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Article Review

The Characteristics Of The *Pseudomonas aeruginosa* And How To Prevention From Them.

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Abstract:

The infections that causes by *Pseudomonas aeruginosa* is usually responsible for the nosocomial infections of the United States. Occurs in the each year approximality 51,000 cases of *P. aeruginosa* infections , and the persons the most risk of infection are those most exposer into equipment of hospital that has not well desinfection such as ventilation of mechanical and catheters.Some strains of *P. aeruginosa* that mutate or those that production of β-Lactamase enzymes that resistance into penicillins.The enzymes of β-Lactamase acts on the disruption into atomic structure of Carbapenems , Penicillins, Monobactams and Cephalosporins , and also the mechanisms that provides to resistance into penicillins such as efflux pumps of genetically encoded that acting as transmembrane proteins that help to secrete toxic materials. The mutations that influence to expression of gene for *P. aeruginosa* provide immune to support antimicrobials. So that results into decrease of specific genes that leads into production wide spectrum of β-Lactamase. The immune increase against penicillin and other antibiotics is important role play to the stay length of a patient's in hospital and rate of mortality.The conjugation of bacteria role play to an increase resistance for the antibiotics and some *P. aeruginosa* strains have become immune against all penicillins.The *P. aeruginosa* of illumination that leds into provides measures of preventative and steps that leads to fight of outbreaks nosocomial . These review aids into address mechanisms of resistance and discuss the preventative measures and its effectiveness that used today.

Keywords: *P. aeruginosa*; Bacterial nosocomial infections .

Introduction :

The bacterial *P. aeruginosa* , is proteobacteria and one of the most commonly for the members of the Pseudomonadaceae family .This bacteria was discovered in 1882 through Carle Gessard (bacteriologist and chemist of French) ,*P. aeruginosa* is a gram-negative bacteria , rod shape , 5-.8 µm in diameter and contain one flagellum that used for the mobilization. *P. aeruginosa* is the most gram-negative bacteria that give oxidase positive reactions , but unable on the lactose fermentation. This bacteria is present in soil , water , plant and also in the animals epidermis.

P. aeruginosa is found in the nature commonly as plankton that swimming in water or through biofilm that are groups of bacteria share at the same chemical phenotype and properties (1). *P. aeruginosa* can survival at the temperatures a variety and nutrition

of infrequent. Through some of previous studies , this bacteria can easily grow in distilled water and its give bacteria a able on the adapting with the change of environments (2). In the case occurs lack in the immune of the host , so the *P. aeruginosa* become pathogen and causes opportunistic infections (3).This is leads to *P. aeruginosa* considers nosocomial threat of sizeable , esipically for patients suffering from cancers or ventilation machines or burns. *P. aeruginosa* is colonizing the respiratory tract and that associate in the most cases with sepsis and may death. In the case immunosuppression or patients exposure into large trauma are high risk with infection colonization. The rate of mortality in the most of patients around 50% who otained with infection (4). *P. aeruginosa* has high able on the destroy human immune cells such as macrophages through exotoxin A production to decrease of the uptake of 3H-thymidine by cells, that leads to give high toxicity of bacteria (5). The infections with *P. aeruginosa* can treated through groups combination of β-Lactams such as penicillin that classified through its four-membered of ring.
These antibiotics consideres bactericidal and its focus on the enzymes that used to constructing of the cell wall such as transpeptdase and carboxypeptidase , so the act of penicillin-binding proteins act on retard peptidoglycan synthesis , this leads to the inhibition of cell's ability on the construction of the cell wall. The β-lactams drugs are has consideres hydrophilic and can pass through small pores in the complex of outer membrane , that considers from propreties of *P. aeruginosa* and also other gram-negative bacteria, and known with porins that important role play into antimicrobials resistance (6) .

This review are intended to focus on the highlighted of mechanisms that used into expression of high able of *P. aeruginosa* to increase resistant for the antibiotics. So, can foucs on the importance measures of preventative and also production and develope new treatments for the *P. aeruginosa*.

- Literature Review .

