Int.J.Curr.Microbiol.App.Sci (2025) *14*(09): 186-194

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 14 Number 9 (2025)**
Journal homepage: http://www.ijcmas.com

Review Article https://doi.org/10.20546/ijcmas.2025.1409.020

The Evolution of Antibiotic Resistance in Opportunistic Pathogens: Mechanisms, Surveillance, and Novel Approaches to Mitigation

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Keywords

AMR-Antimicrobial resistant, AFST-Antifungal susceptibility test

Article Info

Received:
02 July 2025
Accepted:
28 August 2025
Available Online:
10 September 2025

A B S T R A C T

Antibiotics remain the cornerstone of infection management in both humans and animals, targeting a wide spectrum of pathogenic microorganisms. However, the misuse and overuse of these agents have accelerated the emergence of antimicrobial resistance (AMR), posing a global public health threat. Opportunistic pathogens, which are normally harmless under healthy conditions, can become life-threatening when host immunity is compromised. Common opportunistic organisms include *Salmonella spp.*, *Shigella spp.*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, fungal pathogens such as *Candida albicans*, and protozoan parasites like *Cryptosporidium*. These pathogens exhibit resistance through multiple mechanisms, including genetic mutations, modification of target sites and enzymes, activation of efflux pumps, and acquisition of resistance genes via horizontal gene transfer. Such adaptive strategies significantly reduce the effectiveness of conventional antibiotics, complicating treatment and increasing morbidity and mortality rates. To address this growing challenge, novel therapeutic approaches are being explored. Promising alternatives include vaccines that prevent infection before onset, bacteriophage therapy that harnesses viruses to specifically target bacterial pathogens, nanoparticles with potent antimicrobial and biofilm-disrupting properties, and antimicrobial peptides that mimic innate host defense mechanisms. Together, these emerging strategies represent potential breakthroughs in combating AMR and restoring the efficacy of infection management. This review highlights the urgent need for innovative interventions, integrated surveillance, and responsible antibiotic stewardship. By combining conventional and novel approaches, the global community can work towards mitigating the threat of antibiotic resistance and ensuring sustainable therapeutic options for future generations.

Introduction

Opportunistic pathogens are pathogenic organisms that can cause serious infections in people with compromised immune systems but usually do not cause illness in healthy people. These pathogenic organisms advantage of weaknesses including immunosuppression, long-term illnesses, or gaps in the skin's or mucous membranes' protective layers. Patients with HIV/AIDS, cancer, organ transplant recipients, and those on long-term antibiotic or steroid therapy are especially susceptible to opportunistic infections. Reducing the impact of these diseases on public health requires an understanding of their mechanisms and preventative strategies (Mary Smith., 2025). A chemical substances or medication called an antibiotic is used to treat infections caused by microorganisms. Antibiotic-resistant microorganisms are those that exhibit resistance to the drugs used to treat bacterial infections. Antimicrobial resistance poses a serious threat to human, animal, and environmental health. Amr is one of the global problems of the twenty-first century that threatens the entire population of people and animals. Since there is presently no effective treatment, the CDC reports that most bacteria are developing antibiotic resistance over time, lengthening treatment durations and raising the chance of recovery. Methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-resistant *S. aureus*, Toxin-Hyperproducing *Clostridium difficile*, extended spectrum beta lactamase and carbapenemase-producing coliforms, *Mycobacterium tuberculosis* that is resistant to multiple drugs, and exclusive drug resistance are some common antibiotic-resistant pathogens. Antibiotic pathogens exhibit increased virulence and can spread throughout a hospital or community, which can have serious health consequences (Irfan A. Rather et al., 2017). Opportunistic pathogens are various bacteria, fungi, viruses, and parasites that initially do not harm healthy individuals but instead become aggressive and infect those with compromised immune systems. These infections often develop in hospital settings and often afflict patients with weakened immune systems due to medical treatments or underlying disorders. Candida species can produce systemic fungal infections, while *Pseudomonas aeruginosa* causes severe pneumonia. Immunocompromised patients are also affected by viral agents such as herpes simplex virus (HSV) and cytomegalovirus (CMV). People with weakened immune systems are more susceptible to opportunistic microbes, which can lead to severe and even lethal infections. Under the right conditions, normally harmless bacteria, fungi, viruses, and parasites can become harmful. Understanding risk factors, identifying infections early, and treating them quickly are critical to managing these diseases. The main study of this topic is to find out the mechanisms, evolution of the opportunistic functions.

