Review

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Novel and emerging therapeutics for antimicrobial resistance: A brief review

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SUMMARY A pandemic known as anti-microbial resistance (AMR) poses a challenge to contemporary medicine. To stop AMR's rise and quick worldwide spread, urgent multisectoral intervention is needed. This review will provide insight on new and developing treatment approaches for AMR. Future therapy options may be made possible by the development of novel drugs that make use of developments in "omics" technology, artificial intelligence, and machine learning. Vaccines, immunoconjugates, antimicrobial peptides, monoclonal antibodies, and nanoparticles may also be intriguing options for treating AMR in the future. Combination therapy may potentially prove to be a successful strategy for combating AMR. To lessen the impact of AMR, ideas like drug repurposing, antibiotic stewardship, and the one health approach may be helpful.

Keywords anti-microbial resistance, mechanisms, drugs, therapeutics, FDA approved, monoclonal antibodies, anti-microbial peptides, AMR vaccines

1. Introduction

Antibiotics, widely used to treat diseases in both humans and animals, are hailed as the greatest medical discovery of the 20th century. Global antibiotic usage increased by 46% between 2000 and 2018, according to a new analysis that provided longitudinal estimates for human antibiotic consumption across 204 nations (*1*). However, rising levels of antimicrobial resistance (AMR) globally pose a danger to the beneficial health effects of antibiotics. AMR has become one of the main public health issues of the twenty-first century, posing a threat to the efficient prevention and treatment of a growing variety of microbial illnesses (*2*). The relationship between spread of AMR and antibiotic use is well documented (*3*). Additionally, it has been predicted that AMR would be the primary cause of death worldwide by 2050 due to the declining effectiveness of existing antibiotics and the dearth of novel antibiotics available on the market (*4*). It is concerning to note that AMR caused 1.27 million fatalities globally in 2019 alone, more than HIV and malaria combined (*1*). In addition to its direct effects on human health, AMR is linked to a substantial worldwide financial burden because of rising hospitalization and medication-related healthcare expenses (*5*).

Recognizing the seriousness of the situation, the World Health Organization (WHO) drafted the Global Action Plan (GAP) on AMR, which was approved at the 68th World Health Assembly in May 2015 (*6,7*). This was followed by National action plans (NAPs) by many countries. The World Health Assembly recently called on member states to support and encourage basic, applied, and implementation research on infection prevention and control, diagnostic tools, vaccines, therapeutics, and antimicrobial stewardship through cooperation with academia, the private sector, and civil society in its 77th resolution on accelerating national and global responses to AMR (*8,9*). Furthermore, a key dimension to overcome AMR is ensuring that the world has a sustainable supply of antimicrobials. To this end, there is an urgent need to replace drugs rendered useless by the emergence of resistance by new therapeutics. This review will focus on new and emerging therapeutic options to combat AMR.

2. AMR mechanisms

Bacteria can develop acquired or innate antibiotic resistance (*10*). The intrinsic resistance characteristic, which is uniformly shared within a bacterial species, is unrelated to horizontal gene transfer and unaffected by prior antibiotic exposure (*11*). Intrinsic resistance might help bacteria survive an antibiotic through evolution (like changing their structure or components). Intrinsic resistance, for instance, might result from the natural activity of efflux pumps and decreased permeability

of the outer membrane, such as the lipopolysaccharide (LPS) in gram-negative bacteria (*11,12*). Acquisition of genetic material through horizontal gene transfer (HGT) including transformation, transposition, and conjugation or a new genetic mutation can lead to acquired resistance (*11,13*). AMR mechanisms include limiting uptake of a drug, modifying a drug target, inactivating a drug and active drug efflux (*11,14*). Figure 1 represents some AMR mechanisms and some novel and emerging options to tackle AMR.

Antibiotic uptake may be hampered by modifications in the permeability of the outer membrane or by the presence of porins, a subclass of transmembrane pore-forming outer membrane proteins (OMPs) (*11,14*). Drug uptake may be restricted by a reduction in the number of porins or mutations that alter the porin channel's selectivity (*11*). AMR, especially carbapenem resistance, is significantly influenced by outer-membrane remodeling, a key characteristic of many bacterial pathogens (*15*). Recently, the five-protein β-barrel assembly machine (BAM) complex, which is essential for the synthesis of outer membrane proteins in gram-negative bacteria, has become a viable target for drug development (*16,17*).

