CHAPTER 15

TREATMENT OF BACTERIAL INFECTIONS OF ANIMALS: A SHIFT FROM ANTIBIOTICS TO NANOFORMULATIONS

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INTRODUCTION

The history of animal survival is mostly linked to the several existing lethal ailments. However, those caused by bacterial infections, impose the potent threat to animal health and surveillance (Gandhi et al. 2010). The prevention and control of infectious diseases is of basic economic importance in the animal husbandry. The causative agent of bacterial infection is the bacterial species that reside either over the surface or inside the organism, causing damage or death of cells /tissues via metabolic substances and other toxins (Fukuda et al. 2011). Antibiotics have been considered as the first-line therapeutic agent to fight against the invading pathogen hence, reducing the rate of morbidity and mortality of mammals (Martens and Demain 2017) and ultimately leading towards a dramatic progress in the animal production. Moreover, antibiotics have also been introduced as growth promoters in the form of additives to the animal feed leading to further economic advantage of animal production especially in the poultry industry (Wierup 2000).

Up till now, antibiotics have been playing an irreplaceable role in treating bacterial infections and promoting growth in animal production industry. However, the abusive and unattended use of antibiotics lead to increased resistance to them. Another major factor inducing drug resistance is the use of high dose of antibiotics with the common thinking that high dose may provide effective therapy against bacterial infections. However, increasing dose of antibiotics may cause more serious antibiotic resistance (Chen et al. 1999).

The emergence of resistant strains indicated that the antibiotic use should not be the ultimate and only way to control the bacterial infections (Bilal et al. 2021). Multi drug resistant invading organisms are imposing great threat to both animal and human health and need special attentions to control (Lee et al. 2019). The use of antibiotics in animal production need special measures as the emergence of resistant bacterial strains impose a potential threat to human health (Ma et al. 2021). It has also been predicted that the death rate via antibiotic resistance (10 million/year) will exceed to that caused by cancers (8.2 million/year) by 2050 (Liu et al. 2019). The use of antimicrobials especially fluroquinolones and other growth promoting antibiotics has been highlighted because of emergence of resistant microorganisms in animals (Fair and Tor 2014). It has been estimated that the bacterial infection may become the biggest cause of death if new effective antibiotic or other effective therapeutic agents have not been discovered in the next prevailing years. However, unluckily the speed of bacterial resistance against antibiotics is so high that it lagged behind the speed of development of new antibacterial agents and if the resistance issue remains unattended it will lead to return to the pre-antibiotic era, where minor cuts and a common cold could be lethal. Statistically, it was found that the number of newly synthesized therapeutic agents against bacterial infections, decreased sharply since last 30 years and there is even a gap of discovery of new drugs (Liu et al. 2019). World Health Organization (WHO) recommended and endorsed that antibiotics should not be administered as growth promoters and alternative treatment strategies should be used for therapeutic purposes (Manyi-Loh et al. 2018).

There is ultimate requirement to develop new therapeutic agents via advanced technologies (Ling et al. 2015). New treatment strategies using advanced nanotechnology, are immediately needed to tackle the problem of antibiotic resistance. This chapter describes the potent and effective nanomaterials that can considered for treatment of bacterial infections to improve animal production. Excellent properties of nanomaterials such as easy modification, specific physicochemical activity, size effect and so on, make them potent candidates to be considered for treatment of severe drug-resistant bacterial infections. Major bacterial diseases in animals are elaborated in Table 1 along with their potential nanotherapeutics.

Synthesis of Nanoparticles

Several strategies have been considered for the synthesis of nanoparticles. High temperatures are required for physical methods. Other disadvantages of this method are required space, time and harmful environmental effects. Physical methods include the advantage of absence of contamination of solvent and the uniform distribution of NPs in comparison

How to cite this chapter: Altaf S, Ali A, Zafar S, Akhtar T, Iftikhar A, Babar SUR and Anwar M, 2022. Treatment of bacterial infections of animals: a shift from antibiotics to nanoformulations. In: Abbas RZ, Khan A, Liu P and Saleemi MK (eds), Animal Health Perspectives, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. I, pp: 118-125. https://doi.org/10.47278/book.ahp/2022.50

Table 1: Major bacterial diseases in animals along with their potential nano-therapeutic agents

