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RESEARCH ARTICLE

PREVALENCE OF ANTIBIOTIC RESISTANCE IN PSEUDOMONAS AERUGINOSA

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Abstract

One of the main bacteria responsible for hospital-acquired illnesses is Pseudomonas aeruginosa. Through chromosomal changes or the horizontal acquisition of resistant determinants, antibiotic resistance can be easily developed it. High-risk clones, like ST175, are spreading together with the rising frequency of extensively-drug-resistant (XDR) or multi-drug-resistant (MDR) P. aeruginosa isolates. MDR/XDR infections should be taken seriously since they can make it difficult to choose the best empirical and conclusive antimicrobial therapies. New avenues for the treatment of MDR/XDR P. aeruginosa infections have been opened by the introduction of powerful new antibiotics. Pseudomonas aeruginosa strains are known to withstand the majority of antibiotics by utilizing their high levels of intrinsic and acquired resistance mechanisms. Furthermore, recalcitrance and infection recurrence are caused by P. aeruginosa's adaptive antibiotic resistance, a recently identified process that combines biofilm-mediated resistance and the development of multidrug-tolerant persister cells. There is a growing need for and interest in the research and development of alternative therapeutic approaches that offer fresh approaches to combat P. aeruginosa infections. Much recent research has documented various novel therapeutic methods that have proven pronouncedly effective in treating drug-resistant P. aeruginosa strains, but largely at the preclinical stages. This review focuses on the Prevalence of antibiotic resistance in Pseudomonas aeruginosaand also provides an overview of the characteristics of pseudomonas bacteria, various infections caused by them, the mechanism of antibiotic resistance, their clinical implications, Challenges in treatment, strategies for management and control, and future perspectives and research directions.

Introduction:-

Pseudomonas aeruginosa is a Gram-negative common opportunistic bacteria that plays a major role in nosocomial, acute, and chronic infections. When this pathogen infects a patient, it can cause diseases with a high death rate, including cancer, severe burns, cystic fibrosis, and immunocompromised individuals. This bacterium uses its important binding factors, flagella, pili, and biofilms, to thrive on water, various surfaces, and medical devices. As a

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result, P. aeruginosa is widespread in lakes, hospitals, and home washbasin drains, among other natural and manmade settings (Chegini et al., 2020). P. aeruginosa typically exhibits extensive drug resistance (XDR), which occurs when the bacteria are resistant to either one or two antimicrobial categories, as well as multidrug resistance (MDR), which occurs when the bacteria are resistant to at least one agent in three or more antimicrobial categories. The production of biofilms by P. aeruginosa is a potent aggravating factor in an infection. A biofilm is a structure made up of extracellular matrix components released by the constituent cells and an aggregation of microorganisms. It is challenging to eradicate the infection because the biofilm provides a shield for the cells from abiotic stressors, the immune system, and antibiotic action. P. aeruginosa colonization and infection are more common in patients with cystic fibrosis. Lung epithelial cells can consume the invasive P. aeruginosa and then desquamate it, preventing lung infection. On the other hand, P. aeruginosa is phagocytosed less by cystic fibrosis patients. This decreased phagocytosis is linked to an internal system malfunction and the defense of particular P. aeruginosa lipophilic substances found in the bacteria's outer membrane (Lorussoet al., 2022).

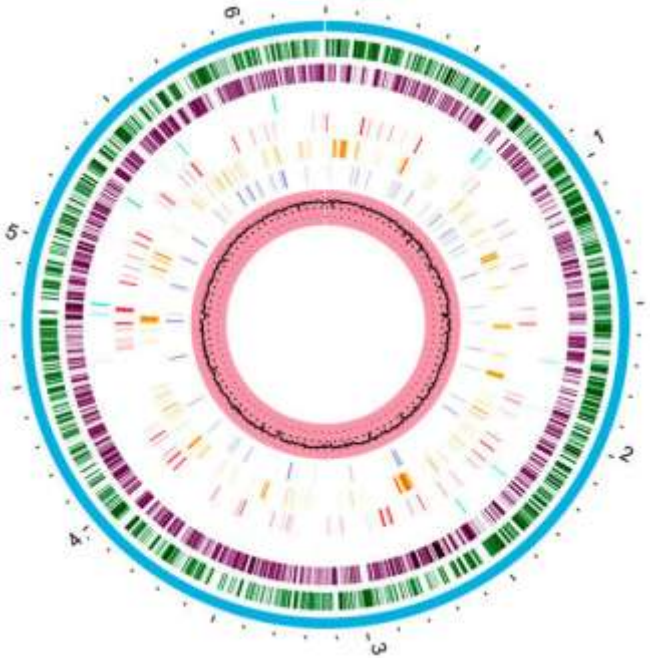
The aforementioned data make it necessary to identify potential therapeutic targets, create fresh therapies, and create potent P. aeruginosa vaccinations to enhance human health. However, the rise of MDR strain cases has made both attempts extremely challenging. This article provides a broad overview of the recent developments in P. aeruginosa research concerning host-pathogen interaction, novel technological advancements, and the regulatory and functional mechanisms of virulence factors, gene expression regulators, secretion systems, quorum sensing, and antibiotic resistance (Qin et al., 2022). The production of biofilms by P. aeruginosa is a potent aggravating factor in an infection. A biofilm is a structure made up of extracellular matrix components released by the constituent cells and an aggregation of microorganisms. It is challenging to eradicate the infection because the biofilm provides a shield for the cells from abiotic stressors, the immune system, and antibiotic action. P. aeruginosa differs from other Pseudomonas species in that it can grow at 42 °C and can grow on the majority of culture media used in routine analysis. In addition, pyocyanin synthesis is another reason why colonies are frequently green. Because pyocyanin is poisonous and increases oxidative stress in cellular systems, it is a significant virulence factor in P. aeruginosa infections. Additionally, pyocyanin is found in significant amounts in the sputum of patients suffering from bacteremia-related chronic lung diseases (Lorussoet al., 2022).

