Maddiboyina *et al.*
Bulletin of the National Research Centre (2023) 47:95
https://doi.org/10.1186/s42269-023-01072-3

Bulletin of the National Research Centre

REVIEW

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Methicillin-resistant *Staphylococcus aureus*: novel treatment approach breakthroughs

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Abstract

Background Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common bacterial infection that is a significant source of illness and mortality globally. The advancements in antibiotic therapies continue to be the critical aspects of treating bacterial infections, and their usage has lowered patient mortality and raised life expectancy.

Main body of the abstract The ideal treatments for MRSA remain challenging, and the quest for new antibiotic targets and advanced drug delivery systems with safety profiles is necessary to ensure treating MRSA infections adequately in the future.

Short conclusion This article primarily focuses on different therapeutic medications and their modes of action for general microbial infections and goes through the latest developments in novel drug delivery technologies, such as hydrogels, lipid particles, nanocarriers, and polymers for MRSA treatment.

Keywords MRSA, Antimicrobial, Antibacterial, *S. aureus*, Drug delivery

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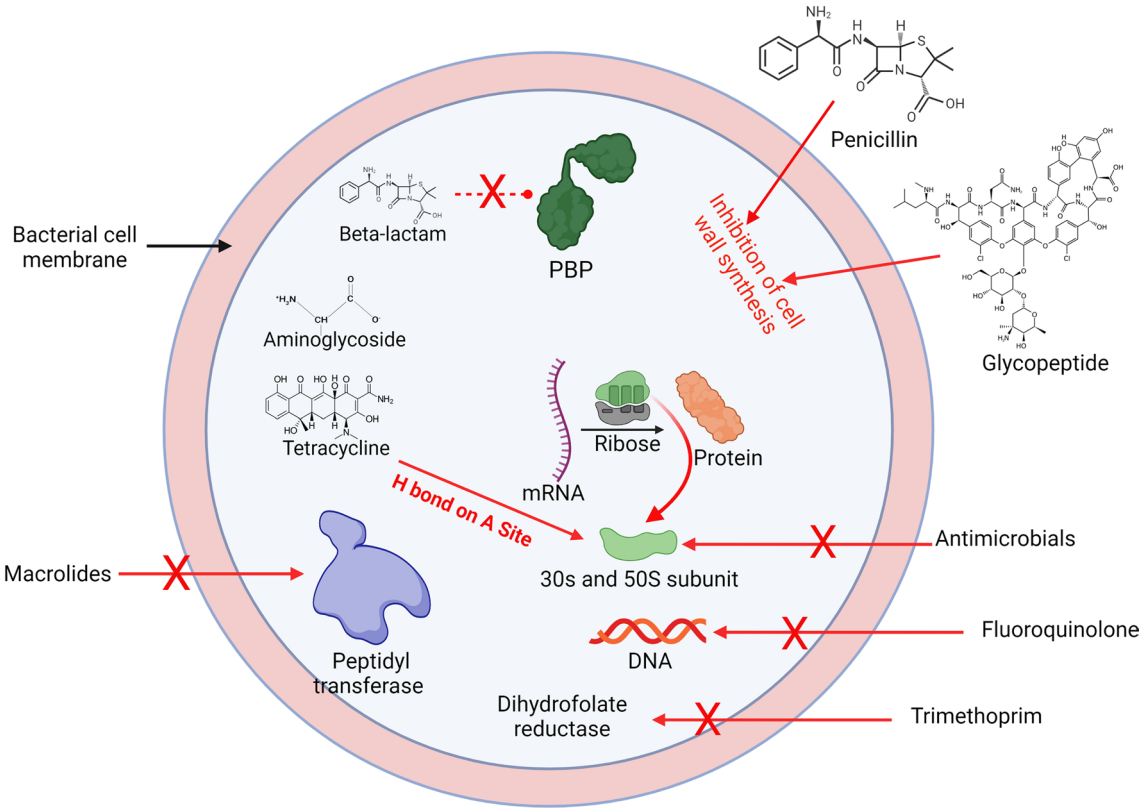
Graphical Abstract



Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an infection seen in many hospitals. It is a type of bacteria that are especially prevalent in hospitals and can cause severe sickness and death (Turner et al. 2019). According to recent prevalence studies, the incidence of MRSA is on the rise in developed countries, both in healthcare settings and in the community (Wan et al. 2021; Maddina et al. 2016). Among nosocomial infections in developed countries, MRSA poses a 60% risk of colonization (Williams et al. 2009). A recent meta-analysis of inpatient admissions for *S. aureus* infection in the USA reported nearly 4,000,000 population admissions per year. MRSA also increases the mortality rate (~19,000) of the hospitalized American population daily (Report NDS 2020; Maddiboyina et al. 2020).

Staphylococcus aureus, gram-positive bacteria in the Stpohylococccеae family with a diameter of about 1 µm, produces grape-like collections. *S. aureus* is a bacterium that lives commensally or often symptomless in healthy individuals' skin and skin glands, nasal epithelial cells, mucous membranes, and gut (Raineri et al. 2022). Several prevalence revisions revealed that 20% of populations remain obstinate nasal carriers, approximately 30% of populations are recurrent carriers, while 50% remain non-carriers. In 1880, Alexander Ogston sequestered *S. aureus* following a surgical wound contagion (Ogston 1882). It has been a long time since MRSA's prevalence and incidence have skyrocketed worldwide. According to recent epidemiology studies, the global incidence of MRSA infection has increased by 7 to 60% between 1964 and 2015 (Cowan et al. 1954; Maddiboyina et al. 2023). Extended hospitalization, intensive care, open wounds, hemodialysis, overdosing on antibiotics, MRSA colonization, and long-term urinary catheter use are all risk factors for MRSA. People suffering from major chronic illnesses are at high risk of contracting MRSA. Detecting MRSA colonization during admission may reduce the risk of developing MRSA infections (Sakr et al. 2018). Increasing antibiotic resistance is a result of MRSA infection. This limits treatment options for MRSA-associated infections. As well as poor infection control, MRSA remains resistant to the utmost powerful antibiotics employed to treat severe MRSA infections, according to

the latest research. Aminoglycosides, erythromycin, and fluoroquinolones are the most commonly prescribed antibiotics for MRSA treatment. Vancomycin remains the most frequently used antibiotic in the therapy of MRSA (Cong et al. 2020). A schematic representation of timeline for novel treatment approach and development of resistance of *staphylococcus aureus* is described in Fig. 1.

