ORIGINAL RESEARCH PAPER

Clinical Microbiology

MECHANISMS AND CLINICAL IMPACT OF ANTIMICROBIAL RESISTANCE IN INFECTIVE ENDOCARDITIS

KEY WORDS: Infective Endocarditis, Antimicrobial Resistance, Mechanisms, Antibiotics

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ABSTRACT

Infective endocarditis (IE) remains a life threatening disease despite advances in therapeutic and diagnostic modalities. Antimicrobial resistance (AMR) has been a major challenge in the treatment of IE with consequences on treatment success and patient outcomes. The review encompasses the microbiologic aetiology of IE with focus on resistance mechanisms of key pathogens like Staphylococcus aureus, Streptococcus species, and Enterococcus species. It encompasses genetic and biochemical determinants like production of beta-lactamase, efflux pumps, and biofilm production that confer resistance and implications for empirical and targeted therapy. Clinical repercussions of AMR in IE like augmented morbidity, extended hospital stay, and elevated mortality are also mentioned. Containment strategies like antimicrobial stewardship, optimization of therapy, and discovery of new agents are also discussed. Clear insight into these mechanisms is needed for the improvement of treatment protocols and patient outcomes in the era of rising resistance.

INTRODUCTION:

Infective endocarditis (IE) remains a potentially life-threatening condition defined by endocardial infection of the heart, most commonly of the heart valves (1). IE continues to be challenging in its complex pathogenesis, heterogeneity of clinical presentation, and associated high morbidity and mortality rates, despite improvement in diagnostics and therapeutics (2). Among the most crucial problems over the last decade is the rise and spread of antimicrobial resistance (AMR) among the etiologic pathogens of IE, which has significantly made treatment and prognosis in affected patients very challenging (3).

Staphylococcus aureus, Streptococcus species, Enterococci, and Gram-negative bacteria continue to be the leading pathogens, while methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococci (VRE) are now more frequent (4). Resistance developed in these organisms by multiple mechanisms like beta-lactamase production, biofilm production, efflux pumps, and genetic mutations. (3, 4).

This paper has been written with the objective of investigating the molecular mechanisms underlying antimicrobial resistance in IE and evaluating the clinical significance of such resistance patterns. Through analysing current trends, treatment hurdles, and emerging therapy, we hope to stress the need for the integration of antimicrobial stewardship, revised treatment algorithms, and novel research to address the escalating drug-resistant threat of infective endocarditis.

Review-

COMMON RESISTANT PATHOGENS

The most common organisms that are resistant to the usual antibiotics include MRSA (methicillin-resistant *Staphylococcus aureus*), VRE (vancomycin-resistant *Enterococcus faecalis/faecium*), *Pseudomonas aeruginosa* (MDR/XDR), *Haemophilus species, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* (HACEK Group), Coagulase-negative staphylococci (CoNS), *Corynebacterium* spp. (resistant strains), and fungal pathogens (Candida spp., Aspergillus).

MRSA is widely known to be resistant to -lactams such as penicillins and cephalosporins and is a prominent cause of prosthetic valve endocarditis. It is acquired notably from healthcare and community settings (5). VRE, particularly *E. faecium,* is apparent in nosocomial IE and immunocompromised patients. These strains exhibit resistance to agents such as aminoglycosides and -lactams. MDR Pseudomonas is notoriously common in IV drug abusers, prosthetic valve IE, and those with prolonged hospital stays or catheter use (6).

HACEK organisms, although usually susceptible to ceftriaxone, may occasionally produce -lactamases, leading to resistance to penicillin. CoNS, especially S.*epidermidis*, are often resistant to methicillin and are a frequent cause of prosthetic valve endocarditis (7). Corynebacterium and fungal pathogens are rare causes of prosthetic valve IE, commonly seen in immunocompromised individuals. In culture-negative cases, zoonotic agents such as *Coxiella burnetii*, *Bartonella,* and *Tropheryma whipplei* are considered as potential etiological agents (6).

