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REVIEW

The contribution of nano-based strategies in overcoming ceftriaxone resistance: a literature review

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Abstract

Antimicrobial drug resistance, including resistance to multiple antibiotics, is continuously increasing. According to research findings, many bacteria resistant to other antibiotics were susceptible to ceftriaxone. However, over the last few years, ceftriaxone resistance has become growing and extremely worrisome challenge to the global healthcare system and several strategies have been initiated to contain the spread of antimicrobial drug resistance. Its extended use for therapeutic or preventative measures in humans and farm animals resulted in the development and spread of resistance. Recent advances in nanotechnology also offer novel formulations based on distinct types of nanostructure particles with different sizes and shapes, and flexible antimicrobial properties. For ceftriaxone, several nanostructured formulations through conjugation, intercalation, encapsulation with lipid carrier, and polymeric films have been investigated by different groups with promising results in combating the development of resistance. This review addressed the existing knowledge and practice on the contribution of nano-based delivery approaches in overcoming ceftriaxone resistance. Evidences have been generated from published research articles using major search electronic databases such as PubMed, Medline, Google Scholar, and Science Direct.

KEYWORDS
antimicrobial resistance, ceftriaxone, ceftriaxone resistance, drug delivery, nanotechnology

1 | INTRODUCTION

Antimicrobial resistance (AMR) has become a mounting challenge and one of the most severe public health threats in the 21st century. The number of resistant microbial strains, the geographical distribution, and the extent of resistance are alarmingly on the rise. The percentages of microbes developing resistance even toward multiple antibiotics is also continuingly increasing. Many drugs that were known to be susceptible to antibiotics therapy are now returning in new habits as resistant to those therapies.[1-3]

Cephalosporins are cell wall synthesis inhibiting and broad spectrum, beta-lactam antibiotics commonly used in the treatment

Abbreviations: AMR, antimicrobial resistance; CL-SLNPs, ceftriaxone-loaded solid lipid nanoparticles; EPS, extracellular polymeric substance; ESBL, extended-spectrum β-lactamases; ESCs, extended-spectrum cephalosporins; LDH, layered double hydroxide; LON, lipid oligonucleotide; MDR, multiple drug-resistant; MIC, minimum inhibitory concentration; MNPs, magnetic nanoparticles; NLC, nanostructured lipid carrier; NMs, nanomaterials; NPs, nanoparticles; SLNPs, solid lipid nanoparticles.

of common microbial infections such as pneumonia, skin and soft tissue infections, bacteremia, and meningitis.[4] Resistance to third generation cephalosporins has also been increasing inflicting significant pressure on the health system in many countries.[5,6] On the other hand, microbial strains that developed resistances were found to be multidrug-resistant, making treatment of infectious disease challenging and calling for the alarming the global community for the search of more effective compounds and delivery modalities. Ceftriaxone, an extended-spectrum third-generation cephalosporin was first released in 1982 for the treatment of severe infections or infections caused by multi-drug-resistant strains.[7,8] Since its launching, ceftriaxone has been one of the commonly utilized antibiotics due to its commendable antibacterial performance, broader spectrum of activity, and lowest toxicity.[1] Ceftriaxone is prescribed for respiratory bacterial infections like bronchitis and pneumonia, bacterial infections in the abdomen, urinary tract, and the bone, etc.[4]

Related to the ever-increasing emergence and spreading of AMR to many of the first line and effective antimicrobial drugs and by virtue of its extensive use, resistance to ceftriaxone has been on the rise over the past decade.[9-11]

At present, ceftriaxone resistance has become an increasing challenge to treat many infections caused by *Salmonella*,[2] *Neisseria gonorrhoeae*,[12] *P. meningitis*,[13] Penicillin-resistant *Streptococcus pneumoniae*,[14] and *Escherichia coli*.[15] AMR has been globally recognized as a first-line threat to public health dwindling the ability to manage and control microbial infections with traditional or conventional antibiotics. On the other hand, there are scientific challenges to develop new treatment options at an equivalent rate including (i) the need to kill rapidly growing organisms that are adept at keeping out xenobiotics; (ii) lack of rapid diagnostics leading to empirical treatment of infections; and (iii) and the need to administer high doses to cover worst-case scenarios.[16]

The integrated use of antimicrobial stewardship programs (ASPs), pharmacokinetic and pharmacodynamic profiles of the antibiotics, data from diagnostic testing and antimicrobial susceptibility testing, and surveys from the clinical response of antimicrobial effects have been considered as supplementary strategies for minimizing AMR. The development of new antibiotics is advocated by the scientific community and public health policy experts together with coordinated effort for the rational use of the existing arsenals at all levels.[17]

As part of the continuing combat of AMR, the use of advanced formulation and delivery platforms including nanotechnology has been under extensive investigation for the effective use of the existing antimicrobial therapeutic agents. There has been an increasing interest in the use of nanomaterials (NMs) coupled with antimicrobial drugs for targeted delivery.[18,19] NMs are used to transport antimicrobials, to specific sites of action or eventually act synergistically by their inherent antimicrobial activity. Moreover, nanoparticles (NPs) may counter mechanisms of bacterial drug resistance by virtue of their antimicrobial potential by inhibiting some important bacterial processes like biofilm formation.[20] However, the use of conjugates or combinations of NMs and conventional antibiotics to combat microbial resistance requires careful investigation.[21]

In this review, we discussed the potential contribution of NMs and nanotechnology-based structures as alternative approaches to circumvent the development and spread of resistance to ceftriaxone. We have tried to review different research and review articles on AMR with special emphasis to ceftriaxone resistance and nanotechnology-based approaches developed to overcome the increasing ceftriaxone resistance. For the development of this review, published research and review articles, and other reports and/or commentaries from relevant organizations related to the issue have been reviewed and summary of specific issues were incorporated. For the purpose, literature resources were generated using major electronic databases and search engines such as PubMed, Medline, Google Scholar, and Science Direct. Some books and related documents were also used when deemed necessary.

2 | HISTORICAL PERSPECTIVES OF CEFTRIAXONE RESISTANCE

Ceftriaxone is an extended-spectrum third-generation cephalosporin with a 72%–97% cure rate. It is a greatly effective antibacterial with high potency covering wide variety of gram-negative and gram-positive specious and has been extensively prescribed in healthcare facilities including for empirical treatment.[2] Twenty-five years back, a study was conducted to investigate the incidence of bacterial species and their susceptibilities to ceftriaxone and other β-lactams from patients with community-acquired infections. The report indicated that all bacterial strains resistant to other antibiotics were found to be fully susceptible to ceftriaxone.[7] Resistance to ceftriaxone by FC428 ceftriaxone-resistant *N. gonorrhoeae* strain was first reported in January 2015 in Japan,[9] 22% of the *Gonococcal* Isolate Surveillance Project member countries reported reduced susceptibility to ceftriaxone among patients with *N. gonorrhoeae* infection.[10] The world's first gonorrhea strain resistant to ceftriaxone was reported in 2018 in England and showing high-level resistance to azithromycin was isolated from a man who sought care in early 2018.[22] A study conducted in Jimma Teaching Referral Hospital, Ethiopia using clinical isolates reported *S. aureus* and *E. coli* reported that 73% and 65% of the clinical isolates were resistant to ceftriaxone and ceftazidime, respectively. The study also demonstrated that among the bacterial strains that were resistant to ceftriaxone and ceftazidime, 44% of *S. aureus* and 43.5% of *E. coli* were found to be resistant to both drugs.[3] Recently, Dr. Moopans' Aster Hospital in Doha, Qatar reported the first cases of ceftriaxone-resistant *Salmonella Typhi* in the Middle East.[11] Over the years, an increasing number of microbial strains have become resistant to ceftriaxone threatening its use.[23-25] Like other first-line antibiotics, resistance to ceftriaxone has become worrisome for many countries in consideration of its historical performance, tolerability, and affordable price. As shown in Figure 1, a 10-year period surveillance study in US revealed that ceftriaxone has become one of the 10 increasing antibiotic resistances by Enterobacteriaceae strains.[16]