Mechanism of antibiotic action and antibiotics resistance

Antibiotics are classified based on their mechanism of action (MoA), as shown in Fig. 2.

Antibiotics that attack the cell wall

This large sugar polymer, peptidoglycan, undergoes crosslinking of the glycan components due to transglycosidases, which crosslink the glycan components. In the incidence of penicillin-binding proteins, glycine deposits crosslink the D-alanine-alanine peptide chain (Maya-Martinez et al. 2019). Unlike β-lactams and glycopeptides, which interfere with the cell wall's construction, β-lactams and glycopeptides do the opposite by blocking the production of the cell wall.

Beta-lactam antibiotics

PBPs continue to be the primary goal of -lactam assistance, and they will continue to be. The PBP binds to the β-lactam ring and cannot be used to produce other peptidoglycans because it interacts with the ring. In this case, disruption of the peptidoglycan stratum indicates that the bacteria are on the verge of lysing (Iyer 2022).

Glycopeptides

Glycopeptides bind to the peptide side chain's D-alanyl D-alanine section in the D-alanyl D-alanine sequence. It prevents D-alanyl subsets from binding to the PBP and thus prevents cell wall synthesis (Blaskovich et al. 2018).

Inhibitors of protein biosynthesis

Translation occurs when the ribosome synthesizes proteins from messenger RNA (mRNA). Ribosomes and cytoplasmic factors are still involved in the protein synthesis process. Antimicrobials aim at the 30S or 50S

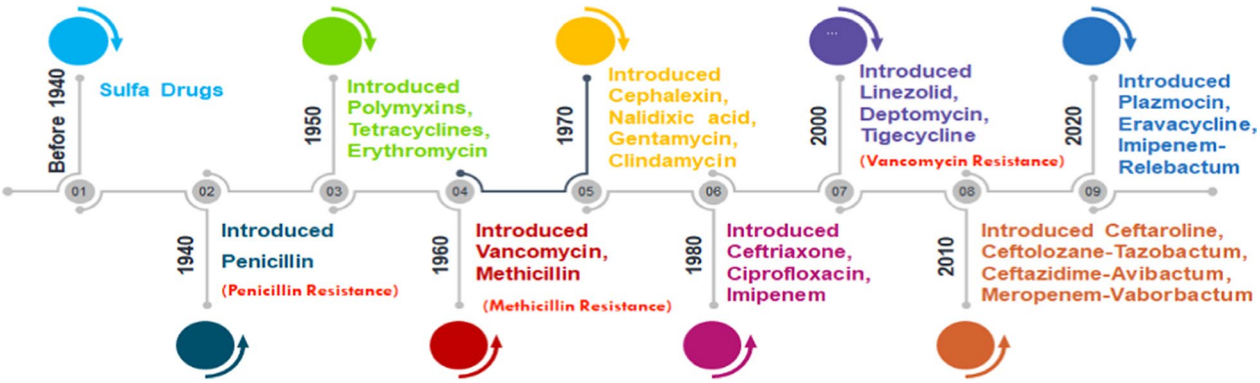


Fig. 1 Schematic representation of timeline of antimicrobial drug development and the subsequent emergence of resistance

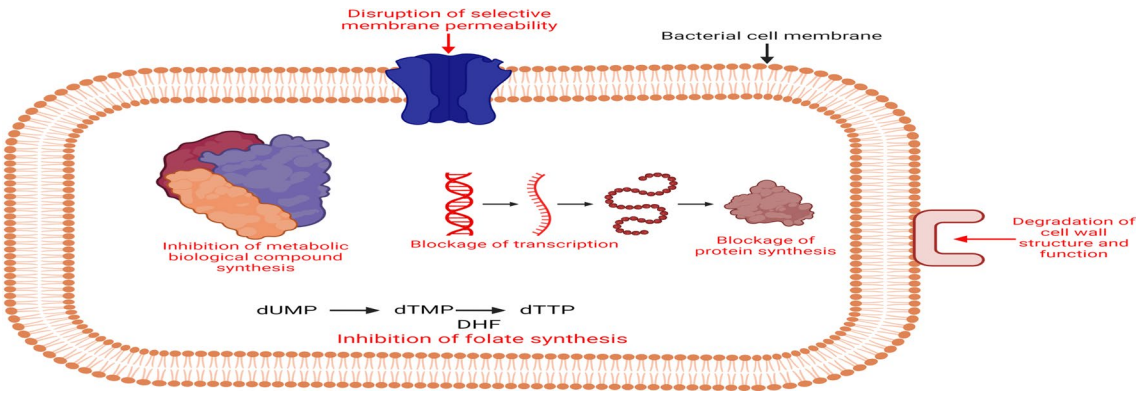


Fig. 2 Different targets of antimicrobials treatment

subunits of the bacterial ribosome to inhibit protein synthesis (Roy et al. 2022).

Inhibitors of 30S subunit

Aminoglycosides (AGs)

AGs are negatively-charged molecules that are charged positively and therefore attach to the outside of the cell's membrane. This allows for the formation of large pores, which allows antibiotics to permeate into the bacterium and kill the bacteria. Bacteria get into the cell via cell wall synthesis; antibiotics that inhibit this process, such as β-lactams and glycopeptides, make it easier for AGs to get into cells at low doses because of the effect of those antibiotics. The AGs' interaction with the 16S r-RNA of the 30S subunit is via a hydrogen bond, which is adjacent to the A site. The diseases cause delusions and random mutations in mRNA.

Tetracyclines

They are derived from the preserved orders of the 30S ribosomal subunit's 16S r-RNA to prevent t-RNA binding toward the A site (Maddiboyina et al. 2022a).

Inhibitors of 50S subunit

Chloramphenicol

This connects via the sealed orders of the peptidyl transferase opening of the 50S subunit's 23S r-RNA. Following that, this inhibits protein synthesis through averting t-RNA from binding toward the A site of the ribosome (Sanga et al. 2022).

Macrolides

This is accomplished by targeting the peptidyl transferase focus of the 50S ribosomal subunit's 23S r-RNA (Zimmermann et al. 2018). All of these macrolides, lincosamides, and streptogramins display the same MoA.

