MRSA), Hospital-acquired MRSA, Community-acquired MRSA and MDR TB (Multidrug resistant tuberculosis) challenge for the clinicians have increased to a greater extent. Recent development in nanotechnology based drug delivery system may prove to be solution for combating these resistance bacteria. However policies and regulations for antibiotic use should be formulated to control the further development of resistance among the microbes.*

Keywords: *Antibiotic resistance, Diseases, MRSA, Multidrug resistance, Superbug.*

INTRODUCTION

The use of antibiotics for combating the infectious agents dated back to the era of Alexander Flemming (1929). With the development of antibiotics to higher synthetics groups, came to fore the emergence of resistant microbes. Antibiotics are used for combating the infectious diseases but their excessive and misuse have given rise the formation of superbugs graving a major problem worldwide. Superbug is a term used to describe the newly evolved bacterial species resistant to antibiotics. This resistance to antibiotics by Super bugs causes economic losses by increasing the duration of infection, treatment cost and decreasing the success of surgical treatments due to hospital acquired infections.[1] This morbidity and mortality loss caused there of indirectly hampers the economic developments in countries. The previous reports say that the cost of medical sectors for treating resistant bacterial infections and MDR TB (Multidrug resistant) reaches to 4-7 dollar billion per year[2] and 180,000 dollar in United State[3]. In developing countries also the misuse and underuse of antimicrobials due to lack of awareness of patients, medical workers and financial problems emerged the antimicrobial resistant strains.[4,5] Due to rapid globalization of human population by travel and other factors these resistant strains spread easily between developed and developing countries making it a global problem.[6,7]

CHRONOLOGICAL DISCOVERIES OF VARIOUS SUPERBUGS

Initially Drug-resistant strains were found on Hospitals due to use of most antibiotics.[8] *Staphylococcus aureus* was the first resistant bug discovered in 1943 against Penicillin.[9] In 1967, *Streptococcus pneumoniae* and after that the *Enterococcus faecium* was found resistant to Penicilin.[10] After Penicilin, Methicillin was the target antibiotic and first Methicilin- resistant *S. aureus* (MRSA) was found in 1961 in UK and became a major bug worldwide in 1980s.[11] After that both Hospital-acquired MRSA (HA-MRSA)[12] and Community acquired MRSA (CA-MRSA)[13]

emerged creating problems worldwide. The first outbreak of CA-MRSA has occurred in the indigenous populations of Western Australia[14] and after that it emerged worldwide. There after MRSA began to develop resistance against glycopeptides like Vancomycin leading to production of Vancomycin intermediately resistant *S. aureus* (VISA) and in 1997 its first case was isolated.[15,16] Resistant gram-negative bugs emerged simultaneously with gram-positive strains. Multidrug resistance was first seen in enteric bacteria like *Escherichia coli, Shigella and Salmonella* in late 1950s-1960s.[17] Extended-spectrum beta-lactamase containing bugs prevailed in Europe and then worldwide.[18,19] After that Carbapenemase-producing gram-negative bugs like extensively drug-resistant *Acinetobacter spp.* and enterobacteriacae producing New-Delhi metallo-protease-1 (NDM-1) *Klebsiella pneumoniae* producing carbapenemases were emerged.[20] In 21st century many multidrug resistance bugs prevaled like *Pseudomonas aeuroginosa* , *Mycobacterium tuberculosis* strains resistant to four and more line of drugs specific for TB called as extremely drug resistant (XDR) strains[21,22] and totally drug resistant (TDR) strains[23] etc. First XDR isolate was discovered in 2001.[24] Newer antibiotics are discovered to combat these resistant strains and simultaneously the bugs mutate their genes and by selection process become resistant to all drugs slowly causing challenge for physicians to treat infections.[25]

MECHANISMS OF RESISTANCE TO ANTIBIOTICS BY DIFFERENT RESISTANT BUGS

The prolonged administration or misuse of antimicrobials resulted in selection pressure which favors the evolution of resistant strains and subsequently their transmission causes spread of the resistant strains in the environment. The long-term use of a single antibiotic favored development of strains resistant to both same antibiotic along with other related antibiotics.[26] The spread of resistance traits occurs among different ecological groups and taxonomical groups by the presence of mobile genetic elements like bacteriophage, plasmids, naked DNA , transposons etc..[27,28] Sequential Mutation of genes help in low to high levels of drug resistances.[29] Due to the selection and mutation of genes these resistant strains hamper the easy passage of drugs through the cellwall, change their targets and inactivate them by producing enzymes.[30] The gram positive super bugs like *S. aureus* resists to Methicillin and Vancomycin by changes in their cell wall and cell membrane while the resistance to Linezolid antibiotic attributed to the mutation of 23 S ribosomal RNA.[31] It has been seen that like Gram positive bacteria Gram negative bugs like *Pseudomonas, Klebsiella, Enterobacter* and *Acinetobacter* resist various antibiotics in various ways. They resist the action of beta-lactam antibiotics by production of enzymes cephalosporinases, carbapenemases and extended spectrum beta-lactamases. By Mutation of target sites they resist the action of Fluoroquinolones and by modification of Aminoglycosides by bacterial enzymes they resist Aminoglycosides.[32,33] MDR, XTR and TDR TB microorganisms show resistance to antibiotics by spontaneous mutation in various genes.[34] Resistance to Macrolides and related antibiotics mostly occurs due to the r RNA modification responsible for their bindings with ribosomes.[35]

PREVENTION AND CONTROL

Antimicrobial resistant bugs are the emerging present day threats. The followings are some control and preventive measures should be taken to minimize their developments, spread and to promote development of new therapeutics.

- Most of the infections spread and occur from the contact of infected persons and lack of hygienic practices. Proper sanitation and hygiene maintenance in food and other things can reduce the spread of superbugs.

- Inappropriate use of antibiotics occurs due to unnecessary length of treatment, wrong prescription and its use without infections.[36] Both physicians and people education about it can check the development of resistant strains.

- Some policies and regulations should be practiced in both developing and developed countries to check the unnecessary drug promotions.[37]

- Antibiotics are used vividly in food animals like chicken, cattle, pigs, agricultural fields and fish farming methods. These uses establish a direct link for the appearance of resistance in humans.[25,38] Dusting of antibiotics as disease prophylaxis and use of antibiotic laden animal manure on croplands also contribute towards the development of resistant strains in

environment.[39] So measures should be taken to follow the WHO rules to minimize the dual-use antimicrobials[40] which are both related to human beings and food promotions.

- Attempts should be taken to check the spread of antimicrobial resistances by restricting human to human transmission of resistant strains, decreasing the use of broad spectrum antimicrobial and developing new and novel antimicrobials.[41]

- Steps should be taken to prevent infections by inhibiting key gene products involved in the infection process.[42]

Novel Newer Technologies to reduce the Superbugs

➢ Vivid research and application of Nanotechnology for identification of resistant bacteria[43] and therapy for combating superbugs should be practiced[44].

➢ Ultraviolet- C irradiation is useful to reduce the load of MRSA in food and Beverage industry as well as in hospital rooms. Hydrogen peroxide vapour is also effective in Hospital wards to reduce the resistant bacteria.[45]

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