Enhancement of anti-bactericidal and anti-biofilm activities of silver nanoparticles against multidrug-resistant enteric pathogens isolated from children with diarrhea

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Abstract

Background: Gastroenteritis has a significant mortality and morbidity incidence in children globally. Antimicrobial resistance in Enterobacteriaceae is a serious public health problem, especially in developing countries.

Objective: The present study aimed to evaluate the anti-bacterial and anti-biofilm activities of AgNPs alone and in combination with kanamycin against multidrug-resistant Enterobacteriaceae and *P. aeruginosa* isolated from diarrheal children.

Materials and methods: 90 Enterobacteriaceae and *P. aeruginosa* isolates from diarrheal children were evaluated against 10 antibiotics. Minimum inhibitory doses of AgNPs and kanamycin were determined using broth microdilution, synergistic was determined using Checkerboard dilution tests, and the Calgary technique was used to analyze biofilm development.

Results: A total of 90 stool cultures were conducted for bacteria associated with diarrhea among children attending some Baghdad hospitals. The findings revealed that bacterial diarrhea was most often caused by *E. coli* 31 (34.5%), followed by *S. typhi* 19 (21.1%), *K. pneumoniae* 14 (15.5%), *P. aeruginosa* 11 (12.2%) and *S. sonnei* 6 (6.7%), and significant variations between the strain's species were discovered using statistical analysis ($P < 0.05$). The present study's findings revealed that bacteria isolated from children with diarrhea were spread significantly in age groups of 37–48 months and significantly different between age groups ($P < 0.05$), with a male/female ratio of 0.57/1. Imipenem and amikacin were the most active antibiotics compared to penicillin, which was the least effective antibiotic. The combination of sublethal doses of AgNPs with sub-MIC (½MIC) of kanamycin exhibited substantial synergistic bactericidal effects against MDR-Enterobacteriaceae. AgNPs inhibited biofilm formation by 55%–65% for diarrhea-causing bacteria, while the combination of AgNPs with kanamycin demonstrated the strongest biofilm inhibition of around 80%–90% against MDR-Enterobacteriaceae with a highly significant variation ($P < 0.05$).

Conclusions: The outcomes of the research show that the combination of AgNPs with kanamycin has remarkable synergistic bactericidal and anti-biofilm effectiveness against MDR-Enterobacteriaceae isolated from diarrheal children.

Keywords: Enterobacteriaceae, diarrheal children, Kanamycin, Silver nanoparticles.

Introduction

The term "gastroenteritis" may be used to refer to symptoms such as diarrhea or vomiting that are brought on by inflammation in the colon or upper small intestine1. There is a possibility that viruses, bacteria, or parasites are the etiologic agents (1). A person is said to have diarrhea if they have three or more loose stools per day or more than they typically do, according to the WHO (2).

There is a high death rate and high morbidity rate associated with gastroenteritis in children worldwide, but this is particularly true in impoverished nations. A high prevalence of bacteria enteritis has been documented (3).
Enterobacteriaceae resistance to antimicrobials is a major public health concern, particularly in underdeveloped nations. Transferable plasmids that encode multidrug resistance have been shown to be a major cause of the issue, and it has been demonstrated that species of enterobacter (4).

Complex colonies of surface-associated microbes are what make up biofilms. Biofilms are encased in a structured, highly hydrated polysaccharide matrix that protects them from the environment (5).

There is a lot of interest in nanoparticles right now because of their many potentials uses in biomedicine, agriculture, optics, and electronics. Researchers are currently focusing on nanomedicine, which is the study of developing safe, biocompatible, effective and inexpensive medications that are non-toxic and do not harm the body (6). For the treatment of infections caused by multi-drug resistant bacteria, silver nanoparticles (AgNPs) may be an alternative to antibiotics (7).