Mechanisms of defense : -

Defense mediated of membrane : *P. aeruginosa* is the gram-negative bacteria and pathogen opportunistic that has membrane who quite complex. The bacteria can product of membrane a very protective ,so due to the environments of harsh that live in. *P. aeruginosa* are both natural and mutant have membranes more permeable and this leads into very susceptible for the antibiotics , Z61 is strain of wild-type that more sensitive into β-lactams, tetracycline, rifampin , aminoglycosides and also chloramphenicol (7). Some of studies proved that outer membrane removal may be causes increase of sensitivity to the antibiotics (8). The *P.aeruginosa* membrane have several of pumps of efflux that could you to prevent influx with antimicrobial agents , due to highly selective of membrane. This studies clarified that remove of the porins may be lead into decrease in minimum inhibitory concentration of antibiotcs (9).
The high selectivity of memrane attributed into proteins that act as porinscalled OprF. Opr F is different from OmpF/OmpC trimeric porins, while can homologous with OprA that present in Escherichia coli , and used for the structure and prevent permeable .The large similarities between for the OprA and OprF phenotypically enhances its ability to the form small porins and also residues of aromatic and

hydrophobic in their structure . Also another advantage for the OprF has ability on the form larger porins than OprA and smaller residues present in OprF that used into ions transport (10 ,11). The OprD of the *P. aeruginosa* that essential role play in amino acids diffusion , so the lack OprD that lead to quality of *P. aeruginosa* resistant of multi-antibiotic (12,13). The several of proteins are expressed in the *P. aeruginosa* outer membrane , although are not usually associated with antibiotics resistanc (14).

- The resistance through pump of efflux :

The efflux pumps are proteins present in the most of bacteria that act on the antimicrobials deport and cosidered another mechanisms for the *P. aeruginosa* resistance. The pumps of efflux classifid into families five , MF is Major facilitator and MATE define as multidrug and toxic efflux , while RND is resistance nodulation-division and SMR know as small multidrug resistance and the last type is ABC define as ATP binding cassette. *P. aeruginosa* contain on the all of these families, the most common of pumps in the *P. aeruginosa* are RND (15). Among the studies conducted in the Department of Microbiology in the Kyoto Pharmaceutical University , the researchers focused on three characteristics of pumps of efflux that detected in the *P. aeruginosa.* MexCD-OprJ and also MexXY-OprM are high expression of mutants that act on the Penicillins expunge , while sulbenicillin and carbenicillin can differentiates them from another penicillins through have negative charges (16). In more than one study, it was shown that MexAB-OprM important role play to the resistance of acquired and intrinsic for the β-lactams , esipically penicillins (17). MexAB-OprM the role play to the mutations of mexR to the repressor of terminate , and added nalC repressor or may be mutations for the PA3721gene (18,19). MexAB-OprM when it happens to him overexpression, this causes increase in the penicillins expulsion (20).The efflux pump of MexAB-OprM have a wide range from substrates of concerning of β-lactams (21,22). The regulation of the MexCD-OprJ occurs through the nfxB gene , this gene that act as controls negatively for the MexCD-OprJ expression (22).The studies conducted on the RND MexCD-OprJ have shown that they do not contribute for the antibiotics intrinsic resistance (23).Depression of nfxB and increase of MexCD-OprJ expression that may be lead to hypersensitivity for the some of β-lactams (24).

Where several studies have shown that MexCD-OprJ act on the extrude of the most of penicillins, so that considers a part from sulbenicillin and carbenicillin. The *P. aeruginosa* contain on only two from of twelve of RND , the pump of efflux of the MexXY RND does not contain on the encodes genes for the proteins of outer membrane ; where he has the ability to interact with OprM and it can perform a function (25).The overexpression of the MexXY OprM through of some experiments that allowed penicillins extrude. The RND transporter may be associated through combin with two of other complexe compounds ; that are MFP define as periplasmic membrane fusion protein and OMF which is outer membrane factor. The full structure may be pass through membrane, so that allow of pumps into toxins extrude. They found are major of two genes in each of operon that acts on the encode for the MFP and RND ; and only half of the twelve operon that have ability to the code of the OMF (26). The explain around of the RND pumps is made it clear that many *P.*

aeruginosa strains have antibiotics resistance when the compare with many gram-negative bacteria (26 ,27).

