Chapter 2

Complications of Antibiotic Therapy and Introduction of Nanoantibiotics

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Additional information is available at the end of the chapter

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Abstract

Oral and maxillofacial surgeons play a major role in therapy, preventing morbidity, mortality from odontogenic and non-odontogenic maxillofacial infections; therefore, it is essential to have knowledge of current advancements in microbiological diagnosis and antibiotic therapy for odontogenic maxillofacial infections. Fortunately, we live in an era where antibiotics are readily available to prevent and treat against infections. The exact cause should be determined once the specific antibiotic is prescribed; additionally, the empirical, definitive treatments, side effects, pharmacokinetics and pharmacodynamics of antibacterial agents have to be considered.

Nowadays, antimicrobial resistance which is spreading rapidly is of great concern, because it is common in hospitals where acquired infections can be perilous. This situation compels scientists to synthesize new antibiotics and treatment modalities. The reason of microbial resistance can be due to increased misuse of antibiotics in foods (livestock, poultry and agriculture). A number of significant factors, such as organism identification, antibiotic sensitivity testing and host factor situations, should be taken into account in order to treat various infections effectively.

Currently, investigations are ongoing to impede antibacterial resistance by nanoscience technology seeking new chemotherapeutic agents. Scientists focusing on microbiological investigations aim to invent novel nanoantibiotic agents with high efficiency, low toxicity and low percentage of resistance. In recent years, nanoantibiotics have been applied against infections intelligently. The average size, polydispersity and composition of generated nanomaterials can be controlled by various methods in order to make them appropriate for biomedical applications.

The goal of this chapter is to provide an overview of the complications of various antibiotics used for therapeutic and prophylactic purposes in the oral and maxillofacial regions; furthermore, some essential nanoantbiotics are introduced and discussed.

Keywords: antibiotics, complications, nanoantibiotics, resistance, adverse effect

1. Introduction

Antibiotics can improve cell defense effectively; some key factors should be considered in antibiotic therapy, including the health of the host, identity of the organism and the antibiotic susceptibility; moreover, adverse reactions, interactions, resistance and other complications should be taken into account. The origin of most orofacial infections is odontogenic. The major relevant organisms of dental origin infections are aerobic and anaerobic Gram-positive cocci and anaerobic Gram-negative rods. The predominant aerobic bacteria in odontogenic infections are *Streptococcus milleri* genus [1]. Oral Gram-negative anaerobic rods are cultured in three quarters of the infections; however, several Gram-positives and Gram-negatives play more important pathogenic roles [1, 6]. Pure aerobic infections are less common (5%) [7]. Brook et al. detected that 50% of odontogenic deep facial infections yielded anaerobes, and only 44% of infections are a combination of aerobic and anaerobic flora [8]. Most sinus infections are viral, and only a small proportion develop a secondary bacterial infection in which the most common bacteria are Gram-positive and anaerobic bacteria [7, 9]. It is reasonable to use narrow-spectrum antibiotics for simple infections and broad-spectrum for complex infections to prevent resistance. Penicillin, clindamycin, metronidazole are narrow-spectrum, while amoxicillin+clavulanic acid, ampicillin+sulbactam, azithromycin, tetracycline, cephalosporin, moxifloxacin, ciprofloxacin and co-trimoxazol are broad-spectrum antibiotics [10]. Recently, there has been an alarming increase in the incidence of resistant bacterial isolates in odontogenic infections. Many anaerobic bacteria have developed resistance to beta-lactam antibiotics via beta-lactamase [7]. Inappropriate use of antibiotics causes the emergence of resistant bacteria. Today, many common and life-threatening infections are becoming difficult or impossible to treat and sometimes turning a common infection into a life-threatening one [11]. The antibiotic resistance is facilitated by repeated exposure of bacteria to antibiotics and access of bacteria to a large antimicrobial pool. Pathogenic and nonpathogenic bacteria are becoming increasingly resistant to conventional antibiotics. The focus has now shifted to multi-drug-resistant Gram-negative bacteria, while initial studies were investigated on antibiotic resistance such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococcus spp. [12]. Gram-negative pathogens are particularly troublesome as they are becoming resistant to nearly all drugs. Bear in mind that resistance occurs for the Gram-positive infections (Staphylococcus and Enterococcus) but not on the same scale [13].

Nanoantibiotic drug delivery with low toxicity and extended release would be an appropriate alternative to reduce antibiotic resistance. When an antibiotic is administered, strains of resistant organisms may proliferate; therefore, the antibiotic becomes ineffective. An antibiotic can act as an antigenic stimulus and produce an allergic reaction. They can kill or

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halt the proliferation of sensitive bacteria. This may include normal flora. Thus, an antibiotic may cause diarrhea, increased risk of bleeding especially in patients taking warfarin. Once the susceptible bacteria are killed, they may be replaced by more resilient organisms such as *Candida albicans* and *Clostridium difficile*; moreover, hepatobiliary dysfunctions and nephrotoxicity are the other complications that may occur [14].

2. Mechanisms of resistance

- Mutations of bacterial genes (chromosomal) leading to cross-resistance.
- Gene transfer from one microorganism to other by plasmids, transpositions (conjugation), integrons and bacteriophages (transduction). After these, they can use various biochemical types of resisting mechanisms (**Figures 1** and **2**).
- Antibiotic inactivation (with cell wall synthesis by beta-lactams and glycopeptide).
- Target alteration (inhibition of protein synthesis for tetracyclines and macrolides).
- Interfering with nucleic acid synthesis for rifampin and fluoroquinolones.
- Altered permeability (modifications of the cell surface for aminoglycosides).
- Bypass metabolic pathway (metabolic route inhibition for co-trimoxazole) [2–4].
- In recent studies, Lee et al. recommended that not all interactions of bacteria with antibiotics can be clarified within the standard theory; however, the new Kin selection hypothesis