Characteristics of Pseudomonas aeruginosa:

Pseudomonas aeruginosa is a common type of bacteria that can be found in both aquatic and terrestrial environments. It is therefore present in a wide variety of meals as well as in healthcare settings. P. aeruginosa is regarded as a bacterium of enormous medicinal significance because of its remarkable environmental adaptability as well as its capacity to infect susceptible individuals with chronic illness. A major worldwide public health concern of the present day is the pathophysiology linked to the rise of generalized pathogenic bacteria. In addition to people, Pseudomonas aeruginosa can infect animals and plants. Because of its many virulence factors, this virus can damage host cells and alter human adaptive immune systems, which can lead to the emergence of new infections. This non-fermentative bacterium breaks down glucose via the glycolytic route when it is in an aerobic environment. Oxygen serves as the last electron acceptor in this pathway. On the other hand, nitrogen can be employed as an electron acceptor in anaerobic environments (de Sousa et al., 2021).

The genome of P. aeruginosa PAO1 is 6.3 Mbp (G + C content: 66.6%) and encodes 5700 genes, including 5584 projected open read frames (ORFs). It is a highly vast and complex genome (fig-1). It is possible to extract the rod-shaped, gram-negative, aerobic bacteria Pseudomonas aeruginosa from a variety of habitats, including soil, plants, and animal tissue. This bacterium uses its important binding components, such as flagella, pili, and biofilms, to thrive on water, various surfaces, and medical equipment. As a result, P. aeruginosa is widespread in both natural and man-made settings, such as hospitals, lakes, and home washbasin drains. Human infections are caused by the opportunistic bacterium Pseudomonas aeruginosa in multiple instances. It is now a significant contributor to antibiotic resistance and nosocomial infections. One of the opportunistic bacteria linked to healthcare infections is Pseudomonas aeruginosa. These infections include ventilator-associated pneumonia (VAP), infections in the intensive care unit, bloodstream infections related to central lines, surgical site infections, urinary tract infections, burn wound infections, keratitis, and otitis media. Pseudomonas aeruginosa is an organism that can produce a range of virulence factors, quickly develop resistance to antibiotics, and adapt to changes in its environment (Tuon et al., 2022).

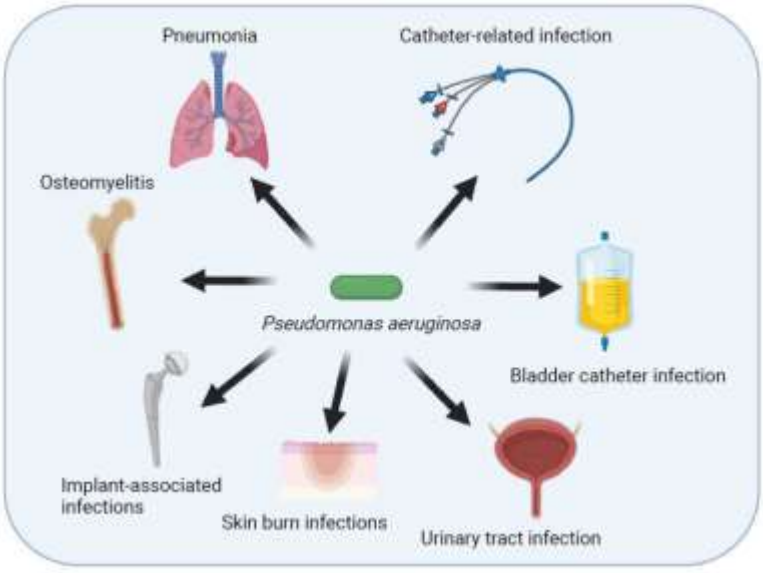
Fig 1:- Circular representation of the Pseudomonas aeruginosa PAO1 genome.



Common infection caused by Pseudomonas aeruginosa:

A significant Gram-negative opportunistic pathogen, Pseudomonas aeruginosa is responsible for numerous serious acute and chronic infections with up to 40% death rates and considerable morbidity. P. aeruginosa presents a unique challenge due to its high level of innate and acquired resistance to numerous antibiotics. P. aeruginosa can cause bloodstream infections (BSIs), osteomyelitis, endocarditis, keratitis and corneal ulcers in contact lens wearers, respiratory tract infections, hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), and urinary tract infections (UTI) (fig-2) (Wood et al., 2023). Globally, invasive infections frequently result in bloodstream infections (BSI), which have a substantial morbidity and fatality rate. The aetiological agent, the site of infection, the right antimicrobial treatment, and the patient's underlying medical conditions are some of the elements that determine their prognosis. In terms of aetiological agents, invasive Pseudomonas aeruginosa infections are linked to high mortality rates; additionally, prognosis is highly correlated with early, aggressive treatment (Pérez-Crespo et al., 2022).

