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Research Article

Risk Factors Associated with Nosocomial Infections and the Emergence of Antibiotic Resistance

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Abstract

Studies of hospital-acquired infections (HAIs) aimed to determine the etiology and microbiology of predominant pathogens and their antimicrobial susceptibility. The evaluation of the percentage of infections in different medical areas and the severity of infection is determined. Based on medical and biological criteria of hospitals involvement of different microorganisms in catheters, bloodstream, prosthetic devices, and in medical interventions lead to the generation of diseases. Ventilator- associated pneumonia (VAP), urinary tract infections (UTI), respiratory tract infections (RTI), and surgical site infections (SSI) are common.

It provides an appropriate discussion on the importance of nosocomial infections and their antibiotic resistance. The adverse effects on patient safety and emergence of complications by multidrug-resistant microorganisms are evaluated and the Limits of antimicrobial therapies by the increasing rates of detection of microorganisms.

It highlights the importance of biofilm formation, enzymatic modifications in microorganisms, production of multidrug-resistant microorganisms from it, and the effect of antibiotics on them. The Biofilm formation in catheters of intensive care units (ICU) leads to a high mortality rate and prevalence's by the contribution of Methicillin resistance Staphylococcus aureus (MRSA), Acinetobacter baumannii, and Clostridium difficile.

The information of emergence of antibiotic resistance from antibiotics like cephalosporins, vancomycin, carbapenems, etc. The process of identification and culture of microorganism and their lab diagnosis is done in different ways. Treatment options by antibiofilm coating particles that are newly present for intracellular targeting and, antimicrobial therapy of different infections by the use of newly emerging antibiotics and drugs.

Keywords: Hospital-acquired infections (HAIs), Nucleic acid amplification test (NAAT), Hospital-acquired pneumonia (HAP), Vancomycin-resistant Staphylococcus aureus (VRSA), Methicillin-resistant Staphylococcus aureus (MRSA), Medical intervention (MI)

LIST OF ABBREVIATIONS

CLABSI.....Central line-associated bloodstream infections

CAUTI.....Catheter-associated urinary tract infections

HAI.....Healthcare-associated infections

HAIs.....Hospital-acquired infections

HIV.....Human immunodeficiency virus

HBV.....Hepatitis B virus

HAP.....Hospital-acquired pneumonia

IV.....Intravascular

ICU.....Intensive care unit

MI.....Medical intervention

MRSA.....Methicillin-resistant Staphylococcus aureus

NV-HA……non-ventilator hospital-acquired pneumonia

NAAT……Nucleic acid amplification test

RTI……Respiratory tract infections

SSI……Surgical site infection

UTI……Urinary tract infection

VAP……Ventilator-associated pneumonia

VRSA……Vancomycin-resistant Staphylococcus aureus

INTRODUCTION

Classification of hospital-acquired infections (HAIs)

Healthcare-associated infections (HAIs) are also termed nosocomial infections which are acquired at the time of admittance into the hospitals. These infections mainly occur after three to thirty days of discharge of an operation or after 48 hours of hospital admission. In developing countries about 75% of infections are nosocomial and they affect every 1 in 10 patients admitted to hospital (Inweregbu et al., 2005)

These infections appear in different regions of hospitals such as after discharge, long-term treatments, and in ambulatory settings, while in new era prosthetic devices and indwelling medical devices are also related to nosocomial infections (Sikora et al., 2021). Illness or infection caused by these medical devices is also referred to as “iatrogenic”. WHO states that worldwide about 15% of infections are hospital-acquired.

The Source of infection depends on causative agents who include multidrug-resistant microorganisms such as bacteria, viruses, fungi, and parasites. In acute settings, these responsible pathogens lead to infections like pneumonia, surgical site infection, gastrointestinal infections, urinary tract infection, and bloodstream infections which are the 6th main leading cause of death. Microbial resistance had made tough the eradication of microbes (Storr et al., 2017).

