Effect of aminoglycosides on the pathogenic characteristics of microbiology

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Abstract
Infections caused by pathogen remain to be one of the most important global health issues, and scientists are devoting themselves to seeking effective treatments. Aminoglycoside antibiotics are one kind of widely used antibiotics because of the good efficiency and broad antimicrobial-spectrum. However, it causes some unexpected effects on the pathogenic characteristics of microbiology during the treatment, such as drug resistance and biofilm promotion. Drug resistance is partly due to antibiotics abuse. Simultaneously, aminoglycoside is documented to make divergent effects on biofilm based on their concentrations. Here, we review the mechanism of drug resistance caused by long-term use of aminoglycoside antibiotics, the effects of antibiotic concentration on biofilm formation and the negative effects on intestinal flora to provide theoretical supports for rational use of antibiotics.

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1. Introduction

Aminoglycoside antibiotics are one kind of widely used antibiotics because of the good efficiency and broad antimicrobial spectrum. Since the first acquisition of streptomycin from fermentation broth produced by Streptomyces in 1944 by Waksman et al. [1], more than 3000 natural and semisynthetic aminoglycoside antibiotics have been reported afterwards. After the discovery of streptomycin, research of aminoglycoside has been expanded through the development of several closely related compounds acquired from actinomycetes such as Streptomyces and Micromonospora. The structure of aminoglycosides is similar to carbohydrate, whose backbone structure consists of an aminocyclitol ring saturated with amine and hydroxyl substitutions. The majority of aminoglycoside antibiotics are semi-synthetic derivatives of the natural products (Fig. 1), excluding amikacin, netilmicin, dibekacin, isepamicin and arbekacin.

Aminoglycoside antibiotics are excellent anti-infective agents of the life-threatening infections caused by gram-negative bacteria [3–5]. They are enhanced in the alkaline environment and produce synergistic action together with other antibiotics [6]. A synergistic action of aminoglycoside antibiotics with various beta-lactams is reported in vitro and in vivo against Enterococi, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella spp. and Proteus mirabilis [103]. Combinations of aminoglycosides and other agents provided powerful broad spectrum tools for the control of infections in increasingly immunocompromised patients with complex infections problems. Reliance on synergistic action grew into the groundwork for current antibiotic therapy practice.

Aminoglycoside antibiotics show significant dose-dependent effects against bacteria. Moreover, the majority of pathogens have been reported to present post antibiotic effect (PAE). The PAE is defined as the length of time that bacterial growth is suppressed following brief exposure to an antibiotic [7]. The greater the magnitude of the PAE, the less likely it is that resumption of bacterial growth will occur during intervals of sub-inhibitory antibiotic concentrations in tissues or serum. Previous studies have found that the PAE of gentamicin, tobramycin and netilmicin against P. aeruginosa is up to 5–8 h, whereas that of E. coli is 2–3 h [8]. This kind of drug might result in some adverse reactions, such as the eighth cranial nerve damage, renal damage and neuromuscular junction block. Furthermore, some unexpected effects of aminoglycosides on the pathogenic microorganisms couldn’t be ignored, including antimicrobial resistance, biofilm formation and the disruption of gut microbes balance.

Antimicrobial resistance refers to the reduction in effectiveness of a drug such as an antimicrobial or an antieoplastic in curing a disease or infection [102]. Bacteria that show resistance to three or more classes of antibiotics are designated as multi-drug resistance (MDR). MDR bacteria encountered currently include P. aeruginosa, E. coli, Klebsiella pneumoniae, Mycobacterium tuberculosis, Acinetobacter baumannii, Staphylococcus aureus [9,17]. As concerned, the prevalence of MDR A. baumannii increased significantly from 2008 (14.2%) to 2012 (46.5%) in Fujian province, China [10]. Aminoglycoside antibiotics abuse in agriculture and veterinary are contributing to the emergence of MDR bacteria [11–15]. According to a report of China, the annual production of antibiotics was 21 million tons in recent years, of which 86% of the production were for domestic use and more than 1/3 of the domesticus usage enters into the human body through food chains [16]. Furthermore, there is an alarming increase of resistance bacteria that cause hospital acquired infections even community infections caused by resistant bacteria. Recent metatranscriptome analyses have revealed that antibiotic resistance genes are expressed in a broad range of natural habitats, even in the absence of obvious antibiotic selection pressure [18–20].