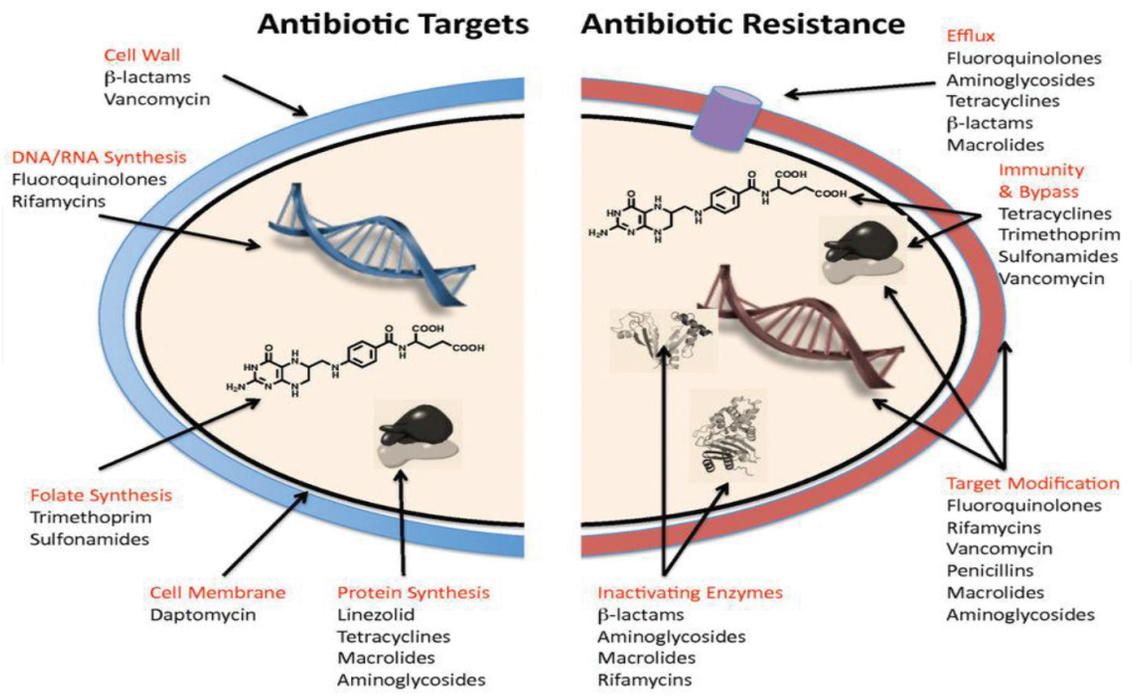

Figure 1. Gerard D Wright. Antibiotic targets and mechanisms of resistance. BMC Biology 2010 8:123.

proposed by W.D. Hamilton in 1964 suggested if one group of microorganisms is going to be resistant or destroyed, then others with similar genes have an opportunity to resist and mutate [15, 16].

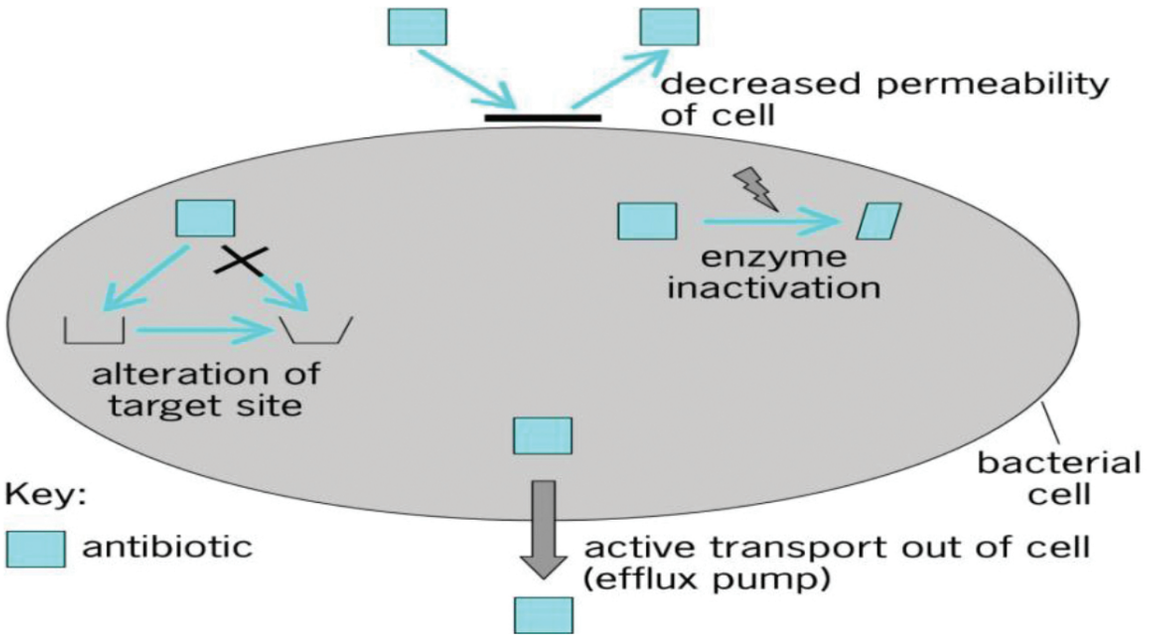

Figure 2. Four common mechanisms of antibiotics resistance. McGraw-Hill Concise Encyclopedia of Bioscience. 2002 by the McGraw-Hill Companies, Inc.

Resistance is formed by the lack of proper diagnosis, the widespread use of antibiotics in hospital, wrong use for patients with a viral infection or still undiagnosed illness and livestock farming and exploiting antibiotics in poultry and food industry (may cause some resistance in the long term) [11]. Clinical signs of resistance include prolonged and chronic infections, increasing disease manifestations and outbreaks, distributing diseases to other organs and increasing the probability of other diseases due to immune system weakening, malnutrition and organ failure. Adverse effects include hypersensitivity reactions to agents, that is, interaction between drugs, cells, organ functions and normal electrolyte concentration. In addition, the presence of background diseases, organ disorders, and physiologic factors such as old age and pregnancy may increase side effects [17].

3. The adverse effects and resistance of the several common antibiotics which are used in oral and maxillofacial surgery

3.1. Penicillins

The base structure of penicillins is a thiazolidine ring which is adherent to the beta-lactam and carries the subordinate amino group (RNH), and in fact, substituents can attach to the amino chain [3]. Natural penicillins are beta-lactam antibiotics and the most important ones are as follows [18]:

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- Penicillins (penicillin G) have little activity against Gram-negative rods, and they are susceptible to hydrolysis by beta-lactamases.
- Anti-staphylococcal penicillins (nafcillin) are resistant to staphylococcal beta-lactamases. They are active against staphylococci and streptococci but not against anaerobic bacteria, Gram-negative cocci or rods.
- Extended-spectrum penicillins (aminopenicillins and antipseudomonal penicillins). They are relatively susceptible to hydrolysis by beta-lactamases [3].

More than 10% of patients receiving penicillin may have some reactions from a mild rash to anaphylaxis. Anaphylaxis is a life-threatening reaction that most commonly occurs with parenteral administration. It appears as severe hypotension, bronchoconstriction and abdominal pain. Other manifestations of hypersensitivity reactions include fever, eosinophilia, angioedema and serum sickness. Before penicillin therapy begins, the patient's history should be assessed for reactions to penicillin, in case of positive background, alternative drugs should be used; however, hypersensitivity reactions may occur even in patients with a negative history [18].

3.1.1. Adverse effects

Penicillins are bactericidal and act by interfering with bacterial cell wall synthesis. They infiltrate well into body tissues and fluids. Penetration into the cerebrospinal fluid is poor except when the meninges are inflamed. Allergic situations happen in 1–10% of patients, but anaphylactic reactions occur in less than 0.05% of treated patients. Patients with a history of atopic allergy are at higher risk of anaphylactic reactions to penicillins. Patients who are allergic to one penicillin will be allergic to all. Patients with the background of immediate hypersensitivity to penicillin may also have a reaction to cephalosporin and other beta-lactam antibiotics. Individuals with a history of a minor rash (non-confluent, non-pruritic) or a rash that occurs more than 72 hours after penicillin administration are probably not allergic to penicillin, and penicillin should not be withheld unnecessarily for serious infections [19]. Other side effects are rare, but serious toxic effects of the penicillins are encephalopathy due to intrathecal injection. In renal failure, the accumulation of electrolytes may occur due to either sodium or potassium content in injection. Diarrhea frequently occurs during oral penicillin therapy, and it can also cause antibiotic-associated colitis in a prolonged case [19]. Penicillins are classified as category B. Penicillin is excreted into breast milk in low concentrations and is considered safe to use in breastfeeding women [20, 21]. Exfoliating dermatitis and Stevens-Johnson syndrome are the most severe dermatologic signs. Gastrointestinal adverse effects are most common in response to ampicillin [22]. Aqueous crystalline penicillin G and procaine penicillin G have been implicated in neurological reactions including seizures, neuromuscular instability, confusion and hallucinations [21]. Rarely, penicillin G causes hemolytic anemia [23, 24]. Candidiasis is more common in patients taking broad-spectrum aminopenicillins. Other side effects of natural penicillins include bone marrow suppression, and with high-dose therapy, seizures may occur [18].