Opportunistic Pathogens

Shigella

Shigella bacteria are gram-negative bacilli that can cause gastrointestinal infections, particularly shigellosis. It causes diarrhea, which is a sign of colitis and is characterized by painful, bloody, or mucus-filled stools. The colon is the primary organ affected by Shigella. The primary pathogen is marcrophages, which phagocytose through transcytosis via M cells. Bacteria use the type 3 secretion system (T3SC) to invade and kill colonic epithelial cells, injecting effector proteins that induce inflammation and bloody diarrhea. Shigella is resistant to first-line antibiotics like ampicillin and methoprim-sulfamethoxazole. Shigella sonnei is susceptible to carbapenems (Sophie lefevre et al., 2023). It resistant to ciprofloxcine, trimethoprim/sulfamrthoxazole, tetracycline, and third-generation cephalosporins. Shigella exhibits the highest level of resistance to ampicillin (82%), and trimethoprim/sulfamethoxazole (77%), according to (Ahmad Farajzadeh Sheikh et al. 2019).

Rhodococcus equi

Rhodococcus equi is a gram-positive coccobacillus that causes most infections in HIV patients. In addition to the primary lung infection it produces in immunocompetent and immunocompromised individuals, it also causes diseases such as bloodstream infections, diarrhea, meningitis, brain abscesses, and soft skin infections. It causes pneumoniae infections (brain abscesses) in AIDS patients. Resistance to amikacine and tobramycine is significantly prevalent in Rhodococcus. It exhibits resistance to macrolides and rifampin (Steeve Giguere et al., 2025).

Salmonella

Salmonella is a member of the Enterobacteriaceae family

of foodborne pathogens. It can live in mammals, amphibians, and reptiles and causes gastroenteritis in humans. When a healthy host consumes contaminated food or water, *Salmonella* gets transferred to them. Globally, salmonella has been having a major effect on both health and the economy. The World Health Organization (WHO) lists *salmonella* as one of the top four causes of diarrhea worldwide. Since *Salmonella* species are thought to be a natural microbiota in the gut or gallbladder, animals might help in the pathogen's direct or indirect transmission to humans. Poultry and poultry products are the main causes of Salmonella infections in humans. Improper treatment of sick organs, such as the stomach and liver, during carcass processing is the most frequent cause of meat contamination (Bibek Lamichhane et al., 2024). It demonstrates resistance to azithromycine, trimethoprim-sulfamethoxazole, ampicillin, and chloramphenicol. It exhibits the lowest rate of resistance to ciprofloxacin, gentamicine, and nalidixic acid. *Salmonella* that was isolated from instances of diarrhea shown resistance to three-generation cephalosporins (Weiweili et al., 2023).

Staphylococcus aureus

The opportunistic pathogen *Staphylococcus aureus* typically colonizes the human anterior nares. In addition, this bacteria is a major contributor to potentially fatal bloodstream infections like endocarditis and sepsis. Methicillin-resistant S. aureus (MR) is one of the most concerning types of *S. aureus* since it has developed an antibiotic resistance. S. aureus is usually harmless on healthy skin. It can, however, result in infections in some situations, such as when the bacteria come into contact with an open wound. The lower respiratory tract (11%), urinary tract (10%), skin/soft tissue/bone (27%), and catheters (46%), are the most frequent sites of bloodstream infections caused by *S. aureus*. There have been reports of vancomycin-resistant *S. aureus* (VRSA), heteroresistant *S. aureus* (hetero-VRSA), and vancomycin-intermediate S. aureus (VISA) (https://isid.org).Penicillin binding protein 2a (PBP2a), which provides resistance to beta-lactam antibiotics, is encoded by the mecA gene. *Staphylococcus aureus* is resistant to oxacillin, amoxicillin, and penicillin. The most resistant bacteria to beta lactamase drugs, including methicillin, amipicillin, and penicillin, are *Staphylococcus* (Olufemi emmanuel Akanbi et al., 2017).

