DISSERTATION SUBMITTED FOR THE MASTER'S DEGREE IN MEDICAL MICROBIOLOGY

TITLE

ASSESSMENT OF BIOFILM FORMATION BY MICROORGANISMS IN MEDICAL DEVICES

SUBMITTED BY

FIZA MUSTAQ MANSOORI

2022

DEPARTMENT OF MICROBIOLOGY

INTEGRAL INSTITUTE OF MEDICAL SCIENCES & RESEARCH

INTEGRAL UNIVERSITY, DASAULI, KURSI

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"ASSESSMENT OF BIOFILM FORMATION BY MICROORGANISMS IN MEDICAL DEVICES"

A DISSERTATION Submitted to INTEGRAL UNIVERSITY in partial fulfillment of the requirements for the award of degree of

Masters of Sciences

In
Medical Microbiology

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TO

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This is to certify that the dissertation entitles **"Assessment of biofilm formation by microorganism in medical devices- A meta-analysis'**s" is a bonafide and genuine research work carried out by **Fiza Mustaq Mansoori** under the guidance of **Dr. Noor Jahan,** Professor & HOD, Department of Microbiology and Co-guides **Dr. Siraj Ahmad** (Professor & HOD) and **Dr. Ausaf Ahmad**, Associate Professor, Department of Community medicine, IIMS&R, Lucknow in partial fulfilment of requirement for the degree of Master of Science in Medical Microbiology.

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CERTIFICATE

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The above mentioned research work has been approved by Institutional Ethics Committee, IIMS&R with consensus in the meeting held on **19 May 2022**.

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INTRODUCTION

INTRODUCTION:-

It is challenging to cure a biofilms with antimicrobial medicines. indwelling medical device comprise a public health risk to population. Formation of biofilm cause a problem in medical amenity as well as in non-medical areas like industries. **Subramanian et.al,(2012)**

History of Biofilm:-

Animalcule is first time observed on the surface of teeth by a Dutch researcher Anton van Leeuwenhoek by use of microscope which was later recognized as the discovery of the microbial biofilm.

In natural world like hotels, bathroom, healthcare institution, laboratories biofilms may be found. Biofilms are habitually develops on submerged or aqueous solutions. It may also be developed on any surface, whether it's habited or uninhabited. **Costertonet.al (1999)**

Extracellular polymeric matrix helps the microbial cells to attach on one another on living as well as non-living surfaces to form a biofilm, which is help in the association of microorganisms.

COMPOSITION OF BIOFILM:-

A colony of microorganisms is known as a biofilm which produces extracellular polymeric substances (EPS) like proteins, enzymes, DNA, and RNA. Like these components, water (which can make up as much as 97 percent of a biofilm) contribute as a major component of the biofilm which is responsible for the nutrients flow within the matrix of the biofilm.

S.No.	Constituents	Percentage (%)
1.	Water	97%
2.	Microorganism cell	Up to 5%
3	Polysaccharides	Up to 2%
4.	DNA & RNA	<1-2%
5.	Protein	<1-2% (comprise enzymes)

Table 1 chemical composition of biofilm

Mechanism of biofilm formation:-

Microorganism cells undergo a transformation from a planktonic to a sessile mode of development during the production of biofilms, which is a noticeably complex process.

Okada et.al,(2005)

In addition to environmental factors, planktonic cells undergo a number of genetic and phenotypic alterations that contribute to biofilm development.

Five different stages have been suggested during biofilm development,

(i) Attachment

(ii) Micro colony formation

(iii) 3D biofilm formation

(iv) Maturation

(v) Dissemination

ATTACHMENT:-

A bacterial cell may create a reversible reference to the floor or have already bonded another type of microbe to the floor when it is so close to the floor that its travel down might be extremely sluggish.

Microorganism can easily proliferate in solid- liquid interface because it provides a

favorable condition to microorganism for biofilm formation. Hydrophilic, rough and covered surfaces provide a better condition for attain maximum biofilm growth and attachment. Water temperature and vitamin concentration promote the early and excessive growth of biofilm. Some locomotory system like flagella, fimbriae, pili are present on the cell surface which play an important role in the development of biofilm.

MICRO-COLONY FORMATION:-

Microorganism attach to the body surface or organic tissue and developed vigorously to form a micro-colony. Inside biofilm microorganism multiply which help in the chemical signaling Genetic pathway is initiated by the production of exopolysaccharide and it initiated when the depth reaches a particular threshold.so, the exopolysaccharide matrix and chemical signaling help in the production of microcolonies. **Mackenney et.al, (1998)**

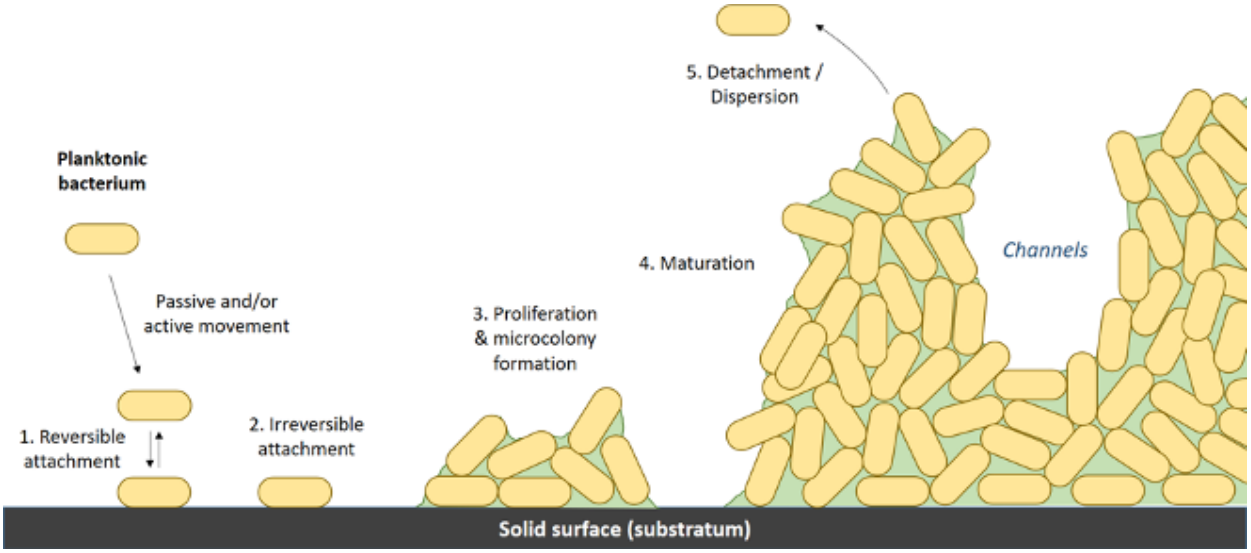
3-DIMENSIONAL MATURATION: -

Positive biofilm associated gene regulate the microcolony development. EPS is the product of biofilm associated gene which form the structural frame of biofilm. Extracellular matrix is help in the bacterial adhesion. in biofilm some water channel are formed for vitamin transport and these vitamins are help in the matrix formation. Water channel are act as a cardiovascular system which help in the transport of vitamins, and eliminate waste product inside the micro-colonies that promote the bio film formation. **Parsek et.al, (2003)**

DISSEMINATION:-

When the recent cells are detach from growing cell and the aggregates flowering effect or quorum- sensing result the dispersion of biofilm cell **Miller et.al,(2001)**

Some cells are eliminated in the biofilm due to the motion of some enzyme that cause digestion of alginate. Dispersal of biofilm show an adverse effect on phenotypic characteristics of organism. Dispersed biofilm cells sustain some biofilm property such as antibiotic sensitivity. Scattered cell form biofilm which helps in the growth and also rapidly regress the planktonic phenotype.