Bacterial disease in animals	Synonym	Animal species	Causing organism	Treatment	Reference
Actinomycosis	Lumpy jaw	cattle, swine	*Actinomyces bovis* or *Streptothrix bovis*	Silver and gold nanoparticles	Hu et al. 2018; Gajdács and Urbán 2020
Anthrax	Splenic fever, Wool-sorter's disease and Malignant pustule	All domestic animals, poultry, cattle and birds	*Bacillus anthracis*	PLGA-dendron nanoparticles, Viral nanoparticles	Manayani et al. 2007; Ribeiro et al. 2007
Bacillary White Diarrhea	Pullorum disease	newly hatched chicks, turkeys, pheasants, ducks and other wild birds.	*Salmonella pullorum*	Silver nanoparticles	Farouk et al. 2020; Schat et al. 2021
Black Quarter	Black leg, Quarter-ill, Emphysematous gangrene, Quarter evil, Symptomatic anthrax	Cattle and Sheep	*Clostridium chauvoei, Cl. septique* and *Cl. oedematiens,*	Not formulated yet	Ziech et al. 2018
Braxy	Braxy	Sheep especially weaned lambs	*Clostridium septique*	Not formulated yet	Alves et al. 2021
Botulism	Food poisoning	Animals and birds	*Clostridium botulinurri*	Silver nanoparticles	Aminianfar et al. 2019
Contagious abortion of Cattle	Brucellosis; Bang's disease; Infectious abortion.	Cattle	*Brucella abortus bovis* or *Bang's bacillus.*	Silver nanoparticles	Alizadeh et al. 2014; Khurana et al. 2021
Actinobacillosis	Wooden tongue	Cattle and sheep	*Actinobacillus lignieresis* *Actinomyces viscosus*	nano-ZnO loaded eggshells	Chen et al. 2021
Botryomycosis	Discomycosis	Horses	*Staphylococcus aureus*	silver nanoparticle-containing polymer composite, Silica nanoparticles	Bhardwaj 2015; Quintero-Quiroz et al. 2020
Pasteurellosis	A group of diseases like hemorrhagic septicemia, fowl cholera, plague, arthritis, influenza	Animals and Birds	Pasteurella group of bacteria: *Pasteurella multocida* Cause of hemorrhagic septicemia in cattle *Pasteurella aviseptica* Cause of fowl cholera *Pasteurella suiseptica* Cause of Swine plague *Pasteurella canis* Cause of otitis, bacterial rhinitis, vertebral osteomyelitis, meningomyelitis, bronchopneumonia, tracheitis, paranasal sinus inflammation and toxicosis in canines. *Pasteurella bovine* Cause of hemorrhagic septicemia in cattle		Csébi et al. 2010; Griffin 2010; Malayeri et al. 2010; Sellyei et al. 2011; Ashraf et al. 2019; Chatelier et al. 2020; Shyam et al. 2020

to chemical method (Abou El-Nour et al. 2010). Chemical reduction is another most common process for preparation of silver NPs by inorganic and organic reducing substances. Other chemical methods of NP synthesis include the micro emulsion assay, photo induced reduction, ultraviolet initiated photo reduction, irradiation methods and electrochemical synthetic methods. Chemical methods provide higher yield as compared to physical methods (Raghavan et al. 2016).

Biological methods of NP synthesis harness the reducing ability of microbial cells, enzymes and biological molecules. The green plants, bacteria and fungi are recently being used to biologically synthesize metal NPs via environment friendly method. For instance, silver nanoparticles have been successfully synthesized from *Pseudomonas aeruginosa* (Peiris et al. 2017), *Staphylococcus aureus* and *Escherichia coli* (Peiris et al. 2019).

Moreover, the fungus Fusarium based silver nanoparticles were analyzed to have long term stability as the fungus secretes an enzyme i.e., nitrate reductase which help in reducing the Ag ions and also involved in secreting capping proteins, which contribute to the long term stability (Ingle et al. 2008). Recently several plants have been considered for biological synthesis of NPs (Ahmed et al. 2016). The extracts of plants are rich in enzymes and phytochemicals, which assist in reducing metal ions into nano sized particulate material. This procedure definitely provides a cost effective and environment friendly alternative method for large scale production of NP over the environment unfavorable chemical and physical methods (Loo et al. 2012).