3.1.2. Significant interactions

Probenecid increases blood levels of penicillins and may be given alongside for this purpose. Antibiotic antagonism occurs when erythromycin, tetracycline or chloramphenicol is given within an hour after taking penicillin. Prolonged reactions may arise in utilizing penicillin G procaine and benzathine. Penicillin G procaine should not be injected into or near an artery or nerve due to possible permanent neurological damage [3, 18].

Penicillinase-resistant penicillin is not hydrolyzed by beta-lactamases. These agents include methicillin, nafcillin, the isoxazolyl penicillin, dicloxacillin and oxacillin. The penicillinase-resistant group can cause hypersensitivity reactions. Methicillin may cause nephrotoxicity and interstitial nephritis. Oxacillin may be hepatotoxic. The most dangerous situation is methicillin-resistant *Staphylococcus aureus* (MRSA). This bacterium resists numerous antibiotics including methicillin, amoxicillin, penicillin and oxacillin [25]. Wide-ranging cross-resistance exists among the penicillinase-resistant penicillins. Methicillin sodium and nafcillin have been reported to be incompatible with aminoglycosides, acidic and alkaline drugs [26]. Aminopenicillins, because of their broader range, are identified as broad-spectrum penicillins. The incompatibility of ampicillin sodium and aminoglycosides appears to be more evident at higher concentrations and with glucose-containing solutions [26].

Extended-spectrum penicillins have the extensive antibacterial spectrum of all penicillins. Also called antipseudomonal penicillins, this group includes the carboxypenicillin and ureidopenicillin [18]. Hypersensitivity reactions are the other penicillins. Ticarcillin may cause hypokalemia. The high sodium content of ticarcillin can pose a danger to patients with heart failure (HF) and inhibits platelet aggregation [26].

3.1.3. Resistance

Modification of drug penicillin-binding proteins (PBPs) impairs penetration of drug to target PBPs and efflux. Beta-lactamase production is the most common mechanism of resistance. Altered target PBPs are the basis of methicillin resistance in staphylococci and penicillin resistance in pneumococci. These resistant organisms produce PBPs which have low affinity for binding beta-lactam antibiotics. PBP targeting is decreased only in Gram-negative species because of their water-resistant outer cell membrane. Reduced penetration is not sufficient to confer resistance because enough antibiotic ultimately enters the cells. However, this barrier can become important in the presence of the beta-lactamase as long as hydrolyzing the drug is faster than entering the cells. Gram-negative organisms may produce an efflux pump that efficiently transports some beta-lactam antibiotics from the periplasm back across the outer membrane [27].

3.2. Cephalosporins

The cephalosporins are a class of beta-lactam antibiotics originally derived from the fungus Acremonium, and they also constitute a subgroup of beta-lactam antibiotics called cephems, and both are based upon the cephem nucleus. Unlike most cephalosporins, cephamycins are a very effective antibiotic group against anaerobic microbes. Cephamycins include cefoxitin,

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cefotetan and cefmetazole which are often grouped with the second-generation cephalosporins. The structure of most of the cephalosporins contains N-methylthiotetrazole side chain, and when it becomes metabolized in the body, it releases free N-methyl-thiotetrazole which can cause hypoprothrombinemia (due to the inhibition of vitamin K enzyme, epoxide reductase) and a reaction with ethanol similar to performing by disulfiram, due to inhibition of aldehyde dehydrogenase [3]. Cephalosporins are similar to penicillins but more stable to many bacterial beta-lactamases; therefore, they have a broader spectrum of activity.

3.2.1. First generation

They are very active against Gram-positive cocci; however, they are not active against methicillin-resistant strains of staphylococci. Oral therapy should not be relied on in serious systemic infections.

3.2.2. Second generation

They have extended Gram-negative efficacy. Cephamycins have activity against anaerobes. The oral second-generation cephalosporins are active against beta-lactamase-producing organisms [3].

3.2.3. Third generation

They have an expanded Gram-negative coverage, and some of them are able to cross the blood-brain barrier. Third generation acts against beta-lactamases; however, they should be avoided in enterobacter infections because of the emergence of resistance [3, 5].

3.2.4. Fourth generation

They are more resistant to hydrolysis by chromosomal beta-lactamases (those produced by Enterobacter) [3].

3.2.5. Fifth generation

Beta-lactam antibiotics with activity against methicillin-resistant staphylococci are currently under progress, for instance ceftaroline fosamil is the first drug to be approved for clinical use. Ceftaroline has better binding to penicillin-binding protein 2a which facilitates methicillin resistance in staphylococci. It is not active against AmpC or extended spectrum beta-lactamase-producing organisms [3].

3.2.6. Adverse effects

Reactions can be allergic or toxic or both [3]. Common adverse drug reactions (>1%) include rash, diarrhea, electrolyte instabilities, nausea, pain and inflammation at injection site. Rare side effects (0.1–1%) include vomiting, headache, dizziness, oral candidiasis, pseudomembranous colitis, eosinophilia, neutropenia, hemolytic anemia, nephrotoxicity, thrombocytopenia and fever. Some other adverse reactions are pruritus, Stevens-Johnson syndrome, vaginitis,

increased hepatic transaminases, thrombocytosis, phlebitis, increased BUN and creatinine, renal failure and anaphylaxis. Some cephalosporins have reactions when they are combined and utilized such as encephalopathy, asterixis neuromuscular excitability, seizure, aplastic anemia, interstitial nephritis, PT prolonged, agranulocytosis, cholestasis and erythema multiform [5]. A potentially life-threatening arrhythmia has been reported in patients who received a rapid bolus cefotaxime injection via central line, and granulocytopenia and more rarely agranulocytosis may develop through long treatment (>10 days) [3, 5]. Secondary to biliary obstruction possibly due to ceftriaxone-calcium precipitates, pancreatitis has been reported rarely by using ceftriaxone [3, 5]. Cross-allergenicity appears to be most common among penicillins, carbapenems, aminopenicillins and early-generation (group I and II) cephalosporins due to sharing the same R-1 side chains. Patients with documented penicillin anaphylaxis have an increased risk to cephalosporins. Previously, extensive warnings of 10% cross-reactivity had been given, but nowadays, in the absence of proper alternatives, oral cefixime or cefuroxime, injectable cefotaxime, ceftazidime and ceftriaxone are used with precaution [4]. Local irritation can produce pain after intramuscular injection and thrombophlebitis after intravenous injection [3, 5, 28]. Cephalosporins may cause increased international normalized ratio (INR) particularly in nutritional-deficient patients, extended treatment, hepatic and renal disease. Long usage may result in fungal or bacterial superinfection particularly with renal impairment [5]. The pregnancy risk factor is B. Small amounts of cephalosporins are excreted in breast milk but most are not harmful, however, have influence on bowel flora [5].