The exposure of resistant microorganisms in hospitals is a major concern. Now a day’s major threat to modern medicine is antibiotic resistance. Resistant microorganisms lead to the change in the target point of antibiotics. Resistant to polymyxins and glycopeptides develop through the chemical modifications and also through enzymatic modification which causes a mutation in genes. A major barrier for antibiotics that do not allow them to reach the target is the microbial population, which is lethal for individuals. Innate resistance to many antibiotics and incidence of infection by multidrug resistance microbes has increased the mortality and morbidity rate which makes the treatment more difficult. Nosocomial outbreaks are spreading worldwide. (Frieri, 2017).

Globally more percentage of nosocomial infections are from the intensive care unit (ICU). The endemic burden of hospital-acquired infection in primary care hospitals is 4.4%, in intensive care units 19.2%, in tertiary care hospitals 7.1% and in long-term care facilities 3.7% approximately. Epidemiological analysis in developing countries about HAIs shows 15.5% prevalence while in Asian countries the prevalence is about 9.1%. This prevalence is mostly less in medical units rather than in surgical wards and intensive care units (ICU) (Sikora et al., 2022).

Socio-economic disturbance, mortality, and antimicrobial resistance have been increased in every hospital of developing countries, mostly in those patients who are neonates, in a burn unit, or organ transplantation. The patients who are affected in intensive care units have a range of more than 51% of resistance along with infection. The latest study and data on antibiotics and resistance will help to treat the infections caused by microorganisms. Current modification by the enzymatic way will give the knowledge about the gene mutation of microorganisms, and how to deal with the newly developed resistant mechanisms.

ETIOLOGY AND MICROBIOLOGY

Based on medical and biological criteria hospital-acquired infections had thirteen different types along with 50%of infection confirmations. Different hospital-acquired infections are caused by different pathogens which originate from a variety of sources such as catheters, prosthetic devices, etc (Khan et al., 2015) (Letica Kriegel et al., 2019).

These infections have been categorized into the following types:

- Surgical site infection or medical interventions (SSI)
- Ventilator-associated pneumonia (VAP)
- Central Line associated bloodstream infection (CLABSI)
- Catheter-associated urinary tract infection (CAUTI)

Some other categories also include respiratory infections, gastrointestinal infections, non- ventilator associated hospital-acquired pneumonia (NV-HAP). Hospital-acquired infections are also related to some other infectious sites these include infection of throat, nose, ear, eye, cardiovascular infections, and lower respiratory tract infections such as infection of bronchiolitis, lung accesses, infection of the central nervous system, and genital infections (Magill et al., 2018). While due to advancement in treatments such as organ transplantation, cancer chemotherapy, prosthetic and invasive devices for diagnosis has changed the nosocomial infectious sites with time. This can be seen in the case of pneumonia. In the last five years prevalence of pneumonia has been increased from 17% to 30% followed by a gastrointestinal infection which is 17.1% (Ewan et al., 2017).

Surgical site infection or medical interventions

Intravascular devices and surgical incisions are the portal

entrance for pathogens. About 2-5%of hospital-acquired infections occur from undergoing surgeries and manifest within the ninety days of intravascular devices and thirty days of surgery. A recent study shows 10-15% of incidence in abdominal surgeries. Heart valves and prosthetic devices provide a safe habitat for bacteria to grow easily. Urinary tract infections caused by urinary catheterization devices. Sometimes location and depth of infection determine what kind of medical or surgical intervention will occur. Subcutaneous tissues and skin are involved in superficial surgical intervention; fascia and muscle include deep surgical intervention. Unsterilized endoscopes led to the transmission of hepatitis viruses, *Mycobacterium tuberculosis,* and *Salmonella typhi* pathogens which had a high mortality rate (Mukagendaneza et al., 2019).