The antibiotic's low potency may result from changes to the drug target that prevent it from binding (*11,13*). Antimicrobial treatments may target several different parts of the bacterial cell, and the bacteria may alter many of these targets to make them resistant to the medications. β-lactam antibiotics target penicillin-binding proteins (PBPs), which are necessary for the bacterial cell wall to form (*18*). The quantity of drug binding to that target will be affected by an increase in PBPs with reduced drug binding ability or a decrease in PBPs with normal drug binding (*11*). Compared to sensitive strains, AMR strains frequently feature chimeric high molecular mass PBPs (HMM PBPs) (*19*). The analysis of 26,465 *S. pyogenes* genome sequences revealed that amino acid alterations in PBP1a, 1b, 2a, and 2x resulted in decreased susceptibility to β-lactams (*19,20*). The *vanA* gene cluster on the transposon *Tn1546*, which is commonly found on plasmids, can give vancomycin resistance by altering the structure of peptidoglycan precursors, which reduces vancomycin's binding capacity (*21*). A 44-bp deletion in the *vanHAX* promoter region that permits the production of *vanHAX* was linked to an enhanced *vanA* plasmid copy number in a study on vancomycin variable enterococci with resistant phenotype (*22*).

Drug inactivation leading to AMR can be achieved by actual degradation of the drug, or by transfer of a chemical group to the drug (*11*). Modified existing bacterial enzyme can interact with an antibiotic making it inactive towards bacteria (*14*). The common structural element of all β-lactam antibiotics, including penicillins, cephalosporins, carbapenems, and monobactams, is the amide bond in the β-lactam ring, which is hydrolyzed by