Fig 2:- Main infection caused by Pseudomonas aeruginosa.



One of the most frequent gram-negative bacteria that cause pneumonia in immunocompromised patients is Pseudomonas aeruginosa. P. aeruginosa pneumonia is very dangerous for ventilated patients, and P. aeruginosa pneumonia causes a much greater fatality rate from ventilator-associated pneumonia (VAP) than from other bacteria. Certain strains of P. aeruginosacan compromise the integrity of the alveolar epithelial barrier, leading to swift lung epithelium necrosis and the spread of bacteria into the bloodstream. Acute lung damage in models of animals P. aeruginosa secretes several harmful byproducts, and research on P. aeruginosa's toxic exoproducts that play significant roles in acute lung injury started. Bidirectional protein transport across the lung epithelial barrier was used to quantify acute lung epithelial damage in animal models. In this model, the introduction of live P. aeruginosa into the airspace led to a twofold increase in the vascular tracer in the airspace, a notable decrease in the lung's ability to clear fluids, and an increase in the migration of the alveolar tracer into the vascular compartment (Sawaet al., 2014). P. aeruginosa is thought to be the primary source of chronic lung infections in those who have the genetic condition cystic fibrosis (CF). P. aeruginosa is the primary cause of death and a significant factor in lung function decline in individuals with cystic fibrosis (CF). Part of the pathophysiology linked to P. aeruginosa chronic infection in CF lung arises from leukocytes invading the lung and causing collateral damage as they fail to remove P. aeruginosa infection. Early in life, either from community or hospital exposure, CF patients become colonized with P. aeruginosa, which remains chronic throughout their lives (Wood et al., 2023).

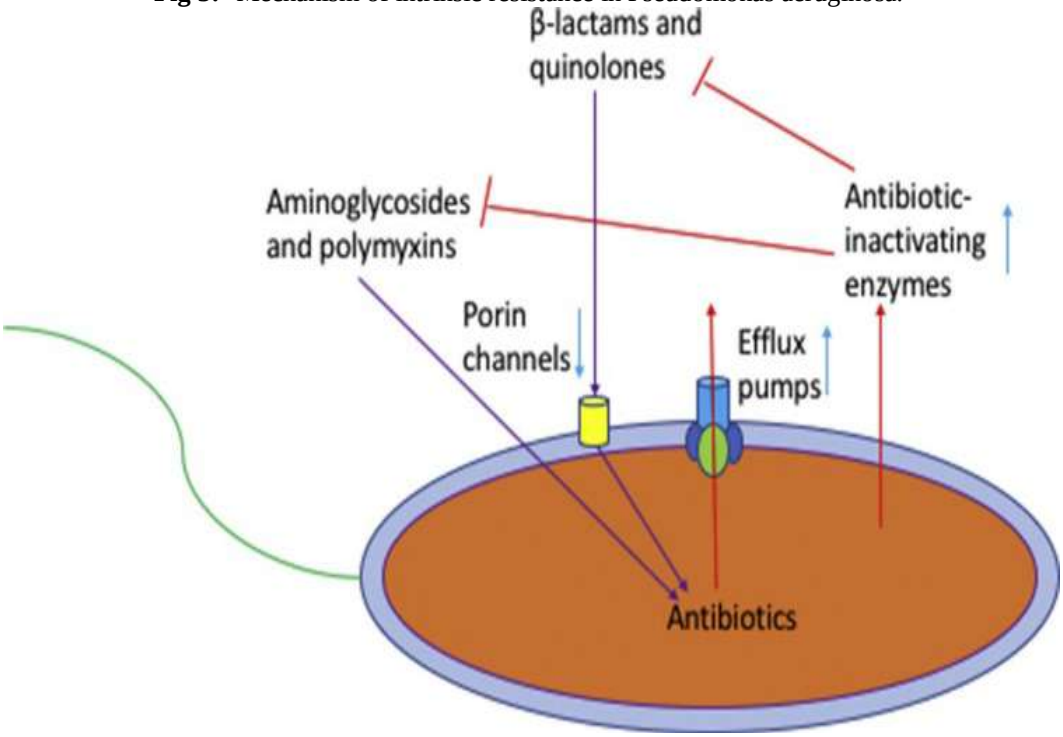
Mechanism of Multi-drug Resistance in Pseudomonas aeruginosa:

There have been numerous reviews of P. aeruginosa's antibiotic resistance mechanisms elsewhere. In summary, P. aeruginosa exhibits multifactorial resistance to antibiotics, resulting from a variety of intrinsic (innate) and extrinsic (acquired) mechanisms. P. aeruginosa's intrinsic pathways of antibiotic resistance include the following: (i) Porin molecules (like OprF) are expressed by P. aeruginosa, which is significantly more resistant to drug entry than other Gram-negative bacteria like E. coli. (ii) a decrease in the expression of porins found on the outer membrane, which further reduces the antibioticpermeability of the bacterial cell wall. (iii)Expression of different efflux pumps (e.g., MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY-OprM), which reduce the effective concentrations of antibiotics in P. aeruginosa cytosol by pumping out these drugs and imparting resistance to β-lactams, fluoroquinolones, and aminoglycosides (Wood et al., 2023). A significant contributor to both chronic infections that last a lifetime and potentially fatal acute infections is Pseudomonas aeruginosa. Because P. aeruginosa chronic infections have a distinctive biofilm mode of life, the effectiveness of antimicrobial therapies is severely limited. This is because biofilm-specific genes can confer temporary protection against antibiotics, which can promote the development of resistance, as well as physical and physiological factors that contribute to intrinsic tolerance. This pathogen's remarkable ability to select chromosomal changes that provide resistance to almost all current antibiotics is a noteworthy characteristic, as demonstrated by its exceptional and adaptable mutational resistome (Fernández-Billónet al., 2023).

Intrinsic resistance mechanism

A bacterial species' inherent capacity to reduce an antibiotic's effectiveness through innate structural or functional traits is referred to as intrinsic antibiotic resistance. It has been demonstrated that Pseudomonas aeruginosa has a high degree of intrinsic resistance to the majority of antibiotics due to its limited outer membrane permeability, efflux systems that remove drugs from the cell, and synthesis of enzymes that inactivate antibiotics, like β-lactamases. To reach intracellular targets, the majority of antibiotics used to treat P. aeruginosa infections must be able to permeate cell membranes.

Fig 3:- Mechanism of intrinsic resistance in Pseudomonas aeruginosa.



As an illustration, the aminoglycoside family of antibiotics, which includes amikacin, gentamicin, and tobramycin, binds to ribosomal 30S subunits to suppress bacterial protein synthesis. Quinolone antibiotics, which include ciprofloxacin and levofloxacin, block DNA gyrase and topoisomerase IV, hence interfering with DNA replication. Penicillin, cephalosporin, carbapenem, and monobactam are among the β-lactam antibiotics that have a β-lactam ring in their molecular structures. By specifically targeting penicillin-binding proteins, which are enzymes involved in the manufacture of peptidoglycan, this class of antibiotics prevents the biosynthesis of bacterial cell walls (Pang et al., 2019).

Acquired resistance mechanism

By mutational alterations or horizontal gene transfer, bacteria can acquire resistance genes and develop resistance to antibiotics. Apart from P. aeruginosa's high degree of intrinsic antibiotic resistance, acquired resistance plays a significant role in the formation of multidrug-resistant strains, making it harder to eradicate the pathogen and increasing the number of cases of chronic infections. Reduced antibiotic uptake, altered antibiotic targets, overexpression of efflux pumps, and the production of enzymes that inactivate antibiotics are all possible outcomes of mutations, and they all contribute to the ability of bacteria to persist in the presence of antimicrobial agents. For instance, a study showed that increasing the mutation frequencies of P. aeruginosa due to inactivation of the DNA oxidative repair mechanism results in increased production of β-lactamase and overexpression of the MexCD-OprJ efflux pump (Pang et al., 2019).

Efflux Pumps and their role in resistance

P. aeruginosa's large intrinsic resistome, limited membrane permeability, and capacity to build biofilms all contribute to its innately low susceptibility to antibiotics. Several antibiotic resistance genes, including blaampC, and the genes encoding the RND superfamily's MexXY, MexAB-OprM, MexCD-OprJ, and MexEF-OprN multidrug efflux pumps (Mex) are found in its core genome (fig-4). One of the main causes of bacteria's multidrug resistance is efflux pumps. P. aeruginosa has four multidrug efflux pumps that are involved in the ejection of hazardous compounds and lower the susceptibility to antibiotics (Lorussoet al., 2022).

These efflux pumps are catalysed drug/proton antiporters called tripartite protein complexes, which extrude their particular substrates from the periplasm through the outer membrane Efflux-pump deletion mutants demonstrated a direct relationship between efflux and antibiotic activity on P. aeruginosa for a core set of RND pumps; this

relationship could be verified by mutants that overexpress particular RND systems. As stated in the Section Introduction, these P. aeruginosa RND pumps have substrate ranges that overlap but are not identical. The substrate specificities of RND efflux pumps vary, encompassing amphiphilic molecules as well as hydrophobic solutes and the hydrophilic polycationic aminoglycosides, which are known to enter cells by a self-promoted process. Keep in mind that while the majority of antibiotics are amphiphilic substances with hydrophobic portions that must partition into a membrane, there are significant variations in the way efflux affects activity even within antibiotic classes (Dreier et al., 2015).