QUORUM SENSING:-

Cell-to-cell communication device is called "quorum sensing machine" which is used to coordinate between various population density. The Auto inducing peptides (AIP) and Agr (Accessory gene regular) are the S. aureus quorum sensing mechanisms that are activated by external ligands. The final stage for creating a biofilm is dispersion. It plays a key role in the growth of the biofilm and also contributes to systemic dispersion. **Boles et.al, (2008); Novick et.al, (2003)**

BIOFILM AFFECTED MEDICAL DEVICES:-

Medical device is any device which help in the advancement of health care and early diagnosis of patient to overcome their sickness. Medical device can be an appliance, tool, equipment and apparatus.

Mainly the biofilm formed by microorganism on medical devices like catheter, prostheses, lenses, fracture fixing device but Microorganism have great affinity for biofilm formation toward catheter, mechanical heart valve and orthopedic device, biofilm formation is also associated with some other infection like endocarditis and osteomyelitis. Biofilm also affect skin, lung and heart. there are 3 most prevalent DRIs centerline associated bloodstream infection (CRBSIs), ventilator-associated pneumonia, and Foley catheter- associated urinary tract infection.**Balaure et.al, (2020); Kwiecinski et.al,(2019)** and nearly 80% of known pathogenic bacteria have been implicated in device-related infections, such as intravenous and urinary catheters , joint prostheses penile prostheses , contact lenses , fracture fixation devices, breast implants, pacemakers , endoscopes , cardiovascular and biliary stents , and coherent implants .Biofilms infections of lungs, heart, skin, teeth ,urinary tract always injurious. there are 3 most prevalent DRIs centerline associated bloodstream infection (CRBSIs), ventilator-associated pneumonia, and Foley catheter- associated urinary tract infection.

Advani et.al, (20S18)

Central venous catheters-

For Injecting parenteral nourishment, blood components, or fluids CVS (central venous catheter) is used. CVS is mainly inserted in a large vein because small peripheral veins are rupture. There are differenttype of hospital acquired infection in which CVS contribute to 33% bloodstream infections. Bacteria facilitae the pathogen for creating more adhesion site which help in the multiplication and production of extracellular matrix (ECM) that help the bioflim for irreversible attachment from the catheter site. Attachment between biofilm and catheter is also depend on the physiochemical properties os catheter.

Urinary catheters:-

During surgery urinary catheterization is frequently used to get urine. Catheterization is also help in the retention of urine in ICU (intensive care unit). After removing the catheter from skin some peri-urethral pore helps in the colonization of bacterial infection which may be migrate to bladder and form a biofilm on catheter. **Sticker et, al. (2008)** pH of urinary bladder is alkaline which proliferate some urease producing microorganism like *Klebsiella* and *pseudomonas* and by using the alkaline environment of bladder microorganism promote the biofilm formation. **Neethirajan et.al, (2014)**. Urinary catheter can be prevented by change the catheter frequently and some other technique is also used. **Talsma et.al, (2007)**

Endotracheal tubes:-

Endotracheal tube is the most common proliferative site for microorganism proliferation to form biofilm. from different clinical site Numerous bacteria form a biofilm on endotrachial tube. Some bacteria that form biofilm on ventilator are *E. coli, K. Pneumoniae, Acinetobacter, P. aeruginosa.* **Bauer et.al, (2002).** Reports suggest numerous microorganisms, from orally related microflora to clinically unique isolates, can shape biofilms in endotracheal tubes. **Vandecandelare et.al, (2015,2012)**

Prosthetic joints:-

In artificial joints (prosthesis) loosening can also be a site for biofilm formation *S. epidermis* or *Propionibacterium* affect the prosthetic joints which lead to morbidity. **Mcminn et.al, (2012); Pozo et.al, (2009)**

Orthopedic implants:-

Hip implant replacement surgery failure have 15% chances to form a biofilm which lead to tissue destruction and inflammation of surrounding tissue that can cause a gingivitis. For preventing biofilm formation during orthopedic implant surgery, we can use plasma spraying, sand blasting and sintering. **Bozic et.al, (2009); Belibasakis et.al, (2014).**

Breast implants:-

Shortening and hardening of muscle and tissue of breast duct can cause a biofilm formation during breast implant. **Bartsich et.al, (2011); Courtiss et.al, (1979); Thornton et.al,(1998)**

Pacemakers and Heart Valves:-

In cardiac implantation like pacemaker implant, *P. aeruginosa, , Klebsiella pneumonia, E. coli, Acinetobacte baumannii P. acnes, and S. epidermidis* commonly cause a biofilm. **Viola et.al,(2011) Darouiche et.al(2004); Vongpatanasin et.al, (1996)** Other microbes, such as *Enterococcus a*nd yeasts, also form biofilms o Biofilm can form in any environment in vitro or in vivo but more thicker biofilm is formed in prosthetic valves, coronary artery bypass graft and defibrillators in in vivo conditions cardiovascular devices Chifiriuc et,al (2011) . systemic biofilm infection is produced by mycobacterium fortuitum on heart valves. When biofilm is formed on heart valves it decrease the blood flow which affect the other organs that ultimately form emboli. Bosio et,al.(2011).

Biofilm forming bacteria:-

Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus viridans, E. coli, Klebsiella pneumoniae, Proteus mirabilis, and *Pseudomonas aeruginosa* are the most frequent types gram- positive and gram –negative bacteria which form biofilm on medical devices. 40 and 50 percent infections of prosthetic heart valves cause by S. *aureus* and *S. epidermidis* as well as 50–70% of catheter biofilm and 87% of bloodstream infections Is also caused by *S. aureus* and S. *epidermidis* **Chen et.al, (2013)**

The staphylococcal species are responsible for two-thirds of implanted device-related infections, with *S. aureus* and coagulase-negative *staphylococci* accounting for the bulk of these infections. **Ribeiro et.al,(2012)** Another common gram-negative bacteria, P. aeruginosa, is well recognised for quickly adapting to severe conditions and medications. It has been frequently utilised as an in vitro model for research on biofilm formation**. Rahim et.al,(2016); Chang et.al,(2018)**

***Staphylococcus aureus*:-**

S. aureus is a multi-drug resistant bacteria causing a number of nosocomial infections. It grows on catheters and chronic *S.aureus* is a multi-drug resistance bacteria causing a number of nosocomial infections. It grows on catheters and chronic wounds as biofilm. **Novick et.al,(2008); Voung et.al,(2002)** *S.aureus* recycles proteins for the formation of the extracellular matrix in the cytoplasm. The cytoplasmic protein also working as matrix protein allow enhanced flexibility and adaptation to *S.aureus* in forming biofilms in infectious condition and could encourage the formation of mixed-species biofilms in chronic wounds**. Foulstone et.al, (2014)**

***Staphylococcus epidermidis*:-**

It is the most common CoNS (75-80%), isolated from clinical samples. It is present as normal flora on the skin, oropharynx and vagina; however, its pathogenic role is greatly enhanced in presence of prosthetic- devices.