Biofilms are microbial communities wrapped in the self-produced matrix or extracellular polymeric substance (EPS), which is ubiquitous either in industrial or medical device filed [21]. The bacteria bedded in EPS are protected from the interference of the external environment. It has been estimated that biofilms may be involved in more than 65% of medically relevant infections, including ventilator and cystic fibrosis-related pneumonia, endocarditis, burn wound infections [22–25]. Therefore, infections caused by biofilms are one of the biggest health issues in food industry and nosocomial treatment. Simultaneously, the effect of aminoglycoside antibiotics on biofilms is significantly compromised by the unique structure and characteristics of biofilms. Furthermore, aminoglycoside antibiotics at the sub-inhibition concentration are reported to promote the biofilm formation.

Normally, the intestinal flora is crucial for various physiological functions and life activities of the organisms, and are closely linked with the status of host’s nutrition, immunity and metabolism [26–29]. Aminoglycoside antibiotics, commonly used in treatment of urinary tract infection, have influence on the dynamic balance of intestinal flora. In this review, we will discuss the unanticipated effects of aminoglycoside antibiotics on the pathogenic characteristics of microbiology in detail.

2. Antimicrobial resistance

Antimicrobial resistance has been recognized as one of the most pressing public health and societal issues nowadays [30–34]. Xu et al. had investigated the antimicrobial resistance rates of three important genus in southern China during 2001–2015, including Staphylococcus, Enterococcus and Streptococcus [35]. Resistance rates against gentamicin were 69.2% in Enterococcus faecalis and 75% in Enterococcus faecium. Slightly increase in coagulate-negative
Staphylococcus (CNS) was observed during the studied period (ranging from 42% to 58%) (Fig. 2). Notably antimicrobial resistance among gram-positive pathogens still remained high in southern China. The reasons of antibiotic-resistance are usually multifaceted, involving both intrinsic resistance mechanisms and adaptive stress response. Therefore, it is necessary to figure out the mechanism of antimicrobial resistance, laying the foundation of proposing new effective measures.

2.1. Decreased permeability of membranes

The outer membrane of gram-negative bacteria is a barrier to both hydrophobic and hydrophilic material. In order to circumvent this permeability barrier, these organisms have evolved porin proteins (such as OmpF in E. coli and OprD in P. aeruginosa) that function as “nonspecific” entry and exit points for antibiotics and other small-molecule organic chemicals. Carbapenem and basic amino acids pass through OprD mutations that decrease expression of the porin contribute to clinical carbapenem resistance [36]. Moreover, a similar study was conducted by Kumar et al. to investigate the relationship between amikacin resistance of Acinetobacter, the expression of oprD gene and porin. According to the research, they found that expression of 33 kDa porin in normal cell was 10 folds higher than that of the resistant bacteria, in accordance with the expression of oprD gene [37]. The decrease of the porin expression led to the decrease of permeability of the cell membrane. And the change of drug uptake was mainly caused by the membrane permeability, which was more common in Pseudomonas, as well as other non-fermentation gram-negative bacilli [38–42]. Moreover, streptomycin shows no antimicrobial activity to P. aeruginosa as it could bind to negatively charged membrane directly, thus decreasing the membrane permeability and limiting the drug enter into the cells [43–46]. Therefore, the aminoglycoside antibiotics use should be carefully in clinical treatment.

2.2. Inactivation of aminoglycoside antibiotics

Bacteria produce aminoglycoside-modifying enzymes (AMEs) which passivate the aminoglycoside antibiotics, resulting in antimicrobial resistance [47,48]. Inactivation of enzymatic modification is the most prevalent resistance mechanism of bacteria to aminoglycoside antibiotics. The AMEs covalently binding to antibiotics with –OH or –NH₂ and other functional groups could interfere the combination of antibiotics to the A site on the 16S rRNA, thus resulting in the decrease of affinity between the antibiotics with ribosyl-tRNA and inactivating the antibiotics [49].