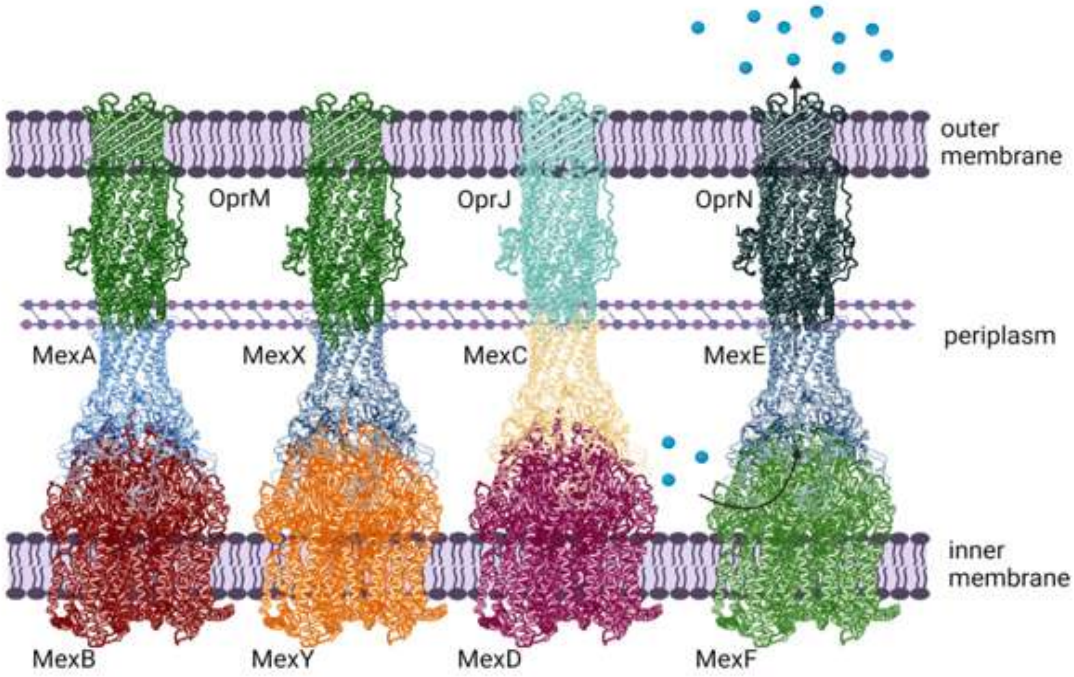


Fig 4:- Structure of the four main efflux pumps involved in antibiotic resistance in Pseudomonas aeruginosa.

Epidemiology:

Nosocomial infections, such as pneumonia, urinary tract infections, surgical site infections, and bacteremia, are frequently caused by P. aeruginosa. The frequency of P. aeruginosa among all illnesses linked to healthcare is estimated to be between 7.1% and 7.3%. P. aeruginosa is the most often found Gram-negative bacteria in nosocomial pneumonia, and pneumonia is the most common location of infection with it. Over the previous ten years, prevalence has increased. P. aeruginosa is accountable for an even greater proportion of infections related to healthcare in patients receiving intensive care unit (ICU) treatment. (Reynolds et al., 2021).

Global awareness of antimicrobial resistance is growing swiftly, especially as the proportion of bacteria resistant to the antimicrobials that are currently on the market increases. Gram-positive and gram-negative bacteria are included, and its global prevalence rate is at least 60%. Drug-resistant Pseudomonas aeruginosa and Acinetobacter baumanii infections are a serious public health risk and an increasing source of hospital-acquired infections. These bacteria can cause a variety of ailments, including wound infections, bacteremia, meningitis, pneumonia, and urinary tract infections. Drug-resistant Pseudomonas and Acinetobacter infections are associated with longer hospital stays and higher death rates. The exceptional resistance of P. aeruginosa to medications has made its eradication more challenging. Because P. aeruginosa strains have high levels of both acquired and natural resistance mechanisms, including biofilm formation, most antibiotics are known to be resistant to them. Novel therapeutic approaches that offer distinct routes against P. aeruginosa infections are being sought after and given more attention (Arayaet al., 2023). Because P. aeruginosa is intrinsically resistant to numerous antibiotics, treating these infections is still a therapeutic issue. Since P. aeruginosa exhibits every known enzymatic (poor outer membrane permeability/oprD loss, chromosomally encoded AmpC, as well as an extensive efflux pump system) and genetic route of resistance, it is classified as antibiotic-resistant. Because the bacterium is widely distributed in both the environment and the

endogenous flora of hospitalized patients, it is crucial to use strong molecular typing technologies to understand its molecular epidemiology and evaluate the patterns of dispersal of resistant strains (Pappa et al., 2020). Although the literature has previously addressed the epidemiological characteristics of critically sick patients with pseudomonal ventilator-associated pneumonia (VAP) or hospital-acquired pneumonia (HAP), there is a dearth of data relevant to Canada. Longer intensive care unit (ICU) stays and mortality rates in the ICU population as high as 43% have been linked to PA VAP or HAP. When PA is found to be the causing pathogen, up to 56% of cases of insufficient empiric antibiotic therapy are recorded. Less research has been done on the features of ICU patients with non-pneumonial PA infections (Kula et al., 2020).