Oxazolidinones

They work by interacting with the 50S subunit's 23Sr RNA and by reducing the 70S inhibition and interaction via peptidyl-tRNA (Roger et al. 2018).

Inhibitors of DNA replication

Quinolones

This enzyme marks double-stranded DNA, familiarizes negative supercoils, and later seals the pilfered ends. Fluoroquinolone (FQ) inhibits this enzyme. This is important to keep excessive positive supercoiling in check after the strands have separated. Their strand-cutting/resealing abilities restrict anatomically similar FQs binding to A subunit. Prior to DNA replication, Topoisomerase IV's nick and split process attacks and breaks up the daughter DNA strands, which are Gram-positive bacteria's primary target. Compared to Gram-positive bacteria, this enzyme may be more effective because it is more similar. Because topoisomerase II is more closely related to FQ than DNA gyrase or topoisomerase IV, it is retained in mammalian cells (Bush et al. 2020).

Folic acid metabolism inhibitors

Sulfonamides and trimethoprim

At different stages of the same biosynthesis pathway, trimethoprim is combined with sulfonamides to create interaction and compact the mutation rate for resistance. Sulfonamides inhibit DHS because they are more similar to the enzyme than their likely substrate, p-aminobenzoic acid. Inhibition of the enzyme dihydrofolate reductase by trimethoprim, for example, occurs at an advanced stage in the production of folic acid (Ovung and Bhattacharyya 2021).

Mechanisms of antimicrobial resistance

Blocked penetration

Depending on the drug's nature, drugs can be delivered to a cell via porin diffusion, bilayer diffusion, or self-uptake. It has been shown that porins can traverse the outer membrane through themselves with the help of slight hydrophilic molecules (β-lactam and quinolones). If the number of porin passages is reduced, β-lactam antibiotics and FQ obsessed are less likely to enter the cell, resulting in later resistance to these antibiotic classes. Antibiotic resistance in *P. aeruginosa* has developed due to its inability to penetrate the bacterium's outer membrane as displayed in Fig. 3.

Efflux pumps

Cellular efflux mechanisms prevent the antimicrobials from reaching their intended target (Reygaert 2018). However, the cytoplasmic membrane still has these pumps, while the outer membrane has distinct porin proteins. In terms of antibiotics, efflux pumps can be quite specific. Because they are multidrug carriers capable of pumping multiple antibiotics such as macrolides, tetracyclines, and FQ, multidrug-resistant organisms are reduced in numbers (Maddiboyina et al. 2015).

Modification of target molecule

They need an imperative impact on antibiotic binding because they're often caused by an unintentional mutation of one of the bacteria's genes on the genome. By interfering with protein synthesis, alterations in the 30S or 50S subunits in the ribosome signpost drug resistance (Lin et al. 2018). Although the adaptations in Gram-positive bacteria favor resistance, Gram-negative bacteria continue to remain resistant, owed toward the production of β-lactamases (Maddiboyina et al. 2021a).

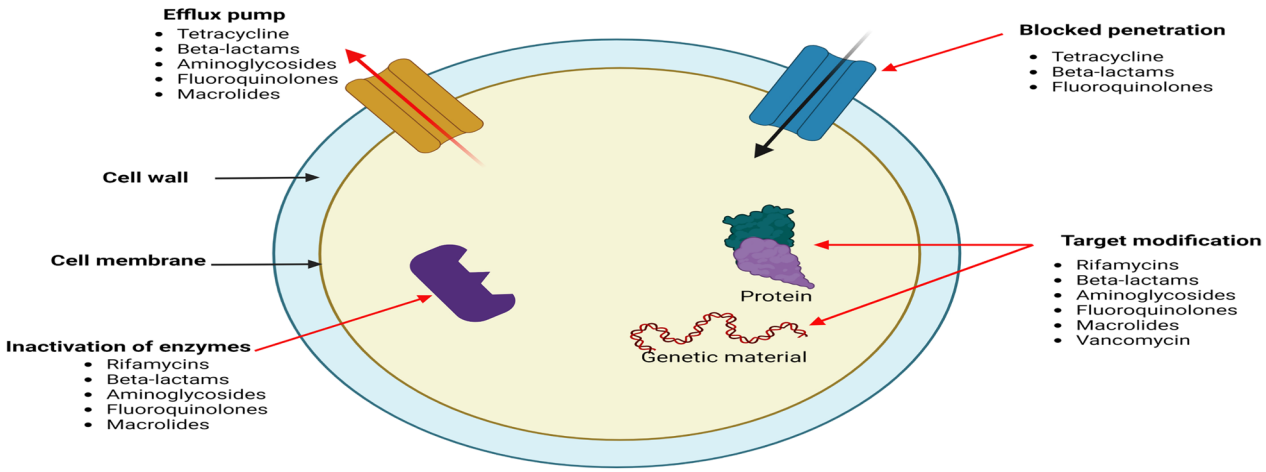


Fig. 3 Antimicrobial drug resistance mechanisms in microorganisms

Gram-positive bacteria can be inhibited by glycopeptides like Vancomycin and teicoplanin, which use D-alanyl-D-alanine residues to prevent the construction of cell walls. However, glycopeptides don't crosslink with D-alanylalanine, resulting in later resistance to them. Mutations in DNA gyrase and topoisomerase IV point to resistance to FQ. Due to mutations in genes gyr A and par C (DNA gyrase and topoisomerase IV), there is a replication standstill (Li et al. 2022). Tetracycline resistance is revealed by ribosomal protection contraption. There are several RNA polymerase mutations responsible for rifampicin resistance.

Inactivation of enzymes

Antibiotics are deactivated by three major enzymes: Chloramphenicol acetyltransferases (AACs), β-lactamases, and aminoglycoside-modifying enzymes.

Beta-lactamases

β-lactamases hydrolyze almost entire β-lactams, such as penicillins, cephalosporins, monobactams, and carbapenems, with an obligate ester and an amide bond.

Aminoglycoside-modifying enzymes (AGEs): AMEs offer broad-spectrum resistance to AGs and FQs as well as the ability to minimize molecular similarity and binding to the 30S ribosomal subunit (Lee et al. 2018).