The purpose of the current research was to assess the anti-bacterial and anti-biofilm properties of AgNPs alone and in combination with an aminoglycoside antibiotic (Kanamycin) against multidrug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* that isolated from children who are suffering from diarrhea.

Materials and Methods

Sample collection and bacterial identification

Children with diarrhea in Baghdad Hospitals provided 90 stool samples for testing in a single-use plastic container between November 2021 and March 2022. Each patient's age, gender, and other pertinent data were recorded. For direct macroscopical and microscopical investigation, the samples were sent to the laboratory. At 37°C, the samples were incubated for 24 hours on MacConkey and blood agar. After that, the colony growth was honed using a variety of selective and differentiated medium. Using morphological and biochemical testing, one may discriminate between different species. BioMérieux, Marcy L'Etoile, France" API 20 E kit was used to complete biochemical testing and verified the final laboratory diagnosis.

Antibiotics and silver nanoparticles (AgNPs)

Bioanalyze (Turkey) provided all of the antibiotics used in this investigation are listed in table1. The following attributes of the silver nanoparticles were acquired from Hongwu International Group Ltd (China): shape "Spherical", appearance "grey black powder", purity (99.99%), particle size (20nm), apparent density (0.97g/ml), and tap density (2.16g/ml) (Fig. 1.).

Antibiotic susceptibility testing

As part of the Clinical Laboratory Standards Institute (CLSI) standards, we modified Kirby-disk Bauer's diffusion technique to evaluate the antibiotic susceptibility of microorganism's isolates. On Müller-Hinton agar (Oxoid, UK), one to three bacteria isolates were cultured overnight for 24 h at 37°C. In order to plate the bacteria on Müller-Hinton agar, we employed the streaking technique, in which the bacteria were transferred to the plate using sterile swabs. The results were declared as sensitive (S) or resistant (R) in accordance with the (CLSI) 2014 standards for reporting results (8).

Minimum inhibitory concentrations (MICs) of Kanamycin and AgNPs

CLI standards were followed while determining Kanamycin and AgNPs MICs. More specifically, the microtiter plates were filled with two-fold serial dilutions of Kanamycin or AgNPs in Müller-Hinton broth and 100 l of bacterial inoculum suspensions in Müller-Hinton broth, "equivalent to 0.50 McFarland standards." Microtiter plates were kept at 37 degrees Celsius for 18 hours. The absorbance at 600 nm of the enzyme-linked immunosorbent assay microtiter reader "Huma Reader-HS, Human GmbH, Wiebaden, Germany" was used to record the minimal inhibitory concentrations results (9).

Biofilm formation assay

Calgary biofilm approach was used to assess AgNPs and Kanamycin at sub-MIC doses. Briefly, bacteria are grown overnight at 37°C and diluted with Müller-Hinton broth to 1x106 CFU/ml. Suspension 180 µl of bacteria in each well of a 96-well microtiter flat-bottom plate for 24 hours. Plates were incubated at room temperature for 4-5h with AgNPs and Kanamycin at sub-MIC doses. The plates were washed three times with PBS and incubated for one hour to fix biofilms. Biofilms are stained with 1% crystal violet for 30-40 minutes at room temperature, and then destained with 96% ethanol at 37°C for 30 minutes. "Huma Reader-HS, Human GmbH, and Wiesbaden, Germany" detected 595nm absorbance. [1(A 595 of AgNP-treated cells/A 595 of non-treated control cells)] 100 was used to determine anti-biofilm activity (10).

Checkerboard dilution

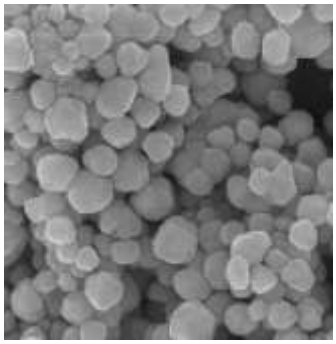
In a 96-well microtiter plate, AgNPs or Kanamycin was diluted 2-fold. Vertical and horizontal 50-microliter aliquots of the first and second antimicrobials were applied. Each well received 100 µl of new bacterial suspension (1 × 106 cfu/ml) and was cultured as previously. FICI = (MIC of antimicrobial agent A in combination/MIC of agent A alone) + (MIC of antimicrobial agent B in combination/MIC of agent B alone). When the FIC index was ≤ 0.5, it was synergistic (11).