Nanoparticles Act as Antimicrobials

In the medical field, nano-scale particles (Medina et al. 2007) are being considered as suitable agents for the treatment and diagnostic purposes (Surendiran et al. 2009) . The recent advances in the development of medicinal nanomaterials may have beneficial role to cover the purpose of antibiotics. The nanoparticles may be considered as a modern class of bacterial antimicrobials. Nanoformulations as antibiotics may play role to efficiently reduce resistance and kill the pathogenic bacteria (Rai et al. 2009). Latest research studies elaborated that several antimicrobial - activated metal

Table 2: Mechanism of action of different types of nanomaterials against specific bacteria

Nanomaterial	Size (nm)	Mechanism of Action	Target organism	Reference
Carbon mediated nanoformulations				
Carbon Nanotubes	1-100	Inhibition of energy metabolism, bacterial membrane and respiratory chain damage	*Escherichia coli*, *Klebsiella pneumonia*, *Yersinia pestis*, *Enterococcus faecium*, MDR *Streptococcus* spp. *Salmonella enterica, Acinetobacter baumannii, Burkholderia cepacia*	Shvero et al. 2015
Fullerene	200	Inhibit energy metabolism and destroy the respiratory chain	*Salmonella, Streptococcus* spp. and *E. coli*	Heredia et al. 2022
Graphene Oxide nanosheet	12	RNA effluxes by damaged cell membranes, methiciline resistantg MDR	*E. coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Enterococcus faecalis, Staphylococcus aureus* *Methicillin-resistant Staphylococcus aureus* (MRSA)	Gao et al. 2021
In-organic nanoformulations				
Silver Nanoparticles	1-100	Inhibit cell division and damage the respiratory chain	almost all bacteria, eukaryotic organisms and viruses as well	Bruna 2021
Gold nanoparticles	1-100	Cell damage via induction of local hyperthermia in the presence of a magnetic field	*Staphylococcus aureus, Enterococcus faecium, Pseudomonas. aeruginosa, E. coli* and *Candida albicans*	Su et al. 2020
Ferric oxide nanoparticles	1-100	Production of reactive oxygen species leading to cell wall disruption	*Methicillin-resistant Staphylococcus aureus,* multi drug resistant *E. coli* and *K. pneumoniae*	Shvero et al. 2015
Aluminum oxide nanoparticles	10-100	Production of reactive oxygen species leading to cell wall disruption	*E. coli*	Manyasree et al. 2018
Magnesium oxide NP	15-100	Generation of reactive oxygen species, Alkaline effect, Peroxidation of lipids	*S. aureus, E. coli*	He et al. 2016
Silicon NP	20-400	ROS production leading to membrane damage	*MRSA*	Selvarajan et al. 2020
Titanium dioxide NP	30-45		*S. aureus, Enterococcus faecium, E. coli, P. aeruginosa,*	Dicastillo et al. 2020
Super-paramagnetic iron oxide nanoparticle (SPIONS)	15-25	NO release Production of reactive oxygen species.	*S. aureus, E. coli*	Gholami et al. 2020
Zinc-oxide nanoparticles	10-100	Lipid and protein damage Adsorption to cell surface ROS production, disruption of membrane	*K. pneumoniae, E. coli, Enterobacteraerogenes, MRSA, Klebsiellaoxytoca*	Emamifar et al. 2010
Copper NP	2-350	DNA damage, Generation of ROS, Cell membrane potential dissipation Lipid and protein peroxidation	*A. baumannii, MDR E. coli*	Chen et al. 2019
Organic nanoformulations				
Poly-ε-Lysine	1-100	Disrupt the cell wall and membrane integrity. Destroy cell membranes or cell walls	Gram-positive and Gram-negative bacteria. Additionally, it acts against spores of *B. subtilis, B. stearothermophilus*, *B. coagulans, S. cerevisiae* *E. coli*	Rodrigues et al. 2020
Quaternary Ammonium Compounds	1-100	Interfere with the function of the cell membrane Lysis, or destruction of the cell Affects DNA ROS release	*Pseudomonas* *Pseudoalteromonas* *Erwinia* *Enterobacter*	Xue et al. 2015
N–Halamine Compounds	1-10	Disrupts the functionality of bacterial cell membrane leading to inactivation	*S. aureus, P. aeruginosa*	Padmanabhuni et al. 2012
Chitosan nanoparticles	200	Loss of permeability of membrane	*S. aureus, E. coli*	Alqahtani et al. 2020
Quaternary bis-phosphonium and ammonium	1-100	Inhibits the growth of bacteria disruption of thecell division mechanisms	*S. aureus, E. coli, B. subtilis, S. epidermidis*	Nikitina et al. 2016
Composite mediated nanoformulations				
Ceramic Matrix Nano-Composites	1-100	Inhibit the growth of bacteria and hinder physical interaction	*S. aureus* *E. coli*	Baaloudj et al. 2021
Polymer Matrix Nano-composites	1-100	Inhibit the growth of bacteria and hinder physical interaction	*A. baumannii* *K. pneumonia* *E. coli* *S. aureus*	Giraud et al. 2021
Metal Matrix Nanocomposites	1-100	Hinder physical interaction and inhibit the growth	*S. aureus* *A. baumannii* *K. pneumonia* *E. coli*	Yang et al. 2018