Chloramphenicol-acetyl-transferases

The enzyme chloramphenicol transacetylase acetylates chloramphenicol hydroxyl groups. Even with adaptations, it remains still inept at connecting with a ribosomal 50S subunit in a proper way (Ghafoori et al. 2021).

MRSA antibiotic resistance and antibiotic action mechanisms

MRSA has remained a foremost global healthcare issue for years (Samia et al. 2022; Maddiboyina et al. 2021b). Vancomycin has remained the medication of choice in treating MRSA infection conditions. In clinical management, *S. aureus* is a multidrug-resistant condition known as a potentially life-threatening superbug (Ahmad-Mansour et al. 2021; Maddiboyina et al. 2021c). The Centers for Disease Control and Prevention (CDC) estimates that more than 75,000 persons in the USA are infected with MRSA every year, with the vast majority of healthcare-associated settings occurring in the geriatric population. The 5-generation cephalosporins and a broad spectrum of antibiotics are beneficial in the management of bacterial infection and MRSA.

Usually, β-lactam antibiotics remain effective against action by *S. aureus*; however, other antibiotic agents are also prime for clinical management of staphylococcus infections. These β-lactam antibiotics can bind the intrinsic PBP2a enzyme, the penicillin-binding protein determined through the MecA gene resistance (Fergestad et al. 2020; Jones et al. 2010). In MRSA infection conditions, Staphylococci express the PCI β- lactamase enzyme adept at hydrolyzing the β-lactam ring, resulting in reduced antibiotic activity and the attainment of an encoding gene-modified penicillin-binding protein (PBP), also identified as PBP2a, as shown in Fig. 4. PBP2a is still innately resistant to β-lactam ring reticence (Fuda et al. 2005). PBP2a detritus plays a part in the growth of β-lactam antibiotics because it neutralizes the PBP enzymes, giving β-lactam antibiotics time to establish cell wall synthesis. It also allows the bacteria to flourish despite the presence of β-lactam inhibitors.

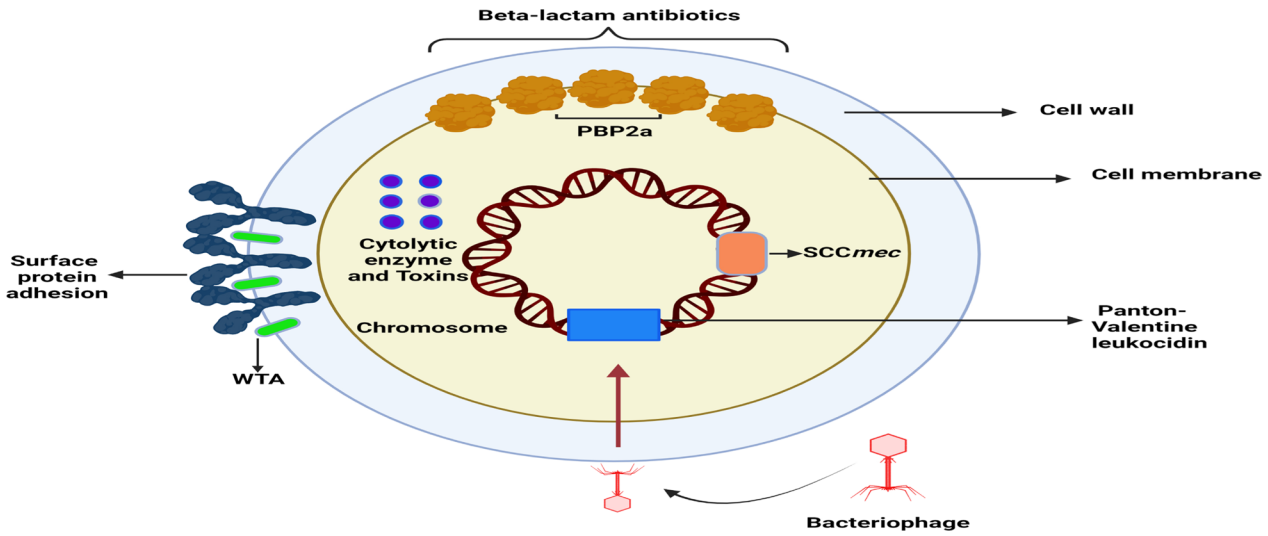


Fig. 4 Mechanism through which methicillin resistance in *S. aureus* evolves

MRSA bacterial infection responds quickly to a modern class of antibiotics and develops a resistance mechanism. MRSA is resistant to primarily endogenous compounds, such as the MecA gene, a novel penicillin-binding protein, and PBP2a. PBP2a endogenous compound, on the other hand, has a low affinity for methicillin conditions; it also allows bacterial cell wall advancement in the presence of antibiotics. Sometimes methicillin resistance improves phenotypes, and PBP2a enzyme production influences antibiotic enzymatic inactivation via inhibition of penicillinase output (Corey et al. 2010). This results in penicillin resistance and resistance toward further anti-staphylococcus agents aforementioned as amoxicillin, ampicillin, penicillin V, and aminoglycosides such as gentamicin and amikacin. We used linezolid, daptomycin, and ceftaroline antibiotics as alternative clinical management therapy in severe MRSA infections such as bacteremia, spinal discitis, and MRSA pneumonia (File et al. 2010).

Various advancements in the treatment strategies for MRSA

Liposomes

Self-assembling lipid bilayers, or liposomes, can deliver large amounts of antimicrobial drugs to the interior of bacteria by fusion with bacterial cell membranes. Rani et al. provided an overview of prospective liposome targeting strategies for MRSA in their study (Mat Rani et al. 2021). Phospholipid nanoparticles synthesized from penicillin G improved cellular uptake of the antibiotic compared to free antibiotic and killed intracellular MRSA in infected A549 lung epithelial cells (Zhang et al. 2019). Increased accumulation in thigh tissues infected with MRSA and decreased accumulation in the kidney were observed after administering folic acid-coated lipid NPs containing vancomycin (VAN) (Vanamala et al. 2021). These results show that this formulation can overcome the limitations of bacterial resistance and adverse side effects in kidneys caused by the free drug.

Solid lipid nanoparticles (SLNPs)

Lipid and polymeric components constitute SLNPs, which can significantly improve medicine administration and bioavailability. Vancomycin-loaded SLNPs with a mean size of 106.9 ± 1.4 nm and a zeta potential of -16.5 ± 0.95 mV inhibited the growth of MRSA biofilm for 5 days (Ibrahim et al. 2021). This was due to the addition of ascorbyl tocopherol succinate, an adjuvant that significantly increased drug release in an acidified environment associated with controls.