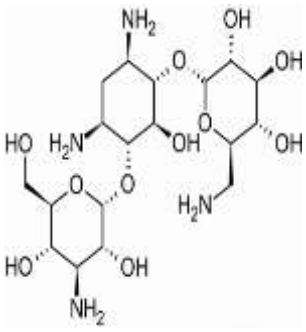
Statistical analysis

We used "GraphPad Program Inc., La Jolla CA, PRISM® 9.4.0 '" statistical software to analyze our data. P-values were derived via the student's t-test. There were two separate trials that yielded all of the data. This level of significance is defined as being at or below the 0.05 threshold.

Table (1): Antimicrobial disks employed against pathogenic bacteria isolates

Class	Antibiotics	Symbol	Concentration µg/ml
Quinolone	Ciprofloxacin	CIP	10
Tetracycline	Tetracycline	TE	25
Penicillin	Amoxicillin	AX	10
aminoglycoside	Kanamycin	K	5
Carbapenem	Imipenem	IPM	10
Aminoglycoside	Gentamicin	CN	10
	Amikacin	AMI	30
Chloramphenicol	Chloramphenicol	C	10
Monobactams	Aztreonam	ATM	10
Monobactams	Azithromycin	AZM	15
β-lactamase Inhibitors	Amoxicillin -clavulanate	AMC	20/10





(A) **(B)**

Figure (1): A-Morphology of Silver nanoparticles (20nm) Hongwu International Group Ltd. B- Structures of aminoglycoside antibiotic (Kanamycin).

Results

During the period of this study, a total of 90 stool cultures were conducted to bacteria associated with diarrhea among children attending some Baghdad hospitals. Traditional biochemical procedures were used to examine the stool samples, as well as antibiotic susceptibility testing for each bacterial isolate.

The findings revealed that bacterial diarrhea was most cause by *Escherichia coli* 31(34.5%) followed by *Salmonella typhi* 19 (21.1%), *Klebsiella pneumonia*14 (15.5%), *Pseudomonas aeruginosa* 11 (12.2%) and *Shigella sonnei* 6 (6.7%) and Significant variations between the strain's species were discovered using statistical analysis ($P < 0.05$) as presented in table (2).

Table (2): Numbers of pathogenic bacteria isolate from children with diarrhea.

	Bacteria	No. (%)
1.	*Escherichia coli*	31 (34.5)
2.	*Salmonella typhi*	19 (21.1)
3.	*Klebsiella Pneumonia*	14 (15.5)
4.	*Pseudomonas aeruginosa*	11 (12.2)
5.	*Shigella sonnei*	6 (6.7)
6.	*Proteus mirabilis*	9 (10)
7.	Total	90 (100%)

The present study's findings revealed that bacteria isolated from children with diarrhea were spread significantly in age groups of 37-48 months and significantly different between age groups ($P < 0.05$).
Furthermore, female patients showed high risk to be contaminated with microorganisms linked to children's diarrhea rather than male patients and the male / female ratio was (0. 57/1) as seen in the Figure (2).

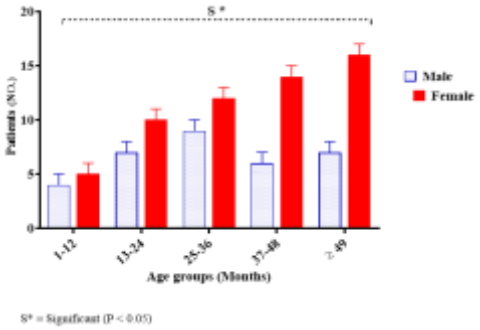


Figure (2): Patient distribution according to age categories (Months).