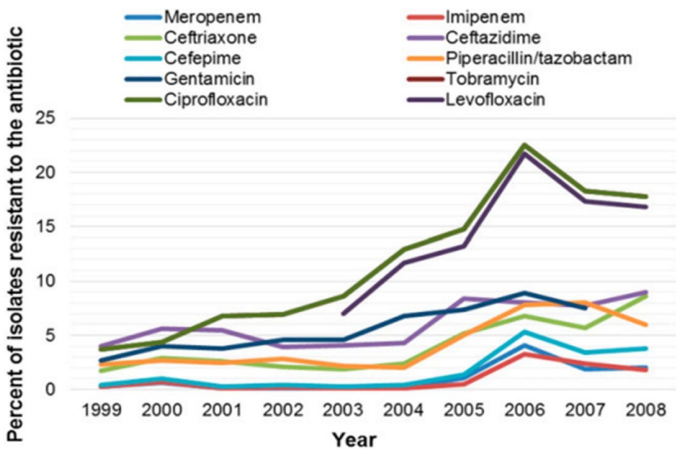

FIGURE 1 Percentage of *Enterobacteriaceae* strains resistance from a US surveillance study[16]

2.1 | Challenges associated with ceftriaxone resistance

Discussions on combating antibiotic resistance have gained greater attention again after WHO urges for new options for the treatment of strains of *gonorrhea* that are resistant to available antibiotics. According to the WHO report, the annual death from drug-resistant microbial infections was estimated to be 700 000 yearly and predicted to increase to 10 million by the year 2050.[26] A review of AMR in East Africa reported a relatively high level of resistance to ceftriaxone (46%–69%) among gram-negative infections, with the most resistant strains being *Klebsiella* species and *E. coli*; whereas gram-positive infections showed extensive resistance to ceftriaxone (50%–100%) with *S. aureus* being the most recorded resistant strain.[27] The frequently used antibiotics like ampicillin, gentamicin, and ceftriaxone are reported to have bacterial resistance, and concerns are rising that they may no longer be prescribed for the treatment of moderate to severe microbial infections in the region. Thus, empirical treatment of bacterial infections needs to be reconsidered and guided by local assessment of AMR.[27,28]

According to Al Kraiem et al.,[2] ceftriaxone resistance from typhoidal and non-typhoidal infections is significantly increasing over time alarming health system experts and professionals. Yang et al.[29] reported that the increasing resistance to extended-spectrum cephalosporins (ESCs) among *Salmonella* had been noted since the late 1980s where the spread of extended-spectrum β-lactamase genes was suspected as the leading factor. In their finding, the group outlined that ceftriaxone resistance in pediatric *Salmonella* infections represents a serious clinical problem since fluoroquinolones are generally not recommended in children. Unless the spreading ceftriaxone resistance is timely countered, it will result in increased prevalence of *Salmonella* infections globally accelerating morbidity and mortality rates from resistant microbial infections.[2]

A review by Browne et al.[30] also reported higher proportions of ceftriaxone and azithromycin-resistant *S. Typhi* organisms with conclusive evidences that resistance among *S. Typhi* and *S. Paratyphi* is worsening and interventions to reduce the number of enteric fever infections is urgently needed. The study report from Jimma University Specialized Teaching Hospital also reported that the rate of bacterial isolates resistant to ceftriaxone was more than 50%, whereas about 44% of ceftriaxone-resistant bacterial strains were found to be resistant to two or more drugs.[3] Similar studies from Shanghai, China also reported that increasing ceftriaxone-resistant *salmonella* strains were found to be multidrug resistant.[31] The ever-increasing AMR to first-line antibiotics including third-generation cephalosporins is associated with increased risk of invasive diseases, longer hospitalization, increased rate of morbidity and mortality, and to the worst scenario the arise of strains that could be resistant to all available treatment options.[12]

2.2 | Mechanism of ceftriaxone resistance development

Infectious microbes use different mechanisms to resist antimicrobials such as mutational adaptations, acquisition of genetic materials, alteration of gene expression, limiting drug uptake, alteration of drug targets, inactivation of drugs, and active drug efflux.[32,33] Other more complex phenotypes, such as biofilm formation and quorum are also related to tolerance to antibiotics in bacteria.[20] As studied by Zhao et al.[34] reported biofilm formation and pathogenesis as major mechanism of resistance by *E. coli*. The most active fractions of bacteria have been recognized to occur as biofilms where cells are adhered to each other on surfaces within a self-produced matrix of extracellular polymeric substance (EPS). The EPS provides the bacterial a barrier that inhibits antibiotic penetration into the cell which further promotes the emergence of antibiotic resistance; which is referred as quorum sensing (bacterial communication for the biofilm integrity).[20] In β-lactam antibiotics, *gonococci* develop resistance through two mechanisms: the first (high level, quickly acquired and easy to transfer among strains) is mediated by a resistance plasmid that produces β-*lactamase*; and the second mechanism is mediated by chromosomal genes which takes a relatively long time for the gradual accumulation of multiple resistance-related gene mutations.[35]

The production of extended-spectrum β-lactamase has been recognized as the most important mechanism of resistance development against ceftriaxone by *E. coli*.[15] A molecular analysis study

in Taiwan also reported that the emergence of ceftriaxone resistance in *Salmonella* isolates was associated with the production of CMY-2 (64%) and CTX-M-3 (27%) β-lactamases.[36] On the other hand, the mechanism of resistance to ceftriaxone by *N. gonorrhoeae* strains was found to be due to chromosomally mediated mutations in the three loci of penA, mtrR, and penB.[37] Generally, the following mechanisms are presumed to majorly contribute to the development and spread of resistance against cephalosporins including ceftriaxone.

2.2.1 | Overproduction of cephalosporinases

Cephalosporinases are enzymes that can degrade cephalosporins. Overproduction of cephalosporins degrading *Cephalosporinases* is one mechanism for *Salmonella* to become resistant to cephalosporins. Since extended-spectrum β-lactamases (ESBL) are located on mobile genetic elements that can spread horizontally between bacteria by obtaining ESBLs genes from resistance bacteria, sensitive bacteria can acquire resistance to cephalosporins.[2] Studies on the mechanism of microbial resistance to third-generation cephalosporins against clinical strains of *Enterobacter cloacae* suggested that ceftriaxone is more commonly linked with the hyperproduction of chromosomal *b-lactamase* in *E. cloacae* clinical isolates than other ESCs.[1,15]

2.2.2 | Expression of antimicrobial-resistant genes

Evidences suggested that non-typhoid *Salmonella* strains (*S. Choleraesuis* and *S. Typhimurium)* produce dissimilar antibiotic resistance genes, which in turn makes them able to persist through hostile antibiotic drug environments; the ability of *salmonella* to integrate new resistance genes in its virulence plasmid poses a serious threat to public health.[2] In an investigational study of ceftriaxone resistance in *Salmonella enterica* serotype *Oranienburg* during therapy for bacteremia, the acquisition of the blaCMY-2-carrying IncI1 plasmid in the *S. enterica* serotype *Oranienburg* appeared to be the major reason for the resistance leading to the subsequent relapse of infection in patients.[29]

2.3 | Triggering factors for ceftriaxone resistance development and spread

Even though the causes for the emergence and spread of AMR pathogens are multifactorial, excessive and inappropriate use of antimicrobials has been recognized as the major one. Extensive production, wide-ranging use, and inappropriate utilization of antibiotics have been contributing to the concern for complicated global public health; the emergence of multiple drug-resistant (MDR) infectious organisms.[21] Hospitals, residential senior care facilities, and sociodemographic factors were suggested among the foci of amplification for ceftriaxone-resistant *E. coli*.[15] Ceftriaxone utilization evaluation reports from Dessie Referral Hospital[4] and Felege Hiywet Referral Hospital[38] in Ethiopia, and University Hospitals in Korea[39] reported a high degree of inappropriate use of ceftriaxone which may further increase the development and spread of ceftriaxone resistance.

