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Review Article

A REVIEW ON EMERGENCE OF ANTIBIOTIC RESISTANCE IN *Pseudomonas aeruginosa*; ITS RISK FACTORS AND CLINICAL IMPACTS

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ABSTRACT

Pseudomonas aeruginosa is one of bacteria which cause dangerous disease and it is mostly rigid or not possible to get rid of infections and so this bacterial infection calls for a novel therapeutic procedure and method. An antimicrobial have been used as an effective therapeutic approach by way of a diversity of mode of action. Aminoglycosides are recognized vanguard antibiotics in the action of Gram-negative bacterial infections there are influential antibiotics that slow down protein synthesis by obligatory in the direction of the bacterial 30S ribosomal subunit. As rising information showed the better occurrence of confrontation in opposition to these drugs as seen, it seems essential to use combinations of aminoglycosides with other antimicrobial agents against *P.aeruginosa.* An interactive combination of aminoglycosides (gentamicin, tobramycin and amikacin), fluoroquinolone (ciprofloxacin) and penicillin (Carbenicillin) has been utilized to treat *P.aeruginosa* infections. Furthermore, an amount of *P.aeruginosa* strains has been reported to contain confrontation to aminoglycoside antibiotics.

Normalization to the creation of the latest generations of antibiotics, clinicians come across antibiotic resistance which has considerably amplified throughout the new years. This difficulty is rising worldwide, striking an enormous burden of costs, morbidity, and mortality. Hence, it is essential towards finding out novel antimicrobial agents to associate to the cases of antibiotic resistance.

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INTRODUCTION

Pseudomonas aeruginosa is a universal Gram-negative bacterium that can be a source of disease in plants and animals, as well as humans. It shows positive results for citrate, catalase and oxidase. It originates in soil, water, skin flora and mainly man-made environments all through the world. It flourishes not only in usual atmospheres, but also in hypoxic atmospheres, therefore occupied numerous natural and artificial environments [1]. It utilizes an extended assortment of organic substances for food; in animals, its adaptability enables the organism to contaminate injured tissues or those with condensed immunity. The symptoms of such infections are generalized inflammation and sepsis. If such colonizations take place in decisive body organs, such as the lungs, the urinary tract and kidneys, the consequences can be fatal [2]. Since it flourishes on wet surfaces, this bacterium is also originate on and in clinical appratures, together with catheters, causing cross-contamination in hospitals and clinics. It is concerned in hot-tub rash. It is also capable to decay hydrocarbons and have been utilized to rupture tarballs and oil from oil spills [3].

Scientific Classification

Domain	:	Bacteria
Phylum	:	Proteobacteria
Class	:	Gammaproteobacteria
Order	:	Pseudomonadales
Family	:	Pseudomonadaceae
Genus	:	*Pseudomonas*
Species	:	*P.aeruginosa*

Identification of Organisms

It is a Gram-negative, rod-shaped, aerobic, unipolar motility bacterium with an opportunistic human pathogen, as well as of plants pathogen [4]. *Pseudomonas* is the genus type and *P. aeruginosa* is the species (Migula) [5]. *P. aeruginosa* secretes a mixture of pigments, together with pyoverdine (yellow-green and fluorescent), pyocyanin (blue-green) and pyorubin (red-brown). King, Ward, and Raney modernized *Pseudomonas*

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Agar P (King A medium) for attractive pyocyanin and pyorubin creation, and *Pseudomonas* Agar F (King B medium) for attractive fluorescein manufacture [6]. *P. aeruginosa* is frequently initially recognized by its gem like manifestation and grape-like or tortilla-like odor *in vitro*. Ultimate medical detection of *P. aeruginosa* furthermore includes identifying the creation of pyocyanin and fluorescein, as well as its capability to grow at 42°C.

P. aeruginosa is able of development in diesel and jet fuel; everywhere it is recognized as hydrocarbon-using bacteria, causing microbial deterioration. It creates dark, gellish mats occasionally rudely called "algae" suitable to their manifestation. Even though classified as an aerobic organism, *P. aeruginosa* is considered by numerous as a facultative anaerobe, as it is well modified to propagate in circumstances of incomplete or total oxygen reduction. This organism can attain anaerobic development with nitrate as a fatal electron acceptor, and, in its nonexistence, it is furthermore capable to ferment arginine by substrate-level phosphorylation [7, 8]. Alteration to anaerobic or microaerobic environments is essential for convincing lifestyles of *P. aeruginosa*, for example, through a lung infection in cystic fibrosis patients, anywhere thick layers of lung mucus and alginate nearby mucoid bacterial cells can bind the distribution of oxygen [9, 10, 11].

Nomenclature

The term *Pseudomonas* means "false unit", from the Greek *pseudo* (Greek- false) and (Latin: *monas*, from Greek-a single unit). The stem word *monas* was utilized near the beginning in the history of microbiology to demote to germs, e.g., kingdom Monera.