S. epidermidis is the most common cause of prosthetic- device related infections, such as endocarditis with insertion of valvular prosthesis and ventricular shunt infection. It is also a common cause of stitch abscess.

***Pseudomonas aeruginosa*:-**

P. aeruginosa is an oxidase positive, pigment producing non- fermenting gram negative bacilli. It is a major pathogen among the hospitalized patient and in patient with cystic fibrosis. *Pseudomonas* is known to possess gene coding for resistance to several antimicrobial agents; thereby helping the bacilli to survive under antibiotic pressure especially in the hospital environment. Biofilm formation is another mechanism by which it prevents the entry of antibiotics into the bacterial cell.

Pseudomonas aeruginosa is notorious to cause infection at almost sites, most common being lungs, skin and soft tissue, most of the infections are encountered in hospitalized patients who get colonized with the organisms either from heavily contaminated hospital staff (through contaminated hands). VAP (ventilator associated pneumonia) develops among patients on ventilator in intensive care units.

***E. coli* :-**

E. coli is a rod shaped Gram negative bacteria causing a large number of nosocomial and community infections such as urinary tract infections (UTIs) and prostatitis. It has the ability to secret toxins, polysaccharide and can form biofilm. It can also form biofilm *in-vitro*. **Naves et.al,(2010)**

E. coli capsules are high molecular weight molecules and are attached to the cell surface. *E. coli* capsule play an indirect role in biofilm by protecting bacterial surface adhesion. Different environmental conditions affect *E. coli*capability to form biofilm. Thickness of *E. coli* biofilm may be of hundreds of microns and posing a difficulty in treatment with antibiotics due to presence of exopolymers**. Larson et.al,(2003)**

Klebsiella pneumonia:

K. pneumoniae is a Gram-negative bacterium, frequently causing nosocomial infections, belongs to the genus *Klebsiella*.

K. pneumoniae is very important species among genus *Klebsiella* and causing a considerable proportion of nosocomial infections such as urinary tract infections (UTI), pneumonia, septicemias and soft tissue infections. **Ellis et.al,(1998).**

In vitro and *in vivo* biofilm detection methods:-

Method	Advantages	Disadvantages	References
In vitro biofilm detection			
Congo red agar Test	High efficiency in the detection of *Staphylococcus* sp. Biofilm Producers	Low reversibility	Melo *et al*. (2013)
Tube biofilm formation test	Low cost	Subjective reading	Halim *et al*. (2018)
Microplate test	Low cost Several tests can be done simultaneously	Lack of standardization in the interpretation of results	Qu *et al*. (2017)
Crystal violet	Low cost Simple technique High replicability	Low specificity	Xu *et al*. (2016)
Safranin	Non-toxic dye	Low replicability and sensitivity	Stepanovic et al. (2007); Ommen *et al*. (2017)

Method	Advantages	Disadvantages	References
XTT	Simple technique High replicability	High cost Low sensitivity salt Retention by the pathogens that can interfere with the result	Costa-Orlandi *et. al.* (2017)
In vivo biofilm detection			
D. melanogaster	High homologies between the *Drosophila* and human genomes Easy to handle Inexpensive to maintain	Preference for and *Escherichiacoli* for small genomes Does not have hemoglobin yeasts having	Yamaguchi and Yoshida (2018)
C. elegans	Powerful methods physiological processes for studying	Nematode culture standardization factors may interfere with its survival	Park *et al*. (2017)

Table no:2

Bacterial biofilm may play a role in the pathogenesis of disease has led to an increased focus on identifying diseases that may be biofilm- related. Biofilm infections are typically chronic in nature, as biofilm- residing bacteria can be resilient to both the immune

system, antibiotics, and other treatments. Biofilm can cause diseases in the auditory, the cardiovascular, the digestive, the integumentary, the reproductive, therespiratory, and the urinary system. **Vestby et.al,(2020)**

Biofilm-associated diseases of different body systems and their affected organs.

Body System	**Affected Organs**	**Disease**
Auditory	Middle ear	Otitis media
	Arteries	Atherosclerotic disease
Cardiovascular		
	Cardiac valves	Endocarditis
Digestive	Salivary glands	Sialadenitis
Digestive	Gall bladder	Cholecystitis

Body System	Affected Organs	Disease
	Gastrointestinal Tract (GIT),	Inflammatory bowel disease (Crohn's disease, Ulcerative colitis) and colorectal cancer & food poising
Integumentary	Skin and tissue	Wound infections
Reproductive	Vagina	Bacterial vaginosis (BV)
Reproductive	Uterus and fallopian tubes	Chronic endometritis, Salpingitis
Reproductive	Mammary glands	Mastitis

TREATMENT OF BIOFILM INFECTIONS:-

As indicated in multiple publications, biofilm infections are challenging to cure and frequently cannot be treated with just antibiotics. In general, the methods can be classified as involving or not a foreign body. If there is no foreign body present, the infection may be completely eradicated with long- term use of high doses and frequently a combination of medicines with particular killing mechanisms. However, removal of the material is typically required if a foreign body is involved in order to achieve success. In other situations, the only treatment options are biofilm depletion, persistent biofilm suppression, or waiting for a biofilm relapse to occur, abscess and foreign body removal.

In animal soft tissues, it has been shown that high inoculums of *Staphylococcus aureus* (108 CFU/mL; CFU, colony forming units) could not cause any abscesses in the absence of a foreign body, whereas 102 CFU/mL of *S. aureus* were sufficient to cause an infection with a foreign body in 95% of the cases. Naturally, a foreign body offers a perfect surface for

bacteria to attach to, hence its presence dramatically raised the risk of biofilm infection. It is currently challenging to treat biofilm infections with conventional antibiotics due to the biofilm characteristics of antibiotic resistance. As a result, the clearance of such biofilm infections becomes critically dependent upon the removal of a foreign body. In the event that it is not possible to remove the infected foreign body, it may be indicated to try to minimise the biofilm load with antibiotics before continuing suppressive antibiotic treatment to stop the biofilm from growing again.