2.4 | Strategies to counter ceftriaxone resistance

There have been continued debates among scholars on whether to strengthen the discovery of new antimicrobial drugs, or to use alternative therapies and/or follow innovative modifications of the existing antimicrobial arsenals to sustain their performance and reduce the development of resistance. Some stand on the logical step forward to developing new antibiotics as the targets can be novel and attacking a completely different aspect of bacterial viability; whereas others argue that microbes will likely become resistant to the new drugs and call for the need of more innovative formulation and delivery approaches of the existing antimicrobial agents.[26]

The hope of overcoming AMR by new antibiotics development has been diminishing particularly in the gram-negative spectrum, and even by the evolving possibility of resistance to the novel antibiotics that pathogens can adapt like the previous antibiotics Calling for effective strategies such as appropriate prescribing, antimicrobial stewardship programs, public education, hygiene & disinfection interventions, the use of advanced formulation and delivery platforms, and still the search for novel antibiotics.[17] Shifting to other drugs of choice based on their efficacy against the multidrug-resistant strains of bacteria has been advised as an alternative to ceftriaxone resistance. However, several strains that developed resistance to ceftriaxone are also showing resistance to other antibiotic treatments.[2] The development of vaccines against resistant strains can be a potential approach. A study in Taiwan reported that more than 90% of ceftriaxone-resistant isolates in the study were seen to be covered by a conjugate vaccine suggesting the use of *pneumococcal* conjugate vaccine can be implemented in developing countries, especially in settings with a high prevalence of resistance.[14]

On the concern of nanotechnology, nanoparticle–antibiotic coupling can be considered as one of the current strategies to combat multidrug-resistant bacteria, as this can inhibit bacterial efflux properties; biofilm processing; bacterial cell communication through quorum sensing; and other related processes in the microbial cell.[20]

3 | THE ROLE OF NANOTECHNOLOGY IN COMBATING CEFTRIAXONE RESISTANCE

3.1 | Nanotechnology in countering AMR

The ever-increasing emergence and spreading of antimicrobial drug resistance are challenging the global health system and signaling the possibility of losing the arms race to bacterial infections and

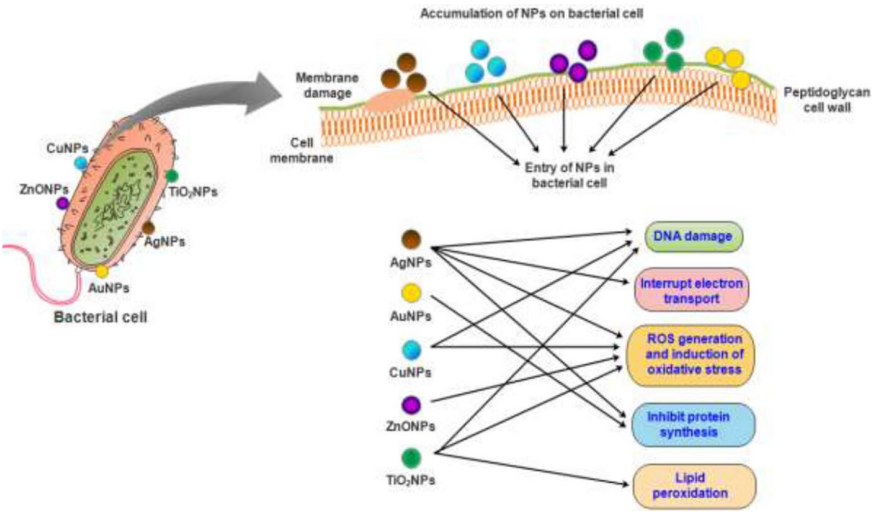

FIGURE 2 Different mechanisms of NPs actions against bacteria[50]

the imminent possibility of post-antibiotic era.[40-42] In the light of such greater threats, several research programs are underway for the containment of AMR worldwide. The application of nanotechnology, especially nanostructures with antimicrobial potential, has been presented as a new possibility in the fight against MDR infectious organisms.[43,44] Debates have been continuing on the use of NMs to either circumvent microbial resistance or for further conducting fundamental research on targeting the molecular mechanisms causing antimicrobial activity in NMs.[21] Current advances in the application of nanotechnology in areas of medicine suggest new scenes of novel drug formulations using the various distinctive properties of NMs such as size, shape, and intrinsic antimicrobial activity. NPs can bring promising solutions as they can directly target the bacteria by themselves or they can act as carrier systems for antimicrobial compounds.[20]

Several NMs are already in use as broad-scale antimicrobial agents in consumer products.[21] Nanoengineered systems offer advanced and superior approaches to overcome limitations in antibiotic drug therapy and to overcome various drug resistance mechanisms by microbes. In addition to their antimicrobial activities, nanostructures can effectively target antimicrobial drugs, can circumvent drug resistance mechanisms, may interfere with quorum sensing and plasmid curing, and inhibit biofilm formation or other important processes including efflux pumps.[20] However, the practical applicability of different nanocarriers has been limited despite the increase in real-world demand in terms of insufficient biocompatibility, lower sensitivity (with respect to temperature and pH), and lack of complete biodegradability.[45]

3.2 | Mechanisms of nanomaterials in combating-resistant bacteria

Nanoparticles-based drug delivery systems introduce a wide range of therapeutics, by either binding to their large surface area or being contained within the structure, to the site of infection effectively and safely with a controlled release rate of delivery. NPs can include a variety of structures including metallic NPs such as Ag, Au, Al, Cu, Ce, Cd, Mg, Ni, Se, Pd, Ti, Zn, super-paramagnetic NPs, other inorganic NPs including silicates, polymeric NPs, and lipid-based NPs. Some inorganic NPs such as NPs of silver are well known for their effect against many bacterial species; whereas other metallic NPs like NPs of Au, TiO, Cu, and Fe_3O_2 are believed to have bactericidal effects.[46-48] As suggested by experimental investigations, NPs can disrupt the bacterial cell membranes and have ability to obstruct the biofilm formation process, thereby decreasing the possibility for the continued existence of the microorganism in the host cell.[20,49]

The use of NMs functionalized with molecular antibiotics where the antibiotics can be dispersed, encapsulated, or conjugated can improve the effectiveness of antibacterial therapy. Such antibiotic-nanomaterial functionalization is thought to be the case for two primary reasons: (i) functionalization of NMs results in improved drug-delivery features, better than the conventional antibiotic alone; (ii) functionalizing the NM with traditional or conventional antibiotic drugs results in a remarkable synergistic activity.[21]

Nanomaterials with intrinsic antimicrobial properties can cause bacterial cell membrane damage, and initiate the generation of reactive oxygen species and release of toxic metals thereby disturbing various cellular processes of the microbe in a less specific manner unlike a particular process as conventional antibiotics do. Such multifaceted mechanisms make it more difficult for microbes to develop resistance.[21] The well-recognized mechanisms of Nps for inhibiting biofilm formation process are targeting the quorum-sensing molecules, disturbing the bacterial communication, and destroying the biofilm integrity.[20] Figure 2 depicts how various classes of NMs elicit their antibacterial activity against MDR pathogens.[50]

4 | THE ROLE OF CEFTRIAXONE NANOSTRUCTURES IN COUNTERING AMR

Nanotechnology-based drug delivery platforms are often characterized by improved bioavailability through enhanced aqueous solubility, improved half-life from prolonged residence time and

better receptor specificity, and targeted delivery to the site of action.[51] Such nano-based platforms can greatly influence some basic microbial cell functions like metabolism and reproduction; can affect membrane permeability and efflux activity; and produce reactive species which result in cellular oxidative stress.[20] Some of the pertinent nanostructure-based ceftriaxone delivery systems are described as follows.

4.1 | Metallic NPs

Silver (Ag), gold (Au), copper (Cu), and inorganic carriers such as silica, alumina have been utilized for the preparation of novel nanocarriers for pharmaceutical formulations. AuNPs are most promising due to their excellent optical and photoelectric properties, inertness, nontoxicity, higher stability, ease of preparation, and possibility of bioconjugation.[52,53] The biomodification property of AuNps with several functional groups such as amines, disulfides, and thiols can considerable advantages including synergistic antibacterial effect.[52]

Metallic NPs functionalized with antibacterial drugs can defend bacterial threats passively by prolonging the retention time of the drug at the target, or actively by conjugating to the active molecules which are capable to bind to the target.[20] In an investigation of conjugation of biogenic AgNPs with ceftriaxone, superior antibacterial effects compared to both ceftriaxone and unconjugated AgNPs were achieved.[54] As shown in Figure 3, biogenic AgNPs conjugated with ceftriaxone demonstrated superior performance against human pathogens which were resistant to ceftriaxone. In a similar study, biosynthesis of AuNPs from the white rot fungi, *Trametes sp* was conducted and conjugated with different antibiotics for their synergistic effect with antibiotics against *S. typhi* and *S. paratyphi*.[55-57] The researchers reported antibacterial activity of ceftriaxone against test strains increased and AuNPs produced from *Trametes* sp. enhanced the reaction rates of the antibiotics in a synergistic mode These results are in line with the other study findings that demonstrated increasing efficacies of ceftriaxone when used in combination with AuNPs against *Bacillus subtilis*, *S. aureus*, *E. coli*, and *Proteus vulgaris* as shown Figure 4.[58] The application of ceftriaxone-conjugated metallic NPs has hence been suggested as an alternative choice for the inhibition resistance pathogens. The dose-dependent cytotoxic activities were observed on increasing the concentration of the AgNPs. Ceftriaxone-conjugated AgNPs showed high activity than unconjugated AgNPs which could be suggested for treating ceftriaxone-resistant microbes.[59]