3.2.7. Drug interactions

Uricosuric agents may decrease the excretion of cephalosporins. Cephalosporins may increase the anticoagulant effect of vitamin K antagonists. Tablets containing sodium caseinate can cause allergic reactions in patients with milk protein hypersensitivity. Cephalexin may increase the serum concentration of metformin. Antacids, H2-antagonists and food may decrease the absorption of cephalosporin [5]. Calcium salts (intravenous) and every fluid containing calcium may enhance the adverse/toxic effect of ceftriaxone due to the formation of an insoluble precipitate. Some test interactions might be changed such as positive direct Coombs, false-positive urinary glucose, false-positive serum or urine creatinine [5, 16].

Resistance to cephalosporin antibiotics can involve either reduced affinity of existing PBP components or the acquisition of a supplementary beta-lactam-insensitive PBP. Currently, some *Citrobacter freundii, Enterobacter cloacae, Neisseria gonorrhea* and *Escherichia coli* strains are resistant [3, 28]. Other beta-lactam drugs such as monobactams and aztreonam are drugs with a monocyclic beta-lactam ring; their spectrum of activity is limited to aerobic Gram-negative rods. Their Gram-negative spectrum is similar to the third-generation cephalosporins.

3.3. Beta-lactamase inhibitors (clavulanic acid, sulbactam and tazobactam)

These substances look like beta-lactam molecules and have weak antiseptic action. They can protect hydrolysable penicillins from inactivation. Beta-lactamase inhibitors are available only in fixed combinations with specific penicillins [5].

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Carbapenems are structurally related to other beta-lactam antibiotics. It is resistant to most beta-lactamases but not carbapenemases or metallo-beta-lactamases. Methicillin-resistant strains of staphylococci are resistant. The dosage must be reduced in the case of renal insufficiency [3]. The most common adverse effects of carbapenems as imipenem are gastrointestinal signs, skin rashes and reactions at the infusion sites. Patients allergic to penicillins may be allergic to carbapenems, but the incidence is low [5].

3.4. Glycopeptide antibiotics

Vancomycin is an antibiotic produced by Streptococcus and *Amycolatopsis orientalis*. It is active only against Gram positives [3]. Resistance to vancomycin is due to reform of the D-Ala-D-Ala binding site of the peptidoglycan building block with conversion to D-lactate and thickened cell wall with increased numbers of D-Ala-D-Ala which serve as dead-end binding sites for vancomycin. Vancomycin is effective against staphylococci, including those producing beta-lactamase and those resistant to nafcillin and methicillin [5, 6, 29].

Adverse reactions take place in almost 10% of cases. Most reactions are rather slight and reversible. Vancomycin is an irritant to tissue because of phlebitis at the site of injection. Chills and fever may occur. Ototoxicity is rare, and nephrotoxicity is uncommon. However, prescribing another ototoxic or nephrotoxic drug increases the risk of these toxicities. Ototoxicity can be minimized by maintaining peak serum concentrations below 60 mcg/ml. The more common reaction is "red man" syndrome which is caused by the release of histamines. It can be prevented by prolonging the infusion period to 1–2 hours or pretreatment with an antihistamine [3]. Other side effects include tinnitus or vertigo which can be the symptoms of vestibular injury and future bilateral irreversible damage. Elongated therapy or total doses above 25 g may increase the risk of neutropenia. Oral vancomycin is only specified for pseudomembranous colitis due to *C. difficile* and enterocolitis due to *S. aureus* and is not effective for systemic infections. Pregnancy risk factor is B for the oral type and C for intravenous type. Vancomycin may develop the neuromuscular-blocking effect. Nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease the elimination of vancomycin [5].

3.5. Other glycopeptides

Teicoplanin is very similar to vancomycin in the mechanism of action and antibacterial spectrum; telavancin is active with Gram-positive bacteria and potentially teratogenic; hence, it must be avoided in pregnant women. Daptomycin is a new cyclic lipopeptide fermentation creation of *Streptomyces roseosporus*. It may be active against vancomycin-resistant strains of enterococci and *S. aureus*. It should be used with care in renal impairment [3, 29].

3.6. Tetracyclines (tetracycline, doxycycline, minocycline, tigecycline)

Tetracyclines chelate divalent metal ions which can restrict their absorption and activity. Tetracyclines are broad-spectrum bacteriostatic antibiotics that inhibit protein synthesis.

3.6.1. Resistance

Three mechanisms of resistance to tetracycline analogs have been described: 1) impaired influx or increased efflux, 2) ribosome shield due to the production of proteins that interfere with tetracycline binding to the ribosome regularly by Gram positives and 3) enzymatic inactivation. The most important of these is the formation of an efflux pump and ribosomal protection [3, 30].

3.6.2. Adverse reactions

Hypersensitivity reactions to tetracyclines are uncommon. Most adverse effects take place due to direct drug toxicity or modification of microbial flora; moreover, gastrointestinal adverse effects are the most common symptoms. Tetracyclines are readily bound to the calcium deposited in newly formed bone or teeth in young children under 8 years and in the fetus. It can accumulate in fetal teeth, leading to fluorescence, discoloration and enamel dysplasia; therefore, tetracyclines are avoided in pregnancy (category D). Tetracyclines in breast milk can chelate with calcium and interferes with growing teeth. Hepatic necrosis has been reported with daily doses of 4 g or more with intravenous injection. Renal tubular acidosis and Fanconi syndrome have been attributed to the administration of outdated tetracycline; if it is given along with diuretics it may cause nephrotoxicity. Intravenous injection can lead to venous thrombosis. Intramuscular injection produces painful local irritation and should be avoided. Demeclocycline can induce sensitivity to sunlight or ultraviolet light mainly in fair-skinned people [3]. An erythematous rash in sun-exposed parts of the body has been reported to appear in 7–21% of people taking doxycycline. Unlike some other members of the tetracycline group, it may be used in those with renal impairment. Doxycycline is contraindicated in the pediatric treatment of acute bacterial rhinosinusitis. Other reactions of doxycycline are similar to other tetracyclines [3, 5, 17]. Oral tetracyclines should be given in an empty stomach. Meals containing aluminum and magnesium may reduce tetracycline absorption. Other side effects include pericarditis, intracranial pressure increase, bulging fontanels in infants, pseudotumor cerebri, paresthesia, pigmentation of nails, exfoliative dermatitis, insipidus syndrome, discoloration of teeth enamel hypoplasia (young children) and anaphylaxis [5].

3.6.3. Drug interactions

Antacids, bile acid, bismuth, iron, magnesium and zinc salts may decrease the absorption of tetracyclines. Tetracycline derivatives can boost the neuromuscular-blocking effect and may diminish the therapeutic effect of penicillin and increase the toxic effect of retinoic acid and the anticoagulant effect of vitamin K antagonists [3, 5].

3.7. Macrolides (azithromycin, erythromycin)

The macrolides are categorized by a macrocyclic lactone ring to which deoxy sugars are attached. Erythromycin loses activity rapidly at 20°C and at acidic pH. Its activity is enhanced at alkaline pH [3, 17].