Prevalence of Multidrug resistance:

The objective of this investigation was to examine the frequency, resistance to antibiotics, and genetic affinity of P. aeruginosa isolates derived from recreational and drinkable water samples, gathered from various locations (swimming pools, healthcare facilities, accommodation facilities, municipal waterworks, and residential buildings). This work has demonstrated that P. aeruginosa is present in a variety of water samples, including resistant strains that are particularly common in swimming pools, and it has verified the contribution of porins to the development of carbapenem resistance in Gram-negative bacteria. P. aeruginosa is hard to control due to its widespread distribution, great adaptability, and intrinsic resistance to a wide range of detergents, disinfectants, and antimicrobial substances. Treatment for infections produced by this disease is frequently challenging due to the drug and multidrug-resistant (MDR) phenotypes of the bacteria. P. aeruginosa has demonstrated rising resistance to a variety of medicines in recent years, including carbapenems, a type of β-lactam antibiotics that are frequently used in clinical settings (Schiavanoet al., 2017). To address the aforementioned problems, the study set out to characterize the frequency of MDR and resistant P. aeruginosa isolates in nine intensive care units (ICUs) of a university hospital. It also sought to characterize the use of antimicrobial agents in the ICUs, utilizing a defined daily dose (DDD), and to look into the relationship between antibiotic resistance and antibiotic consumption. Data from the hospital's Clinical Laboratory were utilized to analyze susceptibility and resistance. Patients admitted to at least one of the ICUs chosen for the study period provided samples. When P. aeruginosa isolates demonstrated resistance to three or more antimicrobial agent classes, with resistance to at least one antibiotic in each class, they were classified as multidrug-resistant (MDR) (Ribeiro et al., 2020).

Determining the background prevalence and antibiotic resistance profile of P. aeruginosa in hot tubs and swimming pools was the goal of this surveillance investigation. 108 samples were collected for convenience from three hot tubs and eight indoor swimming pools. Membrane filtration was used to treat water and swab samples, and polymerase chain reaction was used for confirmation. Even though the conditions are perfect for P. aeruginosa contamination, little research has been done on the background prevalence of the bacteria in indoor recreational water during times when there isn't an epidemic and sufficient chlorine levels should prevent contamination. Establishing the endemicity of P. aeruginosa in indoor hot tubs and swimming pools during times when there isn't an epidemic could have significant effects on infection management and facility upkeep. By gathering water and swab samples, our initial research objective was to determine the frequency of P. aeruginosa contamination in these two indoor recreational waters (Sambrano et al., 2021).

The most common bacteria isP. aeruginosa, which is especially challenging to cure. P. aeruginosa does include a wide range of virulence agents, including homoserine lactone, phospholipase, exotoxin A, and elastase. Furthermore, this organism exhibits a multitude of drug resistance strategies, including the inactivation or suppression of enzyme production, the upregulation of an active efflux pump system, the creation of biofilms, and the reduction or elimination of outer membrane protein expression. As a result, strains that are extensively drug-resistant (XDR) and multidrug-resistant (MDR) are prevalent. P. aeruginosa-infected burn victims have a greater death rate. As a result, our study group has concentrated on creating efficient therapeutic approaches to treat P. aeruginosa infections (Dou et al., 2017).

Clinical implications of Pseudomonas aeruginosa:

The majority of the conductive and respiratory zones are vulnerable to P. aeruginosa colonization, as the body of research clearly shows. However, for a single CF patient, heterogeneity can frequently be found in both P. aeruginosa colonization and disease location. Therefore, in an ideal world, medical professionals could tailor each patient's treatment so that the medication only targets P. aeruginosa-infected areas. To effectively treat P. aeruginosa colonized lung areas, it is necessary to first identify the specific areas affected and then treat them with a single therapy or a combination of therapies that will effectively deposit the drug and achieve eradication, greater bacterial

killing, or other outcome measures like improved lung function, reduced exacerbations, decreased hospitalizations, and improved quality of life (QoL). Sputum cultures are commonly used to detect P. aeruginosa colonization in CF patients. These cultures help confirm infection but provide little detail regarding the precise respiratory zone regions that are impacted. (Moore et al., 2017).

Human infections, especially chronic illnesses, are largely caused by bacterial biofilms. One of the main mechanisms by which P. aeruginosa causes severe and resistant infections that are linked to high rates of morbidity and mortality is its capacity to build biofilms. P. aeruginosa benefits greatly from biofilms because they enable the bacteria to survive on synthetic surfaces, evade the immune system, and become resistant to antibiotic treatment. Here, we'll go over the significance of P. aeruginosa biofilms in CF and device-related lung infections before talking about how resistant these biofilms are to conventional antibiotic treatments. In modern medicine, it has become routine to introduce artificial devices to humans in a range of clinical settings. Endotracheal tubes (ETTs), urinary catheters, vascular catheters, peritoneal catheters, orthopedic implants, prosthetic joints, and prosthetic heart valves are examples of common medical devices. These abiotic devices can enable bacterial attachment as early as one day after insertion by rapidly coating them in a conditioning film of host proteins. After that, biofilm bacteria can spread, which could lead to the planktonic forms of the bacteria possibly causing widespread infection. The CF transmembrane conductance regulator in the submucosal glands and airway epithelium malfunctions, which results in cystic fibrosis. The mutation causes altered airway anatomy, acidification of the airway surface liquid layer, decreased chloride transport across the epithelial barrier, decreased periciliary fluid, increased sputum viscosity, and impaired mucociliary clearance. These illnesses put people at risk for recurrent respiratory infections caused by a variety of microbiological organisms (Maurice et al., 2018).