Effective antibiotic therapies and removal of the infected foreign bodies are critical to curing infections in patients with biofilm infections in biliary stents, endotracheal tubes, dead bones (chronic osteomyelitis), biliary and urinary stones (biliary and urinary tract infections).

EMPTY OF ABSCESSES:-

Although abscesses are not biofilm, they do have certain similarities with it. Antibiotics find it challenging to pass through the abscess wall and reach the focus when an abscess forms. Therefore, it is vital to empty the abscess. Early and competitive antibiotic treatments towards biofilm infections is in vitro research shown that, in contrast to mature biofilm, juvenile biofilm might be easily removed by antibiotic therapy. As a result, prompt and forceful antibiotic treatments are advised for biofilm infections. However, early biofilm infection analysis is difficult at the moment, and the majority of clinical biofilm infections are actually mature biofilms that are difficult to eradicate with antibiotic therapy. In order to effectively treat biofilm infections, it is crucial and essential to use currently available antibiotics.

Selection of antibiotics:-

If the amount of oxygen available is insufficient to satisfy the demand, glycolysis will start, causing acidosis, and pH levels may have an impact on how well antibiotics work. Previous research have shown that effect of rifamycin SV can increase due to low pH values (pH 5.2) while the effects of β -lactam antibiotics decreases. As a result, acid-base balance issues may be critical by treating biofilm infections with antibiotics.

Administration of antibiotics:-

Antibiotic combination therapy against biofilm infection has previously been shown to be significantly superior to the treatment of biofilm infection necessitates sensitive and deeply penetrating antibiotics to guarantee an adequate dose of effective antibiotic is given at the site of biofilm infection. Generally speaking, macrolides, lincosamides, tetracyclines, rifamycins, quinolones, fusidic acid, nitroimidazole, sulfonamides, and oxazolidinones penetrate tissues and cells more effectively than beta-lactam (including penicillins, cephalosporins, and carbapenems), aminoglycosides, glycopeptide, and polymyx Inflammation brought on by sickness is well recognized to increase metabolism and systematic or domestic oxygen intake antibiotic monotherapy. Therefore, antibiotic combination therapy is advised for the management of biofilm infections. High dosages of antibiotics within the safe range of renal and hepatic functions are recommended in light of the characteristics of antibiotic tolerance and resistance in biofilm and the high MIC (Minimum inhibitory concentration) and MBC (Maximum bactericidal concentration) of biofilm cells reported in experimental studies. An appropriate antibiotic treatment course

duration is also crucial. Systemic mixed with topical antibiotic treatment can have better benefits against biofilm infections, such as antibiotic inhalation or direct administration for airway biofilms, for patients with biofilm infections suited for topical treatment with high doses of antibiotics.

PREVENTION OF MICROBIAL GROWTH:-

Chemical modifications are the main strategy for biofilm prevention on indwelling medical devices includes Antibiotics, biocides, and ion coatings are commonly used chemical methods of biofilm prevention. Theyprevent biofilm formation by interfering with the attachment and expansionof immature biofilms.

REVIEW OF LITERATURE

REVIEW OF LITERATURE:-

In a study by M Archana et al.(2022):-Out of 50clinical isolates,48(96%) were found to produce biofilm. Among 10(100%) out of 10 *CONS* , 8(66.8%) out of 12 Gram negative bacteria ,28(96.5%) out of30 *Candida* were biofilm producers.

In a study by Mansabdar et al.(2022):-72 isolates, the predominant biofilm producing isolates were *Staphylococcus aureus* (56%), *Klebsilla spp.(*15.2%), *CONS* (8.3%), *Pseudomonas spp.*(6.9%), *Citrobacter* (5.5%), Non fermenting gram negative bacilli (NFGNB) (4.1%), *E. coli* (2.7*%), Providencia species.* (1.3%).

In a study by Purushottam et al.(2022):- Among 145 bacterial isolates obtained in this study 98 (67.5%) samples showed positive biofilm formation. Among 30 ASB isolates 56.6% have produced biofilm,18(75%) out of 24 *micrococci* isolates, 13(62%) out of 21 *diphtheroid* isolates, 16(88.8%) out of 18 *CONS* isolates, 16(100%) out of 16 *Klebsiella* isolates,

4(33.3%) out of 12 *Proteus* isolates, 4(40%) out of 10 *Citrobacter* isolates, 5(62.5%) out of 8 *Escherichia coli* isolates and 6 (100%) out of 6 *Staphylococcus aureus* also produced biofilm.

In a study by Gogoi et al.(2021):-Out of the 115 bacterial isolates, 71 were biofilm producers. Tissue culture plate method detected the maximumnumber of biofilm producers (61.7%). The maximum number of biofilm producers were isolated from tracheal aspirate and endotracheal tubes (52.1%) followed by blood (17%) and urine (12.6%) respectively. The predominant biofilm producing isolates were *Klebsiella pneumoniae* (39.4%),

Staphylococcus aureus (19.7%) and *Pseudomonas aeruginosa* (16.9%),*Escherichia coli*(9.8%),*Staphylococcus epidermis* (7%),*Enterococcus sp*.(4.2%), *Acinetobacte rbaumanni*(1.4%), *Proteus mirabilis*(1.4%).

In a study by Baidya et al.(2021):- Out of the 71 isolates, 56.3% were biofilm producers. The predominant biofilm producing isolates were *Pseudomonas aeruginosa* (19.7%), *Acinetobacter* (9.9%), *Klebsiella pneumoniae* (9.9%), *Staphylococcus aureus* (2.8%),*E. coli* (2.8%).

In a study by Gunardi et al.(2021):- Out of 109 catheterized patients, 78% of the catheters were culture positive, which was higher than those of the urine samples (37.62%). The most common species isolated from the catheter cultures were *Escherichia coli* (28.1%), *Candida* sp.(17.8%), *Klebsiella pneumoniae* (15.9%),and *Enterococcus faecalis* (13.1%). *E. coli* (83.3%) and *E. faecalis* (78.6%) were the main isolates with a positive CRA (Congo red agar).

In a study by Rajmane (2021):- Gram-negative organisms were predominant (83.24%) of all the isolates. Biofilm production was detected in 47% of the isolates. *Pseudomonas aeruginosa* (51.7%), were the most common biofilm producing Gram negative bacilli followed by *Escherichia coli* (44.32%). Amongst Gram positive cocci, *Enterococcus faecalis* (77.8%) was the most common biofilm producing organism.

In a study by Patel et al.(2021):-Total 61 isolates recovered from 55 patients, 52.4% were biofilm producer. Most common isolates were *pseudomonas aeruginosa* (22.95%) followed by *Enterococcus faecium* (13.11%). *Candida tropicalis* and *Klebsiella pneumoniae* were

seenamong 11.47% each.

In a study by Uzuegbunam et al.(2021):- Out of 217 significant bacteriuria isolated, 38 strains produced biofilms were *E.coli* (52.6%),*S. aureus* (15.7%), *Klebsilla pneumoniae* (13.15%), *CONS* (10.5%), *Pseudomonas spp*.(7.8%).