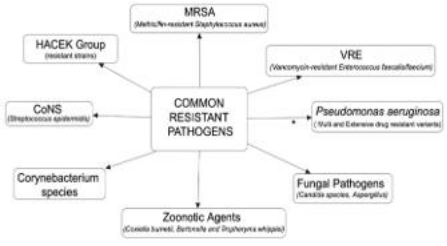
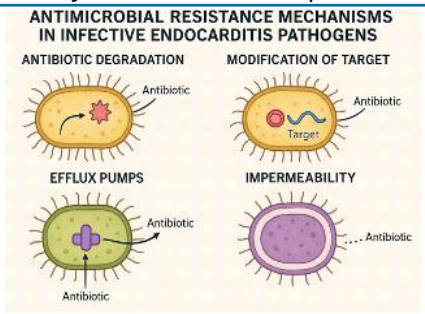


Figure 1: Representation of the most common resistant pathogens

MECHANISMS OF RESISTANCE

Antimicrobial resistance (AMR) of infective endocarditis is a significant problem for both diagnosis and treatment (3). The most frequent offending bacteria, Staphylococcus aureus, Streptococcus species, Enterococcus species, and Gram-negative bacteria, have evolved multiple strategies to counteract antibiotic activity (4). Such resistance mechanisms can be intrinsic, conferred by mutation, or through mobile genetic elements, and are usually further potentiated by biofilm deposits on heart valves and prosthetic devices (3, 4).

Figure 2: Mechanisms of antimicrobial resistance in pathogens causing infective endocarditis



1. Staphylococcus aureus

Methicillin-Resistant Staphylococcus aureus (MRSA) is one of the most commonly encountered drug-resistant pathogens in infective endocarditis (IE), especially healthcare-associated and prosthetic valve IE (8).

Resistance Mechanisms:

a) The mecA gene expresses a modified penicillin-binding protein (PBP2a) with low -lactam binding affinity, making methicillin and other -lactams incapable of acting.

b) Biofilm growth on prosthetic valves and native valves shelters the bacteria from host defences and antibiotic penetration.

c) Efflux pumps are responsible for resistance to macrolides and fluoroquinolones.

d) Enzymatic inactivation, as in -lactamase production, hydrolyses penicillin (9).

2. Streptococcus species

Viridans group streptococci are a typical perpetrator of subacute IE, especially in patients with previous valvular heart disease. Although normally susceptible to penicillins, resistance is on the rise (10).

Resistance Mechanisms:

a) Altered penicillin-binding proteins (PBPs) with decreased affinity for -lactams.

b) Tolerance, where bacteria remain alive after antibiotic exposure but are not killed, particularly to -lactams and vancomycin.

c) Horizontal gene transfer is responsible for the dissemination of resistance genes among oral and bloodstream streptococci (11).

3. Enterococcus species

Enterococcus faecalis and Enterococcus faecium are recognised more and more as causes of IE, particularly in elderly or immunocompromised patients. These bacteria are intrinsically resistant to numerous antibiotics and able to acquire high-level resistance (12).

Resistance Mechanisms:

a) Vancomycin resistance (VRE) is mediated by vanA or vanB genes, which modify the D-Ala-D-Ala target to D-Ala-D-Lac, decreasing vancomycin binding.

b) High-level aminoglycoside resistance (HLAR) is encoded by aminoglycoside-modifying enzymes (AMEs), like acetyltransferases and phosphotransferases.

c) Biofilm formation increases persistence and resistance on valvular tissue and on prostheses.

d) Efflux pumps and stress-response mechanisms resist environmental and therapeutic stresses (4, 13).

4. Gram-negative Organisms (HACEK & Non-HACEK)

Although less frequent, Gram-negative species like Haemophilus, the HACEK group, and non-HACEK Gram-negatives like Pseudomonas aeruginosa can produce IE, especially in intravenous drug abusers and prosthetic valve patients (14).