A comparative study of Au and Ag NPs conjugated with ceftriaxone by Shah et al.[60] demonstrated that the NPs were very stable and resulted in increased antibacterial activity and improved kinetics of ceftriaxone. According to this study, conjugation of ceftriaxone to AgNPs and AuNPs resulted twofold and sixfold activity against *E. coli*, respectively. Another study on the biosynthesis of AuNPs using *Rosa damascenes* petal extract and conjugation with ceftriaxone (Cef-AuNP) against ESBL-producing bacteria offered an in vitro anticancer activity and decreased the minimum inhibitory concentration (MIC) of ceftriaxone with more than 27-folds where the AuNPs could also displayed apoptotic and time-dependent cytotoxic effects in breast cancer cells.[57]

4.2 | Solid lipid nanocarriers

Nanostructured delivery systems have been employed for the encapsulation of lipophilic, hydrophilic, and poorly water-soluble drugs.[61] Solid lipid nanoparticles (SLNs) were introduced in 1991 primarily to reduce some of the limitations of contemporary colloidal carriers such as emulsions, liposomes, and polymeric NPs.[62,63] SLNs are

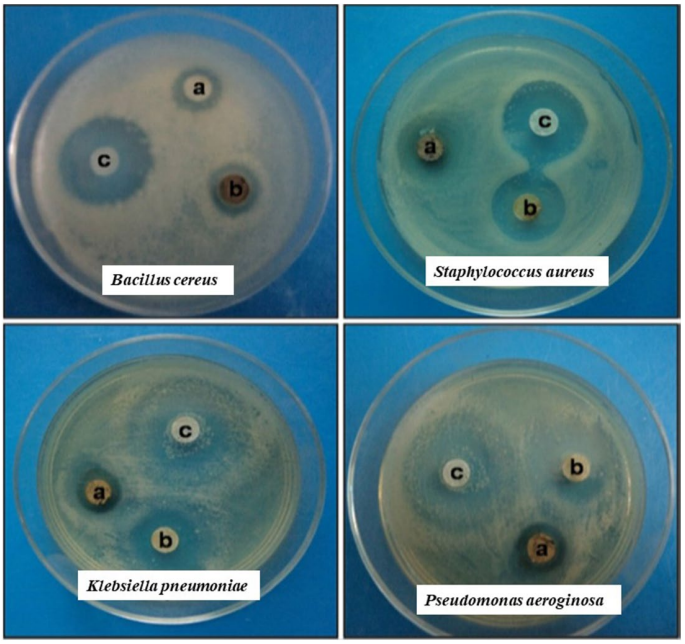

FIGURE 3 Individual and conjugated Ceftriaxone nanoparticles antimicrobial activities against test bacteria.[58] Unconjugated AgNPs (a); ceftriaxone (b), and biogenic AgNPs conjugated with ceftriaxone (c)

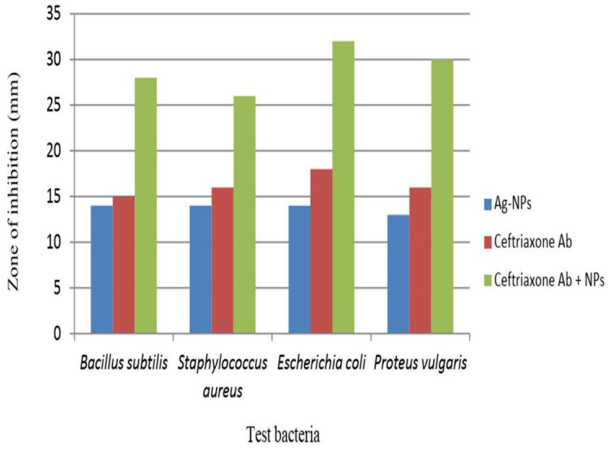

FIGURE 4 Individual versus conjugated effects of ceftriaxone with Ag-NPs[58]

characterized by their essential attributes including the need for inexpensive cheap raw materials, do not require organic solvents for fabrication, prepared using physiological lipids, the ease of scale-up, high biocompatibility, ability to enhance bioavailability, product protection from environmental hazards, suitability for controlled drug-release.[64-66]

The potency of many antibacterial drugs is limited by their poor membrane transport properties, which can be improved by loading the drug into NP vehicles that can enter the host cells via endocytosis. Such platforms also offer the potential for loading multiple drug combinations resulting in highly complex and unpredictable antimicrobial actions where the bacteria could not develop resistance.[20] The possible improvement in antimicrobial activity of ceftriaxone-loaded NPs is due to enhanced intracellular delivery of the poorly-cell-penetrating drug where the NPs are ingested by phagocytic system thereby activating macrophages and boosting the host immune response.[67] The unique size-dependent characteristics of SLNs give incredible opportunities for new therapeutics with improved bioavailability, site targeting, and controlled delivery. Controlled and/or sustained release characteristics with improved performance of poorly water-soluble drugs were demonstrated by formulating as SLNs.[52,68,69] Encapsulation antibiotic drugs with lipid nanocarriers can also prevent issues of overdosage due to the amount of drug required at a desired site, excess dosage, increased frequency of administration, associated side effects, poor patient compliance, the development of resistance, and some biodistribution problems.[45]

Kauss et al.[70] developed a lipid oligonucleotide (LON) therapy as an effective approach to reduce bacterial resistance to antimicrobial drugs. The findings revealed that LON demonstrated a strong antimicrobial activity against *ß-lactamase* producing bacterial both in clinical isolates and laboratory strains suggesting that such lipid conjugation can further be applied to other related antimicrobial drugs. Kumar and colleagues[45] developed ceftriaxone-loaded SLNs by double emulsification process of water-in-oil-in-water (w/o/w) formulation. As depicted in Figure 5 and 6, the SLN formulations offered sustained drug release showing the potential of SLNs as alternative carriers for delivering the drug at a controlled rate.

Hathout and colleagues[71] employed Bio/chemoinformatics software tools and compared nose-to-brain formulations of cefotaxime and ceftriaxone for targeting the treatment of meningitis. The study utilized differences in main structural, topological, and electronic descriptors of the drugs by loading in gelatin and tripalmitin matrices as bases for the formation of nanoparticulate systems. From the result, ceftriaxone showed higher affinity for *S. pneumoniae* bacterial receptors, higher affinity to P-gp efflux pump proteins and higher docking on mucin, less out-of -matrix diffusion, and higher entrapment on the gelatin and the tripalmitin matrices. The group suggested that ceftriaxone-loaded tripalmitin SLNs can be more feasible and efficient nose-to-brain formulation for targeted treatment of meningitis. In a similar study, Haftyzer–Van Krevelen and Hoy's mathematical models were investigated using the double emulsion solvent evaporation method to prepare a nanostructured lipid carrier (NLC) for ceftriaxone sodium and to investigate its effect on eliminating *E. coli*. The findings demonstrated a controlled drug release over time in vitro, and the possibility for effectively killing Escherichia by cutting drug dosage in half using such NLCs.[72]

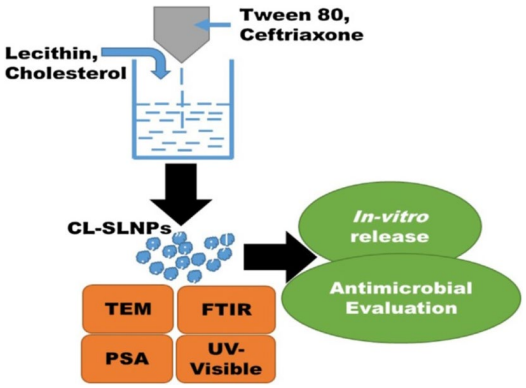

FIGURE 5 Synthesis, characterization, and evaluation of CL-SLNPs.[45] CL-SLNPs, ceftriaxone-loaded solid lipid nanoparticles

4.3 | Polymeric NPs

Polymeric biodegradable NPs have better efficiency and effectiveness over traditional methods of polymeric biodegradable matrix system for drug delivery. Biodegradable polymers used for the fabrication of NPs include chitosan, gelatin, sodium alginate, polycyanoacrylate or poly (D, L-lactide), poly (lactide-co-glycolide), and Chitosan.[52,63] Ceftriaxone-loaded chitosan NPs have demonstrated the potential as a safe delivery system for targeting *salmonella*-infected cells, where the chitosan NPs augmented the antibacterial effect of ceftriaxone against intracellular *S. typhimurium*.[67] In a similar study, synergistic effect of ceftriaxone-loaded chitosan NPs (CNPs) was observed for the treatment of methicillin-resistant *Staphylococcus aureus* and *E. coli* infections by an in vitro study.[73] The findings showed that the drug-loaded CNPs had enhanced antibacterial activity than the conventional antibiotic alone against resistant strains of both gram-positive and gram-negative bacteria. The synergistic effect is also reported at a reduced