There are three types of AMEs, including aminoglycoside nucleotidyl transferases (ANTs), aminoglycoside acetyltransferases (AACs) and aminoglycoside phosphotransferases (APHs) [50]. The reactions catalyzed by these enzymes are usually regioselective, and the modification site is indicated in parentheses. The AMEs are commonly observed across gram-positive and gram-negative bacteria. Remarkably, many subtypes of AMEs have been reported and they are widely distributed, such as E. coli (aac(3)-II, aac(6’)-Ib, in Hong Kong), K. pneumonia (aac(3)-II, aac(6’)-Ib, ant(2’)-Ia, in Norway), and coagulase negative Staphylococci (aac(6’)-Ic-aph(2’)-Ia, ant(4’)-Ia, aph(3’)-lIa, in Iranian) [51–53]. And related research has demonstrated that deletion of aac(2’)-I gene could increase susceptibility of Mycobacterium abscessu to kanamycin, tobramycin, dibekacin and gentamicin. In the meantime, deletion of eis2 could increase its susceptibility to capreomycin, hygromycin, amikacin [54]. The AMEs are usually encoded by plasmids in Staphylococci, R-factors in Enterobacteria and other extrachromosomal elements, including integrons, gene cassettes and transposons. For example, three AACs genes were found in class 1 integron among P. aeruginosa, and they were specifically resistant to carbapenems and sulfonamides as well [55]. The transformation or transduction of plasmids are beneficial for horizontal gene transfer of drug resistance genes among different bacteria. To keep aminoglycosides as useful tools in the clinical treatment, development of new aminoglycosides which cannot bind to AMEs or inhibitors are of great necessity [56,57].

2.3. Altered target sites

The ribosome is the target of aminoglycoside antibiotics, and ribosomal RNA plays a key role in the binding of antibiotics to ribosome [58,59]. With more clearly structure of ribosome being known, it is likely to understand the mechanism of bacteria resistance against aminoglycoside antibiotics at molecular level, which will contribute to monitoring these antibiotics and design new antibiotics. Antibiotics cannot combine with ribosome due to the alternation the target site. Though this situation happened rarely. However, previous studies have proved that some specific mutation of ribosomal RNA was related to antibiotic resistance. For example, certain mutations at positions 1400 and 1401 of the rrs were found...

Fig. 2. Gentamicin resistance rate of important gram-positive isolates in southern China [35].
in kanamycin-resistant isolates of M. tuberculosis [60].

Moreover, other studies have shown that mutations of the rpsL gene encoding the 512 ribosomal protein and the rrs gene encoding 16S rRNA altered the target site in M. tuberculosis, making the bacteria resistant to streptomycin at significant level [61,62]. S12 protein is a component of the 30S subunit, which mainly controls the binding of streptomycin to the 30S subunit and plays a remarkably role in stabilizing the highly conserved fake structure formed by 16S rRNA. The amino acid substitution caused by the mutation of rpsL gene resulted in the change of advanced structure of 16S rRNA which interacts with streptomycin. The mutation in the rrs gene, associated with streptomycin resistance in M. tuberculosis, affected two highly conserved regions, the 530 loop and the region around nucleotide 921, according to E. coli numbering, and resulted in decreased affinity for streptomycin. The structure of the streptomycin-30S ribosomal subunit complex revealed specific interactions between antibiotics and the backbone phosphate or ribose hydroxyl groups of nucleotides, C526 and G527 of helix 18 and A913 and A914 of helixes 27 and 28 [63], respectively, providing a rational for the location of mutations previously identified and their effect on streptomycin binding. Moreover, according to a genetic analysis of new 16S rRNA mutations conferring aminoglycoside resistance in M. abscessus conducted by Rachid et al., three new substitutions in rrs of M. abscessus kanamycin mutants resulted in the change of resistant phenotype in addition to the position 1408 of 16S rRNA, including T to A at 1406, C to T at 1409, G to T at 1491, respectively. The gene mutation of 1406 and 1408 showed a resistant phenotype, while the mutation of 1409 and 1491 were susceptible [64].

2.4. Efflux pump

MDR efflux systems are widely distributed among prokaryotic microorganisms, and it plays a vital role in the intrinsic resistance of gram-negative bacteria [65–67]. Most drug efflux proteins belong to five distinct protein families: the resistance nodulation cell division (RND), major facilitator (MF), staphylococcal/small multidrug resistance (SMR), ATP-biding cassette (ABC), and multidrug and toxic compound extrusion (MATE) families [68]. On the condition of constant presence of antibiotics, RND-AmrB/AcrD (resistance nodulation cell division family) efflux pump, MexXY-OprM and other transporter efflux system will express its function, thus the bacteria presents resistance to it. The expression level of MexXY efflux pump gene, commonly mediated by aminoglycoside antibiotics, can be influenced by many factors. Sebastien et al. have found that the expression of MexXY of PA5471 gene in P. aeruginosa was upregulated significantly when the bacteria were exposed to ROS (reactive oxygen species), enhancing the bacteria tolerance to aminoglycoside antibiotics [69].