Resistance Mechanisms:

a) Extended-spectrum -lactamases (ESBLs) hydrolyse a broad range of -lactams, such as penicillins and cephalosporins.

b) Carbapenems, particularly in non-HACEK species like Klebsiella pneumoniae or Pseudomonas spp., provide resistance to carbapenems.

c) Efflux pumps and porin mutations reduce intracellular drug levels.

d) Biofilm production, particularly in Pseudomonas, introduces an additional mechanism of resistance and chronicity (3, 4).

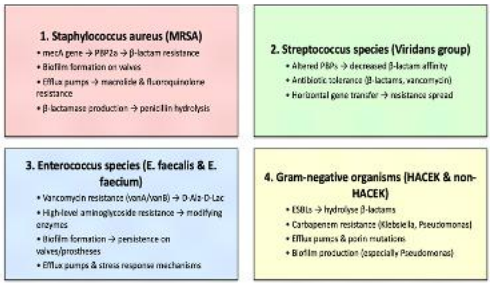


Figure 3: Mechanism of resistance in the most common species causing infective endocarditis

IMPLICATIONS FOR TREATMENT

Antibiotic strategies

The primary goal of antibiotic treatment is to eliminate the infection, including the sterilisation of vegetation; however, the unique characteristics of infected vegetation may pose a number of difficulties (15). A study from JAMA Internal Medicine demonstrated that adherence to appropriate antibiotic protocols and a multidisciplinary approach significantly reduced the 1-year mortality rates from 18.5% to 8.2% (16). The treatment of IE by a multidisciplinary medical-surgical team following a standardised protocol was associated with a notable reduction in mortality rates (16).

The American Heart Association advises a regimen of vancomycin and rifampin for at least six weeks, with gentamicin administered during the first two weeks, particularly for prosthetic valve endocarditis caused by *Staphylococcus aureus*. In cases where coagulase-negative staphylococci (CoNS) exhibit resistance to gentamicin, alternative aminoglycosides or fluoroquinolones may be considered based on susceptibility. The combination of ampicillin and ceftriaxone has shown superior efficacy and reduced nephrotoxicity for *Enterococcus faecalis* IE compared to conventional regimens involving aminoglycosides (17).

The Partial Oral Treatment of Endocarditis (POET) trial proposed switching clinically stable patients with infective endocarditis from intravenous to oral antibiotics (18). They were found to be non-inferior in efficacy and also reduced adverse events like prolonged hospital stays, increased costs, and nosocomial IE. After the first two weeks of treatment, Outpatient Parenteral Antibiotic Therapy (OPAT) can facilitate certain patients to be discharged from the hospital early (19). However, OPAT is contraindicated in patients with heart failure, complicated infections, high risk of embolism, neurological sequelae, or renal insufficiency (19).

Surgical Intervention

Surgical intervention, particularly early surgery, has been linked to improved long-term survival, especially in patients without significant comorbidities (14). There are three main indications for cardiac surgery: heart failure, uncontrolled infection, and preventing septic embolisation. A study conducted by Heiro et al. in a Finnish teaching hospital found that heart failure within 3 months of admission for the index episode of IE was a major predictor of poor long-term outcomes. Patients who underwent surgery for IE during their initial hospitalisation had much better outcomes than those who did not (20). The overall survival rate for 1-year survivors was 66% at 10 years, 51% at 15 years, and 45% at 20 years (20).

Infective endocarditis may cause complications that can only be treated with cardiac surgery. In these circumstances, surgical therapy has a survival advantage of up to 20% (21). Risk stratification models, like the Society of Thoracic Surgeons Endocarditis Score, can help with patient counselling and decision-making by predicting the risks of morbidity and mortality in IE patients following valve surgery (22).