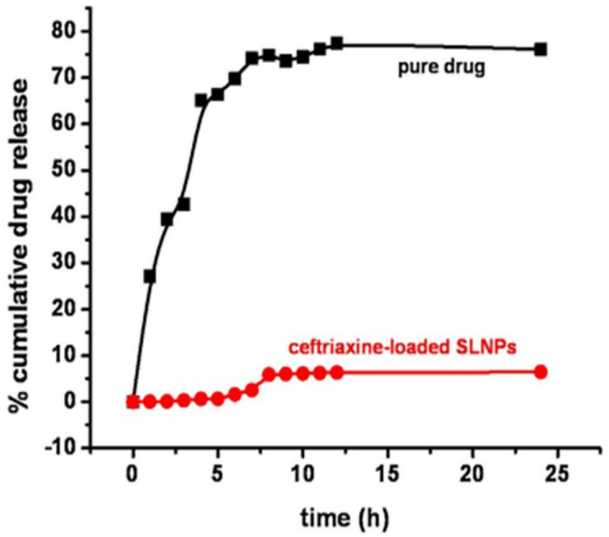

FIGURE 6 In vitro drug release of ceftriaxone-loaded SLNPs[45]

ceftriaxone dose which can be a cost-effective treatment against resistant microbes. In a similar in vitro study, Manimekalai et al.[74] claimed higher loading efficiency and sustained delivery of ceftriaxone sodium from CNPs. Similarly, sustained drug release with enhanced biocidal activity against resistant bacterial strains was also reported by other researchers.[75-77]

A study done on copolymeric NPs for the delivery of a hydrophilic drug, ceftriaxone by encapsulating within poly (ε-caprolactone)-poly (ethylene glycol)-poly (ε-caprolactone)/PCL-PEG-PCL/NPs by a double emulsion technique. The results showed that in vitro release of ceftriaxone was remarkably sustained suggesting that polymersomes may be considered as an effective treatment strategy to improve the therapeutic effect of ceftriaxone.[78] Ceftriaxone-loaded NPs of bovine serum albumin (BSA) were prepared and evaluated for their physicochemical and pharmacodynamic characteristics.[51] The findings revealed that the drug-loaded BSA NPs could effectively sustain drug release over 12 hours and required lower MIC values against *S. aureus* and *E. coli* compared with the conventional drug formulation. Hosseinzadeh et al.[79] investigated a novel nanocellulose-based superabsorbent polymer nanocomposites (SAPCs) using poly (acrylic acid-co-2-hyderoxy ethyl methacrylate)-grafted cellulose nanocrystal composites using ceftriaxone and crystal violet as model drugs. In vitro results showed maximum drug encapsulation efficiency suggesting the potential of the polymeric hydrogels for effective therapeutic application.

In the fight against antimicrobial drug resistance, nanostructured synthetic polymers with antimicrobial activity demonstrated promising results against resistant microbial strains.[80-83] Judzewitsch et al.[84] demonstrated enhanced antimicrobial effect comparable to antimicrobial peptides using linear high-order quasi-block copolymers consisting of aminoethyl, phenylethyl, and hydroxyethyl acrylamides developed through photo-induced electron transfer-reversible addition-fragmentation chain transfer technique; highlighting the possibility for tuneable antimicrobial and hemolytic activities. In another study, linear random copolymers comprising oligoethylene glycol and amine groups in a single-chain polymeric NPs showed better performances against *Pseudomonas aeruginosa* and *E. coli* gram-negative with better capability of killing both planktonic microbial cells and biofilm compared to colistin, the last line of defense against gram-negative pathogens.[85]

On the other hand, the combination of mechanistically different antimicrobial drugs has been suggested for better efficacy and reduction of AMR with minimum dose and side effects. With this established hypothesis, different researchers investigated the potential of combining antimicrobial synthetic polymers with commercial antimicrobial agents.[86-88] Nguyen and colleagues[89] developed gentamicin-loaded polymeric NPs capable of storing nitric oxide which could provoke antibiotic susceptible planktonic formation which resulted in synergistic better bactericidal effect against *P. aeruginosa* biofilm and planktonic cultures. Similarly, a potent synthetic antimicrobial polymer comprising oligoethylene glycol, ethylhexyl, and cationic primary amine groups, in combination with doxycycline and colistin demonstrated improved bacteriostatic and bactericidal effect against MDR *P. aeruginosa strains*.[90] Enhanced antimicrobial and antibiofilm activities against drug-resistant strains have also been reported using combination of synthetic antimicrobial polymers with nitric oxide and essential oils.[91,92]

4.4 | Magnetic NPs

Magnetic NPs are novel nanostructures that involve binding of the therapeutic or diagnostic molecule with magnetic nanoparticles (MNPs) such as oxidized iron or magnetite.[93,94] As a precondition for using magnetic carriers for biomedical applications, they must be aqua-based, biocompatible, nontoxic, and nonimmunogenic. Application of MNP drug delivery systems helps to define and target the specific treatment sites, which will reduce the target and non-target drug amount. These will in turn prevent toxicities from target over dosage and severe side effects from the non-target concentrations.[95]

Iron oxide has been used as a magnetic nanocarrier due to its biodegradability, biocompatibility, super paramagnetic properties, and ability to serve as a contrast magnetic resonance imaging material.[52] Because of their intrinsic antimicrobial activity, iron oxide nanoparticles (IONPs) provide promising treatments for infectious illnesses by targeting specific and hard-to reach sites where pathogens are harbored. In addition, their low cost of synthesis and high versatility make IONPs feasible solution to overcoming barriers on treatment of infectious diseases.[95] The successful synthesis of a new nanocarrier-grafted magnetic NPs was reported as an effective and appropriate sorbent for ceftriaxone delivery by Alipour et al.[96] using modified Fe_3O_4 MNPs in n-vinylcaprolactam 3-allyloxy-1,2-propandiol (Fe_3O_4@[NVC][AP]). Effectively sustained

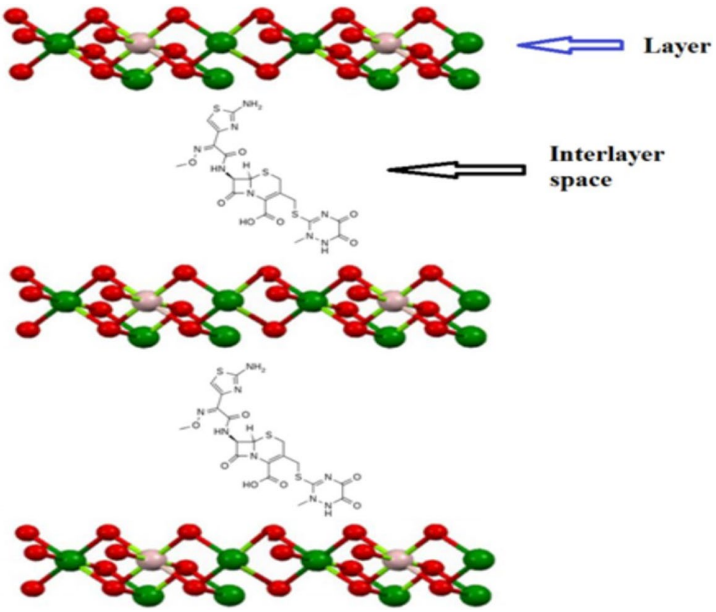

FIGURE 7 Antibiotic/LDH nanohybrid schematic view[100]

drug release was observed from simulated gastric and intestinal fluids. Similarly, Kawish et al.[97] demonstrated higher drug entrapment, sustained rug release and suitability for enhancing the oral delivery ceftriaxone using ceftriaxone loaded highly functionalized magnetic IONPs.

4.5 | Intercalated nanostructures

Intercalation is simply the process of inserting one molecule or chemical compound into a differently layered structure.[98] Layered double hydroxides (LDHs) and their complexes with several materials offer a key group of resources suitable for a number of current and future uses for biochemical and environmental developments. The compositional variety, lamellar structure, and biocompatibility characteristics of LDHs, together with their simplicity for larger scale synthesis attracted the interest of many groups in the field.[99]

Ceftriaxone intercalated nanostructures were investigated by Duceac et al.[100] as controlled drug delivery systems (Figure 7). The result indicated that inclusion of the active within the inorganic matrices offered advantages such as high drug loading and sustained release. In addition, intercalation of ceftriaxone into the layered structure of anionic clays improved antibiotic efficiency through controlled drug release. The authors predicted that ceftriaxone-LDH nanohybrids can have a huge potential for the delivery of antibiotics and improve medical treatment.