The antibiotic susceptibility of all Enterobacteriaceae and *Pseudomonas aeruginosa* strains isolated in this study was examined using a modified Kirby- Bauer disk diffusion method with ten antibiotics with diverse mechanisms of action.
Carbapenem antibiotics (Imipenem) and aminoglycoside (Amikacin) was most active antimicrobial agent against bacterial isolated, while the majority of bacterial isolates showed a high level of resistance to β -lactamase inhibitors (Amoxicillin-clavulanate) and penicillin derivative (Amoxicillin) as indicated in the table (3).
All microorganisms isolate in this study were evaluated for their propensity to produce biofilms employing a Calgary method with some improvements. According to the findings of the provided study, the majority of MDR-bacteria displayed a great proclivity (+++) to form biofilms especially *E. coli, S. typhi* and *Pseudomonas aeruginosa* as indicated in table (3).
In this study, the most common types of multi-drug resistant (MDR) Enterobacteriaceae bacteria *Escherichia coli* and *Salmonella typhi* that cause diarrhea were selected to treat with AgNPs and compared to untreated cell. Interestingly, AgNPs exhibit superior antibacterial action against multi-drug resistant (MDR) Enterobacteriaceae (*E. coli and S. typhi*) with MIC from 10 -15 µg/ml and disrupts growth with inhibition around 50%- 60 % for *E. coli* and *S. typhi* respectively as shown in table (4) and as illustrated in figure(3). Moreover, combination of sublethal doses of AgNPs with sub-MIC (½MIC) of aminoglycoside antibiotic (Kanamycin) exhibited substantial synergistic bactericidal effects against multi-drug resistant Enterobacteriaceae with FIC index range 0.21 –0.5 for *E. coli* and 0.2-0.45 for *S. typhi* as shown in the table (4).

Table (3): Antibiotics Susceptibility profile (%) and biofilm production propensity score of bacteria isolate.

Bacteria	IPM	TE	CN	K	AX	AMI	CIP	C	ATM	AMC	Biofilm Propensity score
E. coli	7.3	70.3	61.6	40.7	63.5	10.6	40.1	34.3	25.7	66.7	+++
S. Typhi	3.8	80.4	30.0	20.6	30.7	30.8	33.0	70.6	40.3	50.2	+++
K. Pneumonia	16.2	33.6	66.2	37.1	66.4	20.3	50.9	20.6	44.1	88.6	++
P. aeruginosa	33.8	67.1	60.6	55.4	50.1	30.9	40.3	70.1	33.7	90.8	+++
S. sonnei	5.9	44.6	25.4	50.9	60.6	10.7	55.8	27.0	34.9	44.6	+
P. mirabilis	6.1	80.5	68.0	50.2	72.0	40.1	36.8	55.9	20.1	97.1	+

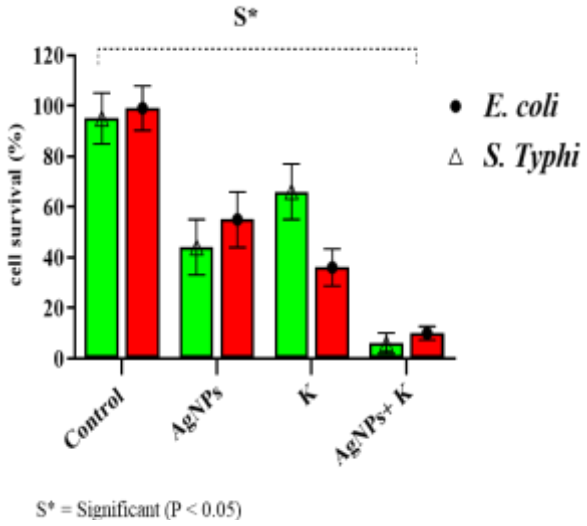


Figure (3): Antimicrobial Activity of AgNPs alone and in combination with Kanamycin against MDR-Enterobacteriaceae.