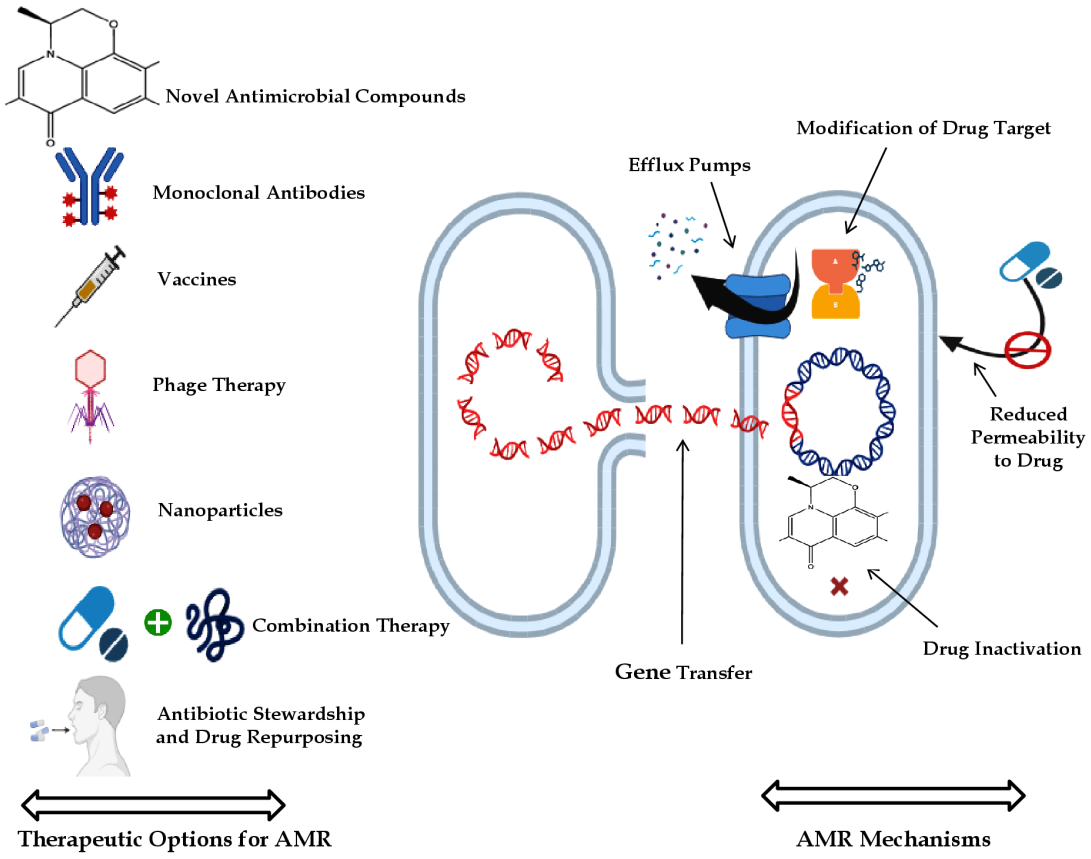

Figure 1. AMR mechanisms and some novel and emerging options to tackle AMR.

β-lactamases, a superfamily of hydrolyzing enzymes with over 2,000 members, rendering them ineffective (*23*). Aminoglycoside-modifying enzymes (AMEs) catalyze enzymatic modification of aminoglycoside antibiotics leading to their inactivation. AME-encoding genes were found in 48 out of 619 clinical isolates of *P. aeruginosa* in a recent study using bioinformatics analysis. The most prevalent of these genes were *ant(2')-Ia* and *aac(6')-Ib3*, which are linked to tobramcyin and gentamicin resistance (*24*). Macrolide phosphotransferases (MPHs) are enzymes that add a phosphate to the 2'-OH group of macrolides thereby modifying and inactivating them (*25*). Macrolides interact with 23S rRNA at the A2058 residue within the nascent peptide exit tunnel around the peptidyl transferase center to inhibit protein synthesis (*25*). The substitution of 23s rRNA in the A2058 or A2059 positions leads to macrolide resistance in both Enterobacteriaceae and gram-positive isolates alike (*26*).

Efflux pumps decrease the intracellular concentration of drugs and function at the frontline to protect bacteria against antimicrobials (*27*). Efflux transporters are mainly categorized five superfamilies: ATP-Binding Cassette (ABC) superfamily, Multidrug and Toxic Compound Extrusion (MATE) superfamily, Major Facilitator Superfamily (MFS), Resistance Nodulation and Cell Division (RND) superfamily, and Small Multidrug Resistance (SMR) superfamily (*27*). The tripartite complex MacAB-TolC efflux pump, an ABC-type transporter that has been extensively explored in gram-negative bacteria, actively extrudes macrolides and polypeptide virulence factors that are driven by the ATPase MacB (*27*). The efflux of cationic dyes, including the efflux of fluoroquinolone medications, is facilitated by the MATE efflux family, which uses the Na^+ gradient as its energy source (*27*). In gram-positive microorganism, MFS family is the largest characterized family of transporters with 12 or 14 transmembrane segments (*27*). MFS pumps like Lde and NorA in *Listeria monocytogenes* and NorA in *Staphylococcus aureus* extrude hydrophilic fluoroquinolones like norfloxacin and ciprofloxacin (*27*). In many gram negative bacteria, substrate efflux *via* substrate/H^+ antiport mechanism is catalyzed by RND efflux family members (*27*). Pumps like MexAB-OprM in *P. aeruginosa*, AcrAB-TolC in *E. coli*, OqxAB in *K. pneumoniae* and AdeABC in *A. baumannii* are some examples of RND superfamily pumps (*27*). Energized by the proton-motive force (H^+), SMR efflux family are hydrophobic, efflux mainly lipophilic cations having a narrow substrate range (*27*). The SMR superfamily member EmrE protein, which is found in *E. coli* and *P. aeruginosa*, detects and facilitates the extrusion of harmful poly-aromatic chemicals (*27*).