5 | CONCLUSION

Microbial resistance to third-generation cephalosporins have been increasing significantly with those strains which developed resistance to third-generation cephalosporins being also resistant to multiple drugs. Ceftriaxone resistance is now becoming an increasing challenge to many antibiotic therapies. In light of this pressing issue, there has been much interest in possible alternative antimicrobial therapies, including the use of nanotechnology. Ceftriaxone–NP conjugation (with metallic and/or magnetic NPs), intercalation (with LDHs), encapsulation (with solid lipid carriers), and polymeric film formation (like chitosan) were among the different nanotechnology-based approaches to combat ceftriaxone resistance discussed in this review. Very luckily, most of these approaches have promised a huge potential for use in some formulations of ceftriaxone and also for other antibiotics in order to improve medical treatment in the future time. Especially, the synergistic activity of polymeric NPs against resistant strains of both gram-positive and gram-negative bacteria with their beneficial physicochemistry as a carrier such as their biodegradability & biocompatibility, higher stability, simple synthesis, high loading capacity, and cost-effectiveness is very promising and interesting for further investigations and alternative setting approaches. Combination of antimicrobial drugs and antimicrobial synthetic polymers in nanostructured delivery platforms have demonstrated synergistic therapeutic performance against MDR bacterial strains with better tolerability and similar approaches can also be exploited for the delivery of ceftriaxone.

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The authors report no conflict of interest.

AUTHORS' CONTRIBUTIONS

All the authors were involved in the design and write-up of the review, and AT conducted the actual review and the analysis with

the manuscript preparation. GB participated in the topic selection and review of the final work-up. TM made the final review of the manuscript. All the authors approved the submitted version of the manuscript.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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REFERENCES

1. Muller A. Relationship between ceftriaxone use and resistance to third-generation cephalosporins among clinical strains of *Enterobacter cloacae*. *J Antimicrob Chemother*. 2004;4(1):173-177.
2. Al Kraiem AA, Yang G, Al Kraiem F, Chen T. Challenges associated with ceftriaxone resistance in *Salmonella*. *Front Life Sci*. 2018;11(1):26-34.
3. Gashe F, Mulisa E, Mekonnen M, Zeleke G. Antimicrobial resistance profile of different clinical isolates against third-generation cephalosporins. *J Pharm*. 2018;2018:1-7. https://doi.org/10.1155/2018/5070742
4. Ayinalem G, Gelaw B, Belay A, Linjesa J. Drug use evaluation of ceftriaxone in medical ward of Dessie Referral Hospital, North East Ethiopia. *Int J Basic Clin Pharmacol*. 2013;2(6):711-717.
5. Meyer E, Schwab F, Schroeren-Boersch B, Gastmeier P. Dramatic increase of third-generation cephalosporin-resistant *E. coli* in German intensive care units: secular trends in antibiotic drug use and bacterial resistance, 2001 to 2008. *Crit Care*. 2010;14(3):1-9.
6. Adesoji AT, Onuh JP, Okunye OL. Bacteria resistance to cephalosporins and its implication to public health. *J Bacteriol Mycol*. 2016;3(1):1021.
7. Goldstein FW, Pean Y, Gertner J. Resistance to ceftriaxone and other beta-lactams in bacteria isolated in the community. The Vigil'Roc Study Group. *Antimicrob Agents Chemother*. 1995;39(11):2516-2519.
8. EMA. Rocephin and associated names: assessment report by Committee for Medicinal Products for Human Pursuant to Article 30 of Directive 2001/83/EC. 2014. https://www.ema.europa.eu/en/documents/referral/rocephin-article-30-referral-assessment report_en.pdf. Accessed February 14, 2021
9. Nakayama S, Shimuta K, Furubayashi K, Kawahata T, Unemo M, Ohnishi M. New ceftriaxone- and multidrug-resistant *Neisseria gonorrhoeae* strain with a novel mosaic penA gene isolated in Japan. *Antimicrob Agents Chemother*. 2016;60:4339-4341.
10. Tien V, Punjabi C, Holubar MK. Antimicrobial resistance in sexually transmitted infections. *J Travel Med*. 2019;27(1):1-11.
11. Bharathan GK, Kurian B. First reported case of ceftriaxone-resistant typhoid fever in the Middle-East. *Int J Travel Med Glob Health*. 2021;9(1):39-41.
12. Lefebvre B, Martin I, Demczuk W, et al. Ceftriaxone-resistant *Neisseria gonorrhoeae*, Canada, 2017. *Emerg Infect Dis*. 2018;24(2):381-383. https://doi.org/10.3201/eid2402.171756
13. Mizrahi A, Marvaud JC, Pilmis B, et al. Emergence of ceftriaxone resistance during a case of *Pneumococcal meningitis* with fatal evolution. *Antimicrob Agents Chemother*. 2019;64(3):e01958-19. https://doi.org/10.1128/AAC.01958-19
14. Chiu CH, Su LH, Huang YC, et al. Increasing ceftriaxone resistance and multiple alterations of penicillin-binding proteins among penicillin-resistant *Streptococcus pneumoniae* isolates in Taiwan. *Antimicrob Agents Chemother*. 2007;51(9):3404-3406.
15. Chua KYL, Stewardson AJ. Individual and community predictors of urinary ceftriaxone-resistant *Escherichia coli* isolates, Victoria, Australia. *Antimicrob Resist Infect Control*. 2019;8:36. https://doi.org/10.1186/s13756-019-0492-8
16. Baker SJ, Payne DJ, Rappuoli R, De Gregorio E. Technologies to address antimicrobial resistance. *Proc Natl Acad Sci USA*. 2018;115(51):12887-12895.
17. Lee CR, Cho I, Jeong B, Lee S. Strategies to minimize antibiotic resistance. *Int J Environ Res Public Health*. 2013;10(9):4274-4305.
18. Varier KM, Gudeppu M, Chinnasamy A, et al. Nanoparticles: antimicrobial applications and its prospects. In: Naushad M, Rajendran S, Gracia F, eds. *Advanced Nanostructured Materials for Environmental Remediation. Environmental Chemistry for a Sustainable World*. Vol. 25. Springer; 2019. https://doi.org/10.1007/978-3-030-04477-0_12
19. Teixeira MC, Carbone C, Sousa MC, et al. Nanomedicines for the delivery of antimicrobial peptides (AMPs). *Nanomaterials*. 2020;10(3):560. https://doi.org/10.3390/nano10030560
20. Baptista PV, McCusker MP, Carvalho A, et al. Nano-strategies to fight multidrug resistant bacteria-"A Battle of the Titans". *Front Microbiol*. 2018;9:1441. https://doi.org/10.3389/fmicb.2018.01441
21. Aruguete DM, Kim B, Hochella MF, et al. Antimicrobial nanotechnology: its potential for the effective management of microbial drug resistance and implications for research needs in microbial nanotoxicology. *Environ Sci Process Impacts*. 2013;15(1):93-102.
22. PHE. Multi-drug resistant gonorrhea in England: 2018. Public Health England (PHE); 2018. Accessed December 24, 2020. https://www.gov.uk/government/publications/multi-drug-resistant-gonorrhoea-in-england-2018
23. Unemo M, Golparian D, Hestner A. Ceftriaxone treatment failure of pharyngeal gonorrhoea verified by international recommendations, 2011;Sweden. *Euro Surveill*. 2011;16(6):19792.
24. Medalla F, Hoekstra RM, Whichard JM, et al. Increase in resistance to ceftriaxone and nonsusceptibility to ciprofloxacin and decrease in multidrug resistance among *Salmonella* strains, United States, 1996–2009. *Foodborne Pathog Dis*. 2012;10(4):302-309. https://doi.org/10.1089/fpd.2012.1336
25. Durham SH, Wingler MJ, Eiland LS. Appropriate use of ceftriaxone in the emergency department of a Veteran's Health Care System. *J Pharm Technol*. 2017;33(6):215-218.
26. Hrvatin V. Combating antibiotic resistance: new drugs or alternative therapies? *Can Med Assoc J*. 2017;189(37):E1199. https://doi.org/10.1503/cmaj.109-5469
27. Ampaire L, Muhindo A, Orikiriza P, Mwanga-Amumpaire J, Bebell L, Boum Y. A review of antimicrobial resistance in East Africa. *Afr J Lab Med*. 2016;5(1):432. https://doi.org/10.4102/ajlm.v5i1.432
28. Wangai FK, Masika MM, Lule GN, et al. Bridging antimicrobial resistance knowledge gaps: the East African perspective on a global problem. *PLoS One*. 2019;14(2):e0212131. https://doi.org/10.1371/journal.pone.0212131
29. Yang WC, Chan OW, Wu TL, Chen CL, Su LH, Chiu CH. Development of ceftriaxone resistance in *Salmonella enterica* serotype Oranienburg during therapy for bacteremia. *J Microbiol Immunol Infect*. 2016;49(1):41-45.
30. Browne AJ, Kashef HBH, Kumaran EAP, et al. Improved antibacterial activity of cephalosporins loaded in magnetic chitosan microspheres. *Int J Pharm*. 2012;436:201-205.
31. Kuang D, Zhang J, Xu X, et al. Increase in ceftriaxone resistance and widespread extended-spectrum β-lactamases genes among *Salmonella enterica* from human and nonhuman sources. *Foodborne Pathog Dis*. 2018;15(12):770-775.