nanomaterials play significant role to treat infectious diseases (Goodman et al. 2004). Such synthetic nanomaterials may indeed provide benefits of lower cost, lower toxicity and good pharmacokinetic factors while supporting to eradicate drug-resistant bacteria. Their major advantage is that they provide longer efficacy than traditional antibiotics, which is

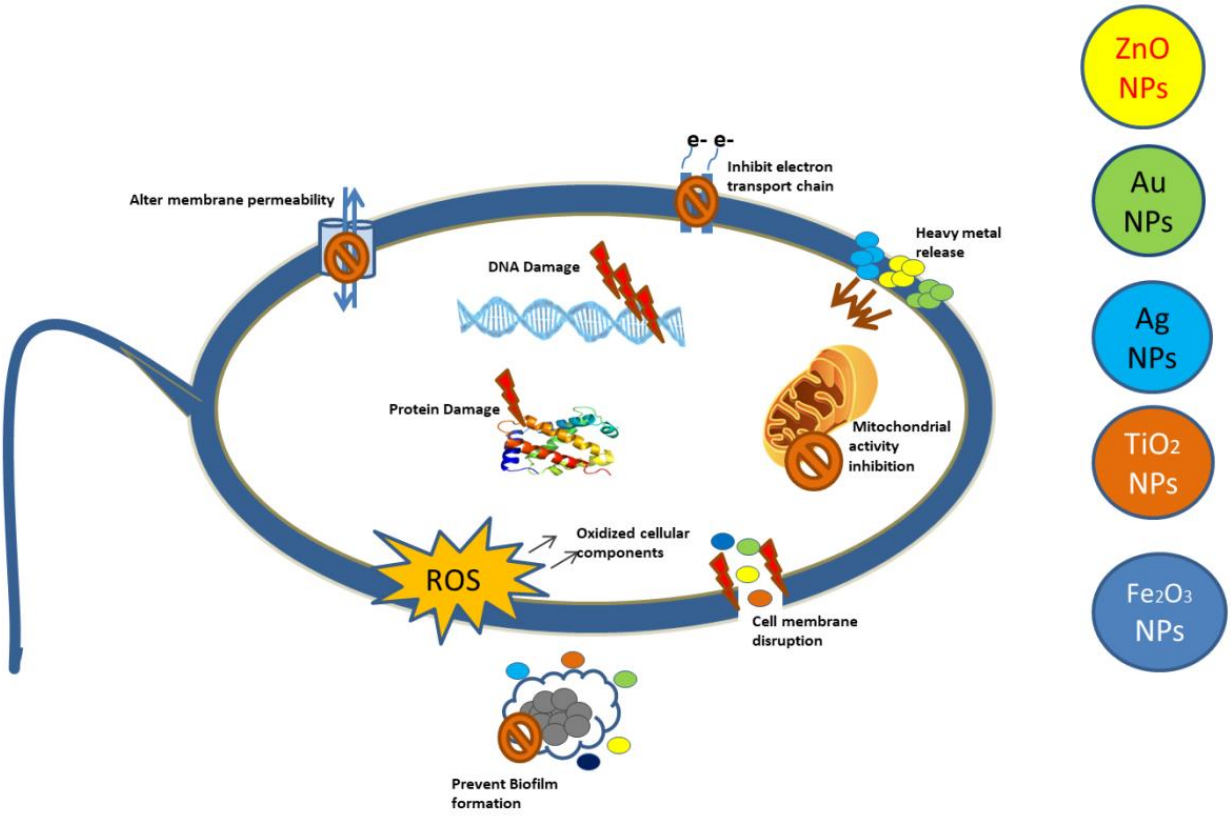

Figure 1: Different pathways for nanoparticles antimicrobial behavior.

highly required in the long-term sustained therapeutic effect (Pal et al. 2007). Moreover, the synthetic therapeutic nanoparticles are biomimetic to biological molecules and are highly specific in their action (Medina et al. 2007). Thus, these features of nanomaterials enhance the effectiveness and reduce adverse effects associated to them. These nanomaterials are categorized into several categories including carbon-based, organic, inorganic, polymeric and composite-based nanoformulations (Table 2).

Possible Mechanism of Action of Antibacterial Nanomaterials

Nanomaterials are used as a fairly modern strategy to resolve the global problem of antibiotic resistance. These nanosystems show antimicrobial activity without the involvement of antibiotics and show their actions via several destroying pathways involving multiple targets. The antibacterial mechanisms of these nanoparticles involve ATP depletion, reactive oxygen species (ROS) production, membrane disruption and inhibition of DNA synthesis (Slavin et al. 2017; Tamara et al. 2018). The adsorption of nanoparticles to surface of the cell causes bacterial wall degradation, leaking out the cytoplasmic material (Shmarakov et al. 2014) (Figure 1).

The metallic nanoparticles are well-known for their effective antimicrobial activity against a wide variety of resistant bacterial species. They work through several mechanism of actions to fight against bacteria. The silver nanoparticles show their action by producing large number of silver ions, which alter the cell membrane permeability and inhibit energy transport chain of electrons. Moreover, silver ions have also been identified to damage the microbial cell DNA (Donaldson et al. 2006; Kumar et al. 2019; Aunkor et al. 2020). Zinc oxide nanoparticles emit Zn^{+2} ions in the cells and are involved