In a study by Kovalchuk et al.(2021):-: Results showed that in standard medium (trypto-soy broth), strains of *P. aeruginosa* (90%) and *A. baumannii* (60%) obtained high biofilm forming activity.

In a study by Raveendra et al.(2021):- Out of 35 patients, 57% of the isolates were biofilm producers and 43% were non biofilm producers. The organisms found were *Acinetobacter baumannii* (45%) was the commonest, followed by *Klebsiella pneumonia* (20%) and *Staphylococcus aureus* (10%). *Klebsiella pneumonia* (40%) was the commonest non biofilm forming organism, followed by *Pseudomonas aeruginosa* (33%).

In a study by Diriba et al.(2020):-From 127 bacterial isolates screened for bioflm formation, 84 (66.1%) of them were biofilm producer and most common isolates were *S.aureus* (22.8%),*CONS* (32.2%), *S. pyogenes* (3.9%), *S.agalactiae* (3.9%), *S. viridians* (2.3%),*Pseudomonas aeruginosa* (7.8%), *K. Peumoniae* (7%), *P. mirabilis* (3.9%),*P. vulgaris* (3.1%), *S. marcescens* (2.3%),*Citrobacter spp*.(3.9%), *Enterobacter spp*. (2.3%), *E. coli* (3.9%).

In a study by Almalki et al.(2019):-In this study, out of 585 isolates from 350 samples were subjected to biofilm detection. Among this, 63.9% of them were non-biofilm forming

organism and 36% of the isolates were found to form biofilm. Out of 211 isolates, significant biofilm producers were *E coli* (24%), *ESBL E.coli* (2%), *Klebsiella* (19%), *E.. fecalis* (8%), *S. aureus* (3%), *P. mirabilis* (18%), *Pseudomonas aeruginosa* (17%) and *Citrobacter* (9%).

In a study by Awoke et al. (2019):-From all bacterial isolates among urinary catheterized patients, forty-three (79.7%) of them were biofilmformers. From among Gram-negative and Gram-positive bacterial isolates, 34 (81%) and 9 (75%) of them were biofilm formers, The most common species isolated from the catheter cultures were *E.coli* (42.8%), *Klebsilla spp*.(28.5%), *P.aeruginosa (*7.1%),*Proteus spp*.(9.5%),*Citrobacter spp.* (7.1%), *Enterobacter spp*. (4.2%).

In a study by Jirawatnotai et al.(2019):- 33 paired samples of capsular tissue and silicone implants were analyzed. Biofilms were detected in 10%.The organisms found were *Staphylococcus epidermidis* (47.10%), coagulase-negative *staphylococci* (35.30%), and *Staphylococcus aureus* (17.60%).

In a study by Dumaru et al.(2019):-A total of 197 (62.73%) isolates were biofilm positive as detected by either tube adherence or Congo red agar method. The organism found were *E. coli* (60.33%), *Acinetobacter spp*. (53.97%), *Klebsilla spp.* (77.55%), spp. (73.68%), Enterobacter spp.(59.26%), *Citrobacter spp*. (62.50%), *Proteus spp*.(40%).

In a study by Meshram et al.(2019):-Out of 116 isolates, biofilm production was seen in 17 (14.66%) isolates and species were 9(18.75%) out of 48 *S.aureus* isolates, 2(66.67%) out of 2 *S.epidermidis* isolates, 1(50%) out of *2 E.faecium* isolates, 2(28.57%) out of 7 *C.koseri*

isolates, 1(20 %) out of 5 *E. coli* isolates, 1(100%) out of 1 *P.mirabilis* isolates, 1(7.69%) out of 13 *A. baumannii* isolates also produced biofilm.

In a study by Siddhiqui et al.(2018):- Out of 112 isolates, *Pseudomonas aeruginosa* showed maximum biofilm production 70%, followed by *Staphylococcus aureus* (59.46%), *Klebsiella spp* (44%),*Staphylococcus epidermidis* (42.85%), Lastly *E coli* showed biofilm production in only (32.14%) of isolates.

In a study by Oliva et al.(2018):-Biofilm production was evaluated in 22 staphylococcal strains: 15 (69%) strains were biofilm producer, bacterial species were 73% of *S. epidermidis*, 67% of *S. aureus*, and *S. hominis* produced biofilm.

In a study by Surekha et al.(2018):- For detection of biofilm formation, out of the 100 indwelling devices processed, 52 bacterial isolates showed growth and these were subjected for biofilm production detection by tissue culture plate (TCP) method, Tube method (TM) and Congo red agar (CRA)method. Of the 52 bacterial isolates, 42 isolates (80.7%) were found to be biofilm producers.

From intravenous catheters (80%), of isolates were biofilm producers, the majority of the organisms associated with biofilm production were *Staphylococcus epidermidis* (45%), *Pseudomonas aeruginosa* (15%), *S. aureus* (10%), *E. coli* (5%).

From Endotracheal tubes (86%) of isolates were biofilm producers, the majority of the organisms associated with biofilm production were *Klebsilla pneumonia* (36%), *Acinetobacter baumanii* (21%), *Pseudomona s aeruginosa*(14%), *E.coli* (7%), *Staphylococcus epidermidis* (3%) ,*S.aureus* (3%).

From Nasogastric tubes, 1 isolate of *Klebsiella pneumonia* (25%) was a biofilm producer. From intercostal drain tubes, 1 isolate of *Acinetobacter baumanii* (50%) was a biofilm producer.

In a study by Tiwari et al.(2017) :-Total 368 bacterial uropathies isolates biofilm producer were *Pseudomonas aeruginosa* (41.84%) *Enterococcus faecalis* (19.02%) and *Staphylococcus aureus* (16.84%) were strong biofilm forming.

In a study by Shrestha et al.(2017):-Among 52 isolates, *S. epidermidis* (52%) was the most common species which was followed by *S. saprophyticus* (18%) and *S. haemolyticus* (14%).

In a study by Shinde et al.(2017):-

A total of 50 isolates are recovered from 148 catheter tips. Amongthese, 24 (48%) were biofilm producers and species were *S.aureus* (75%), *S. epidermidis* (75%), Pseudomonas aeruginosa (60%), *Acinetobacter baumannii* (50%), *Klebsilla pneumoniae* (42.8%), *Enterobacter cloacae (*40%).

In a study by El-Ganiny et al.(2017):-All isolates were tested for biofilm production. Only 12 isolates (10.8%) were moderate biofilm forming, 25 isolates (22.5%) were weak biofilm forming and 74 (66.6%) were non biofilm forming, and species were *Pseudomonas aeruginosa*(59.4%), *S.aureus* (21.6%), *S.epidermidis* (10.8%), *S.saprophyticus* (5.4%), *Klebsilla spp*. (2.7%).