32. Munita JM, Arias CA. Mechanisms of antibiotic resistance. *Microbiol Spectr*. 2016;4(2):1-37. https://doi.org/10.1128/microbiolspec.VMBF-0016-2015
33. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiol*. 2018;4(3):482-501.
34. Zhao F, Yang H, Bi D, Khaledi A, Qiao M. A systematic review and meta-analysis of antibiotic resistance patterns, and the correlation between biofilm formation with virulence factors in uropathogenic *E. coli* isolated from urinary tract infections. *Microb Pathog*. 2020;144:104196.
35. Gong Z, Lai W, Liu M, et al. Novel genes related to ceftriaxone resistance found among ceftriaxone-resistant *Neisseria gonorrhoeae* strains selected *in vitro*. *Antimicrob Agents Chemother*. 2016;60(4):2043-2051.
36. Su LH, Wu TL, Chia JH, Chu C, Kuo A, Chiu CH. Increasing ceftriaxone resistance in *Salmonella* isolates from a university hospital in Taiwan. *J Antimicrob Chemother*. 2005;55(6):846-852.
37. Tanaka M, Nakayama H, Huruya K, et al. Analysis of mutations within multiple genes associated with resistance in a clinical isolate of *Neisseria gonorrhoeae* with reduced ceftriaxone susceptibility that shows a multidrug-resistant phenotype. *Int J Antimicrob Agents*. 2006;27:20-26. https://doi.org/10.1016/j.ijantimicag.2005.08.021
38. Sewagegn N. Evaluation of ceftriaxone use for hospitalized patients in Ethiopia: the case of a referral hospital. *Int J Pharm Sci Res*. 2017;3(2):26-31.
39. Lee H, Jung D, Yeom JS, et al. Evaluation of ceftriaxone utilization at multicenter study. *Korean J Intern Med*. 2009;24(4):374-380.
40. WHO. *Antimicrobial Resistance: Global Report on Surveillance*. World Health Organization (WHO); 2014. Accessed December 30, 2020. https://apps.who.int/iris/bitstream/handle/10665/112642/9789241564748_eng.pdf;jsessionid=F83D7935B2B06494D93D1BC6F356541B?sequence=1
41. Ventola CL. The antibiotic resistance crisis part 1: causes and threats. *P T*. 2015;40(4):277-283.
42. OECD. Antimicrobial resistance: policy insights. Organization for Economic Cooperation and Development (OECD); 2016. Accessed December 30, 2020. https://www.oecd.org/health/health-systems/AMR-Policy-Insights-November2016.pdf
43. Pelgrift R, Friedman A. Nanotechnology as a therapeutic tool to combat microbial resistance. *Adv Drug Deliv Rev*. 2013;65(13–14):1803-1815. https://doi.org/10.1016/j.addr.2013.07.011
44. CORDIS. New weapons to combat antibiotic resistance. Community Research and Development Information Service (CORDIS), European Union Luxembourg; 2018. Accessed December 25, 2020. https://publications.europa.eu/portal2012-ortlet/html/downloadHandler.jsp?identifier=ac3699e2-74fc-11e8-9483-01aa75ed71a1&format=PDF&language=en&productionSystem=cellar
45. Kumar S, Bhanjana G, Kumar A, Taneja K, Dilbaghi N, Kim KH. Synthesis and optimization of ceftriaxone-loaded solid lipid nanocarriers. *Chem Phys Lipids*. 2016;200:126-132.
46. Morones JR, Elechiguerra JL, Camacho A, et al. The bactericidal effect of silver nanoparticles. *Nanotechnology*. 2005;16:2346-2353.
47. Gold K, Slay B, Knackstedt M, Gaharwar AK. Antimicrobial activity of metal and metal-oxide based nanoparticles. *Adv Ther*. 2018;1:1700033. https://doi.org/10.1002/adtp.201700033
48. Singh P, Garg A, Pandit S, Mokkapati VRSS, Mijakovic I. Antimicrobial effects of biogenic nanoparticles. *Nanomaterials*. 2018;8:1009. https://doi.org/10.3390/nano8121009
49. Wang L, Hu C, Shao L. The antimicrobial activity of nanoparticles: present situation and prospects for the future. *Int J Nanomedicine*. 2017;12:1227-1249. https://doi.org/10.2147/IJN.S121956
50. Rai M, Paralikar P, Jogee P, et al. Synergistic antimicrobial potential of essential oils in combination with nanoparticles: emerging trends and future perspectives. *Int J Pharm*. 2017;519(1–2):67-78.
51. Bali GK, Singla S, Kashyap Y, et al. Preparation, physico-chemical characterization and pharmacodynamics of ceftriaxone- loaded BSA nanoparticles. *J Nanomed Nanotechnol*. 2018;9:509. https://doi.org/10.4172/2157-7439.1000509
52. Panda BP, Patnaik S, Maharana RL. Current trends in design and development of nanopharmaceutical dosage forms. *Bioequiv Bioavailab Int J*. 2017;1(1):000104.
53. Kong FY, Zhang JW, Li RF, Wang ZX, Wang WJ, Wang W. Unique roles of gold nanoparticles in drug delivery: targeting and imaging applications. *Molecules*. 2017;22(9):1445. https://doi.org/10.3390/molecules22091445
54. Shanmuganathan R, Mubarak AD, Prabakar D, et al. An enhancement of antimicrobial efficacy of biogenic and ceftriaxone-conjugated silver nanoparticles: green approach. *Environ Sci Pollut Res*. 2017;25(11):10362-10370.
55. Gudikandula K, Vadapally P, Singara CMA. Biogenic synthesis of silver nanoparticles from white rot fungi: their characterization and antibacterial studies. *OpenNano*. 2017;2:64-78. https://doi.org/10.1016/j.onano.2017.07.002
56. Sengani M, Grumezescu AM, Rajeswari VD. Recent trends and methodologies in gold nanoparticle synthesis – a prospective review on drug delivery aspect. *OpenNano*. 2017;2:37-46.
57. El-Rab SM, Halawani EM, Hassan AM. Formulation of ceftriaxone conjugated gold nanoparticles and their medical applications against extended-spectrum β-lactamase producing bacteria and breast cancer. *J Microbiol Biotechnol*. 2018;28(9):1563-1572.
58. Gudikandula K, Metuku RP, Burra S, Nidadavolu SVSL, Pabba SK, Alha SCM. Fungus-mediated synthesis of silver nanoparticles and their activity against gram positive and gram negative bacteria in combination with antibiotics. *Walailak J Sci Tech*. 2015;12(7):613-622.
59. Harshiny M, Matheswaran M, Arthanareeswaran G, Kumaran S, Rajasree S. Enhancement of antibacterial properties of silver nanoparticles–ceftriaxone conjugate through *Mukia maderaspatana* leaf extract mediated synthesis. *Ecotoxicol Environ Saf*. 2015;121:135-141.
60. Shah MR, Ali S, Ateeq M, et al. Morphological analysis of the antimicrobial action of silver and gold nanoparticles stabilized with ceftriaxone on *Escherichia coli* using atomic force microscopy. *New J Chem*. 2014;38(11):5633-5640.
61. El-Salamouni NS, Farid RM, El-Kamel AH, El-Gamal SS. Effect of sterilization on the physical stability of brimonidine-loaded solid lipid nanoparticles and nanostructured lipid carriers. *Int J Pharm*. 2015;496(2):976-983.
62. Muller RH, Mader K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art. *Eur J Pharm Biopharm*. 2000;50(1):161-177.
63. Manimekalai P, Manavalan R. Selection of excipients for the formulation of ceftriaxone sodium loaded chitosan nanoparticle through drug-excipient compatibility testing. *Int J PharmTech Res*. 2015;8(1):5-10.
64. Mehnert W. Solid lipid nanoparticles production, characterization and applications. *Adv Drug Deliv Rev*. 2001;47:165-196.
65. Jores K, Mehnert W, Mader K. Physicochemical investigations on solid lipid nanoparticles and on oil-loaded solid lipid nanoparticles: a nuclear magnetic resonance and electron spin resonance study. *Pharm Res*. 2003;20:1274-1283.
66. Qu J, Zhang L, Chen Z, et al. Nanostructured lipid carriers, solid lipid nanoparticles, and polymeric nanoparticles: which kind of drug delivery system is better for glioblastoma chemotherapy? *Drug Deliv*. 2016;23(9):3408-3416.