Mycobacterium tuberculosis

Mycobacterium tuberculosis generally has a small, rod-like shape that ranges in length from 2 to 6 microns and width from 0.2 to 0.5 microns. It can be straight, although it usually looks a little bent. *Mycobacterium tuberculosis*, the germ that causes tuberculosis (TB), typically affects the lungs. People with lung TB spread the TB bacteria into the air when they cough, sneeze, or spit. Transmission of Tuberculosis: Tiny droplets containing the germs are released when a person with TB coughs, sneezes, talks, laughs, or sings. You can contract it if you inhale these germs. Compared to those without HIV, those living with HIV have a 19 (15–22) times higher risk of developing active TB illness. In 2018, 1.1 million children aged 0 to 14 contracted TB, and 230 000 children—including those with HIV-associated TB passed away from the illness. Patients with multiple drug resistant tuberculosis are resistant to at least isoniazid and rifampicin (Anuru Sen et al., 2020).

Candida albicans

C. albicans has two types of hyphae (lin-ear and sinusoidal), a pseudohyphae, chlamydospores, and several yeast-like morphologies (white, opaque, gray, and intestinal). Like hyphal cells, pseudohyphae produce mycelia following several rounds of cell division and stay linked following cytokinesis. Apart from its wide range of morphologies, Candida albicans may also develop in microcolonies, biofilms, and single-cell cultures. More than 80% of vaginal and oral yeast strains identified from asymptomatic humans are C. albicans, a commensal fungus that asymptomatically colonizes healthy people's skin, vagina, gastrointestinal tract, and mouth mucosa. The number of potentially lethal Candida infections has significantly increased. The primary pathogenic fungus that affects humans, Candida albicans, is distinguished by a complicated interaction between the immune system, bacterial microbiota, and host cells. The chance of having yeast infections is rising as more patients deal with predisposing factors like HIV infections, organ transplants, and cancer chemotherapy (Ignacio Uriel Macias-Paz et al., 2023).

Evolution and Mechanisms of Antibiotic Resistant

Horizontal gene transfer occurs when a mutation in an antibiotic-resistant gene spreads from one

microorganism to its offspring. An evolutionary toolbox of ready-made genes that may be transferred from one species to another and impart resistance to any antibiotic that could be employed to battle diseases in people and animals is provided by the resistome, a sizable collection of pre-existing resistance determinants discovered in the biosphere. Resistance genes will be transferred by conjugation transfer of plasmids, conjugative transposone, transduction by bacteriophages, and transformation of naked DNA extracted from the environment. Amplification of native resident genes, gene rearrangements, and point mutations are other mutation methods. The qnrA gene encoded by the plasmid was probably transferred from freshwater and marine *Shewanella* algae to different species of *Enterobacteriaceae*, highlighting the function of aquatic habitats as reservoirs of resistance. A recent example is the presence of the Tetx gene in Bacterioides and other obligatory anaerobes (Dan I. Andersoon et al., 2017). Bacteria may become resistant to particular antibiotics due to spontaneous genetic alterations. Antibiotic misuse and overuse lead to selective pressure, which only permits resistant microorganisms to endure and grow. This selective pressure is particularly severe in situations like hospitals where people are frequently exposed to antibiotics. Public health is significantly impacted when bacteria that are resistant to antibiotics are found in the human microbiome (Leo Pedras 2024). A structured collection of bacteria immersed in an extracellular matrix of DNA, polysaccharides, and proteins is called a biofilm which is found on surfaces of most bacteria and fungi. Bacterial biofilms are resistant to phagocytosis, disinfectants, antibiotics, and other components of the body's innate and adaptive inflammatory defense system. For instance, it is well known that biofilm formation is the cause of staphylococcal infections linked to leftover foreign items. Mucoid strains of P. aeruginosa that form biofilms are the source of chronic lung infections in individuals with cystic fibrosis (Marianne Frieri et al., 2017). Many elements, including surface conditions, chemical and physical growth agents, cellular architectures, and any other challenge, might affect the creation of biofilms.

Enzymatic change of the drug, alteration of the antibacterial target, and inhibition of drug penetration or accumulation are some common mechanisms for drug resistance. Bacteria can alter the targets the required for drug binding, preventing the medication from fully or partially attaching to the modified target. These alterations are often caused by spontaneous mutations in the gene or genes encoding the protein that the drug targets. For example, mutations affecting the quinolone resistance-determining region (QRDR) in DNA gyrase (topoisomerase II) and topoisomerase IV cause quinolone and fluoroquinolone resistance in both gram positive and gram negative bacteria (Wubetu Yihunie Belay et al., 2024).