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Clarithromycin is derived from erythromycin by the addition of a methyl group and has an improved acid stability, but erythromycin-resistant streptococci and staphylococci are also resistant to clarithromycin. The advantages of clarithromycin are lower incidence of gastrointestinal intolerance and less regular dosing [3].

Macrolides resistance to erythromycin is usually plasmid encoded. Three mechanisms have been recognized: 1) Reduced permeability of the cell membrane, 2) production of esterases that hydrolyze macrolides and modification of the ribosomal binding site and 3) efflux and methylase production are the most important resistance mechanisms in Gram-positive organisms. Fundamental methylase construction confers resistance to structurally unrelated but systematically similar compounds such as clindamycin which share the same ribosomal binding site. However, constitutive mutants which are resistant can be selected and emerge during therapy with clindamycin [3, 17].

3.7.1. Adverse reactions

Anorexia and gastrointestinal signs are common, and they occur due to a direct stimulation of gut motility, and it is the most common reason for discontinuing erythromycin and substituting another antibiotic. Erythromycins, particularly the estolate type, can produce acute cholestatic hepatitis probably as hypersensitivity reaction but is reversible. Macrolides have been associated with rare (QTc) = QT Interval of the electrocardiogram prolongation and ventricular arrhythmias, including torsade de pointes; extensive use may result in fungal or bacterial superinfection [3, 5].

3.7.2. Disease-related concerns

Macrolides should be used with caution in coronary artery disease (CAD), in the elderly, myasthenia gravis, with narrowing of the gastrointestinal (GI) tract (may cause obstruction) and severe renal impairment. Pregnancy risk factor is B for erythromycin and C for clarithromycin. Macrolides can decline the metabolism of benzodiazepines, calcium channel blockers, carbamazepine, cisapride, antifungal agents, clozapine, colchicine, corticosteroids, cyclosporine, theophylline derivatives and vitamin K antagonists and may increase the serum concentration of alosetron, cardiac glycosides, fentanyl, salmeterol and tacrolimus. Macrolides may diminish the therapeutic effect of clopidogrel, the metabolism of HMG-CoA reductase inhibitors and some SSRIs [3, 5, 17].

Azithromycin is derived from erythromycin by the addition of methylated nitrogen into the lactone ring and different from clarithromycin mainly in pharmacokinetic properties. However, azithromycin penetrates into most tissues (except cerebrospinal fluid) and phagocytic cells extremely well. Antacids do not alter the bioavailability but delay absorption and reduce peak serum concentrations. Because they have a 15-element (not 14) lactone ring, they do not inactivate cytochrome P450 enzymes [3]. Other reactions are similar to macrolides [5, 17].

Ketolides are semisynthetic 14-membered-ring macrolides, differing from erythromycin by substitution of a 3-keto group for the neutral sugar L-cladinose which is permitted for limited clinical use. It is active in vitro against *Streptococcus pyogenes, S. pneumonia* and *S. aureus*. Many

macrolide-resistant strains are susceptible to ketolides because the basic modifications of these compounds change as poor substrates for efflux pump-mediated resistance, and they bind to ribosomes of some bacterial species with higher affinity than macrolides. It may slightly prolong the QTc interval. The use of ketolides can cause hepatitis and liver failure and are also contraindicated in patients with myasthenia gravis [3, 17].

3.8. Lincosamides

Clindamycin is a chlorine-substituted derivative of lincomycin, an antibiotic that is produced by *Streptomyces lincolnensis* [3]. Clindamycin, like erythromycin, inhibits protein synthesis by interfering with the formation of initiation complexes and with aminoacyl translocation reactions. The binding site for clindamycin is on the 50S subunit. It is often active against community-acquired strains of methicillin-resistant *S. aureus* [5, 17]. Ordinary adverse effects are diarrhea, nausea and skin rashes. Impaired liver function and neutropenia occur occasionally [3]. Physicians must use clindamycin carefully in patients with hepatic impairment. Some products may contain benzyl alcohol which has been related to "gasping syndrome" in neonates, and some others may have tartrazine which causes allergic reactions in certain persons. Elderly patients have a higher risk of developing severe colitis. Clindamycin is excreted in breast milk, and thus it is suggested to suspend drug intake. Lincosamide may diminish the therapeutic effect potential of erythromycin [3, 5, 17].

3.9. Streptogramins

They share the same ribosomal binding site as macrolides and clindamycin, and it is active against Gram-positive cocci, multidrug-resistant strains of streptococci, penicillin-resistant strains of *S. pneumoniae*, methicillin-susceptible and resistant strains of staphylococci. Resistance may occur due to alteration of the quinupristin binding site (MLS-B type resistance), enzymatic inactivation of dalfopristin or efflux. Quinupristin-dalfopristin is permitted for the treatment of infections caused by staphylococci or by vancomycin-resistant strains of *E. faecium*. The major toxicities are infusion-related events, such as pain at the infusion site and an arthralgia-myalgia syndrome [3, 31].

3.10. Oxazolidinones

Linezolid is an affiliate of the oxazolidinones, a novel class of synthetic antimicrobials. It is active against Gram-positive organisms. Its resistance is caused by the mutation of linezolid binding site on 23S ribosomal RNA. Linezolid is confirmed for use in vancomycin-resistant *E. faecium* infections, health care-associated pneumonia and community-acquired pneumonia. Tedizolid is a next-generation oxazolidinone with high potency against Gram-positive bacteria such as methicillin-resistant *S. aureus*. Possible benefits over linezolid include bigger impact against staphylococci and one daily dosing [3, 6]. The main toxicity of linezolid is hematologic which is reversible and commonly minor. Thrombocytopenia is the most common sign when the drug is ordered for use more than 2 weeks. Optic and peripheral neuropathy and lactic acidosis have been reported with long courses of linezolid. There are reports of serotonin syndrome arising when linezolid is co-participated with serotonergic drugs [3, 5].

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3.11. Aminoglycosides

They are used broadly in combination with a beta-lactam antibiotic in serious infections with Gram-negative bacteria and with vancomycin or a beta-lactam antibiotic for Gram-positive endocarditis. Acidic pH and anaerobic conditions inhibit the passage across the cell membrane into the cytoplasm by reducing the gradient. Transport may be improved by cell wall-active drugs such as penicillin or vancomycin [3, 32]. Aminoglycosides are absorbed very poorly from the intact gastrointestinal tract.

3.11.1. Adverse effects

The threshold is not precisely defined for the beginning of toxicity, but concentrations above 2 μg/mL are perilous [5]. All aminoglycosides are ototoxic and nephrotoxic, and they are more likely to emerge when therapy is persistent for more than 5 days, with higher doses, in the elderly and in renal failure. Parallel consumption with loop diuretics or other nephrotoxic antimicrobial agents (vancomycin or amphotericin) can create nephrotoxicity. Ototoxicity can appear as auditory damage (tinnitus and high frequency hearing loss) or as vestibular impairment (vertigo, ataxia, loss of balance). Neomycin, kanamycin and amikacin are the most ototoxic drugs. Streptomycin and gentamicin are the most vestibulotoxic. Neomycin, tobramycin and gentamicin are the most nephrotoxic. Aminoglycosides can produce a curare-like effect, in high doses, with neuromuscular blockade. This reaction is usually reversible by calcium gluconate or neostigmine. Hypersensitivity occurs intermittently [3, 5].