67. Zaki NM, Hafez MM. Enhanced antibacterial effect of ceftriaxone sodium-loaded chitosan nanoparticles against intracellular *Salmonella typhimurium*. *AAPS PharmSciTech*. 2012;13(2):411-421.
68. zur MuEhlen A, Mehnert W. Drug release and release mechanism of prednisolone loaded solid lipid nanoparticles. *Pharmazie*. 1998;53:552-555.
69. Singh A, Neupane YR, Panda BP, Kohli K. Lipid based nanoformulation of lycopene improves oral delivery: formulation optimization, ex vivo assessment and its efficacy against breast cancer. *J Microencapsul*. 2017;34(4):1-38.
70. Kauss T, Arpin C, Bientz L, et al. Lipid oligonucleotides as a new strategy for tackling the antibiotic resistance. *Sci Rep*. 2020;10(1054):90-101. https://doi.org/10.1038/s41598-020-58047-x
71. Hathout RM, Abdelhamid SG, El-Housseiny GS, Metwally AA. Comparing cefotaxime and ceftriaxone in combating meningitis through nose-to-brain delivery using bio/chemoinformatics tools. *Sci Rep*. 2020;10:21250. https://doi.org/10.1038/s41598-020-78327-w
72. Ebrahimi S, Farhadian N, Karimi M, Ebrahimi M. Enhanced bactericidal effect of ceftriaxone drug encapsulated in nanostructured lipid carrier against gram-negative *Escherichia coli* bacteria: drug formulation, optimization, and cell culture study. *Antimicrob Resist Infect Control*. 2020;9:28. https://doi.org/10.1186/s13756-020-0690-4
73. Mushtaq S, Khan JA, Rabbani F, Latif U, Arfan M, Yameen MA. Biocompatible biodegradable polymeric antibacterial nanoparticles for enhancing the effects of a third-generation cephalosporin against resistant bacteria. *J Med Microbiol*. 2017;66(3):318-327.
74. Manimekalai P, Dhanalakshmi R, Manavalan R. Preparation and characterization of ceftriaxone sodium encapsulated chitosan nanoparticles. *Int J Appl Pharm*. 2017;9(6):10-15. https://doi.org/10.22159/ijap.2017v9i6.16317
75. Hammond PT. Building biomedical materials layer-by-layer. *Mater Today*. 2012;15(5):196-206.
76. Alshubaily FA, Al-Zahrani MH. Appliance of fungal chitosan/ceftriaxone nano-composite to strengthen and sustain antimicrobial potentiality against drug resistant bacteria. *Int J Biol Macromol*. 2019;135:1246-1251.
77. Kızıltay A, Gündoğan Z, Erel Gİ, Hasirci N. Multilayer polymeric films for controlled release of ceftriaxone sodium. *Turk Bull Hyg Exp Biol*. 2019;76(3):303-312.
78. Hossein D. Preparation and characterization of PCL-PEG-PCL copolymeric nanoparticles as polymersomes for delivery of hydrophilic drugs. *Iran J Pharm Sci*. 2018;14(4):21-32.
79. Hosseinzadeh S, Hosseinzadeh H, Pashaei S. Fabrication of nanocellulose loaded poly (AA-co-HEMA) hydrogels for ceftriaxone controlled delivery and crystal violet adsorption. *Polym Compos*. 2018;41(S1):E559–E569. https://doi.org/10.1002/pc.24875
80. Lam SJ, Wong EH, Boyer C, Qiao GG. Antimicrobial polymeric nanoparticles. *Prog Polym Sci*. 2017;76:40-64.
81. Judzewitsch PR, Zhao L, Wong EHH, Boyer C. High-throughput synthesis of antimicrobial copolymers and rapid evaluation of their bioactivity. *Macromolecules*. 2019;52(11):3975-3986.
82. Judzewitsch PR, Corrigan N, Trujillo F, et al. High-throughput process for the discovery of antimicrobial polymers and their upscaled production via flow polymerization. *Macromolecules*. 2020;53(2):631-639.
83. Namivandi-Zangeneh R, Wong EHH, Boyer C. Synthetic antimicrobial polymers in combination therapy: tackling antibiotic resistance. *ACS Infect Dis*. 2021;7(2):215-253. https://doi.org/10.1021/acsinfecdis.0c00635
84. Judzewitsch PR, Nguyen TK, Shanmugam S, Wong EHH, Boyer C. Towards sequence-controlled antimicrobial polymers: effect of polymer block order on antimicrobial activity. *Angew Chem*. 2018;57(17):4649-4654.
85. Nguyen TK, Lam SJ, Ho KKK, et al. Rational design of single-chain polymeric nanoparticles that kill planktonic and biofilm bacteria. *ACS Infect Dis*. 2017;3(3):237-248.
86. Cottarel G, Wierzbowski J. Combination drugs, an emerging option for antibacterial therapy. *Trends Biotechnol*. 2007;25:547-555.
87. Fischbach MA. Combination therapies for combating antimicrobial resistance. *Curr Opin Microbiol*. 2011;14:519-523.
88. Ng VWL, Ke X, Lee ALZ, Hedrick JL, Yang YY. Synergistic co-delivery of membrane-disrupting polymers with commercial antibiotics against highly opportunistic bacteria. *Adv Mater*. 2013;25:6730-6736.
89. Nguyen TK, Selvanayagam R, Ho KKK, et al. Co-delivery of nitric oxide and antibiotic using polymeric nanoparticles. *Chem Sci*. 2016;7(2):1016-1027.
90. Namivandi-Zangeneh R, Sadrearhami Z, Dutta D, Willcox M, Wong EHH, Boyer C. Synergy between synthetic antimicrobial polymer and antibiotics: a promising platform to combat multidrug-resistant bacteria. *ACS Infect Dis*. 2019;5(8):1357-1365.
91. Namivandi-Zangeneh R, Sadrearhami Z, Bagheri A, et al. Nitric oxide-loaded antimicrobial polymer for the synergistic eradication of bacterial biofilm. *ACS Macro Lett*. 2018;7(5):592-597.
92. Namivandi-Zangeneh R, Yang Y, Xu S, Wong EHH, Boyer C. Antibiofilm platform based on the combination of antimicrobial polymers and essential oils. *Biomacromol*. 2020;21(1):262-272.
93. Veiseh O, Gunn JW, Zhang M. Design and fabrication of magnetic nanoparticles for targeted drug delivery and imaging. *Adv Drug Deliv Rev*. 2010;62(3):284-304.
94. Akbarzadeh A, Samiei M, Davaran S. Magnetic nanoparticles: preparation, physical properties, and applications in biomedicine. *Nanoscale Res Lett*. 2012;7(1):144. https://doi.org/10.1186/1556-276X-7-144
95. Rodrigues GR, López-Abarrategui C, de la Serna GI, Dias SC, Otero-González AJ, Franco OL. Antimicrobial magnetic nanoparticles based-therapies for controlling infectious diseases. *Int J Pharm*. 2019;555:356-367.
96. Alipour A, Tehrani MS, Aberoomand AP, Givianrad MH. Preparation of modified magnetic nanoparticles for in vitro delivery of ceftriaxone. *Nanomed Res J*. 2019;4(2):84-90.
97. Kawish M, Elhissi A, Jabri T, Iqbal KM, Zahid H, Shah MR. Enhancement in oral absorption of ceftriaxone by highly functionalized magnetic iron oxide nanoparticles. *Pharmaceutics*. 2020;12(492):1-17. https://doi.org/10.3390/pharmaceutics12060492
98. Chiou JY, Hsu RS, Chiu CW, Lin JJ. A stepwise mechanism for intercalating hydrophobic organics into multilayered clay nanostructures. *RSC Adv*. 2013;3:2847-12854.
99. Szilagyi I. Layered double hydroxide-based nanomaterials-from fundamentals to applications. *Nanomaterials*. 2019;9(8):1174. https://doi.org/10.3390/nano9081174
100. Duceac LD, Luca AC, Mitrea G, et al. Ceftriaxone intercalated nanostructures used to improve medical treatment. *Mater Plast*. 2018;55(4):613-615.

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