Thromboembolic risks and antithrombotic management
Anticoagulation in IE patients is controversial, particularly in mechanical valve IE (23). For patients with mechanical valve IE who have had a CNS embolic event for at least two weeks, the American Heart Association advises discontinuation of all forms of anticoagulation. Aspirin or other antiplatelet drugs should not be started as supplementary therapy for IE; instead, long-term antiplatelet therapy should be continued at the onset of IE without any bleeding problems. Although most emboli occur during the first two to four weeks of antimicrobial therapy, they can occur prior to diagnosis, during therapy, or after therapy is completed (24).

RECENT DEVELOPMENTS IN THE MANAGEMENT OF DRUG RESISTANT INFECTIVE ENDOCARDITIS

Newer Antibiotics
Daptomycin: A lipopeptide antibiotic active against MRSA and VRE. Frequently utilised in combination with other drugs for synergy, particularly in prosthetic valve endocarditis (25).

Ceftaroline: A fifth-generation cephalosporin with MRSA activity. Due to its binding to PBP2a, it is active, whereas vancomycin is not (26).

Linezolid: Active against resistant Gram-positive organisms such as MRSA and VRE. Long-term use, however, can result in haematologic toxicity and neuropathy (27).

Dalbavancin & Oritavancin:
Long-acting lipoglycopeptides under investigation for IE. Their long half-life could decrease hospital stay and increase adherence (28).

Combination Therapy Strategies
Dual -lactam therapy (e.g., ampicillin + ceftriaxone) has been promising for the treatment of Enterococcus faecalis endocarditis, decreasing the use of aminoglycosides and their nephrotoxicity (26).

Daptomycin + -lactam combinations have been found to increase daptomycin's bactericidal activity against resistant *S. aureus* by augmenting membrane permeability (27).

Targeting Biofilms
Rifampin-containing regimens are occasionally employed for prosthetic valve endocarditis because of their biofilm penetration. Resistance, however, rapidly develops when employed as monotherapy (28,29).

Investigation of anti-biofilm drugs, including quorum-sensing inhibitors and extracellular polymeric substance-degrading enzymes, continues.

Bacteriophage Therapy (Experimental)
Bacteriophages (bacteriolytic viruses) are being explored as adjuncts to antibiotics, especially in multidrug-resistant *S. aureus* and *Pseudomonas sp.* causing IE. Early series and trials indicate possible benefit, particularly in refractory cases to standard therapy (30,31).

Advances in Surgery
Early surgery is commonly indicated for resistant cases with extensive valvular destruction, abscess, or embolic potential. Enhanced intraoperative diagnosis and bioprosthesis material decrease postoperative risk of infection (31).

Stewardship & Precision Medicine
Rapid molecular testing (e.g., PCR, next-generation sequencing) accelerates detection of resistance genes, which inform personalised treatment. Antimicrobial stewardship programmes facilitate the optimisation of antibiotic use, minimising unnecessary exposure and resistance development delay (32).

ANTIMICROBIAL STEWARDSHIP

Antimicrobial Stewardship (AMS) refers to the optimal selection, dose, and duration of antimicrobial treatment resulting in the best therapeutic outcome with minimal side effects for patients and low impact on eventual resistance (33). Implementing antimicrobial stewardship programmes has improved adherence to standard care practices. For instance, Brock et al. demonstrated that after introducing an antimicrobial stewardship protocol for *Staphylococcus aureus* bloodstream infections, there was a significant increase in follow-up blood cultures, infectious disease consultations, transoesophageal echocardiography usage, and appropriate antibiotic adjustments. These interventions collectively enhanced the management of IE cases (34).

The growing antibiotic resistance is predicted to result in higher mortality rates if alternatives are not discovered soon, according to Budea et al., who found that the resistance pattern between Gram-positive and Gram-negative bacteria was not significantly different (6).

AMS in paediatric IE
In a paediatric cardiac intensive care unit, a multidisciplinary antimicrobial stewardship programme sought to reduce the needless usage of broad-spectrum antibiotics (35). Interventions included provider education, alternate antibiotic use, overall mortality, sepsis-related mortality, and modifications to the electronic medical records (35). Over the course of 24 months, the program significantly and sustainably reduced the usage of vancomycin and meropenem without increasing mortality or the use of other broad-spectrum antibiotics (35).