3. Novel and emerging therapeutics for AMR

In the light of above information, it is imperative to look for new therapeutics to combat AMR. Some emerging options include monoclonal antibodies (mAbs), antimicrobial peptides (AMPs), novel antibiotic compounds, phage therapy, vaccines, combination drug therapy and nanoparticles to name a few. Many mAbs against bacteria have entered clinical trial but only few have succeeded (*28,29*). Obiltoxaximab and raxibacumab against *Bacillus anthracis*, actoxumab and bezlotoxumab against *Clostridium difficile*, edobacumab and nebacumab against *Escherichia coli*, aurograb against *Staphylococcus aureus* are few important examples (*28,29*). Bezlotoxumab has recently obtained FDA approval for preventing recurrent *Clostridium difficile* infections, while obiltoxaximab and raxibacumab for the treatment of inhalational anthrax (*30,31*). Being distinct from conventional small-molecule antibiotics, mechanisms of action of mAbs is less prone to drug resistance. AMPs are peptide sequences linked to biological action that typically contain 10–60 amino acid residues and lack any particular consensus amino acid patterns (*32,33*). Dalbavancin, daptomycin, telavancin, telaprevir, bacitracin and polymyxins are some examples of AMP approved by FDA (*34*). Phage therapy, an alternative therapy to combat bacterial infections has also been extensively investigated (*35*). Phage therapy registered clinical trials seek to exploit the bacteriocidal activity of lytic phages. Furthermore, focus on the ability of phages to disrupt biofilms is also under consideration (*36*). List of some novel and emerging therapeutics to treat AMR is given in Table 1.

Zoliflodacin, a compound based on a new benzisoxazole scaffold containing the pyrimidinetrione spirocyclic pharmacophore is in phase III trial since 2019 for the treatment of multidrug-resistant *N. gonorrhoeae* (*37,38*). Ridinilazole, a bis-benzimidazoles class of synthetic antibiotic has been reported to have rapid bactericidal activity and is in phase II trial for effective clinical response in the eradication of *C. difficile* compared to vancomycin (*39*). Recently, a new potential combination therapy to combat AMR by targeting two key bacterial enzymes involved in resistance was published (*40*). Triple combination of meropenem (MEM), a novel metallo-β-lactamase (MBL) inhibitor (indole-2-carboxylate 58 (InC58), and a serine-β-lactamase (SBL) inhibitor (avibactam (AVI) showed a much wider spectrum of activity against different carbapenemase-producing bacteria, revealing a new strategy to combat β-lactamase-mediated AMR (*40*). Ceftolozane-tazobactam (C-T) and ceftazidime-avibactam (CAZ-AVI) are two novel antimicrobials that retain activity against resistant *Pseudomonas aeruginosa* (*41-43*).

Carbon-based nanoparticles (NPs) including carbon quantum dots (CDots), nanotubes and 2-D materials, including graphene have been proven to be effective with their bactericidal action against *Klebsiella oxytoca*, *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* (*44*). 2,2-(ethylenedioxy)bis(ethylamine)

Table 1. List of some novel AMPs, mAbs and antibiotics (approved/clinical trials) for AMR