- The resistance through of the biofilm :

The biofilms acts to the contribute on immunity of increase and resistance against the antibiotics (27). In the some studies that conducted on the *P. aeruginosa* colonies when were exposed into penicillins ; while with our study was used piperacillin ; where the study explained does not any one of colonies were have complete of resistant into penicillins. After that, *P. aeruginosa* was able to develop resistance with 25% for the piperacillin , but when acquired *P. aeruginosa* on the biofilm , that lead into increase resistance to piperacillin with 50 % (28). From what we mentioned above , we concluded that there is a direct relationship between formation of biofilm and resistance.When the effects of penicillin and other β-lactam antibiotics were examined on the *P. aeruginosa* colonies ; β-lactams function on the ability inhibit of growing cells for the peptidoglycan production.To measure the β-lactam effects on the biofilm , the biofilm it must grow actively and actively (29). Some studies have shown that there is no relationship between biofilm present and antibiotic resistance increase (30). Although there is some evidence indicating a relationship between *P.aeruginosa* biofilm and increase of expression of efflux pumps of hypothetical and proteins other that act on antibiotics resistant an undiscovered (31). Therefore, *P. aeruginosa* biofilms, which is associated with diseases, is responsible for many problems , colonies of biofilm plays a role in the mc-resistant with patients who suffering from fibrosis of cystic , and also pulmonary of chronic obstructive disease (32) .This explains the high ratemortality of *P.aeruginosa* in these patients (33). *P.aeruginosa* biofilm can be associated with adaptations to increase the chance of infection in UTIs (34).Biofilms of *P.aeruginosa* it plays an important role in the spread of nosocomial infections (35).As biofilms have the ability to cluster on medical equipment and instruments used by patients, which increases the risk and lethality of *P.aeruginosa* (36). The β-lactamase of *P. aeruginosa* especially OXA type is responsabile on the hydrolysis for the esters and amides that present inside and around β-lactam ring of the four-membered of β-lactam antibiotics (37).The antibiotics of β-lactam that act on the inhibits growth of prokaryotes that construction of a peptidoglycan layer.The antibiotics contain substrates that include penicillin-binding proteins and DD-carboxypeptidase and also DD-transpeptidase (38,39). The common antimicrobials include cephalosporins , penicillins, penems , carbapenems and also monobactams , and used usually against gram-negative bacteria and *P.aeruginosa* (40).The OXA-type is the most type of β-lactamase common that present in P. aeruginosa , and called oxacillinase. These enzymes usually share by chlorine characteristic that inhibit its actions of ordinary with the β-lactams (41). *P. aeruginosa* act to the encode of the PER-type and β-lactamases that have extended spectrum , and also in rare cases for the some strains of *P. aeruginosa* from the TEM type (42,43). These β-lactamase enzymes are classified through amino acids structure (44).These include groups A, B, C, and D .The class of D OXA β-lactamase (OTBL) that has some of substrates only with penicillins , that acts on hydrolyze for the penicillins as well as oxacillin (45). In the some of studies, OTBL has the ability to develop resistance to other antibiotics.To the identify and detect properties of the antimicrobial resistance of the *P.aeruginosa* , where has been isolated ESBLs inside the bacteria (46,47).The OXA of 10 β-lactamase that include OXA-13 ; OXA-14 ;

OXA-16 ; OXA-17 ; OXA-19 and OXA-28 (48).The numbers of identify for the oxilliase strain that indicates the order in which they were discovered, and that provide of defenses for the multible for the antibiotics and has highly resistant for all penicillins (49).Some recent epidemiological studies indicate that ESBLs of OXA β-lactamase are present only in the *P. aeruginosa* (50).The types OXA 40 and OXA 24 as well as OXA 25 that provide resistance of β-lactam in the P. aeruginosa, called penicillins.The structure of crystalline into OXA 40, the substrate was found to be specific to penicillin , and weakly acts against cephalosporins (51).

- TEM type : TEM it is considered another type of β-lactamase on the spectrum of ESBL , which was first its discovered in Greece in 1960 , and TEM it got its name when it was extracted from a patient called Temoniera. Where TEM is considered one of the most common plasmids mediated strain for the ESBLs that present in the gram-negative of bacteria (52,53). Where it was discovered in the beginning in bacteria *E. Coli* , where properties allow of plasmid-mediated of the ESBL into speed spread to other species , that include most family strains of *Enterobacteriaceae* as well as *P. aeruginosa*.TEM it is commonly found in the gram-negative of bacteria , and very rarely in bacteria *P. aeruginosa* that contain only a strain of type TEM-2 (TEM-42) (54-55).The type TEM-2 of the isolates more like TEM-1, where differenitiate through their isoelectric point and also by their promoter (56,57).Where he found that isolation of PAe1100 contain on the TEM-42 and can penicillins resistant and another antimicrobials of antipseudomonal of β-lactamb (58). In one of the research papers he wrriten of Poirel, where are the bacterial strains of *P. aeruginosa* that harboring on the ESBL genes. The changes of mutational for the blaTEM-1 or through acquire of resistance by blaTEM-4 absorption , in the *P. aeruginosa* there is a similar concept with ESBLs of OXA-type (59).