Long term suppressive therapy
In cases where surgical intervention is not feasible, long-term suppressive antimicrobial therapy (SAT) is employed. Beaumont et al. determined that SAT was primarily prescribed to patients with cardiac devices who were unable to undergo surgery despite clinical indications. However, there were instances of breakthrough IE episodes, indicating the need for careful patient selection and monitoring during SAT (36).

Guidelines adherence and gaps
Despite the fact that most of the global experts in IE management participated in and co-signed the guidelines, a study by Tissot et al. found that they do not adhere to international consensus guidelines on the particular topic of antibiotic use. (37). Three of four clinical practice guidelines agree that the benefits of preventing infective endocarditis exceed the risks of antibiotic resistance (38). Despite the fact that the guidelines were changed more than 15 years ago, there is still a lack of adherence to current guidelines. The question of whether or not to recommend prophylactic antibiotics in specific patient groups is still up for argument and is largely reliant on expert consensus opinion due to a lack of high-quality evidence, conflicting results from observational studies, and a lack of randomised clinical trials (39).

RESEARCH AND FUTURE DIRECTIONS

Antimicrobial resistance represents an increasing threat to successful management of infective endocarditis, especially with the use of pathogens like *Staphylococcus aureus, Enterococcus spp*., and viridans group Streptococci. Recent research has been focused on clarifying mechanisms of

resistance, particularly those related to biofilm formation and horizontal gene transfer, and on combining genomic methodologies for identification of pathogens and resistance genes.

Developments in near-patient diagnosis, such asmetage nomic sequencing and CRISPR-based technologies, are facilitating earlier and more accurate detection of resistant organisms. Concurrent therapeutic research is looking into new antimicrobials, bacteriophage treatment, and biofilm-disrupting compounds. Personalised medicine strategies, such as pharmacogenomics and therapeutic drug monitoring, are increasing in prominence to maximise treatment effectiveness.Preventive measures, such as antibiotic stewardship, vaccine production, and optimisation of prophylaxis guidelines, are necessary to prevent the emergence of resistance. Intraoperative technologies and antimicrobial-coated implantable devices are adjunctive options for refractory cases. Last, worldwide surveillance networks and multinational research networks are needed to track AMR trends and provide data for policy decisions.

CONCLUSION

Despite advancements in diagnostics and treatment, infective endocarditis (IE) continues to be a major health threat owing to increased antimicrobial resistance. Antimicrobial resistance in IE-causing bacteria like MRSA, VRE, the HACEK group, CoNS, and Pseudomonas sp. originates from their intrinsic resistance mechanisms and their ability to create biofilms on heart valves and prosthetic devices.

Research shows that using empirical and standardised antibiotics in a multidisciplinary approach lowers mortality rates in patients with IE. The POET trial found oral antibiotics to be non-inferior to intravenous antibiotics, reducing hospital-acquired IE risk and hospital stay. Surgical procedures with appropriate patient selection have enhanced the survival rates of patients without major comorbidities.

New IE management includes antibiotics, such as daptomycin, ceftaroline, and linezolid, and combination therapies, such as dual -lactam treatments. Medical treatment for prosthetic valve endocarditis has included the use of rifampin-containing regimens. Experimental bacteriophage therapy and surgical advancements have shown promise in treating IE.

Antimicrobial stewardship programmes have been shown to improve adherence to standard care practices. With rising resistance among gram-positive and gram-negative bacteria, research warns of increased mortality rates without alternative treatments. The decision to recommend antibiotic prophylaxis for specific patient groups has not been established because of insufficient evidence and contradictory research outcomes without randomised trials based on expert consensus. Hence, a multidisciplinary, evidence-driven approach remains crucial to counter the rising resistance trends and improve patient outcomes in infective endocarditis.

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