Antibiotic efflux is one of the most common mechanisms of resistance among a wide range of pathogenic bacteria. Efflux pumps are transport proteins localized in the cytoplasmic membrane of bacteria that actively trans-locate the chemical across the membrane. ATP-binding cassette transporter family members MsrA and MsrC are efflux pumps that cause macrolide resistance in Gram-positive organisms. Efflux Pumps for Multiple Antibiotic and Toxin Extrusion (MATE) are found in both Gram-positive and Gram-negative bacteria contain members of the MATE family. Antibiotics that differ structurally, including ampicillin, ciprofloxacin, kanamycin, chloramphenicol, and norfloxacin, can be transported by MATE pumps. NorM was first described in *Vibrio parahemolyticus* and is the best researched pump from the family. It has been determined that other bacteria, such as *N. gonorrhoeae,* contain NorM homologues. MATE pumps use a Na+ gradient coupling to obtain the energy needed for transfer. Other bacteria, including YdhE from *E. coli*, HmrM from *Haemophilus influenzae*, PmpM from *P. aeruginosa*, CdeA from *Clostridium difficile*, and AbeM from *A. baumannii,* have been found to have 27 MATE efflux pumps (Maelle Duffey et al., 2024). The SMR family is a proton-driven group of efflux frameworks that exhibits a twofold topology, modest size, and simple structure. Members of this family are made up of transport proteins that exist in the cell's inner layer. The inward film of Gram-negative bacteria contains polypeptide chains of SMR efflux pumps, which are 100–140 amino acid accumulations long and have four transmembrane helices. The most frequently considered SMR efflux pumps include *Bacillus subtilis*'s EbrAM, *P. aeruginosa*'s EmrE, *S. marcescens*' SsmE, and E. coli's EmrE. The major facilitator superfamily (MFS) is the most significant membrane transporter family involved with drug efflux. Contributors of this family are found in all spheres of life, including microbes, archaea, and eukaryatoes (Fatema Saabir et al., 2022). Three metabolic pathways can lead to fluoroquinolone resistance, and these pathways may coexist in the same bacteria at the same time, resulting in an additive effect and frequently increasing resistance levels such as i)

overexpression of efflux pumps that expel the drug from the cell; (ii) mutations in the genes that encode the fluoroquinolone target site (DNA gyrase and topoisomerase IV); and (iii) a protein called Qnr that protects the fluoroquinolone target site.

Target site alterations are among the most prevalent ways that bacterial infections develop antibiotic resistance, and they impact practically every family of antimicrobial drugs. Point mutations in the genes encoding the target site, enzymatic modifications of the binding site (such as the addition of methyl groups) or replacement or bypass of the original target are some examples of these target changes.The development of rifampin resistance is an example of mutation modified resistance. A rifamycin called rifampin inhibits the DNA-dependent RNA polymerase, a complex enzyme with an α2ββ′σ subunit structure, preventing bacterial transcription (Jose M. munita et al., 2025). Antibiotic resistance can also be attributed to the alteration of enzymes in the target site. For instance, methylation of the ribosome by enzymes expressed by erm genes results in antibiotic resistance to macrolides.