in production of hydrogen peroxide and destruction of membrane of the cells (Pinto et al. 2013; Karwowska 2017). Titanium dioxide nanoparticles work by producing reactive oxygen species and ultimately affect the stability of cell membrane (Klasen et al. 2000; De Aberasturi et al. 2015; Liao et al. 2019). In addition to metal nanoparticles, there are several other nanomaterials including liposomes, polymers, or carbons, each of which has its own antibacterial action against bacterial pathogens. Chitosan nanoparticles show their action by boosting permeability and inactivating the enzymes of the microbial cells (Li et al. 2008; Zhang et al. 2008). Carbon nanotubes show their action primarily by membrane damage via production of reactive oxygen species (Sondi and Salopek-Sondi, 2004). Another group of nanoparticles involving fullerenes functions by enhancing neutrophil infiltration and disruption of cell membrane (Dastjerdi and Montazer 2010; Tania and Ali 2021). Thus, there are various action pathways in which nanoparticles can effectively attack the machinery of microbes (Figure 1).

Nanoparticles Derived Antibacterial Vaccines

Vaccines may provide protection and treatment against bacterial infections by linking the host's immune system. Successful control over former epidemics world widely has been counted as the most effective public health intervention ever achieved (Plotkin 2005; Germain 2010). The prevention and treatment strategy via vaccine development, provides a promising effect to control antibiotic resistance by decreasing the use of antibacterial agents (Wenzel and Edmond 2000; Mishra et al. 2012). On the other hand, the majority of

existing vaccines predominantly neutralize or opsonize antibodies against invading pathogenic organism, a mechanism that is not effective to prevent or treat a variety of bacterial infections (Levy and Marshall 2004). The development of vaccine is further become challenging due to lack of complete understanding of complex human immune system and the principal protective mechanisms (Fauci and Morens 2012). To overcome these hard challenges, nanoparticles have been considered as strong antibacterial candidates bearing unique feature of immune modulation against microbial infections (Swartz et al. 2012; Irvine et al. 2013).