- The type of PER :

The strains of PER-1 it was discovered for the first time in the *P. aeruginosa*, where it is the only type of PER of β-lactamase who is defined in the *P. aeruginosa* (59,60). As these strains are widespread in parts of the Europe and cause many nosocomial infections. In one study, it was found that 11% of nosocomial infections are caused by *P. aeruginosa* that encod for the blaPER-1 gene.Where there is about 20-25% of strains contain a PER (60).Where there is a share 25-26% of homology with studied of TEM and also enzymes of SHV (61). The enzymes of PER have highly effective for the hydrolyzing with the ring of β-lactam of penicillins and oxacillin exclusion (62). The TEM β-lactamase we can transcend her traits through inhibition of clavulanic acid , and some strains have ability with clavulanic acid resistance (63). At first it was believed that PER-1 present on the *P. aeruginosa* chromosome, but in the 1995 one of the studies was done which demonstrated the possibility of transferring this gene from one sample to another (64). There are some opinions and suggestions about the coupling of resistant plasmids between *Acinetobacter* and *P. aeruginosa* which may be similar to the conjugation of plasmids between PER-1 and produced by *S. typhimurium* (65). This indicates that the genes that encode PER-1 beta-lactamase is controlled through plasmid.The epidemiologically, it is *P. aeruginosa* that produce of PER-1, it is widespread in Europe and the north of Africa , as most strains are clinically isolated in intensive care

units and surgical wards in many countries, including Italy , France , Poland , Egypt and Turkey (66).

- The type of SHV: the first species of discovered of SHV type of beta lactamase is SHV-1 , that who are usually resistant to penicillin and other antimicrobials of beta lactam .Where there are about 189 strains from the type of SHV enzymes , as these enzymes are widespread in gram-negative bacteria as well as in some clinicains of *P.aeruginosa*.Where a limited number of strains of nosocomial infections have been isolated and that have the ability to produce SHV-2a, SHV-5, and SHV-12 (67 , 68). Among the studies conducted on the strain of SHV-5, as the patients were treated from the infection by giving them tazobactam and piperacillin. As the strain when it was studied was sensitive to piperacillin-tazobactam , penicillins and ticarcillin-clavulanate (69).The region -35 of SHV-2a of the left inverted repeat of IS26 and also found −10 region of the blaSHV-2a promoter that produce to form promoter of composite of the SHV-2a. AS the DNA that surrounds the promoter of blaSHV-2a SHV-2a usually homologous with plasmid pMPA2a of the KpZU-3 of *Klebsiella pneumoniae*.Therefore, the analysis of the evidence and some genetic features that are shared between the DNA sequences is evidence that *K. pneumoniae* which may be potential of origin of SHV-2a (69,70).The ESBLs and plasmids that act on the ability on create spread of ESBLs by environment through the food of chain , and that form high risks for the humans (70).

- Preention :

P. aeruginosa is considered one of the main causes of nosocomial infections, with a total number of about 51,000 cases reported each year , where it found about 13% every year, of which 6000 cases of these isolates were found to be multi-drug resistant. Drug-resistant bacteria are defined as bacteria that are resistant to three or more drugs (71). As 400 cases out of 6000 cases eventually lead to death , when making the comparison, it was found that there is a significant increase in the mortality rate of multidrug-resistant strains by 30% compared to non-resistant strains, which were 17% (72,73). Out-of-hospital exposure to *P.aeruginosa* is widespread and rarely leads to infection. Newborns are the only group at risk of infection, as well as people who are constantly exposed to water, such as in heated pools as well as the use of contact lenses for a long time.Therefore, this infection does not pose any threat to human life, unlike nosocomial infection of *P. aeruginosa* , which poses a real threat to individuals (74). It is known that hospital infections are common, with about 1.7 million infections only in the United States alone each year, and 99,000 deaths due to infection. Urinary tract infections are one of the most common causes of health care-acquired infections , after that, surgical site infections come in second place (75). Where catheters such as external catheters for men, proper as well as removal of catheters and antimicrobial catheters were used to reduce the number of infections (76). Some studies were conducted in 2008 to measure the rate of infection of catheters, where there was a decrease in rates that ranged in 2003 from 7.0 cases out of 10,000 cases to 5.1 cases out of 10,000 cases in 2008 (77). As the speed in discovering the causative agent of the disease before it turns into an invader is successful in treating the pathogen.This causes major problems for people with chronic sinusitis with *P. aeruginosa* , as these bacteria are commonly isolated from