The species name *aeruginosa* is a Latin word meaning verdigris ("copper rust"), as seen with the oxidized copper patina on the Statue of Liberty. This species also describe the blue-green bacterial pigment seen in laboratory cultures [12] blue-green pigment is a grouping of two metabolites of *P. aeruginosa*, pyocyanin (blue) and pyoverdine (green), which convey the blue-green distinguishing colors of cultures. Pyocyanin biosynthesis are regulated by quorum sensing, as in the biofilms related to migration of the lungs in cystic fibrosis patients. An additional declaration is that the word may be original as of the Greek prefix *ae-* meaning "old or aged", and the suffix *ruginosa* means wrinkled or bumpy.

The derivations of pyocyanin and pyoverdine' are of the Greek, with *pyo-*, meaning "pus", *cyanin*, meaning "blue", and *verdine*, meaning "green". Pyoverdine in the absence of pyocyanin is a fluorescent-yellow color [13].

Genome

The genome of *P. aeruginosa* is comparatively big (6-7 Mb) and encodes approximately 6,000 open reading frames, depending on the strain. The 5,021 genes are preserved diagonally all five genomes analyzed, with at least 70% sequence uniqueness. This set of genes is the *P. aeruginosa* central part of the genome [14].

The G+C-rich *P.aeruginosa* chromosome consists of a preserved nucleus and a uneven addition part. The nucleus genomes of *P. aeruginosa* strains are mainly collinear, show a low rate of sequence polymorphism, and include few loci of high sequence variety, the mainly distinguished ones individual the pyoverdine locus, the flagellar regulon, *pilA*, and the O-antigen biosynthesis locus [15]. Unpredictable segments are speckled all through the genome, of which concerning one-third are without delay next to tRNA or tmRNA genes.

The three recognized hot spots of genomic variants are caused by the addition of genomic islands of the pKLC102/PAGI-2 family into $tRNA^{Lys}$ or $tRNA^{Gly}$genes [16]. The individual islands deviate in their variety of metabolic genes, but distribute a set of syntenic genes that award their straight spread to other clones and species. Migration of unusual disease habitats predisposes to deletions, genome rearrangements, and gathering of loss-of-function mutations in the *P. aeruginosa* chromosome. The *P. aeruginosa* inhabitants are categorized by a few leading clones extensive in disease and environmental habitats. The genome is prepared up of clone-typical segments in the center and addition, genome and of blocks in the central part of the genome through open gene flow in the inhabitants [17].

Cell Surface Polysaccharides

Cell-surface polysaccharides participate varied roles in the bacterial "lifestyle". They provide as an obstruction among the cell wall and the environment, arbitrate host-pathogen communications, form structural apparatus of biofilms. These polysaccharides are synthesized from nucleotide-activated precursors, and, in general cases, all the enzymes essential for biosynthesis, gathering and movement of the finished polymer is defined by genes prearranged in devoted clusters inside the genome of the organism. Lipopolysaccharide is one of the main significant cell-surface polysaccharides, as it acts as a key structural role in outer membrane veracity, as well as being a significant moderator of host-pathogen interactions.

The inheritance for the biosynthesis of the so-called A-band (homopolymeric) and B band (heteropolymeric) O antigens contain evidently distinct, and a large amount of development has been completed toward sympathetic the biochemical pathways of their biosynthesis. The exopolysaccharides alginate is a linear copolymer of β-1,4-linked D mannuronic acid and L-glucuronic acid residues, and is reliable for the mucoid phenotype of late-stage cystic fibrosis disease. The *pel* and *psl* loci are two newly discovered gene clusters, which also determine exopolysaccharides create to be significant for biofilm configuration. A rhamnolipid is a bio-surfactant whose construction is firmly synchronized at the transcriptional level, but the exact role it acting in disease is not well unspoken at there. Protein glycosylation, in meticulous of pilli and flagellum, is a new focal point of investigation by numerous groups, and it has been exposed to be significant for bond and attack through bacterial infection [18].

Pathogenesis

Plants and Invertebrates

In privileged plants, *P. aeruginosa* stimulates symptoms of soft rot, for example, in *Arabidopsis thaliana*. *Thale cress* and *Lactuca sativa* (lettuce), it is also pathogenic to invertebrate animals, causes the nematode *Caenorhabditis elegans*, the fruit fly *Drosophila* [19] and the moth *Galleria*

mellonella. The relations of virulence factors are the similar for plant and animal infections [20].

Diagnosis

Depending on the temperament of infection, a suitable specimen is composed and sent to a bacteriology laboratory for recognition. As among the majority bacteriological specimens, a Gram stain is performed, which may demonstrate Gram-negative rods and/or white blood cells. *P. aeruginosa* produces colonies with a distinguishing "grape-like" or "fresh-tortilla" odor on bacteriological media. In assorted cultures, it can be isolated as obvious colonies on MacConkey agar (as it does not ferment lactose) which will test positive for oxidase [258]. Assenting tests comprise making of the blue-green pigment pyocyanin on cetrimide agar and growth at 42°C. A TSI slant is frequently used to differentiate non-fermenting *Pseudomonas* species from enteric pathogens in fecal specimens [21, 22].