Gentamicin is effective against both Gram-positive and Gram-negative organisms and has no activity against anaerobes. Resistance emerges in staphylococci during monotherapy. Gram-negative bacteria resistance is most commonly due to plasmid-encoded aminoglycoside-modifying enzymes. Gram negatives which are gentamicin-resistant generally are vulnerable to amikacin. Low pH and low oxygen pressure create poor environment for drug activity [5, 32].

3.11.2. Gentamicin adverse reactions

Nephrotoxicity is usually reversible. It occurs in 5–25% of patients consuming gentamicin for longer than 3–5 days. Ototoxicity, which is permanent, shows itself as vestibular dysfunction. Gentamicin has a rare hypersensitivity reaction. Pregnancy risk factor is C (ophthalmic, topical) and D (injection).The nephrotoxic effect of aminoglycosides may be enriched with amphotericin B, cisplatin, cyclosporine, colistimethate, loop diuretics and vancomycin. Aminoglycosides may increase the hypocalcemic effect of bisphosphonate derivatives and the neuromuscular-blocking effect of Botulinum toxin type A and Botulinum toxin type B. Some penicillins may accelerate the degradation of aminoglycosides in vitro. This may be clinically significant for certain penicillin (ticarcillin, piperacillin, carbenicillin) and aminoglycoside combination therapy in patients with significant renal impairment. Close monitoring of aminoglycoside levels is warranted [5, 32].

Tobramycin, like other aminoglycosides, is ototoxic and nephrotoxic. Nephrotoxicity of tobramycin may be slightly less than that of gentamicin.

Amikacin is semisynthetically derived from kanamycin; it is less toxic than the near relative molecule. It is resistant to many enzymes that inactivate gentamicin and tobramycin; therefore, it can be used against some resistant microorganisms. Similar to all aminoglycosides, amikacin is nephrotoxic and ototoxic [3, 5, 17].

3.12. Sulfonamides

The basic structure of the sulfonamides has similarity to p-amino benzoic acid (PABA). Sulfonamides are more soluble in alkalosis than in acidosis. It can be prepared with sodium salts which are utilized for intravenous injection. Sulfonamides deter Gram-positive and Gram-negative bacteria. Its activity is reduced against anaerobes. *Pseudomonas aeruginosa* is certainly resistant to sulfonamide antibiotics. A mixture of a sulfonamide with an inhibitor of dihydrofolate reductase (trimethoprim) is synergistic due to sequential inhibition of folate synthesis [3, 5].

3.12.1. Resistance

Several bacteria, like mammal cells, do not have the crucial enzymes for folate synthesis from PABA and depend on exogenous sources; therefore, they are not vulnerable to sulfonamides. Sulfonamide resistance may take place by mutations that cause high production of PABA and production of a folic acid-synthesizing enzyme that has low affinity for sulfonamides or impermeability to the sulfonamide. In significant renal failure, the dosage must be reduced. The previous susceptible species such as meningococci, pneumococci, streptococci, staphylococci and gonococci are now resistant [3, 5, 32].

3.12.2. Adverse reactions

Traditionally, drugs with the basic structure of sulfonamide including antimicrobial sulfas, diuretics, diazoxide and the sulfonylurea hypoglycemic drugs are measured to be cross-allergenic. The most common adverse effects are fever, skin rashes, exfoliative dermatitis, photosensitivity, gastrointestinal signs and difficulties due to urinary tract problems. Stevens-Johnson syndrome is uncommon, and potentially fatal type of skin or mucous membrane eruption may be appeared. They may precipitate in acidic urine producing crystalluria or obstruction. This is rarely a problem with the more soluble sulfonamides such as sulfisoxazole. Sulfonamides have also been associated in various types of nephrosis. They can cause hemolytic or aplastic anemia and may incite hemolysis in patients with G6PD. Sulfonamides taken near the end of pregnancy increase the risk of kernicterus [3, 5].

3.13. Trimethoprim and trimethoprim-sulfamethoxazole

Trimethoprim selectively inhibits bacterial dihydrofolic acid reductase for repelling the synthesis of purines and DNA. Trimethoprim or pyrimethamine by merging with a sulfonamide can block folate synthesis (synergism). It is active against most *Staphylococcus aureus* strains, both methicillin-susceptible and methicillin-resistant and against respiratory tract pathogens.

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Resistance to trimethoprim results from reduced cell permeability, overproduction of dihydrofolate reductase or production of an altered reductase with reduced binding. Mutation due to plasmid-encoded causes rapid and widespread trimethoprim resistance.

3.13.1. Adverse effects

Anti-folate activity causes megaloblastic anemia, leukopenia and granulocytopenia, and with the trimethoprim-sulfamethoxazole mixture, all reactions connected to sulfonamides may occur. Patients with AIDS and pneumocystis pneumonia have a particularly high frequency of reactions to this mixture (fever, rashes, leukopenia, diarrhea, hepatic enzymes rising, hypoglycemia, hyperkalemia, hyponatremia) [3, 5, 29]. It should be used with cautiousness in patients with allergies or asthma, hepatic and renal impairment, thyroid dysfunction, in the elderly, G6PD deficiency and folate deficiency. Trimethoprim can increase the hyperkalemic effect of ACE Inhibitors and the adverse effect of amantadine. It may decrease the metabolism of thiazolidinedione, repaglinide, procainamide and the excretion of lamivudine. Sulfamethoxazole can boost the myelosuppressive effect of azathioprine and cyclosporine. Procaine may reduce the activity of trimethoprim. Sulfonamides and trimethoprim may decrease the metabolism of phenytoin [5, 29].

3.14. Fluoroquinolones—DNA gyrase inhibitors

Quinolones are synthetic fluorinated analogs of nalidixic acid. They are active against Gram-positive and Gram-negative bacteria. Methicillin-resistant strains of staphylococci are often resistant [3, 33]. Quinolones as whole are divided into three groups including nalidixic acid, the first generation with better effect on Gram negatives, ciprofloxacin as the second and moxifloxacin as the third generation. In some references they are divided into two groups based on antimicrobial spectrum and pharmacology [3, 34]. Gemifloxacin and moxifloxacin have better action against Gram-positive organisms while older fluroquinolones have moderate effects on Gram positive as well as Gram negative [3, 34].

Resistance appears in around one of every 107–109 bacteria, especially staphylococci, *P. aeruginosa* and *Serratia marcescens*. Resistance will be appeared in the quinolone-binding region of the target enzyme with mutations or by changing the permeability; recently, two forms of plasmid-mediated resistance have been defined. The first utilizes Qnr proteins which protect DNA gyrase from the fluoroquinolones; the second is an aminoglycoside acetyltransferase capable of modifying ciprofloxacin. Resistance to one fluoroquinolone normally confers cross-resistance to all of this class [3, 34].