Challenges in the treatment of Pseudomonas aeruginosa:

Gram-negative Pseudomonas aeruginosa is a prevalent source of clinically persistent infections such as cystic fibrosis, urinary tract infections, and burn infections. It is one of the main bacteria linked to human opportunistic infections. P. aeruginosa's capacity to release extracellular polymeric materials during invasion, including exopolysaccharides, matrix proteins, and extracellular DNA, is the primary cause of the infections' ongoing persistence. These materials stick to and encircle bacterial cells to create a biofilm. P. aeruginosa develops multiple antibiotic resistance because of biofilm formation, which presents a serious obstacle to traditional single antibiotic treatment strategies. Therefore, the development of anti-biofilm medications has become especially crucial. To treat P. aeruginosa infectious biofilms, several new alternative medications have been created recently, such as quorum-sensing inhibitors, bacteriophage therapy, antimicrobial photodynamic therapy, and antimicrobial peptides. To propose fresh directions for the treatment of P. aeruginosa biofilm infection, this paper analyses numerous developed anti-biofilm treatment methods and provides a brief introduction to the process and regulation of P. aeruginosa biofilm formation. Despite the widespread use of antibiotics to treat biofilm infections, drug resistance, drug-microbe interactions, and biofilm matrices that impede drug penetration continue to pose significant difficulties to clinical therapy. As a result, numerous novel anti-biofilm technologies have been created to prevent the production of biofilms. These technologies include phage therapy, gallium, and the combination of antibiotics with novel approaches (Yinet al., 2022).

Strategies for management and control:

Despite the widespread use of antibiotics to treat biofilm infections, drug resistance, drug-microbe interactions, and biofilm matrices that impede drug penetration continue to pose significant difficulties to clinical therapy. As a result, numerous novel anti-biofilm technologies have been created to prevent the production of biofilms. These technologies include phage therapy, gallium, and the combination of antibiotics with novel approaches. outlines the various action mechanisms of related anti-biofilm compounds and the strategies that have been found in recent years for treating P. aeruginosa biofilm infection (Yin et al., 2022).

Table 1:- Different strategies to treat Pseudomonas aeruginosa infection.

Strategy	Mechanism
Antibiotics	To break down biofilms and stop the emergence of antibiotic resistance, antibiotics are used in conjunction with other drugs or substances.
AMPs	interact with and break through the bacterial cell

	membrane to kill the bacterium
QSIs	suppress the QS system and tamper with receptor proteins and signaling chemicals.
Ga^{3+}	serves as a "Trojan horse" to impede P. aeruginosa growth and interfere with bacterial Fe metabolism.
Bacteriophage therapy	To degrade the extracellular matrix, encode enzymes

Infection prevention and control measures:

P. aeruginosa rates have dropped during the previous 20 years as a result of the use of successful eradication strategies. For healthier populations, definitions of chronic P. aeruginosa infection have to be modified. Future research on eradicating P. aeruginosa will be difficult because CFTR modulators are becoming more widely available and are undergoing competing clinical trials. The accepted standard of therapy for cystic fibrosis (CF) is treatment with antipseudomonal antibiotics (tobramycin or colistin) to remove primary or early P. aeruginosa infection; a single course of inhaled antibiotics is typically advised. Early P. aeruginosa identification usually indicates worse outcomes. While early P. aeruginosa can be effectively eliminated by inhaling a tobramycin solution (TIS). In addition to the usual TIS treatment, either a placebo or azithromycin was administered. Due to a 44% decrease in pulmonary exacerbations in patients receiving continuous azithromycin as opposed to placebo, enrollment was halted early (Zemanicket al., 2019). The goal of the research has been to develop a vaccine against P. aeruginosa infections for about 50 years, however, there is currently no approved vaccine on the market. Considerable progress has been achieved in the identification of putative vaccination antigens. Animal models have been used to evaluate the efficacy of both mucosal and systemic immunizations in treating acute illnesses. To date, severalP. aeruginosa antigens have been identified as viable candidates for vaccination. These include the lipopolysaccharide (LPS) O-antigen, polysaccharides, polysaccharide-protein conjugates, outer membrane proteins F and I, the type III secretion system component PcrV, flagella, pili, DNA, and whole killed cells. in addition to several potential antigens for non-integral outer membrane proteins (Grimwood et al., 2015).

While combination therapy is typically advised for severe infections like pneumonia and bacteremia, monotherapy is typically advised for simple urinary tract infections. However, the benefit of combination therapy is still up for question, at least in certain situations. The use of antibiotics increases the possibility of P. aeruginosa resistance, particularly when it comes to certain agents (such as carbapenems and fluoroquinolones). To stop the spread of resistance, antimicrobial rotation, and agent limitation strategies can be effective. In light of the lack of new options against multidrug-resistant P. aeruginosa strains shortly, similar measures, along with the prudent use of antibiotics and compliance with infection control measures, are essential to preserve the efficacy of the currently available anti-pseudomonal agents (Zhao et al.,2020). Following the abrupt spike in P. aeruginosa infections in the fourth quarter of 2005, several focused infection control initiatives were implemented. The emergence of a multi-drug resistant P. aeruginosa phenotype in two out of the three infections was a serious concern for the infection control team. Additionally, all strains of P. aeruginosa that were isolated from clinical samples as well as any strains that could be obtained from surveillance swabs were gathered for genotyping. Following the implementation of these control measures, the rate of infection declined marginally, but the rate of patients colonized rose over time (Bongiovanni et al., 2023).