Treatment

P. aeruginosa is oftenly isolated from non-sterile sites (mouth swabs, sputum, etc.) and under these conditions; it frequently represents migration and not infection. Hence, be interpreted carefully, and the recommendation of a microbiologist or infectious diseases physician/pharmacist have to be required earlier to start treatment. Regularly treatment is not required [23].

When *P. aeruginosa* is isolated from a sterile site (blood, bone, deep collections), it must be engaged critically, and approximately constantly requires treatment. *P. aeruginosa* is obviously resistant to a bulky collection of antibiotics and might reveal extra confrontation following ineffective treatment, in exacting, during alteration of a porin. It has to frequently be potential to direct healing according to laboratory sensitivities, rather than choosing an antibiotic empirically. If antibiotics are taking place empirically, then each attempt must be complete to get cultures (before administering first dose of antibiotic), and the option of antibiotic used must be reviewed when the culture results are accessible [24].

Antibiotics contain movement in opposition to *P. aeruginosa* might comprise:

- ✓ Aminoglycosides (gentamicin, amikacin, tobramycin, but *not* kanamycin)
- ✓ Quinolones (ciprofloxacin, levofloxacin, but not moxifloxacin)
- ✓ Cephalosporins (ceftazidime, cefepime, cefoperazone, cefpirome, ceftobiprole, but *not* cefuroxime, cefotaxime, or ceftriaxone)
- ✓ Anti pseudomonal penicillins: carboxypenicillins (carbenicillin and ticarc illin), and ureidopenicillins (mezlocillin, azlocillin, and piperacillin). *P. aeruginosa* is intrinsically resistant to all other penicillins.
- ✓ Carbapenems (meropenem, imipenem, doripenem, but *not* ertapenem)
- ✓ Polymyxins (polymyxin B and colistin)
- ✓ Monobactams (aztreonam)

These antibiotics are required for everyone to be given by injection, through the exclusion of fluoroquinolones, aerosolized tobramycin and aerosolized aztreonam. For this cause, in several hospitals, fluoroquinolone employ is strictly limited to avoid the growth of opposing to strains of *P. aeruginosa*. On the unusual occasions everywhere disease is external and inadequate (for example, ear infections or nail infections), topical gentamicin or colistin might be used [25].

Antibiotic Resistance

One of the major troublesome descriptive of *P. aeruginosa* is its low antibiotic vulnerability, which is attributable to a concentrated act of multidrug efflux pumps through chromosomally determined antibiotic resistance genes (e.g., *mexAB*, *mexXY* etc.) and the low permeabileness of the bacterial cellular envelopes. In accumulation to this inherent confrontation, *P. aeruginosa* simply develops acquired confrontation also by mutation in chromosomally determined genes or by the horizontal gene transfers of antibiotic resistance determinants. Expansion of multidrug resistance by *P.aeruginosa* isolates requires any dissimilar genetic proceedings, as well as gaining of dissimilar mutations and or horizontal transfer of antibiotic resistance genes.

Hypermutation favors the assortment of mutation-driven antibiotic confrontation in *P.aeruginosa* strains producing chronic infections, while the clustering of numerous dissimilar antibiotic resistance genes in integrons favors the concentrated acquisition of antibiotic resistance determinants. Several modern studies comprise exposed phenotypic resistance linked with biofilm configuration or to the appearance of small-colony variants might be significant in the reaction of *P. aeruginosa* populations to antibiotics treatment *[26]*.

Mechansim of Antibiotic Resistance

The mechanisms of action of antibiotics are categorized based on their activity on the bacteria:

- Inhibition of cell wall synthesis; E.g. Cephalosporins and Penicillin.
- Inhibition of cell membrane function; E.g. Polymixins
- Inhibition of protein synthesis; E.g. Gentamycin, Aminoglycosides, Chloramphenicol, etc.
- Inhibition of Nucleic acid synthesis; E.g. Rifampicin
- Inhibition of Folic acid synthesis; E.g. Sulphonamides.

Prevention

Probiotic prophylaxis can stop migration and the hold-up onset of *Pseudomonas* infection in an ICU location. Immuno-prophylaxis in opposition to *Pseudomonas* is individually investigated. Avoiding burning tubs since *Pseudomonas aeruginosa* is able to stay alive in hot temperatures. Avoiding pools that might be badly maintained and stay get in touch with lens apparatus and solutions from flattering infected. Washing your hands frequently can advantage as well through get in touch with numerous previous pathogen infections. Nevertheless, readily available are most excellent method to stop attainment *Pseudomonas aeruginosa* the most excellent treatment is to diminish contact [27].

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Conflict of interest statement

We declare that no conflict of interest.

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