3.14.1. Adverse effects

Fluoroquinolones are typically well tolerated. The most common side effects are nausea, vomiting and diarrhea. Intermittently, some interactions are headache, dizziness, insomnia, skin rash and high liver function tests. Prolongation of the QTc interval may occur with levofloxacin, gemifloxacin and moxifloxacin; therefore, it must be used with care to QTc interval prolongation and hypokalemia. Due to impaired cartilage growth and arthropathy by

fluoroquinolones, they are not prescribed for patients under 18 years. Nevertheless, if arthropathy is reversible, it may be feasible for the treatment of pseudomonal infections in some patients with cystic fibrosis. Fluoroquinolones should be suspended during pregnancy due to lack of data verifying their safety. Neuropathy can appear and may continue for several months or years during and after treatment; in some cases it may be perpetual [3]. Fluoroquinolones have been related to serious and occasionally fatal hypoglycemia especially in elderly patients with diabetes, but it has been reported in cases without a previous history of diabetes [5, 33].

3.15. Moxifloxacin

It is effective on Gram-positive bacteria. Side effects include tremor, restlessness, confusion and rarely hallucinations or seizures; must be used with caution in cases with known or suspected CNS disorders [5]. Reactions may present as typical allergic symptoms or can present as severe idiosyncratic dermatologic disorder (Stevens-Johnson, toxic epidermal necrolysis, vasculitis). Pneumonitis, nephritis, hepatic failure or necrosis and cytopenias are frequently seen after multiple doses. Patients must avoid excessive sunlight because of moderate-to-severe phototoxicity reactions [5, 6]. Prolonged use can produce fungal or bacterial superinfection. It should be used carefully in patients with significant bradycardia or acute myocardial ischemia, hepatic impairment, myasthenia gravis, rheumatoid arthritis, elderly and G6PD deficiency. Safety and efficacy of moxifloxacin have not been established in children, but in pregnancy, the risk factor is category C [5]. All these adverse effects are rare or about 1–2%, and it may also have some other reactions less than 1% such as hyperlipidemia, hyper or hypotension, hypoesthesia, laryngeal edema, nightmares, paresthesia, pelvic pain, peripheral neuropathy, decreased prothrombin time, speech disorder, taste loss, abnormal thinking, tinnitus, tongue discoloration, arrhythmia and vision abnormalities [3, 5]. It may increase the QTc-prolonging effect. Antacids, magnesium, iron and zinc salts may decrease the absorption of quinolone antibiotics (oral tables), but it is not affected by taking with a high-fat meal, yogurt or sodium bicarbonate. Quinolone antibiotics may expand the toxic effect of corticosteroids (systemic) and the effect of vitamin K antagonists. Insulin and sulfonylureas may increase the hyperglycemic or hypoglycemic effects. The neurotoxicity or seizure-potentiating effect might increase with NSAIDs [5, 33].

3.16. Ciprofloxacin

It has moderate effects on both Gram-negative and Gram-positive bacteria. In consequence of its extensive usage even for minor infections which are curable with older and narrower spectrum antibiotics, many bacteria have developed resistance in recent years. Numerous pathogens, including enterococci, *Streptococcus pyogenes* and *Klebsiella pneumonia*, have become resistant [33]. Most side effects are similar to other fluoroquinolone drugs above. Alkaline urine may escalate the risk of crystalluria. In patients over 60 years, rupture of the Achilles' tendon may take place. Due to secretion in breast milk and because of damage to joint cartilage, it should be avoided during breast feeding; the pregnancy risk factor is C [3, 5, 17]. Intravenous injection must be slow to avoid the risk of venous irritation. Oral tablets should be taken with

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food to minimize GI distress. Consuming large quantities of caffeinated drinks may pose a danger due to cardiac or CNS reactions. Ciprofloxacin can reduce the serum concentration of phenytoin and theophylline derivatives [3, 5].

3.17. Metronidazole

It is a nitroimidazole antibiotic and antiprotozoal drug. Metronidazole is absorbed selectively by anaerobic bacteria and sensitive protozoa and does not affect any human cells directly or aerobic bacteria [3, 17].

3.17.1. Adverse reactions

It has been found to be carcinogenic in rats [35]. Chronic treatment causes seizures and neuropathies; if this occurs, therapy must be withdrawn. It should be used with restriction in patients with a history of seizure disorder and CNS disease. Metronidazole should be utilized carefully in patients with blood dyscrasias, the elderly, heart failure or other sodium-retaining states, liver impairment and severe renal failure (creatinine clearance less than 10 mL/min). The pregnancy risk factor is B and should be avoided in the first trimester. Other reactions include flattening the T-wave, flushing, ataxia, dizziness, fever, headache, insomnia, irritability, seizure, vertigo, erythematous rash, Disulfiram-like reaction, dysmenorrhea, nausea (very common), abdominal cramping, constipation, diarrhea, furry tongue, stomatitis, metallic taste, xerostomia, cystitis, darkened urine (rare), incontinence, neutropenia (reversible), thrombocytopenia (reversible), peripheral neuropathy, nasal congestion, rhinitis, sinusitis, pharyngitis, flu-like syndrome and moniliasis [3, 5, 35].

Metronidazole can increase the toxic effect of alcohol (ethyl). It may augment the toxic effect of amprenavir, tipranavir, disulfiram and mebendazole (risk for Stevens-Johnson syndrome). It may increase the serum level of busulfan, fentanyl and salmeterol. This drug may reduce the metabolism of calcineurin inhibitors and vitamin K antagonists. It may affect the enzymes aspartate transaminase (AST), and alanine transaminase (ALT) for Liver function test, triglycerides, glucose and LDH tests. Metronidazole may possibly cause mood fluctuation [36].

4. Nanoantibiotics

4.1. Introduction

Nanoscience in association with medicine can bring new opportunities for scientists to introduce novel solutions against medical complications. In recent years, the development of innovative drugs to combat multi-drug resistant (MDR) bacteria is growing strongly [28–30, 32, 37–40]. The advantage of nanoantibiotic therapy is to proficiently decrease a variety of side effects which originate from conventional antibiotics; furthermore, a specific nanostructure can be synthesized for a distinctive goal since the production process is safe, inexpensive and innovative.

As biocompatibility, low toxicity and noticeable purity of antibacterial nanoparticles are vital for medical treatments, in the near future the conventional methods of nanoantibiotic assembly such as sonication [41–43] and chemical routes [44] will be replaced by laser-assisted generation of nanoparticles (NPs) in liquids since no chemical precursors are required [45–49]. Shape and size of the nanoparticles play an essential role in the antibacterial behavior of nanoparticles, as a case in point the average size of 1–10 nm demonstrated a dominant antibacterial activity [50]; therefore, laser ablation in particular liquids along with controlled laser parameters can design nanomaterials with desired shape, size and composition in a very strategic mechanism without using surface active agents which can trigger surface impurity and toxicity. The large surface area to volume ratio is a main property of nanomaterial which increases the antibacterial activity. Co-delivery process of two or more drugs can be efficiently achievable by using nanomaterials [51]; antibiotic resistance is significantly avoided since nanoparticles do not enter the bacterial cell, and its mechanism of killing bacteria is fundamentally done via direct contact with the bacterial cell wall [52]. There are critical procedures which occur during nanoantibiotic therapy; as nanomaterials electrostatically bind to the bacterial cell wall, they can induce membrane destruction and depolarization which initiate cell death [53–55]. Nanomaterials with extremely high surface area can catalyze the production of reactive oxygen species (ROS) which have a critical potential to damage bacterial cells [56].