Drug Name	Type	Phase	Bacterial Species/Clinical Target	Reference
Dalbavancin	AMP[†]	FDA Approved	Methicillin-resistant *Staphylococcus aureus*	*(47,48,49,51)*
Raxibacumab	mAb[*]	FDA Approved	*Bacillus anthracis*	*(51,52,53,54)*
Obiltoxaximab	mAb	FDA Approved	*Bacillus anthracis*	*(51,52,53)*
Bezlotoxumab	mAb	FDA Approved	*Clostridium difficile*	*(51,52,54)*
Polymyxins	AMP	FDA Approved	Drug resistant *Enterobacterales, Acinetobacter baumannii and Pseudomonas aeruginosa*	*(55)*
TNP-2092	Antibiotic	Phase 2	Bacterial skin infection	*(60)*
Edobacumab	mAb	Phase 3	*Escherichia coli*	*(52)*
Tefibazumab	mAb	Phase 2	*Staphylococcus aureus*	*(52)*
Aurograb	mAb	Phase 3	*Staphylococcus aureus*	*(52)*
Oritavancin	AMP	FDA Approved	Gram-positive bacteria	*(52, 56,57)*
Telavancin	AMP	FDA Approved	*Staphylococcus aureus* and other gram-positive bacteria	*(52, 58)*
Afabicin	Antibiotic	Phase 2	Bacterial skin infection	*(59,60)*
Benapenem	Antibiotic	Phase 2	Anti-Bacterial	*(60)*
Cefiderocol	Antibiotic	FDA Approved	Gram-negative bacteria	*(59,60)*
Zoliflodacin	Antibiotic	Phase 3	Gram-negative bacteria	*(59,60)*
Levonadifloxacin	Antibiotic	Phase 3	MRSA	*(60)*
Sulopenem	Antibiotic	Phase 3	Anti-Bacterial	*(60)*
Gepotidacin	Antibiotic	Phase 3	Gram-negative bacteria	*(59,60)*
Ceftobiprole	Antibiotic	Phase 3	MRSA	*(61)*
Imipenem	Antibiotic	FDA Approved	Anti-Bacterial	*(62)*
Pretomanid	Antibiotic	FDA Approved	Anti-Bacterial	*(62)*
Lefamulin	Antibiotic	FDA Approved	Anti-Bacterial	*(62)*
Cefilavancin	Antibiotic	Phase 3	Bacterial skin infections	*(62)*
LTX-109	AMP	Phase 2	MRSA	*(63)*
Surotomycin	AMP	Phase 3	*Clostridium difficile*	*(63)*
Murepavadin	AMP	Phase 3	*P. aeruginosa*	*(63)*
Opebacan	AMP	Phase 2	Meningococcal infections	*(63)*
Plazomicin	Antibiotic	FDA Approved	Enterobacteriaceae infections	*(62)*
Sarecycline	Antibiotic	FDA Approved	Anti-Bacterial	*(62)*
Eravacycline	Antibiotic	FDA Approved	Anti-Bacterial	*(62)*
XOMA-629	AMP	Phase 2	Endotoxins of gram-negative bacteria	*(63)*
Novarifyn	AMP	Phase 1	Bacterial infection	*(63)*
AMP PL-18	AMP	Phase 1	Bacterial vaginosis	*(63)*
Omiganan	AMP	Phase 3	Staphylococcus species	*(63)*
Salvecin	mAb	Phase 2	*Staphylococcus aureus*	*(52)*
MEDI4893	mAb	Phase 2	*Staphylococcus aureus*	*(52)*
MAB-T88	mAb	Phase 2	*Escherichia coli*	*(52)*
Brilacidin	AMP	Phase 2	Broad spectrum antibacterial therapy	*(63)*

[†]Anti-Microbial Peptide; [*]Monoclonal Antibody.

carbon quantum dots (EDA-CDots) were reported to be effective and treatment at 0.1 mg/mL for 1 h reduced 3.26 logs of viable cells (*44*). PEI_{600}-CDots and PEI_{1200}-CDots treatment at 0.1 mg/mL for 1 h reduced > 7 logs and 1.82 logs viable cells, respectively (*45*). Potential effectiveness of CuO NPs against biofilms has been recently demonstrated in many microorganism groups (*44*). Recently, TiO_2 NPs were reported to be effective against MRSA (*46*). After 12 hours of incubation, it was shown that the most effective dose was 2 mM TiO_2 nanoparticles, however the combination of erythromycin and 3 mM TiO_2 nanoparticles was more efficient and considerably reduced the MIC of erythromycin to 2–16 mg/L (*46*). List of some novel and emerging therapeutics to treat AMR is given in Table 1 and Table 2.

Combination therapy, the concurrent use of multiple antimicrobials in clinical practice has been successfully used to prevent resistance evolving during the treatment of diseases like tuberculosis and HIV (*64,65*). In a report on laboratory evolution of *E. coli*, three pairwise combinations of antibiotics that included amikacin, chloramphenicol and enoxacin significantly suppressed the resistance acquisition (*66*). Zheng *et al*. (2018) reported that vancomycin in combination with beta lactams: piperacillin-tazobactam, cefazolin, and meropenem effectively prevented the development of vancomycin intermediate *S. aureus* (*67*).

Four vaccine candidates in phase 3 clinical trials against *M. tuberculosis* were recently identified in a paper that offered insight into mapping vaccination options against pathogens prioritized owing to AMR. Phase 3 trials for VPM1002, GamTBvac, MTBVAC, and Immuvac are presently underway. Immuvac is a therapeutic vaccine that employs a heat-killed *Mycobacterium indicus pranii* and is undergoing a phase 3 trial in India; MTBVAC is a live attenuated *M. tuberculosis* candidate; and VPM1002 is a preventive recombinant BCG vaccine (*68*). ExPEC9V, a nine-

Table 2. List of some emerging vaccines, nanoparticles (NPs) and combination therapies for AMR