The data in the figure (5) confirmed that AgNPs had 55%- 65% inhibitory action on biofilm development for pathogenic bacteria isolated from children with diarrhea.

The biofilm production classified as strong, moderate, and weak according to ability of microorganism to developing of the biofilms. About 15% of the *E. coli* strains developed strong biofilm production and compared to approximately 10% of *S. typhi*; moreover, moderate biofilm production recorded about 10% and 5% for *E. coli* and *S. typhi* respectively as described in figure (4).

Table (4): Minimum inhibitory concentration of AgNPs and kanamycin for E. coli and S. Typhi with fractional inhibitory concentration index (FICI) values.

Microorganism	AgNPs MIC (µg/ml) Range	kanamycin MIC (µg/ml) Range	FIC index Range	Interaction
E. coli	5-15	0.2-0.5	0.21 –0.5	Synergistic
S. typhi	5-10	0.25-1	0.2-0.45	Synergistic

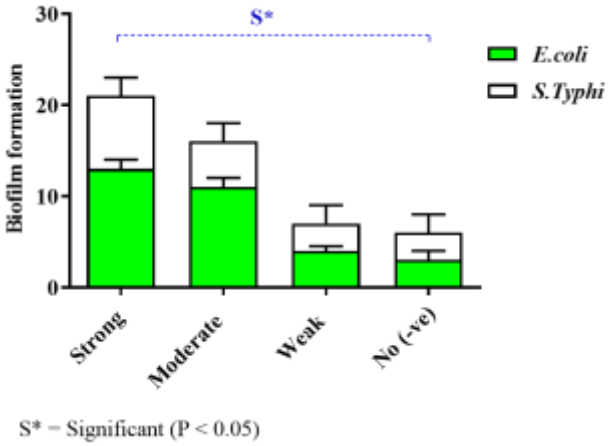


Figure (4): Biofilm propensity score of MDR-Enterobacteriaceae isolates.

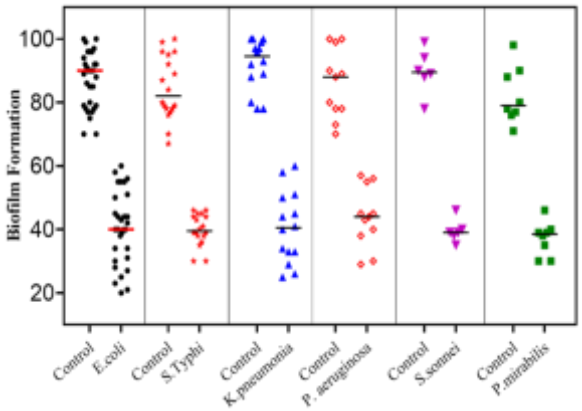


Figure (5): Estimate the biofilm formation level of each bacterium isolate after treated with AgNPs.

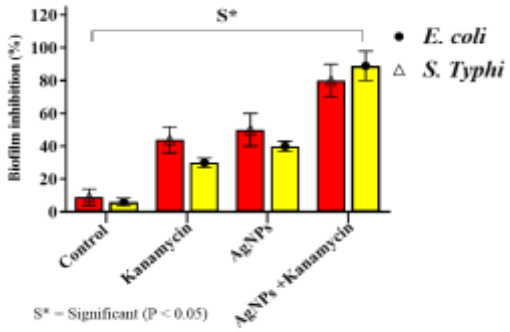


Figure (6): Anti-biofilm inhibitory ability of AgNPs alone and in combination with Kanamycin against MDR-Enterobacteriaceae.