In a study by Murugan et al.(2016):- From 50 culture positive urinary catheters *S. aureus* (24%), *P. aeruginosa* (18%), *E. faecalis* (14%) andothers (44%) were isolated.

In a study by Neeli et al.(2016):-49 samples showed culture positivity; out of which, 18 produced biofilms were *Escherichia coli* (44.44%), *Klebsiella spp*. (33.33%), *Pseudomonas sp.*(11.11%) and *Candida* (11.11%).

In a study by Patel et al.(2016):- Of the 50 clinical isolates, 42 were biofilm producers, in which 24 were strong producers, 15 were moderate and 3 were weak producers. Catheter blood yielded the highest 38% ofbiofilm producers. *Acinetobacter spp*. (30%), *Klebsiella pneumoniae* (22%), *Pseudomonas aeruginosa* (16%), *Staphylococcus spp.* (14%), and *E. coli* (12%) were the most common isolates.

In a study by Tayal et al.(2015):- A total of 200 urine specimens, biofilm production was detected in 27% isolates. Maximum biofilm production was seen in *Enterococcus spp.* (71%), followed by *Escherichia coli* (26%) isolates showed biofilm formation followed by 18% of *K. pneumonia* isolates.

In a study by Hedayati et al.(2014):-Overall, 54 (71%) IVCs were colonized and 76 bacteria were isolated among which, (84.2%) were coagulase negative *staphylococci* (CoNS), (3.9%) *S. aureus*, (3.9%) *Enterococcus spp.* , (2.6%) *E. coli*.

In a study by Chatterjee et al.(2014):-Of all strains, (89.33%) were found to be biofilm positive . Predominant organisms were *Pseudomonas aeruginosa* (30.67%) followed by *Staphylococcus aureus* (15.11%), *E. coli* (13.78%), *Klebsiella pneumoniae* (12%),

Staphylococcus epidermidis (8.44%).

In a study by Gurung et al.(2013):-A total of 46 of the 109 isolates (42.2%) showed biofilm production. Biofilm was detected in (33%) of *P. aeruginosa* and (50%) of *A. baumannii*.

In a study by Prasmodhini et al.(2012): -Total 100 urine samples from catheterized patients, *E. coli* was found to be the most frequently isolated uropathies 70%, followed by *Klebsiella pneumoniae* 16%, *Pseudomonas aeruginosa* 4%, *Acinetobacter spp.* 2%, coagulase negative *Staphylococci* 6% and *Enterococci Spp* 2%.

In a study by A Summaiya et al.(2012):- In this study,56 isolates 37 (66.1%) isolates were MDR and from them 27 (48.2%) isolates were associated with strong biofilm formation. Acinetobacter spp. was the most common organism isolated (26.8%) and also associated with strong biofilm formation (33.3%). It was also the most common multidrug resistant organism (35.1%) followed by *Pseudomonas aeruginosa* (18.9%), *Klebsiella pneumoniae* (18.9%), *E-coli* (13.5%) and *Staphylococcus aureus* (10.8%).

In a study by Mulla et al.(2011):- Out of the total 100 bacterial isolates tested, 88 of them were biofilm formers in which 25% *Acinetobacter baumanni,* 20.4% *Pseudomonas aeruginosa,* 22.7% *Klebsiella pneumoniae* sub spp. *pneumoniae,* 12.5% *E.coil,* 9.0% Coagulase negative *Staphylococci,* 4.5% *Enterobacter cloacae,*3 .4% *Enterococci* , and 2.2% *Staphylococcus aureus* .

In a study by Hassan et al.(2011):- Among 110 isolates, TCP, the standard method, detected 25 as strong and 45 as moderate biofilm producers. The majority of the organisms

associated with biofilm production were *S.epidermidis* (37.1%) followed by*E.coli* (27.1%), *K.pneumoniae* (15.7%), *S. aureus* (11.4%), *E. faecalis* (4.2%) and *P. aeruginosa* (4.2%).

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES:-

AIM:-

The aim of this study is to provide a comprehensive analysis of the literature on biofilm formation by microorganisms in medical devices.

OBJECTIVE:-

- To determine the most common microorganism in biofilm formation.
- To determine the various microorganisms that cause biofilmformation.

MATERIAL AND METHOD

MATERIAL AND METHOD:-

TYPE OF STUDY:-Meta analysis

PLACE OF STUDY:-

Department of Microbiology, Integral Institute of Medical Science andResearch.

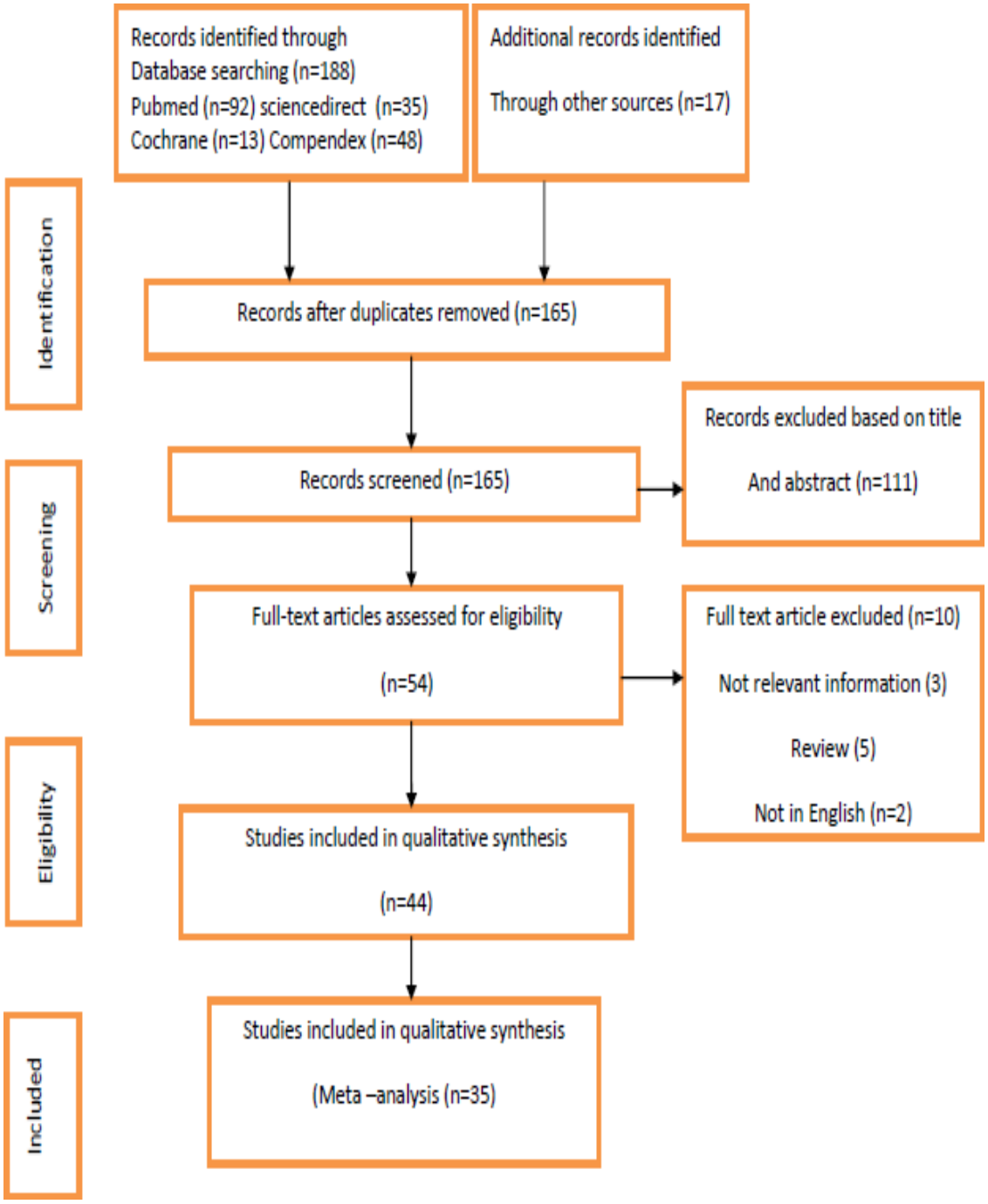
SAMPLE SOURCE:-Pubmed, Hindwi, Google scholar