Studies have reported that MexZ regulated the expression of MexXY. After removing MexZ in vitro, the expression level of MexXY up-regulated and presented aminoglycoside resistance. And a variety of specific and aspecific mutations affecting three distinct regulatory pathways actually lead to the over-expression of efflux system MexXY, and to increase aminoglycoside resistance in clinical strains of P. aeruginosa. These pathways involve the local repressor MexZ (agrZ-type mutants), the MexZ antirepressor ArmZ (agrW1-type mutants), and the two-component regulatory system ParRS (agrW2-type mutants). The expression level of mexY in two mutant strains was 15-folds higher (agrW1-type mutants) and 16-folds higher (agrW2-type mutants) than that of wild type, respectively [70]. Furthermore, another study has found that the expression level of MexXY-OprM down-regulated after knocking out a base fragment of 3bp between the merR and mexA genes, resulting in aminoglycoside resistance in P. aeruginosa [71].

2.5. Other mechanism of drug resistance

In addition, there are many other factors that can lead to aminoglycoside antibiotics resistance, such as 16S rRNA methylation and biofilm formation [72,73]. The 16S rRNA methylation is mainly found in streptomycin. Enzymatic methylation of the rRNA at N1-A1408 or N7-G1405, results in a high level resistance to aminoglycoside antibiotics. Biofilms enable the bacteria to adapt to the living environment. There are three theories related to biofilm resistance, including nutrition limitation, antibiotic permeation disorders and phenotypic structure.

3. Effects on biofilm formation

Once bacteria embedded in biofilm, the phenotype and physiology of bacteria change profoundly, contributing to their highly tolerance to aminoglycosides and host immune response [74]. The efficacy of aminoglycoside antibiotics against biofilms are significantly reduced, and concentration of the antibiotics needed to inhibit biofilm formation is much higher than that of single-cells. Biofilm formation impairs treatment efficacy and requires frequent therapeutic removal of colonized devices, leading to increased morbidity and medical costs. At the same time, there is growing evidence that bacteria respond specifically and defensively to sub-inhibitory concentration of aminoglycoside antibiotics by promoting the biofilm formation, which contributes to bacteria persistence in chronic infections. Therefore, the effects of different aminoglycoside antibiotics on biofilm formation (either inhibition or promotion) are summarized in Table 1.

3.1. Inhibition of biofilm

Aminoglycoside inhibition of biofilm formation is nutrient dependent. Michelle et al. had investigated the effect of nutrient concentration on the susceptibility of developing biofilms [77]. S. aureus biofilm were incubated overnight at different concentration (1/3 ×, 1 × and 3 × TSB, respectively) of nutrient, supplemented with 5 μg/ml (at the bactericidal concentration) of gentamicin and 32 μg/ml of streptomycin. They found that biofilm incubated in 1/3 × and 1 × TSB were inhibited, but samples incubated in 3 × TSB were not inhibited. Additional experiments showed that the ability of nutrient-rich to weaken the antibacterial effects of gentamicin was associated with decreasing uptake of gentamicin by S. aureus. In case of nutrient-rich, increasing biofilm biomass might result in reducing the interactions between antibiotics and bacteria And the experiment indicated that increasing nutrient concentration increased survival and growth of both gentamicin-treated S. aureus planktonic cells and biofilm. It is demonstrated that nutrient availability alone may exert a profound effect on the susceptibility of S. aureus to aminoglycoside antibiotics [78,81].