Drug Name	Type	Clinical Target	Reference
ZnONPs	Nanoparticles	Fungal feet infection	*(74)*
FeONPs	Nanoparticles	Anti-biofilm treatment	*(74)*
PLGANPs	Nanoparticles	*E. fecalis* infections	*(74)*
Tridecaptin B + rifamcipin	Combination Therapy	*A. baumannii*	*(75,63)*
Nisin + Colistin	Combination Therapy	*Pseudomonas biofilms*	*(76,63)*
Ranalexin + Endopeptidase lysostaphin	Combination Therapy	*S. aureus (MRSA)*	*(76,63)*
Lactoferricin + Ciprofloxacin+ Ceftazidime	Combination Therapy	*P. aeruginosa*	*(76,63)*
Gad-1+ Kanamycin+ Ciprofloxacin	Combination Therapy	*P. aeruginosa*	*(77,63)*
Ceftolozane + tazobactam	Combination Therapy	Bacterial infections	*(78)*
Ceftazidime + avibactam	Combination Therapy	Bacterial infection	*(78)*
Meropenem + vaborbactam	Combination Therapy	Bacterial infection	*(78)*
ETVAX/dmLT	Vaccine	Enterotoxigenic *E coli*	*(68)*
GlycoShig3	Vaccine	*S flexneri*	*(68)*
WRSS2/WRSS3	Vaccine	*Shigella sonnei*	*(68)*
iCVD1000	Vaccine	S *Typhi*	*(68)*
KlebV4	Vaccine	*K pneumoniae*	*(68)*
Bexsero	Vaccine	*N gonorrhoeae*	*(68)*
PF-06425090	Vaccine	*C difficile*	*(68)*
ExPEC9V	Vaccine	Extra-intestinal pathogenic *E coli*	*(68)*
H56:IC31	Vaccine	*M tuberculosis*	*(68)*
VPM1002	Vaccine	*M tuberculosis*	*(68)*
GamTBvac	Vaccine	*M tuberculosis*	*(68)*
MTBVAC	Vaccine	*M tuberculosis*	*(68)*
Immuvac	Vaccine	*M tuberculosis*	*(68)*
FmOC + Phenylalanine	Combination Therapy	*S.aureus and P. aeruginosa*	*(79,80)*
Fosfomycin + Colistin	Combination Therapy	*E.coli, K. pneumonieae*	*(79,81)*
NAC + Ciprofloxacin	Combination Therapy	*P.aeruginosa*	*(79,82)*
Light Stimuli Responsive Therapy	Combination Therapy	*E.coli, E.cloacae, S.aureus*	*(79,83)*

valent-O-polysaccharide conjugate vaccine is currently in a phase 3 clinical trial against extraintestinal pathogenic *E. coli* (*68*). PF-06425090 is a recombinant toxin vaccine targeting *C. difficile*, consisting of genetically and chemically detoxified TcdA and TcdB toxins (*68*). For *Klebsiella pneumoniae, a* tetravalent bioconjugated vaccine candidate, KlebV4, is being assessed with and without the AS03 adjuvant in a phase 1/2 trial (*68*). Besides these, next generation approach, CRISPR-Cas9 antimicrobials, nanoparticle based strategies, artificial intelligence (AI) approaches also offer as potential options to tackle AMR in future (*69-71*).

4. Conclusions

AMR's emergence poses a serious threat to global public health, requiring the creation of novel antibiotics and multifaceted approaches to effectively combat it. An attempt was made to educate researchers and physicians about new and developing treatments for AMR in this review article. While creating novel antimicrobials is a crucial part of treating AMR, other viable future solutions to address AMR include enhancing surveillance systems, repurposing current medications, antibiotic stewardship, and one health approach (*72*). Additionally, new synergistic drug interactions to combat AMR can be found with the aid of machine learning (ML) algorithms that are being used to predict and create innovative treatments (*73*). By using AI and ML, it is possible to take use of the potential to create new medicine combinations to control the growth of AMR. Because AMR affects people all around the world and crosses national borders, international cooperation is essential to combating its worldwide scope. Governments, international organizations, and stakeholders must encourage worldwide collaboration on AMR in order to share best practices, harmonize regulations, and coordinate efforts to successfully combat AMR.

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