Micelle-like structures

Supramolecular hydrogels, supramolecular micelles, and cyclodextrin (CD) inclusion complexes are some of the most common CD-based controlled release approaches (Gadade and Pekamwar 2020). Amphiphilic copolymers of poly(ethylene glycol) and poly(-caprolactone) (PCL) connected with CD that has been capped with adamantane light-triggered and stimulus-responsive release of antibiotics and activation of phenylboronic acid-lactamase inhibitors killed MRSA biofilms by creating reactive oxygen species. β-Cyclodextrin-capped phenylboronic acid-tetraphenylethylene conjugates and are coupled with ampicillin (Chen et al. 2021).

Chitosan nanocarriers

Wounds that have bacterial biofilms on them take longer to heal and tend to remain open for longer than they should. The antibacterial activity against MRSA was greatly enhanced by a chitosan (CS) film created by Choi et al. that released nitric oxide (NO) (Choi et al. 2020). It was three times as effective as the control film and CS film at inhibiting the growth of biofilms, and it reduced bacterial viability by a factor of 10. Wounds infected with MRSA biofilm treated in vivo with NO-releasing CS film showed increased epithelialization, collagen deposition, decreased wound size, and accelerated biofilm dispersal relative to both untreated and CS film-treated MRSA biofilm-infected wounds (Fahimirad et al. 2021). Researchers Vijayakumar et al. observed that CS-Ag nanocomposites had a potent bactericidal impact on MRSA in vitro and in vivo, and that CS-AgNPs with diameters between 10 and 50 nm prevented biofilm formation by MRSA and *P. aeruginosa* at 100 g/ml (Vijayakumar et al. 2020). A nanoscale combination of curcumin and CS placed on a hexagonal ZnO with average particle sizes of 48 nm outperformed amoxicillin against MRSA and *E. coli* (Karthikeyan et al. 2020).

Alginate-loaded nanoparticles

Composite nanofibers (38–105 nm) of alginate and oregano essential oil (EO) with 2–3 wt% of oregano EO showed improved antibacterial activity against *Listeria monocytogenes*, *K. pneumoniae*, and *Salmonella enterica* and significantly improved antibacterial activity against MRSA compared to EO without alginate (Lu et al. 2021). The antibiotics amikacin and naproxen were encased in a hydrogel created by grafting phenylboronic acid onto the side chain of an alginate polymer. The hydrogel's ability to react to changes in pH and reactive oxygen species (ROS) allowed it to inhibit bacterial growth and inflammation (Hu et al. 2020).

Cellulose nanoparticles

Natural polymer cellulose is both non-toxic and biodegradable. It is functionalizable, and functionalized derivatives are effective in treating wounds (Momin et al. 2021). Norrrahim et al. discovered that dialdehyde nanocrystalline cellulose with increasing amounts of aldehyde groups had potent antibacterial action against Gram-positive pathogens in vitro and reduced the number of MRSA germs on the skin of infected mice models (Norrrahim et al. 2021). Bacterial cellulose/polyvinyl alcohol hydrogels loaded with ampicillin killed bacteria more effectively than *S. aureus* and *E. coli* because they released 30% of the antibiotic's entire dose over 120 h (Tamahkar 2021).

Hyaluronic acid-based nanocarriers

Hyaluronic acid (HA) polymersomes were used to encapsulate vancomycin (Placha and Jampilek 2021). These polymersomes were spherical in shape, self-assembled, and had a negative zeta potential. These polymersomes were 72 times more effective in combating MRSA than free medication, had a larger effect on the bacterium's membrane, and released their contents steadily over the course of three days. Self-assembling conjugated oligo(thiophene ethynylene) (OTE)-covalently modified HA (OTE-HA) NPs have been discovered that they prevent the premature release of the bactericide (Yuan et al. 2021).

Silver nanoparticles

Particle sizes of the colloidal Ag produced from the Corymbia maculata aqueous leaf extract were 40 mm and 11–16 nm, respectively, when the colloidal Ag was prepared, and 11–16 nm when the dried Ag was utilized. The MIC and MBEC values against plantonic *P. aeruginosa* chronic rhinosinusitis clinical isolates ranged from 0.2 to 3, indicating improved antibacterial action (Feizi et al. 2021). Similarly, green AgNPs NPs (3–25 nm) derived from extracts of Pyrenacantha grandiflora tuber demonstrated significant antibacterial action against methicillin-resistant *Staphylococcus aureus* and other MDR bacteria (Murei et al. 2021). To kill *P. aeruginosa, L. monocytogenes*, and MRSA, researchers found that using a 50-mW 400-nm femtosecond laser in conjunction with AgNPs was more effective than using AgNPs alone (El-Gendy et al. 2021). Gentamicin-filled gentamicin-virus-shaped mesoporous SiO2-coated Ag nanocubes are more effective than other antibiotics at killing Escherichia coli and methicillin-resistant *Staphylococcus aureus* (Wang et al. 2021). For optimal MRSA killing, hybrids of graphene quantum dots (GRQDs) and silver nanoparticles (AgNPs) were shown to be most effective (Zhong et al. 2020).

MRSA transmission and colonization; the role of animals and the environment in resistance transmission

Despite being found in most people and animals, *S. aureus* is still one of the utmost customary bacterial infections (Chang et al. 2003). Around 30% of the population is infected with methicillin-resistant *S. aureus*, and these bacteria increase healthcare expenditures while making people sick. This case's transmission involves nasal epithelial cells and components related to the synthesis of proteins and the cell's surfaces. MRSA

colonization is still heavily reliant on nasal carriage, with up to 80% of the human population's transmissions occurring because of this. Persistent carriers of MRSA remain at greater risk of infection than surgical patients, intensive care unit patients, and patients on dialysis (Wong et al. 2023). It is nose-picking patients, however, who recurrently increase the colonized *S. aureus* infection from one individual to another through direct hand contact, as shown in the study's results. As well humans, MRSA colonization occurs in animals such as dogs, cats, birds, and cows (Crespo-Piazuelo and Lawlor 2021). Direct contact with infected animals or humans has stood reported as a means of spreading MRSA infection. A high rate of MRSA illness in humans has also been found in recent prevalence studies due to close contact with animals (Garoy et al. 2019).