Bacterial cells were cultivated to produce biofilms and then treated with AgNPs alone or in combination with aminoglycoside antibiotics (Kanamycin) to investigate the synergistic effects. The results in the figure (6) it has been proven combination of AgNPs with aminoglycoside antibiotics (Kanamycin) demonstrated the strongest biofilm inhibition around 80% and 90% for *E. coli* and *S. typhi* respectively with a high significant variation ($P < 0.05$).

Discussion

Children's health in Iraq, as well as in other countries with high rates of poverty, is a serious issue due to the prevalence of diarrheal infections. It is vital to have knowledge of the circulating enteropathogenic in order to conduct suitable public health strategies to reduce diarrheal illnesses (12).

According to the findings of our research, diarrheal infections were most common in children between the ages of 37 and 48 months. This may be the result of their immature immune system, which is unable to create an efficient immunological response owing to its lack of development. In addition, physiological phenomena like as teething and crawling, both of which occur at this age, considerably increase the danger of inserting infected fingers and fomites in the mouth (13).

On the other hand, fewer cases of diarrheal infection were seen in older age groups, which is in line with the findings of earlier investigations (14). This means that children with low immunity, which is generally caused by inadequate nutrition, are more likely to be susceptible to infections that cause diarrhea.

A study by (15) reported that *E. coli* and it is the most common bacteria isolated from children with diarrhea in Iraq. The results in this research confirmed that this Enterobacteriaceae *Escherichia coli* is the main cause of diarrhea in children. In our country it's possible that widespread drug-resistant bacteria or people who medicate themselves are to blame for the high prevalence of antibiotic resistance shown in Enterobacteriaceae isolates. According to the findings of this research, the typical level of bacterial resistance to some antibiotics was rather high. The study's methodology and its findings are recorded by (16). AgNPs are active against Gram-negative and Gram-positive bacteria. Several studies suggest that AgNPs have strong antibacterial action against multidrug-resistant pathogens including MRSA, VRE, and TB (17, 18). The outcomes of this investigation confirm these conclusions, AgNPs showed antibacterial efficacy against multidrug-resistant bacteria isolated from diarrheal infants.

On the other hand, (19) discovered that AgNPs enhanced the antimicrobial activities of antibiotics and revealed synergistic effect when combined with chloramphenicol, nalidixic acid, and tobramycin against Enterobacteriaceae isolated from Iraqi hospitals. An interesting synergistic bactericidal and anti-biofilm effect was shown in our studies with AgNPs and the aminoglycoside antimicrobial Kanamycin when used together against MDR-Enterobacteriaceae identified from diarrheal children.

The synergistic antibacterial and antibiofilm activity of AgNPs and kanamycin may be attributable to the diverse modes of action. Protein synthesis is blocked by kanamycin. It binds the 30S ribosomal subunit. This leads to improper alignment with the mRNA and a misread that places the erroneous amino acid into the peptide (20). This causes inactive peptide chains. The AgNPs' influence on distinct molecular targets, among others. Ions of silver are capable of penetrating bacterial cells, denature ribosomes, and inhibit the synthesis of enzymes and proteins necessary for ATP generation, so causing cell death. Silver may also block DNA from unwinding by attaching to it, so preventing bacterial multiplication. Targeting the bacterial membrane also causes proton motive force to dissipate (21,22).

Conclusions

The outcomes of the research show that the combination of AgNPs with the aminoglycoside antibiotic (Kanamycin) has remarkable synergistic bactericidal and anti-biofilm effectiveness against MDR-Enterobacteriaceae isolated from diarrheal children. The enhancement of the antimicrobial activity due to AgNPs-Kanamycin complex would enable the use to treat multidrug-resistant Enterobacteriaceae infections, according to the study. Future research is needed on AgNPs' molecular processes and in vivo tests to combat multidrug-resistant bacteria causing pediatric diarrhea.