On the other hand, inhibition caused by antibiotics mainly occurs at the adhesion stage and the antibiotics killed the planktonic bacteria directly. However, the appearance of a subpopulation of non-growing persistent bacteria, characterized by high, but reversible, tolerance to otherwise lethal concentrations of antibiotics, will contribute to biofilm tolerance [82]. This kind of persistent bacteria are not resistant mutants, which may grow again and repopulate biofilm induced by effective antibiotic treatment, thereby leading to infection occurrence. Hence, in addition to identification of anti-biofilm compounds, inhibition of persistent bacteria approaches that are capable of killing planktonic and biofilm are currently being investigated [83]. For example, use of accessory factor such as mannositol or fructose was demonstrated to increase aminoglycoside antibiotics uptake, thereby enhancing
their efficacy against persistent bacteria in vitro and in vivo. As aforementioned, the sensitivity of planktonic bacteria exposed to aminoglycosides was increased in alkaline media. A recent study conducted by David et al. suggested that L-arginine (0.4%), might be a good accessory factor for killing biofilm persistent cells (S. aureus, E. coli, P. aeruginosa) combining with gentamicin with 99% mortality through raising pH of the media [79]. Indeed, biofilm tolerance to antibiotics of P. aeruginosa was significantly reduced with a supplementation of tobramycin and L-arginine in vitro. The research of Duan et al. also demonstrated that combination of specialized chitosan with aminoglycoside antibiotics could effectively inhibit Listeria biofilm formation by Listeria and disrupt the established biofilms. The established biofilm biomass was significantly reduced by treating with amikacin (25 μg/ml) and chitosan (200 μg/ml), suggesting that this strategy might be useful to treat Listeria biofilm-related infections and prevent the spread of antibiotic resistance through improving antibiotics effectiveness [80].

### 3.2. Promotion of biofilm formation

The sub-inhibitory concentration of certain antibiotics are reported to stimulate biofilm growth. The difficulty in preventing biofilm formation has become more and more complicated because of the presence of this phenomenon. Studies have proved that sub-inhibitory concentration of tobramycin (0.3 μg/ml) stimulated the biofilm formation by P. aeruginosa and E. coli. Moreover, the azithromycin could promote the biofilm formation by Kocuria and Dietzia, at the concentration of 0.001 μg/ml and 0.04 μg/ml, respectively [84]. Furthermore, a real-time biofilm formation curve of S. aureus conducted by Ferrer et al. showed that the cell index reached to 1/3 MIC and 20 h after adding the antibiotics was increased by 40% relative to the control. And the greatest significant increase in biofilm formation for the Staphylococcus epidermidis (75% relative to the control) was produced by gentamicin at sub-inhibitory concentrations [85].

The mechanism of stimulation of biofilms formation by aminoglycosides remains unclearly. Transcriptome research has revealed that aminoglycosides have influence on the signaling pathway. Cyclic diguanosine monophosphate (c-di-GMP), a second messenger, is known to stimulate biofilm formation in a wide range of bacteria [75]. Hoffman et al. had investigated the relationship between arr gene (an aminoglycoside response regulator, encoding an inner-membrane phosphodiesterase whose substrate is c-di-GMP) and c-di-GMP. The results demonstrated that membranes from arr mutant cells were 54% less active in degrading c-di-GMP than membranes from normal cells. Furthermore, they also found that biofilm formation of wild-type cells induced by aminoglycoside was inhibited by exogenous CTP-a-c-di-GMP phosphodiesterase inhibitor. Based on the results, they concluded that tobramycin enhanced the phosphodiesterase activity of the Arr cytoplasmic EAL domain, resulting in c-di-GMP inactivation and promoted biofilm formation (Fig. 3).

Stimulation of adhesion synthesis associated with the "ribosomal stress" is probably another mechanism to promote the biofilm formation [86]. Boehm et al. found that exposure to sub-inhibitory concentration of ribosome-targeting antibiotics leads to strong biofilm induction in E. coli. And the effect is elicited by the ribosome in response to translation stress. Biofilm induction involves upregulation of the cell surface-exposed poly-GlcNAc adhesion, and two components of the poly-GlcNAc biosynthesis machinery, PgaA and PgaD. Poly-GlcNAc control depends on the bacterial signal molecules, guanosine-bis 3’, 5’(diphosphate) (ppGpp) and c-di-GMP. Treatment with translation inhibitors causes a ppGpp hydrolase (Spot5)-mediated reduction of ppGpp levels, resulting in specific derepression of PgaA. Based on the results, they found a novel regulatory mechanism that relies on ppGpp signaling to relay information about ribosomal performance to the Pga machinery, thereby inducing adhesion production and biofilm formation.

For both gram-negative and gram-positive bacteria, sub-inhibitory antibiotics treatment can stimulate production of exopolysaccharides and promote the biofilm formation [87–90]. Furthermore, a recent study suggested that the antibiotics directly or indirectly affect transcription and translation may imitate the action of stress factors triggering the processes of the “biofilm phenotype” formation involving the RpoS sigma factor and other activators, which requires further investigation [91]. Overall, much attention should be paid on low dosage of aminoglycoside antibiotics which may stimulate the biofilm formation, contributing to the difficulty of curing the infections. Moreover, the importance of following the rational regimes of antibiotic treatment has been highlighted.