Antibiotics resistance as other languages of microbial communication

The clinician has extensively identified that microbial communication-specific bacteria, viruses, and fungi remain distressingly resistant to the antibiotics employed to tackle them. In 2015, a World Health Organization survey in 12 nations emphasized people's unawareness of the languages of antibiotic resistance (Michaelidou et al. 2020). Antibiotic drug resistance is caused by the fact that half of the world's population has never heard of the languages of antibiotics. A small amount of clear and explicit phrasing words helps protect the overall effort, while antibiotic resistance remains intense in language. Antibiotic resistance is interconnected with the bacterial cell of identical or diverse species through the language used by these bacterial cells. This language is intended to obstruct novel treatments by reducing antibiotic resistance in distinct bacteria and preventing the correspondence of specific resistance amid diverse bacteria. A person's healing time is shortened when bacterial contagions are considered. A more widespread indication will be more helpful in achieving this goal if the inhibitors can mark a particle specific to a particular bacterial group. So, putrescine and further polyamines seem to remain likely targets for specific inhibitors assumed distinct environments and distinct recently recognized functions in the correspondence of antibiotic resistance. Polymyxin B resistance was reduced in *B. cenocepacia* when ornithine decarboxylase was pharmacologically inhibited (ornithine is converted into putrescine). There is a greater chance that similar inhibitors, such as putrescine, and further small particles corresponding to antibiotic resistance, will remain reliable for human use as antibiotic auxiliaries due to this study. Investigating the molecular source of antibiotic resistance chemical correspondence will be necessary to explain the intricate chemical indications and their part in the extent of antibiotic resistance amid bacteria prominent toward the failure of antimicrobial remedy (Jhawat et al. 2020).

Current MRSA clinical executive recommendations

Despite its ubiquity, treating MRSA is still a severe problem for the global public (Guo et al. 2020). Diagnoses were made after a thorough examination of symptoms, and of those diagnosed, the cases of those suffering from the most severe infections were treated first; MRSA treatment has evolved. The *Enterococcus, Staph aureus, Klebsiella pneumoniae,* and *acinetobacter* species in question are ESKAPE pathogens, meaning they are complicated to treat. There are various methods for diagnosing MRSA, including clinical symptoms, tissue samples (or) nasal secretions expending the microbial culturing practice, and antibiotic resistance of bacterial infections. MRSA skin infections and nasal colonization conditions were responsible for 60% of the population's diagnosis. There are two types of antibiotics available to treat MRSA (Choo and Chambers 2016).

An older antibiotic agent for MRSA treatment

Some outpatients continue to receive oral antibiotics for monotherapy, such as clindamycin, trimethoprim-sulfamethoxazole, doxycycline, and aminocycline, despite these antibiotics' ineffectiveness. For systemic MRSA, the majority of clinicians commonly prescribed vancomycin antibiotics. The Infectious Disease Society of America also endorses Vancomycin (2 μg/ml) as the first medication to cure MRSA. In numerous global surveillance studies, vancomycin dosing (to a maximum of 15 μg per millilitre per day) was also beneficial in treating MRSA (Hindy et al. 2022).

Newer antibiotics for the treatment of MRSA

S. aureus is still a Gram-positive bacterium notorious for its unusually severe pathogenic constitution (Yuan et al. 2021). MRSA remains liable for various ailments, including skin infections and the development of multiple organ diseases; it remains the second prominent source of illness and death worldwide, and healthcare professionals face complex challenges in managing MRSA infections in multiple drug-resistant conditions, which can be fatal (Lee et al. 2018). As a result, there is still a significant need to advance novel and expedient drug management therapy for MRSA infection. A new promising antibacterial therapeutic management system was introduced through the FDA to treat MRSA infection conditions, and the therapy management system is also used in different microbial resistance conditions (Maddiboyina et al. 2022b).

Table 1 FDA-approved anti-infective drugs versus MRSA treatment management

Antibiotic agent	MOA	Therapeutic dose	Advantages	Adverse effects
Vancomycin	Slow bacterial action (dose cell wall inhibition independent of concentration)	500 mg q6h or 1000 mg q12h per oral/1 µg/ml in IV	Inexpensive and 50 years of clinically prescribed drug	Nephrotoxicity, red man syndrome
Linezolid	Protein synthesis inhibition; Bacteriostatic (23 s RNA at 50S ribosomal subset)	IV or PO 600 mg q12h	100% bioavailable oral preparation, upright drug permeation into the lung and beside VRE	Thrombocytopenia and anemia lactic acidosis, serotonin syndrome occurs long term uses
Daptomycin Bactericidal	Bactericidal; membrane depolarization (ca++ dependent)	IV: cSSSI:4 mg/kg (total body weight) OD; *S. aureus* bacteremia, 8 to 10 mg/kg in endocarditis indications	Swiftly bactericidal active for MRSA blood flow infection and endocarditis	Cpk elevation, myopathy, neuropathy diseases, eosinophilic pneumonia
Tigecycline	Bacteriostatic, which means the inhibition of protein synthesis happens at the 30S ribosomal subunit	IV: 50 mg q12h	Active against VRE	GI complications such as nausea and vomiting
Telavancin	Cell Wall Inhibition and Membrane Depolarization; (dose concentration-dependent); bactericidal	IV: 10 mg/kg (total body weight) OD	Swiftly bactericidal beside MRSA, active alongside Strains of MRSA which are no longer susceptible to Vancomycin, linezolid, and daptomycin	Mild QT prolongation, nephrotoxicity, GI side effects
Ceftaroline	Cell Wall Inhibition (with Bactericidal Effects): Time-Dependent	IV:600 mg q12h	Bactericidal agents, moderately expensive	Diarrhea, nausea and skin rash

The FDA has permitted five anti-infective agents for treating MRSA-related multidrug resistance: linezolid, daptomycin, tigecycline, telavancin, and ceftaroline. Linezolid, one of the new antibiotic agents available in intravenous formulation, is still available in oral and intravenous preparations. This antibiotic could be used as a first-line treatment for beta-hemolytic streptococci and MRSA. However, it has been clinically prescribed to be selective in treating acute MRSA, and these antibiotic agents are used as a secondary choice based on the patient's financial budget (Wunderink et al. 2012). Table 1 summarizes the therapeutic management outcomes of these agents when compared to vancomycin. Many new antibiotic agents have remained familiarized in the market to tackle MRSA, and all of them represent promising options for improving the antibiotic mechanism of action.