Nanoparticles may also have characteristics to overcome the undesirable systemic biodistribution, instability, and toxicity associated with the soluble molecule administration (Tan et al. 2010; Gu et al. 2011). It has been analyzed that nanoparticle surfaces conjugated with antigens and facilitated the activation of B-cell (Villa et al. 2011) as higher number of antigens were provided to antigen presenting cells (APCs) (Nembrini et al. 2011). The improvement of antigen loading has been achieved by the advancement in nanotechnology leading to establishment of fabrication technique for formulation of nanoparticle-based drug delivery systems such as facile spray-drying process (Dierendonck et al. 2010), layer-by-layer assembly procedure (De Rose et al. 2008; De Geest et al. 2012) and soft lithography-based PRINT technique (Perry et al. 2011).

Moreover, cell membrane-enveloped nanoparticles have also been coated to impede membrane-damaging toxins and distract them away from their specific cell targets (Hu et al. 2013). Such a toxin-detainment technique was applied to safely deliver staphylococcal α-hemolysin to antigen presenting cells and induced immunity against toxins in the mice in comparison to vaccination of heat-denatured toxins (Hu et al. 2013). This methodology aid in maintaining a faithful antigenic presentation while removing virulence of toxins.

In addition to delivery of antigens, nanoparticles may also involve in carrying adjuvants to mimic natural microbes to improve the efficacy of vaccine (Little 2012). Predominantly, several ligands of toll-like receptor (TLR) such as DNA, RNA, carbohydrates and other small molecules in combination of antigens may be delivered via nanoparticles, leading to equivalent response of immune system in comparison to soluble antigen formulations (Demento et al. 2009).

More notably, nanoparticles especially designed to assist in programmable presentation of adjuvants and antigens to immune cells to get desirable immune responses. One such example is of combinations of TLR agonists which have been concomitantly loaded into specific nanoparticles to get the combinatorial TLR activation, similar to that occurring in natural infections, leading to more vigorous immune responses (Mount et al. 2013; Orr et al. 2014).

Another example involves encapsulation of antigens and TLR agonists in prepared nanoparticles to induce effector T-cell responses (Zhu et al. 2010; Mount et al. 2013; Orr et al. 2014) in the same manner as the antigen processing takes place in the dendritic cells (Blander and Medzhitov 2006). On the other hand, delivery of both TLR agonists and antigens in separate nanoparticles showed beneficial effect in producing antibody responses (Kasturi et al. 2011).

Developing vaccines for specific required target sites to induce effective and safe immune responses is a major advantage of use of nanoparticles for delivery of vaccine. For example, *Clostridium botulinum* type-A neurotoxin loaded cationic nanogel has been analyzed to assist antigen to persistently adhere to the nasal epithelium and then effectively up taken by mucosal dendritic cells (Nochi et al. 2010). The newly synthesized nanogel not only showed immune responses, but also protected central nervous system and upper respiratory tract from exposure to toxic antigens. Moreover, nanoparticles sensitive to the pH of the gastrointestinal tract play protective role and prevent antigen deterioration in the stomach and release antigens as soon as nanoparticles reach the lower gastrointestinal tract of high pH medium, for successive translocation across the epithelium of intestine (Zhu et al. 2012). A similar approach has also been considered for nanoparticle-mediated vaccines which may efficiently target lymph nodes. Nanoparticles which are smaller in size can be transported faster to the lymph node (Reddy et al. 2007), whereas, larger nanoparticles may stay for longer duration in the lymph node (Jewell et al. 2011). Such distinct features show the size optimization importance in lymphatic system for inducing required immune responses.

Conclusion

A number of promising nanotherapeutic agents have been discovered and developed for treatment of resistant bacterial infections in animals. Optimal strategies and measures must be adopted related to prevent and treat antibiotic resistance. Studies elaborated that the nanotherapeutics and nanovaccines contributed in upgrading the status of health and economy of animal production, without introducing antibiotics to the animals. There is dire need to rethink that antibiotics should not be introduced as first line agents. The use of antibiotics should only be considered when other management strategies have failed or are not responsive.

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