![Fig. 3. Schematic view of the augmented biofilm formation induced by tobramycin of P. aeruginosa. Copyright: Lucas R. Hoffman et al. [78].](image-url)
confirmed since the initial treatment will result in the aforementioned problems.

4. Effects on intestinal flora

The intestinal flora lives independently or competitively with each other to realize a dynamic balance of intestinal flora, and it mainly consists of anaerobic bacteria, including *Bifidobacterium, Bacteroides* and *Lactobacillus lactis*. *Lactobacillus* is a beneficial probiotic that has important physiological function in vivo, regulating the balance of intestinal flora and enhancing body's immunity [92,93]. Intestinal flora, a complex ecosystem which mainly dominated by anaerobic bacteria, benefit human health by fermenting nondigestible dietary residues, breaking down carcinogens and synthesizing biotin, folate, and vitamin K. Under normal circumstance, the composition of the gut microbes is relatively stable, but the balance can be disrupted due to external factors, such as antibiotics treatments.

Aminoglycoside antibiotics are used to cure infections caused by gut pathogens since they are not absorbed by the intestinal tract. Unfortunately, it has been reported to presented negative effects on the intestinal flora during the medicine treatment. Numerous studies have confirmed that aminoglycoside antibiotics have a tremendous impact on the composition and functionality of the human microbiota. One study documented that the antibiotic-resistance strains among gut microbiota were insurgenstly and its resistance genes were upregulated after being treated with aminoglycosides for 2 years [95]. Compared with healthy people, the proportion of intestinal flora have changed a lot (Table 2), and the amounts of beneficial bacteria is obviously different between healthy and a volunteer treated for 6 months (*Bifidobacterium, 7.4%* that of healthy people, 3.4% that of unhealthy people). The research have demonstrated that not only the sensitive pathogens were effectively disturbed, but also some resident bacteria were eliminated. Remarkably, disruption of gut microbes due to antibiotics treatments can lead to 5–35% of the Antibiotic-Associated-Diarrhea (AAD). Furthermore, the effects of different concentrations (1 μg/ml and 10 μg/ml) of antibiotics on composition of gut microbes have been investigated. The higher dose of the antibiotics, the stronger changes in the microbiota composition will be observed [94].

Longer duration of antibiotics use led to the risk of imbalance of intestinal flora. It is of great necessary to consider the type of antibiotic and bacteria resistance, as well as the course of treatment, avoiding abuse of antibacterial agents [96]. The nutritional status and intestinal function of the patients should be taken into consideration to decrease the probability of alternation of intestinal flora.

5. Concluding remarks

Nowadays, pathogens have been regarded as one of the major culprits for life-threatening infections [97–101]. And aminoglycoside antibiotics are widely used for its superior performance of curing the infections. However, it also brings about some potential risks, including antimicrobial resistance, biofilm promotion and the disruption of gut microbes balance. Antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections, thus elucidating the characteristics and mechanisms of aminoglycoside antibiotics resistance is imperative. Aminoglycoside antibiotics are usually combined with β-lactam antibiotics as they showed good synergistic action to decrease the PAE time and improve the therapeutic efficacy. In addition, we could design AMEs inhibitors and antisense RNA to control the resistance of bacteria based on the resistance mechanism. Furthermore, the concentration of antibiotics should be taken into consideration when the aminoglycosides are used to treat the infection caused by biofilms. Sub-inhibitory concentration of aminoglycosides could promote the biofilm formation. Antibiotic exposure, even for a short periods of time and especially during infancy, has long-lasting effects on the gut microbiota, and this can predispose the host to a variety of disease. In terms of the treatment of intestinal tract infections caused by intestinal pathogens, unnecessary aminoglycoside antibiotics use should be avoided to prevent any potential adverse consequence on the host. To sum up, excessive use of antibiotics is not good for human beings. And scientists are supposed to develop new antibiotics with good efficiency because of the presence of superbug. At the same time, study of the mechanism of bacterial and biofilm resistance to aminoglycoside antibiotics should be continued, as well as the influence on the dynamic balance of intestinal microflora, providing theoretical supports for rational use of aminoglycoside antibiotics in clinical treatments.

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