Nanotechnology in MRSA theranostic applications

Nanoparticle-based antibiotic formulation paradigms have unavoidably adopted a prevalent extent of exploration in clinical biomedical disciplines. Clinical research has primarily focused on nanochemistry to control infectious diseases (or) multiple drug resistance bacterial infection conditions and cancer therapy. The primary application of nanoscience and nanotechnology drug delivery systems is controlling contagious diseases (Tong et al. 2015). One of the major clinical problems is *S. aureus* associated with MRSA infection, so the determining prerequisite for novel approach therapy for efficiently allocating through MRSA infection is emphasized. They are working on developing a nanoparticle antibiotic drug delivery system. The unique size and properties of nanobiotic drugs improve antibacterial activity, increase the antibacterial drug agonist mechanism of action, and decrease systemic toxicity (Mosselhy et al. 2021). The nanoparticles also increase the bioavailability of the drug in the serum.

MRSA detection using nanomaterial's

This includes photodynamic therapy, light-oxygen therapies, and reactive oxygen species (ROS). Nanomaterials significantly increase accuracy and precision in diagnostic colorimetric assays and PCR markers. Advances in nanomaterials have facilitated the development of biosensor devices characterized by excellent optical, electrochemical, and mechanical properties. Several electrochemical, fluorescence, and mechanical sensors are still developed to detect MRSA biomarkers. Numerous advanced practices must remain engaged in identifying and exemplifying exceptional in a clinical drawing, MRSA (Gill et al. 2019).

Excellent results are achieved using colorimetric nanomaterial-based MRSA sensors and outcomes without the need for complex equipment. Despite rapid advancements in nanomaterial-based biosensor mechanisms, no suitable MRSA sensor has been found since overlooked and has yet to be addressed. One issue is that several advanced biosensors require intensifying genes or DNA before they can be recognized. Nanomaterial-based biosensors should retain several essential characteristics, including time, selectivity, and reduced sensitivity.

Nanomaterial-based MRSA treatment therapy

New therapeutic management causes irreversible damage to bacteria's bimolecular synthesis processes, such as DNA, mRNA, and lipid synthesis. The US Food and Drug Administration also approved nanoparticulate system therapy for MRSA infection. A novel nanoparticle biodegradable polymer-based drug delivery system can improve permeation, 100% bioavailability, good controlled release, and improved clinical outcomes index. This nanotechnology treatment also has lower therapeutic toxicity levels when compared to crude drugs. Only a few drugs are available in a nanoform, such as Vancomycin, gold therapy, amoxicillin, and chloramphenicol. The drugs have specific targeting properties and a completely bioavailable compound. Most hospital clinical management of MRSA life-threatening conditions employs nanotechnology formulation therapies (Singh et al. 2021).

Despite the commitment of several years, work has centered on improving the treatment of MRSA with a focus on increased activity and efficacy. Nano-technology, which the FDA permitted to treat MRSA and *S. aureus* infection in 1994, has now been implemented in other therapeutic applications. The increased effects result from their size, structure, and protective inner environment, and the nanosubstance improves drug action in cell sites, organs, and tissues.

The nanoparticles also improve serum solubility, which prolongs the drug's therapeutic effects and is a sustained, controlled-release dosage form, capsule-based delivery formulation. This means that nanoparticles can remain employed in the therapy of intracellular microbial ailments. In 1994, vancomycin and teicoplanin antibiotics were reported in a nanoparticle formulation to treat MRSA infections (Onyeji et al. 1994). The medication remains multilamellar liposome, which has improved beside MRSA bacteria positioned sites contained by human macrophages, whereas liposomes enclosing vancomycin (200 and 800 g/ml concentration) drug reduced MRSA survival.

Esmaeili et al. used poly-D,L-lactic-co-glycolic acid (PLGA) nanoparticles to deliver rifampicin. Rifampicin remains employed to cure mycobacterium ailments and

Table 2 A new antibacterial agent is tested in clinical trials to treat MRSA and other drug-resistant bacterial infections

Name of drug	Mechanism of action	Therapeutic effects	Adverse Effects	Clinical phase	Route	Investigators
Dalbavancin	PG biosynthesis inhibition	Staphylococcus skin infection, surgical site infection	Rash, tachycardia and nephrotoxicity	Phase III	IV	Pfizer (Parasippany, NJ, USA)
Mupirocin and chlorhexidine	Inhibition of bacteria t- RNA synthesis	MRSA skin infection	Rash, itching/swelling, severe dizziness	Phase III	Body wash, intranasal	Los Angeles biomedical research institute (USA)
Iclaprim	Inhibition of dihydrofolate reductase	Skin and skin structure infection	Nausea, diarrhea, and headache	Phase III (development terminated)		Acino holding (Switzerland)
Tedizolid	Bacterial protein synthesis inhibition by targeting the 50 s ribosomal	Skin and skin structure infection	Nausea, headache, diarrhea, vomiting, and dizziness	Phase III	Oral, IV	Trius Therapeutics (USA)
Delafloxacin	Bacterial gyrase inhibition	Acute Skin and skin structure infection	Diarrhea, nausea, vomiting, and headache	Phase II	Oral, IV	Rib –X pharmaceutical (ICN)
Tomopenem	Bacterial cell wall synthesis inhibition	MRSA infection and gram-positive bacterial infections	Dizziness, dyspepsia, and flatulence	Phase II	IV	Daiichi sankyo (Japan)
Cethromycin	Bacterial protein synthesis inhibition by targeting the 50 s ribosomal	MRSA infection	Diarrhea, nausea, dysgeusia and headache	Phase III	Oral	Abbott/advance life sciences (USA)
LBM-415	Bacterial protein synthesis inhibition by targeting the PDF substance	CA- respiratory tract infection	No adverse effects were observed upon administration of a single 3 g dose	Phase I (development terminated)	Oral	Novartis
Lacilex	Enhance the membrane permeability	Diabetic skin infection include MRSA infection	Rash, itching/swelling	Phase II	Topical	Dipexium pharmaceuticals (USA)
OligoG	Immunomodulation activity	Lung infection in MRSA	Nausea, headache	Phase I	Inhalation	Algi pharma (Norway)
Oritavancin	PG biosynthesis inhibition	Wound infection with MRSA, Systemic inflammation	Diarrhea, nausea, vomiting, and headache	Phase III	IV	Pfizer (USA)
Omadacycline	Inhibition of bacterial protein synthesis	Active against MRSA and extended-spectrum β-lactamase-producing positive bacteria	Rash, itching, hoarseness, trouble breathing, trouble swallowing	Phase III	Oral, IV	Paratek Pharmaceuticals, Inc. Boston, MA, USA