4.2. Essential nanocarriers for drug delivery

Antibacterial drugs due to their fast degradation, low water-solubility, cytotoxicity to healthy tissues and weak membrane transportation are fairly hard to manage; nanoparticles including dendrimers, liposomes and polymer-based nanoparticles can simplify drug delivery against infectious diseases. Dendrimers as a tree-like structure with many branches with typical size of 10 nm were used in drug delivery and diagnostic systems. Liposome nanoparticles in the size range of 50–200 nm were broadly used for drug delivery system initially proposed in the 1970s [57]. Liposomes with a distinctive bilayer lipid structure are able to transfer hydrophobic and hydrophilic compounds without any chemical alteration; they can proficiently combine with bacterial membranes and release antibacterial agents to their cell membranes. In order to extend liposome longevity and stability in the blood stream, they can easily be functionalized with biocompatible polyethylene glycol (PEG) by forming a stealth layer on the liposome surface [58, 59]. Biocompatible chitosan nanoparticles with nontoxic nature, high antibacterial activity and high stability can encapsulate or embed drugs in the polymeric network. Hydrogels with biocompatible hydrophilic networks allow delivery of hydrophilic and small-molecule drugs. Highly porous silica nanoparticles are well known for local drug delivery to reduce cytotoxicity and side effects [60–62].

Metal-based nanoparticles including nickel, tungsten, gadolinium, gold, silver, zinc oxide, titanium dioxide and iron oxide nanoparticles were commonly used for diagnosis and delivery. A critical disadvantage is toxicity from the accumulation of metal nanoparticles in the human body after treatment; therefore, drug delivery process should be performed in a very strategic way.

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Zinc oxide nanoparticles (ZnO NPs) with potent antibacterial activity were designed as enzyme-nanoparticle conjugates in order to improve mono-dispersity and stability of nano-antibiotics during treatment; extremely greater antibacterial behavior was obtained by using positively charged lysozyme enzyme covalently bonded to ZnO nanoparticles [63].

Interestingly not only nanoparticles but also ions can demonstrate very strong antibacterial activity. Researchers at Rice University discovered that only silver ions behave destructively to the bacteria. Delivered silver ions can stimulate lysis in which the membrane of the bacterial cell breaks down and causes bacterial cell death [64].

The release of antibiotics can be prolonged by using nanocarriers for drug delivery systems to reduce extremely antibiotic resistance. Gold nanoparticles capped with glutathione can bring a higher rate of gentamicin loading; these capped gold nanoparticles which were covalently attached to gentamicin revealed strong antimicrobial activity with extended release of antibiotic over several days [65].

4.3. Antibacterial activity of core-shell nanoparticles

Recently, scientists were accentuated over designing of biocompatible core-shell nanoparticles for antibacterial activity, controlled drug release and targeted drug delivery [66]. Core-shell nanoparticles are advantageous in contrast to single nanoparticles because of their advanced properties such as high stability, great dispersity and efficient functionality.

Silver-titanium dioxide (Ag-TiO_2) core-shell nanoparticles presented strong antibacterial activity against infectious diseases as a result of releasing silver ions from silver cores through the porous matrix of titanium dioxide shells; one can assume in such a core/shell assembly is the extension of the release time of silver ions which can be beneficial for a persistent antibacterial effect [67].

Gold-copper sulfide (Au-CuS) core-shell nanoparticles demonstrated extreme capability to deactivate *B. anthracis* cells by disordering and damaging its cell membrane; furthermore, antibacterial activity depends on nanoparticle concentration and treatment time [68]. The antimicrobial activity of nanoparticles and microbial cell death can be related to the electrostatic interaction between negatively charged bacterial cells and positively charged nanoparticles which stimulates the loss of membrane integrity [69]. The negatively charged bacterial cell wall composition has a thick layer of peptidoglycan which is linked to teichoic acid. Osmotic imbalance and cytoplasmic content leakage of the damaged membrane probably initiate the cell disintegration.

Alumina-coated iron oxide magnetic nanoparticles (Fe_3O_4-alumina core-shell MNPs) as a photothermal factor under near-infrared (NIR) illumination were used to selectively destroy bacteria. Alumina coating triggers the targeting ability of Fe_3O_4 magnetic nanoparticles in the direction of bacteria. The magnetic behavior of Fe_3O_4/alumina nanoparticles allows them to accumulate in the desired region under a magnetic field and photothermally destroys them by NIR irradiation at the populated region. Remarkably, the cell growth of nosocomial bacteria (Gram positive, Gram negative) and antibiotic resistance can be efficiently avoided in over

95% by applying 10 minutes irradiation via NIR laser beam at the accumulated region of core/shell Fe3O4-alumina MNPs [70].

Core-shell silica-gold nanoparticles were represented loading a significant amount of gentamycin about 87 μg/mg for drug targeting process. Silica core particles were prepared by Stober's method and functionalized with amine groups. Amine group of gentamycin was attached to the gold nano shell surface, and the drug releasing from core-shell nanoparticles was simply prepared by breaking the gold-gentamycin coordinate linkers [71].

Core-shell silica-polyrhodanine nanoparticles were synthesized by chemical oxidation polymerization; they revealed brilliant antimicrobial activity against Gram-positive *Staphylococcus aureus*. In fact, biocidal activity of these nanoparticles was improved by increasing the surface area to volume ratio; core/shell NP size can be experimentally modified by changing the silica core diameter [72].

Novel mesoporous silica nanoparticles were efficiently loaded with chlorhexidine (CHX) which is generally used as antimicrobial agent in dentistry; they were synthesized with an average particle diameter of 140 nm and pore size of around 2.5 nm. Nano-CHX core-shell nanoparticles exhibited promising antimicrobial activity against critical oral pathogens including *S. mutans, S. sobrinus, F. nucleatum, A. actinomycetem comitans* and *E. faecalis* [73].

Hybrid core-shell zinc oxide-silver (ZnO-Ag) nanorods presented remarkable antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Silver nanoparticles with an average size of about 7 nm were designed on heterojunctions at the surface of the ZnO nanorods. The probable mechanism derives from the generation of reactive oxygen species due to electron transfer between zinc oxide nanorods and silver nanoclusters which triggers physical destruction of the bacterial cell wall [74].

5. Conclusion

The normal human body has an intrinsic order which is known as physiology; when a bacterial infection occurs, human cells occasionally need help to defend themselves; therefore, various antibiotics have roles to assist cells, and at the same time, some interactions may take place among antibiotics and human cells then side effects appear. Adverse reactions can be predicted by recognizing the normal situation, background diseases, spectrum of antibiotic effects and mechanism of action. Nowadays, due to extensive use of antibiotics in many fields such as veterinary, agriculture, farming, food industries, and exaggerative prophylaxis, bacteria have a greater chance to resist with mutation, selection and gene transferring; therefore, action against bacterial infection should be with caution, proper drug doses, good background hygiene, adequate therapy, synergism, novelty in treatment and enhanced diagnosis should be considered; one of these innovative treatments is nanoantibacterial therapy. Nanoantibiotics revealed innovative mechanisms against infectious diseases in comparison with conventional drug delivery procedures. Biocompatibility, low toxicity and pronounced purity of antibacterial nanomaterials have prepared them appropriately for therapeutic processes as an

auspicious alternative in medicine to decrease antibiotic resistance and cytotoxicity in a very efficient way.

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