TIME FILM:-The research paper that have been included are from 2011to 2022.

METHODOLOGY:-

The articles included in the study are selected from various websites such as PubMed; Google scholar etc. by using Preferred Reporting Items for Systematic Review and Meta-Analysis PRISMA guidelines. Last 10 years (2011 – 2022) articles that were published in high impact journals were included in the study .This method for analysis of articleswas proved to be more helpful for the systematic literature review. Moreover, the reference sections of the articles included in the study was done by using database search however the articles that are not found through this are identified by using Mendeley, Google scholar etc. for précised referencing. The articles that mainly focuses on various forms species of microorganisms which causes biofilm formation were taken into an account for this study. Peer-reviewed full-text articles were also assessed to obtained are liable data related to different forms of bacteria. The study not only emphasize on those articles that have discuss only about different forms of bacteria causing biofilm formation but also those studies that have briefly explained about the medical device and others related devices that can be used for detection of such bacteria that results in biofilm formation. Moreover, Data for study was also taken from review articles.

STUDY SELECTION:-



RESULTS

RESULT:-

A total of 205 studies were received and 70 full texts were reviewed from publicly available databases (Web of Science, PubMed, and Google Scholar). Thirty-one studies met our inclusion criteria . The final data set included studies covering 13 countries (most of them from India). All available and relevant data were extracted of each study, more exactly, biofilm prevalence, biofilm forming microorganisms. The majority of studies were included published in the last 5 years (2021 onward, 8/35 [22.8%]).Based on our findings, *Pseudomonas aeruginosa*was the most highly isolated micro-organism that was demonstrated in variousstudies such Dumaru et al.(2019),Kovalchuk et al.(2021,Rajmane(2021),Shinde et al.(2017), El-Ganiny et al.(2017) and so on.

So based on our findings we conclude that *Pseudomonas pneumonia* was highly isolated organisms and other were *Klebsilla pneumonia S.aureus, E. coli, S.epidermidis , Acinetobacter baumannii, CONS* **.**

S.NO	Author and Year	Settings	Duratio-n of Data Collection	Country	Design	Medical Device	Method of Detection	Total Sample	Positive Sample
1	M Archana et al,2022	Tertiary care Hospital	12 months	India	PS	Catheters	TCP method	50 Isolate	96%
2	Mansabdar et al,2022	Tertiary care Hospital	12 months	India	PS	Orthopedic implants	TCP,TM,CRA	120 Isolates	60%
3	Purushottam et al,2022	Tertiary care Hospital	20 months	India	CS	Contact lenses	CRA	145 Isolates	67.50%
4	Gogoi et al,2021	Tertiary care Hospital	12 months	India	PS	ICU medical devices	TM,CRA,TCP	117 Isolates	60.68%
5	Baidya et al,2021	Intensive care unit	7 months	India	CS	Ventilators	TCP	71 Isolates	90.01%
6	Gunardi et al,2021	Tertiary care Hospital	5 months	Indonesia	CS	Urinary Catheters	CRA	109 Isolates	78%
7	Rajmaneet al,2021	Tertiary care Hospital	18 months	India	PS	NA	CRA	352 Urine sample	47%
8	Patel et al,2021	Intensive care unit	18 months	India	OS	Catheters	TCP	60 Isolates	79.70%
9	Uzuegbunam et al,2021	National obsteric fistula centre	7 months	Nigeria	CS	Silicon implants	Ultrasonication	33 samples	10%
10	Kovalchuk et al,2021	Burn and surgery department	NA	Ukraine	NA	NA	TCP	10 clinical strains	100%
11	Raveendra et al,2021	Tertiary care Hospital	12 months	India	PS	Tracheostomy tubes	TCP	35 samples	43%
12	Diriba et al,2020	Medical centre	4 months	Ethiopia	CS	NA	TCP	127 Isolates	66%
13	Almalki et al,2019	Tertiary care Hospital	NA	Saudia Arabia	PS	Catheters	TM	585 Isolates	36%
14	Awoke et al,2019	Medical centre	7 months	Ethiopia	CS	Catheters	TCP	60 Isolates	79.70%
15	Jirawatnotai et al,2019	Plastic and surgery unit	24 months	Thailand	PS	Silicon implants	Ultrasonication	33 samples	10%
16	Damaru et al,2019	Tertiary care Hospital	24 months	India	PS	NA	CRA,TM,TCP	116 Isolates	14.66%