leprosy, and fusidic acid remains to medicate MRSA ailments (Esmaeili et al. 2007). In vitro antibacterial activity, an identical explore by Duran et al. in 2008 revealed that such rifampicin assimilated into rifampicin nanoparticles (20–60 m) formulation maintains anti-MRSA bioactivity while decreasing cytotoxicity of rifampicin(Durán et al. 2008).

Clinical aspects and recent advancements of MRSA

MRSA infection has increased medication resistance over the last few decades, and only a few antimicrobial drugs are available to treat MRSA infections. Anti-staphylococcus drugs should be used more widely in the therapy of MRSA ailments. Several clinical trials have continued to develop new-generation antibiotics to combat MSRA.

The researchers are continuing to develop a currently available antibiotics arsenal to be effective drug resistance bacterial infections, in here drug discovery processes considered the four essential points, mainly (i) reformulation of infections diseased remedy, (ii) curtailment of the curative supervisions, (iii) reduced the drug side effects and increased the drug effectiveness parameters, and (iv) minimizing the practice of drugs. The ultimate goal of a clinical trial is to find (or develop) a new antibacterial agent to treat MRSA infection. Table 2 contains the most recent clinical trials on anti-staphylococcal drugs and the infection against bacterial growth inhibitory activities drugs against gram-positive bacteria, including MRSA infections (Kurosu et al. 2013).

The cell wall glycopolymer wall teichoic acid (WTA) has been identified as a dominant surface antigen, and immunoproteomics studies have assisted in elucidating the most immunogenic and protective *S. aureus* antigens. In addition to vaccinations, bacteriophages or lytic proteins produced from bacteriophages may be employed for novel preventive measures, such as nasal MRSA decontamination in a time of rising mupirocin resistance (Ahmed 2022). Bacterial two-component systems play a central role in the adaptative response of bacteria to their ever-changing environment. The maleimide-based compounds are evaluated against a model histidine kinase, HK853, in vitro and in silico. The most potent leads were then assessed for their ability to decrease the pathogenicity and virulence of MRSA (Espinasse et al. 2023). Aaron et al. developed the purine-derived signaling molecules c-di-AMP and (p)ppGpp control mecA/PBP2a-mediated β-lactam resistance in MRSA raise the possibility that purine availability can control antibiotic susceptibility(Nolan et al. 2023). Fan et al. found that uracil could synergize with aminoglycosides to kill MRSA (USA300) by 400-fold. Reprogramming metabolomics displayed uracil reprogrammed bacterial metabolism, especially enhanced the tricarboxylic acid (TCA) cycle to elevate NADH production and proton motive force, thereby promoting the uptake of antibiotics. Furthermore, uracil increased cellular respiration and ATP production, resulting the generation of reactive oxygen species (ROS). Thus, the combined activity of uracil and antibiotics induced bacterial death. Inhibition of the TCA cycle or ROS production could attenuate bactericidal efficiency. Moreover, uracil exhibited bactericidal activity in cooperation with aminoglycosides against other pathogenic bacteria (Fan et al. 2023).

Conclusions

MRSA remnants among multidrug-resistant entities unquestionably necessitate increased efforts for discovering and advancing novel antibiotics and advanced anticipatory practices. MRSA is still considered a foremost risk to public health because of its extreme adaptability and ability to progress resistance. It has designed its public home and established an innovative environmental niche in animals. As a result, it remains imperative for prevailing MRSA exploration to describe aspects outlining the virulence of the intact type of contagious MRSA strains. Substitute therapeutic procedures for MRSA are still developing, but there is no timetable or guarantee that they will be effective in a clinical trial. Clinicians and researchers are constantly reminded that preventing MRSA infections is preferable to treating them. A temporary state of well-being may be provided by the current therapeutic array and the total number of medications in advance, but this assumption could lead to the demise of the healthcare organization. MRSA will be a critical area of investigation and advancement for the foreseeable future to stay ahead of the problem.

Auxiliary research is still required to constantly revise MRSA's ability to source contagion and antibiotic resistance conduits and maintain the progress of innovative drugs other than MRSA contagion. The advancement of innovative medicines has given doctors more options for dealing with MRSA infections, providing superior fortification for human health. However, the efficacy and safety of medications necessitate further clinical investigation.

Abbreviations

MRSA	Methicillin-resistant *Staphylococcus aureus*
AGs	Aminoglycosides
FQ	Fluoroquinolone
AGEs	Aminoglycoside-modifying enzymes
CDC	Centers for Disease Control and Prevention
PBP	Penicillin-binding protein
VAN	Vancomycin
SLNPs	Solid lipid nanoparticles
CD	Cyclodextrin
PCL	Poly(-caprolactone)
CS	Chitosan
NO	Nitric oxide
ROS	Reactive oxygen species

HA	Hyaluronic acid
OTE	Oligo(thiophene ethynylene)
AgNPs	Silver nanoparticles
PLGA	Poly-lactic-co-glycolic acid

Acknowledgements
The authors thank Freyr Solutions for providing the opportunity and resources; Nirmala College of Pharmacy for support. The figures were created with the support of BioRender.com.

Author contributions
BM involved in conceptualization, data curation, supervision, writing–original draft and review & editing; HR took part in supervision, writing—review & editing; R involved in data curation, conceptualization, supervision; SC involved in project administration, validation; SK took part in investigation, supervision; RN involved in data curation, supervision, writing—original draft; BN took part in supervision, writing—review & editing.

Funding
No funds, grants, or other support was received.

Availability of data and materials
Data available on request from the authors.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Received: 16 March 2023 Accepted: 20 June 2023
Published online: 30 June 2023

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