people who have neutropenia and those with sinusitis (78).The pathogen is usually recurrence after successful treatment with antibiotics or through surgery.Thus, high-quality imaging techniques reduce costs for patients and prevent the spread of the pathogen .To distinguish the bacterial lesion from other lesions, (MRI) high-quality magnetic resonance imaging is used, which is combined with (CT) computed tomography ,Thus, we can quickly prevent severe infection (79). As a result of the foregoing , modern technologies are an urgent necessity for planning the treatment of lesions of the head and neck (80).

- Discussion :

P. aeruginosa poses the greatest threat to the health of patients with cystic fibrosis (CF) , as well as patients who are most susceptible to ventilator-related or associated pneumonia (VAP) , the VAP it is most commonly caused by *P. aeruginosa* (81). Cystic fibrosis patients, about 80-95% of them suffer from acute respiratory failure caused by bacterial infection accompanied by inflammation (82).Where it is considered the main cause of acute pneumonia in hospitals through ventilation, at a rate of about 86%, which is responsible for most deaths in intensive care units (83,84). The diagnosis of VAP is very difficult, where patients can be admitted multiple times in hospitals.The functions of the Centers for Disease Control include giving instructions on sterilization and methods needed to reduce the spread of acute pneumonia in hospitals and VAP, conducting educational seminars for employees on methods for preventing infection and monitors of microbiological and disinfection and sterilization operations, as well as the maintenance of equipment and devices , as well as preventing direct transmission of bacteria from one person to another and increasing of the host's defenses against pathogen , addministrate of the values of immune rates and preventing the occurrence of pneumonia after surgical operations (85). Where the comparison between rates was studied of VAP through the period between 2005 into 2013 (86). Where there is little research on prevention methods and their effectiveness in preventing of VAP. Where studies showed a significant decrease in the rates of VAP which has modern methods and methods for the prevention of VAP (87,88). One of the most famous and latest technologies used in the medical field to combat VAP are the bundles, as science continues to find the best ways to develop more effective antibiotic treatment, this leads to a reduction in nosocomial infections with *P. aeruginosa* and also lower rates of VAP (89). Adequate and complete support from hospital administration as well as patients' guests have the ability to impede the spread of *P. aeruginosa* and other nosocomial pathogens.Continuing education courses are conducted for hospital staff to ensure the success of infection control programs and appropriate training for these programs. In order for the patient to receive the appropriate care , highly experienced infection control personnel are sent to their hospitals and clinics, in addition to determining the appropriate doctor/nurse ratio to the patient (90).

Many hospital infections can be prevented by following the instructions in hospitals, however, visitors often carry infectious bacteria with them when entering the hospital. Where *P.aeruginosa* is commonly spread in water, ground soil, plants and plumbing, where hospitals cannot prevent such things with visitors when they

enter the patient. Where there is a set of guidelines and instructions that help in the spread of hospital infection in the Centers for Disease Control so that the public and the administration can avoid it. As well as identifying the trends of resistance and identifying the surrounding areas, and tracking the places of spread of regional and local infections and eliminating them. Doctors, nurses, staff and visitors must wash and clean hands well before they visit and touch the patient, as well as take only the required antibiotics.

From this it can be concluded that *P. aeruginosa* is opportunistic and lethal gram-negative bacteria, possessing many acquired and intrinsic defenses that allow resistance to huge numbers of antibiotics. As the medical and health field wages war and fight against *P.aeruginosa*, the persistently high death rate associated with bacteria remains. As modern antibiotics have become highly effective, with the increase in information about the pathogen and the increase in awareness about its spread methods and the increase in scientific research on combating these pathogenic bacteria. It is possible in the near future to contain and completely eliminate of these opportunistic pathogens .

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