Surveillances for Antibiotic Resistant

Antimicrobial resistance has been a worldwide response to the World Health Organization's global surveillance research on tuberculosis, which focused on particular strains. There are five types of surveillance: 1) active; 2) passive; 3) sentinel; 4) laboratory; and 5) syndromic. Active surveillance is typically used for rare diseases, during epidemics, and for diseases that are in the process of being eradicated. The most popular surveillance method is passive monitoring, which is also affordable, widely accepted, and simple to implement. The data recipients await information from the data providers regarding illnesses or incidents related to the diseases in issue. One method for monitoring illness patterns over time is sentinel surveillance. A few chosen hospitals are prepared to submit the data and report every single case of the particular illness. Nationally representative data was gathered in 2013 by the Antimicrobial Resistance Surveillance and Research Network (AMRSN), which was established by the Indian Council of Medical Research (ICMR) in New Delhi. This information includes the processes by which antibiotic resistance develops and spreads. Establishing a network of hospitals to monitor AST profiles for clinically significant bacteria and fungi is the primary objective of this ICMR-AMRSN. Additionally, this surveillance aims to better understand drug-resistant infections through genetic investigations that show how they spread (Kamini Walia et al., 2019). The ICMR performed comprehensive research on infections related to healthcare, including ventilator-associated pneumoniae (VAP), urinary tract infections (UTI), and bloodstream infections (BSI). This study was carried out at 39 hospitals around India between January and December of 2023. This surveillance's major goal is to get high-quality HAI data in order to assess the impact, control, and prevention of HAI-causing strains, as well as primary and secondary BSI and urine infections related to catheters and non-catheters (Antimicrobial Resistant Research and Surveillance network annual report 2023). Global Antimicrobial Resistant Surveillance (GLASS) was established by WHO since surveillance is a vital tool. GLASS-AMR offers a standardized method for gathering, interpreting, and distributing national AMR data in clinically acquired samples for a group of pathogens that commonly cause bacterial infections in humans. Antimicrobial consumption (AMC) can be measured and reported at the national, regional, and international levels using a common and standardized set of techniques offered by GLASS-AMC. Emerging resistance can be promptly detected, reported, risk assessed, and monitored with the help of GLASS-EAR, the emerging AMR reporting (EAR) module. The primary goal of GLASS-FUNGI is to monitor invasive fungal bloodstream infections caused by Candida species. The National AMR Surveillance Network (NARS-Net) was created in 2013 to assess the prevalence and patterns of AMR in the various areas of the nation. NARS-Net lab includes government medical colleges. AMR surveillance data of nine priority bacterial pathogens of public health importance *Staphylococcus aureus, Enterococcus species, Klebsiella species, Escherichia coli, Pseudomonas aeruginosa, Acinetobacter baumannii/Acinetobacter calcoaceticus complex, Salmonella enterica serotypes Typhi and Paratyphi, Shigella species, and Vibrio cholerae* must be submitted by the network's gradually increased number of affiliated labs. Among the fungal pathogens that need to be submitted to the NRL for AMR in fungal pathogens for AFST are Candida species from bloodstream infections (National center for diseases control). The National Center for Disease Control (NCDC) and the Ministry of Health and Family Welfare published Guidelines for building State Action Plans for Antimicrobial Resistance (SAP CAR) in July 2018. Three sizable AMR networks are in place in India to gather AMR data from tertiary hospital settings. The

National Programme on Containment of Anti-Microbial Resistance (AMR) is being implemented through the National Center for Disease Control (NCDC) network, which gathers data from a network of about 60 tertiary hospitals (Jasleen Kaur et al., 2022*)*. This network has developed a web-based tool for data collection.

Novel Approaches to Mitigation

Antimicrobial Peptides

An alternative to antibiotics for attacking dangerous bacteria is the use of antimicrobial peptides (AMP). Higher animals, plants, insects, and prokaryotes all have innate immune systems that depend on short, positively charged peptides called AMPs. Because of their broad-spectrum antibacterial, antiviral, and antifungal properties, AMP-based therapies are expected to eventually replace antibiotics. AMPs target the bilayer structures seen in both Gram-positive and Gram-negative bacteria's cell walls to produce their antimicrobial actions. Because AMPs have a positive charge, they can interact with both the negatively charged lipoteichoic acid and the negatively charged polysaccharides found in Gram-positive and Gram-negative bacterial cell membranes (Irene Berger et al., 2024). Colistin is effective against a variety of Gram-negative bacteria, such as *Acinetobacter species, Klebsiella pneumoniae, and Pseudomonas aeruginosa*. In 2003, the FDA authorized daptomycin, a cyclic AMP, to treat infections of the skin and soft tissues brought on by Gram-positive bacteria like Staphylococcus aureus. Cubicin, a daptomycin derivative, is allowed to treat Staphylococcus aureus-induced bloodstream infections as well as infections of the skin and soft tissues. Vancomycin, the source of oritavancin, dalbavancin, and telavancin, has been approved by the FDA as an oral solution in 1983.

Phage Therapy

Phage therapy has been used to treat bacterial diseases for nearly a century. It involves using bacterial viruses, or phages. Traditionally, phage therapy uses naturally existing phages to lyse and infect bacteria at the infection site (Derek M Lin et al., 2017). Bacteriophages can display three distinct life cycles after entering their target bacterial cells: the lytic cycle, the lysogenic cycle, and chronic infection. Lytic phages are most often used to investigate the therapeutic effect of phages. The three families of the Caudovirales order—Myoviridae, Podoviridae, and Siphoviridae—are home to 96% of the lytic phages that have been characterized.