17	Shiddquiet al,2018	Tertiary care Hospital	3 months	India	PS	Indwelling devices	CRA,TCP, TM	112 Isolates	50.9% - TCM,TM - 29.4%,CRA-14.25%
18	Oliva et al,2018	NA	NA	Italy	Ps	Pacemaker	Christensen method	22 bacterial strains	69%
19	Surekha et al,2018	Tertiary care Hospital	6 months	India	CS	Indwelling devices	TCP,TM,CRA	52 Isolates	80.70%
20	Tiwari et al,2017	Tertiary care Hospital	12 months	India	RS	Urinary Catheters	TCP	368 Isolates	24.78%
21	Shrestha et al,2017	Tertiary care Hospital	11 months	Nepal	CS	CVC ,Trachesto my tubes	TM,CRA,TCP	52 Isolates	65.38%
22	Shinde et al,2017	Tertiary care Hospital	6 months	India	PS	Catheters	TCP	50 Isolates	48%
23	El-Ganiny et al,2017	Benha Universi ty and hospital	NA	Egypt	PS	Contact lenses	TCP	111 Isolates	100
24	Muruganet al,2016	Headqua ter Hospital	24 months	Saudia Arabia	PS	Catheters	TCP,TM,CRA	50 Isolates	14%
25	Neeli et al,2016	Tertiary care Hospital	6 months	India	PS	Urinary Catheters	TCP,TM,CRA	49 Isolates	36.70%
26	Patel et al,2016	Tertiary care Hospital	8 months	India	PS	Indwelling catheters	TCP	50 Isolates	84%
27	Tayal et al,2015	Tertiary care Hospital	12 months	India	PS	Urinary Catheters	TCP	200 urine specim en	27%
28	Hedayatiet al,2014	Tertiary care Hospital	12 months	Iran	PS	Itravenous catheters	TCP ,CRA	76 Isolates	64.50%
29	Chatterjee et al,2014	Tertiary care Hospital	24 months	India	PS	Catheters	Christensen method	225 Isolates	89.33%
30	Gurung et al,2013	Intensive care unit	4 months	India	PS	NA	Test tube method	109 Isolates	42.20%
31	Prasmodh ini et al,2012	Tertiary care Hospital	6 months	India	PS	Catheters	TM,CRA	100 Isolates	60%
32	A Summaiya et al,2012	Tertiary care Hospital	6 months	India	PS	Endotrache al tubes	TCP	56 Isolates	48.20%

33	Mulla et al,2011	Tertiary care Hospital	NA	India	PS	Catheters	TCP	100 Isolates	88%
34	Hassan etal,2011	Tertiary care Hospital	6 months	Pakistan	PS	Catheters tip,intravenous catheters	TCP,TM, CRA	110 Isolates	TCP-22.7%

TCP-Tissue culture plate, CRA- Congo red agar, TM – Tube method,PS-Prospective study, CS-Crosssectional ,RS-Retrospective study

DIFFERENT STUDIES IN MEDICAL DEVICES

DISCUSSION

DISCUSSION:-

Bacterial biofilm has long been recognized as a virulence factor generatinghospital acquired infections and being linked to infections caused by a variety of medical equipment.

Bacterial biofilm has long been recognized as a virulence factor producing nosocomial infections and contributing to infections linked to numerous medical devices.

The prevalence of biofilm-related illnesses reflects a current and expanding unmet medical need as the usage of indwelling medical devices (IMDs) rises. We looked at 35 articles in all that dealt with the formation ofbiofilms and its detection using one of three techniques, namely:

1. Tissue culture plate method
2. Tube technique
3. Congo red agar

According to our analysis, catheters are the medical instrument that are used most frequently. For the provision of fluids, blood products, medications, and nutritional solutions, catheters may be placed. *Pseudomonas, Acinetobacter, Klebsiella, Staphylococcus, Enterobacter* and *E. coli* are the most common causes of nosocomial infections, and that may be common cause of colonization in indwelling medical devices Theseare commonly associated with biofilm production .

Based on our study we deduce that *Pseudomonas aeruginosa* was mostly associated with biofilms. We found 73.68% in a study by Dumaru et al.(2019),59.4% in a study by El-Gainny et al.(2017),60% in a study by Shinde et al.(2017) and so on, and other were

Klebsilla pneumoniae ,S.aureus, E. coli, S.e pidermidis ,Acinetobacter baumannii, CONS.

CONCLUSION

CONCLUSION:-

This study revealed that *Pseudomonas aeruginosa Klebsilla pneumoniae , S.aureus,E. coli, S.epidermidis ,Acinetobacter baumannii, CONS* are most commonly associated with biofilm infections,these organism are a threat pose a serious challenge to the clinicals in treatment and cure of the hospitalized patients.

The discovery of biofilm-producing bacteria in the urinary catheters may be a sign that biofilms are beginning to form. In order to prevent nosocomial infections linked to the device in patients, standard operating procedures on the management of catheters must be established for all hospital units, as biofilm creation was found in many of our isolates.

The three methods TCP, CRA, and TM can all be employed to find biofilm.

TCPM is a low-cost phenotypic technique that can be regularly used to identify the production of biofilms. Antibiotics used to treat UTIs are becoming less effective due to biofilms. Therefore, it is advised that all patients who come with chronic or recurrent illness have biofilms detected.

This study led us to the conclusion that patients with indwelling deviceswere highly segregated from biofilm producers.

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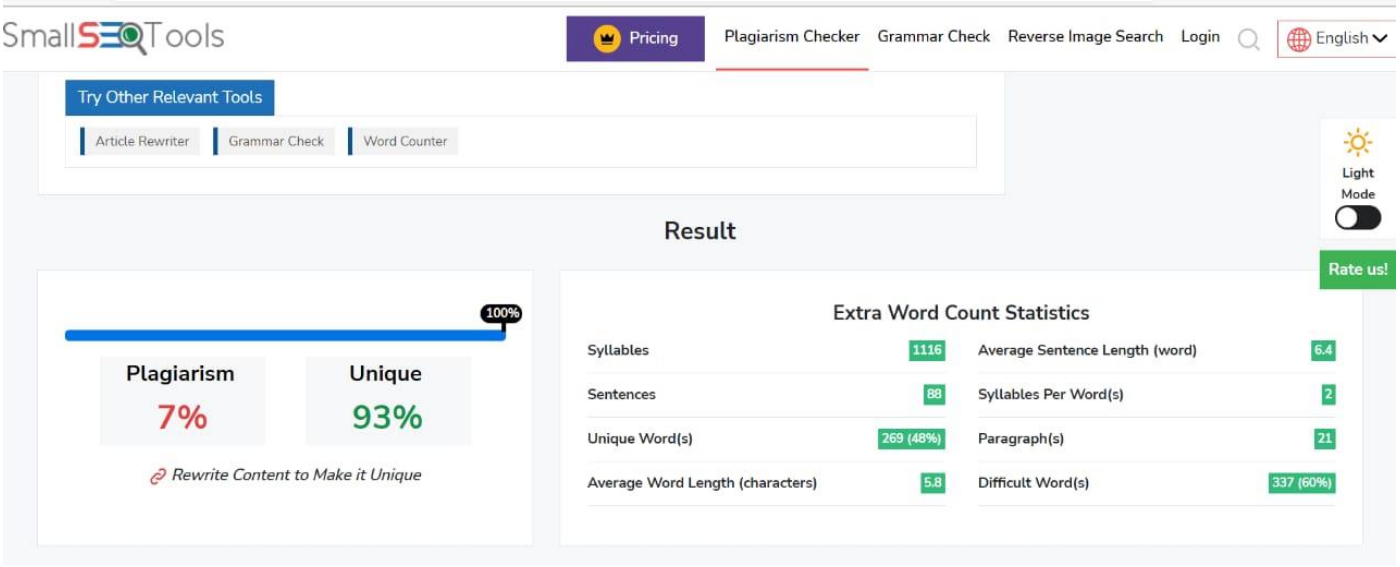
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Syllables Per Word(s) 2
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Paragraph(s) 21
Average Word Length (characters) 5.8
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