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تعزيز الأنشطة المضادة للجراثيم والغشاء الحيوي لجزيئات الفضة النانوية ضد مسببات الأمراض المعوية المقاومة للأدوية المتعددة والمعزولة عن الأطفال المصابين بالإسهال

عصام جمعة ناصر

قسم تقنيات المختبرات الطبية / كلية الصحة والتقنيات الطبية / الجامعة التقنية الوسطى

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الملخص

الخلفية: التهاب المعدة والأمعاء له معدل وفيات ومراضه كبيرة بين الأطفال على مستوى العالم. تعتبر مقاومة مضادات الميكروبات في البكتريا المعوية مشكلة صحية عامة خطيرة، لا سيما في البلدان النامية.

الهدف: هدفت الدراسة الحالية إلى تقييم الأنشطة المضادة للبكتيريا والمضادة للأغشية الحيوية لجزيئات الفضة النانوية وحدها وبالاقتران مع الكاناميسين ضد البكتريا المعوية المقاومة للأدوية والزائفة الزنجارية المعزولة من الأطفال المصابين بالإسهال.

المواد والطرق: تم تقييم 90 عزلة من بكتيريا المعوية والزائفة الزنجارية من الأطفال المصابين بالإسهال مقابل 10 مضادات حيوية. تم تحديد الجرعات المثبطة الدنيا من جسيمات الفضة النانوية والكاناميسين باستخدام التخفيف الدقيق للمرق، وتم تحديد الجرعات التآزرية باستخدام اختبارات التخفيف، واستخدمت تقنية كالجاري لتحليل تطور الأغشية الحيوية.

النتائج: تم إجراء 90 مزرعة براز للبكتيريا المصاحبة للإسهال بين الأطفال الذين يترددون على بعض مستشفيات بغداد. أظهرت النتائج أن الإسهال البكتيري كان سببًا في الغالب للإشريكية القولونية 31 (34.5٪) يليه السالمونيلا التيفية 19 (21.1٪)، الكلبسيلة الرئوية 14 (15.5%)، الزائفة الزنجارية 11 (12.2٪)، والشيغيلة سوني 6 (6.7%) واكتشاف اختلافات معنوية بين أنواع السلالة باستخدام التحليل الإحصائي ($P < 0.05$).
ظهرت نتائج الدراسة الحالية أن البكتيريا المعزولة من الأطفال المصابين بالإسهال قد انتشرت بشكل ملحوظ في الفئات العمرية من 37 إلى 48 شهرًا وتفاوتت بشكل ملحوظ بين الفئات العمرية ($P <0.05$) وكانت نسبة الذكور / الإناث (1/57 .0). كان Imipenem و amikacin أكثر المضادات الحيوية نشاطا مقارنة بالبنسلين كان المضاد الحيوي الأقل فعالية. أظهر الجمع بين الجرعات شبه المميتة من جسيمات الفضة النانوية مع (½MIC) MIC من كاناميسين تأثيرات تآزرية كبيرة ضد البكتيريا المعوية المقاومة للأدوية المتعددة.
ثبط جزيئات الفضة النانوية تكوين الأغشية الحيوية بنسبة 55٪-65٪ للبكتيريا المسببة للإسهال، بينما أظهر الجمع بين جزيئات الفضة النانوية والكاناميسين أقوى تثبيط للغشاء الحيوي حوالي 80٪ و90٪ ضد المعوية المقاومة للأدوية المتعددة مع تباين كبير للغاية ($P <0.05$).

الاستنتاجات: تظهر نتائج البحث أن الجمع بين الجسيمات النانوية الفضية والكاناميسين له فعالية ملحوظة في مبيد الجراثيم ومضادة للأغشية الحيوية ضد البكتيريا المعوية المقاومة للأدوية المتعددة المعزولة من الأطفال المصابين بالإسهال.

الكلمات المفتاحية: البكتيريا المعوية، الأطفال المصابون بالإسهال، الكانامايسين، الجسيمات النانوية الفضية.