Vaccine

Vaccine helps to reduces Antibiotic resistant both directly and indirectly. Antimicrobial use is predicted to decrease by 1·9 billion DDD yearly and up to 135 000 AMR-related causes of death could be prevented by vaccines in late-stage clinical research. Among the late-stage vaccinations under development, a vaccine against *Mycobacterium tuberculosis* given to teenagers is predicted to avert up to 71, 000 fatalities and 1.2 billion DDD per year. Antibiotic use is decreased and chances for the formation and spread of resistance are limited as a result of vaccines' ability to lower the incidence of both drug-sensitive and drug-resistant illnesses.

A comprehensive strategy for infection prevention, diagnosis, and treatment is needed to combat AMR. Along with infection prevention and control, water, sanitation, and hygiene, vaccines are an essential part of preventive (Timothy Jesudason et al., 2024). Vaccination is a key component of several methods aimed to lower antibiotic resistance while decreasing the direct health effects of AMR infections. Vaccination can lower healthcare expenses, including expensive hospital stays, avoid fatalities and complications, and stop the direct health effects of dangerous infectious diseases that can be prevented by vaccination.

Nanopraticals

Antibiotics are being replaced with nanoscale particles (NPs) in the fight against bacterial diseases. NPs are widely used in antibiotic delivery systems, medicinal materials to prevent infection and promote wound healing, antimicrobial coatings for implantable devices, and bacterial detection for diagnostic purposes. As antibacterial agents, nanoparticles are employed. The physical and chemical characteristics of antibacterial nanoparticles vary depending on their composition. Some use organic-based liposomes and capsules, known as nano-carriers, that are loaded with new RNAs or traditional antibiotics, while others use cation leaching from metal colloid surfaces as their primary antibacterial agent. Commonly used metal-based nanoparticles, such as copper (Cu), zinc (Zn), and silver (Ag), are among the most investigated and employed in the field of antimicrobial nanotechnology (Suresh K. Mondal et al., 2024).

CRISPR- Cas

CRISPR technology, which stands for clustered regularly interspaced short palindromic repeat, has shown promise in addressing this difficult situation. Originally inspired by the bacterial immune system, this ground-breaking genetic engineering technique provides remarkable accuracy in identifying and altering pathogen genomes.

Through targeted genetic alterations, CRISPR offers a fresh approach to restricting and diminishing antibiotic resistance in bacteria, despite the fact that traditional antibiotic development has slowed significantly. By selectively inactivating or activating particular genes, CRISPR may interfere with the mechanisms by which bacteria develop resistance to antibiotics. Short repeating DNA sequences (CRISPR) that are separated by spacer regions corresponding to viral or plasmid DNA sequences are known as CRISPR-Cas systems.

The three main stages of these systems' functioning are interference, expression, and adaptability. The Cas1, Cas2, and Cas4 proteins help bacteria integrate a 30-base pair DNA fragment from foreign DNA into the CRISPR locus during the adaptation phase. The Protospacer recognizes the new spacer. Motif Adjacent (PAM). During the expression phase, DNA is converted into pre-crRNA, which uses palindromic repeats to produce a hairpin shape. To create mature crRNA, the Cas6 protein cleaves the 5′ end. A complex formed by the proteins crRNA and Cas recognizes and cleaves the invasive DNA during the interference phase, preventing further infection (Mohamed Mustaf Ahmed et al., 2024).

Author Contributions

S. Aruljyothy: Investigation, formal analysis, writing—original draft. M. Prakash: Validation, methodology, writing—reviewing. K. Arivazhagan:—Formal analysis, writing—review and editing. R. Sabarish: Resources, investigation writing—reviewing.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Conflict of Interest The authors declare no competing interests.

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How to cite this article:

Aruljyothy,S., M. Prakash, K. Arivazhagan, S. Saranya, SelvaSuresh and Sabarish, R. 2025. The Evolution of Antibiotic Resistance in Opportunistic Pathogens: Mechanisms, Surveillance, and Novel Approaches to Mitigation. *Int.J.Curr.Microbiol.App.Sci.* 14(09): 186-194. **doi:** https://doi.org/10.20546/ijcmas.2025.1409.020