Antibiotic stewardship:

Unrestricted use of antimicrobial agents: this is appropriate for antibacterial medications that have long been shown to be affordable, safe, and effective in clinical settings and to have minimal impact on bacterial resistance. The antibacterial medication is available for the doctor to use without restriction and can be prescribed following an assessment. Restricted use of antimicrobial agents: when it comes to antibiotics that contribute to bacterial resistance, there exist restrictions based on the drug's effectiveness, safety, cost, and other factors. Their usage ought to be restricted as a result.

After completing training and testing, doctors who hold intermediate-level or above qualifications are authorized to administer antimicrobial drugs with restricted usage. Specific application of antimicrobial agents: this is relevant for antibiotics where the side effects are readily apparent. To avoid the germs being too resistant and having serious effects in such situations, the medicines should be recommended cautiously. There is a paucity of clinical research on the effectiveness, safety, or superiority of novel antibiotics over existing ones. These medications are costly as well, so usage needs to be closely regulated. Sub-senior or above sub-senior qualified medical professionals are

authorized special use of these antimicrobial medications and may prescribe them following assessment and training (Liu et al., 2018).

Future perspective:

Pseudomonas aeruginosa is one of the therapeutic bacteria that benefit from its big, easily accessible genome, ability to produce virulence factors with strong anti-tumor actions, and ability to express a variety of immunogenic molecules on its membrane. The low toxicity and MSHA fimbriae of the peritrichous P. aeruginosa strain PA-MSHA have made it a viable therapeutic agent for the direct destruction of tumors through the induction of tumor cell death, inhibition of tumor growth, and stimulation of host immunological responses. Furthermore, therapeutic trials combining inactivated PA-MSHA with chemotherapy have been initiated. For the individuals who showed tolerance to PA-MSHA stimulation, however, the PA-MSAH treatment seemed to be ineffective. Consequently, it is advised that cancer patients undergo a pre-test to determine their tolerance to PA-MSHA. Patients who experience mild adverse responses will be sent on to additional therapy. By providing tumor antigens to DCs, the genetically modified P. aeruginosa strain can stimulate CD8+ T cells that are specific to tumors, resulting in the induction of durable anti-tumor immunity. Furthermore, live attenuated P. aeruginosa strains should be quickly removed after treatment and should not be able to multiply, as a matter of safety concern. When creating recombinant immunotoxins, PE is the P. aeruginosa toxin that is most frequently employed. Even though almost all tumor types have demonstrated notable in vitro and in vivo anti-tumor effects due to PE-based immunotoxins.

Only a few number of them have advanced to clinical use, and a significant obstacle that still has to be addressed in clinical applications is their low efficiency and unexpected toxicity to patients. The creation of novel PE-based immunotoxins with reduced immunogenicity and good specificity ought to be a primary focus in the demanding but fruitful field of bacteria-based cancer treatment in the future. All things considered, P. aeruginosa-based cancer medicines are promising approaches to treating cancer, and they work especially well when combined with traditional cancer medications (Pang et al., 2022).

Conclusion:-

P. aeruginosa exhibits multifactorial antibiotic resistance, which can be caused by innate, acquired, or adaptive mechanisms. Conventional antibiotics are no longer effective in treating P. aeruginosa infections due to the variety of antibiotic resistance mechanisms that lead to the emergence of multidrug-resistant strains. Moreover, P. aeruginosa biofilms and persister cells are the cause of CF patients' resistant and persistent infections. The last few decades have seen advancements in the creation of novel antibiotics with unique modes of action, resistance to bacterial enzyme modification, and increases in the effectiveness of drug delivery. But P. aeruginosa has an amazing ability to create or acquire new resistance mechanisms to these novel antibiotics, therefore the overuse and abuse of antibiotics provide major health risks to the general public (Pang et al., 2019). A significant Gram-negative pathogen is P. aeruginosa, especially in patients with chronic lung illness and those who are susceptible to nosocomial infections. In hospital-acquired and ventilator-associated nosocomial pneumonia, it is a particularly significant pathogen. P. aeruginosa is skilled at creating defense mechanisms against antibiotics and possesses a variety of virulence factors that allow it to target respiratory epithelial cells. Combination therapy with two antibiotics that are known to be active against pseudomonas is frequently used to treat P. aeruginosa infections; this early and proper antibiotic therapy is linked to better results. Because CF patients have high rates of chronic P. aeruginosa infection, antimicrobials active against P. aeruginosa are also commonly used to treat CF flare-ups (Reynolds et al., 2021). The world is facing a severe problem with antibiotic resistance, and aquatic flora is contributing significantly to this problem. Since we only looked at one species of Pseudomonas in our study, we can infer that contaminated freshwater springs could serve as a source of infections resistant to antibiotics. To clarify additional factors that contribute to aquatic flora's resistance to antibiotics, more research is required (Pappa et al., 2020). A single antibiotic is the most widely used treatment for P. aeruginosa biofilm infections, yet drug resistance presents numerous difficulties for this clinical approach. Numerous promising therapeutic approaches have been developed in response to the emergence of drug-resistant strains. These approaches include the combination of antibiotics, the targeting of biofilms by enzymes or quorum-sensing systems, the use of novel photodynamic therapies, and the use of other compounds to block or prevent P. aeruginosa biofilm formation by preventing the diffusion of biofilm formation (Yin et al., 2022).

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