Ventilator-associated pneumonia

Ventilator-associated pneumonia and hospital-acquired pneumonia occur after 48 hours of endotracheal intubation and admission into hospitals respectively. About 15% of the patients acquired infection of ventilator pneumonia. The major cause of ventilator-associated pneumonia is the high use of fourth-generation antibiotics after 90 days of hospitalization which led to the growth of multidrug-resistant microorganisms. Some other causes are also related to this infection such as poor oral care, supine positioning, and sedation. Common microorganisms that spread this infection are *Candida* species, *Klebsiella oxytoca, Staphylococcus aureus, Enterococcus,* and *Klebsiella pneumonia (*Klompas et al., 2016).

Central line-associated bloodstream infection

Central venous line infection occurs in 24% of non-ICU patients and 55% of ICU patients. This infection mainly occurs contamination occurs during the process of insertion of the catheter. Bacteria move from the external part of the catheter to the intravascular part and lead to infection. These microorganisms got virulence characteristics due to the formation of biofilm, which increases proliferation. Risk factors of catheter-associated bloodstream infection can be catheters and host. The host is included in risk factors because they had neutropenia, immunosuppressed, chronic illness, and transplantation of bone marrow. While catheter risk factors are prolonged catheterization, sterilization of catheters, and urgent insertion of catheters. Microorganisms related to bloodstream infection are *E. coli* which causes 8% of infection, *S. aureus* causes 23% of infection, and *Streptococcus* species causes 12% of infection (Baier et al., 2020).

Catheter-associated Urinary tract infections

Various medical indications lead to the setting of urinary catheters which cause urinary tract infections. Normally 25% of patients in every hospital have urinary catheters due to various diseases. These urinary catheter infections can have two ways of infections intraluminal and extraluminal. Extraluminal way of infection occurs when catheters are inserted from urethral meatus to bladder, bacteria are present on the external surface of catheters, intraluminal infection occurs when catheters got contaminated due to blockage or drainage that happens in the case of urinary stasis or any kind of ascending infection. In indwelling devices, bacteria and fungi use the mechanism of biofilm for proliferation. Common pathogens that cause catheter-associated urinary tract infections are *E. coli, Pseudomonas aeruginosa, Candida* species*, Klebsiella oxytoca, Klebsiella pneumonia,* and *Enterococcus* species (Kriegel et al., 2019) (Tasbakan et al., 2013).

CAUSATIVE AGENTS OF HOSPITAL-ACQUIRED INFECTIONS

Bacteria, viruses, fungi, protozoa, and mycobacteria are the most responsible pathogens for causing infection while 90% of the infection is mostly caused by bacteria. The prevalence of these infections depends on the susceptibility of the host along with particular pathogen and healthcare settings.

Bacteria

In microorganisms' bacteria are the leading microbes that cause 90% of hospital infections related to healthcare settings. Bacteria are a part of the natural flora of humans but some bacteria are opportunistic. When our immune systems become weak, they get a chance to cause infection exogenously and endogenously in susceptible hosts. Gram +ve species of bacteria that are related to HAIs are *Streptococcus* species, *Staphylococci*, *Enterococcus* species (e.g.*, E. faecalis, E. facial),* and *Staphylococcus aureus* (Magill et al., 2018).

The responsible *S. aureus* coagulase-negative pathogen is the causative agent of blood-borne infections. While the reported agent which causes 15% of the hospital infection is *C. difficile* along with urinary tract infection and inflammation of the colon. Gram –ve species of bacteria mostly cause urinary tract infections, respiratory infections, and surgical site infections. *Enterobacteriaceae* is the main of these infections include *Escherichia coli, Acinetobacter baumannii, Enterobacter* species, *Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus mirabilis,* and *Klebsiella oxytoca* (Sievert et al., 2013).

The improper and excessive use of broad-spectrum antibiotics has created drug-resistant microorganisms which are associated with a significant mortality rate. From reported agents, 20% are drug-resistant in the 1960s *E. coli* and *Klebsiella spp* were associated with HAIs but with the high use of broad-spectrum antibiotics, *P. aeruginosa* and *Acinetobacter* created many clinical difficulties from 1975 to 1980. Species that are multi-drug resistant are associated with high mortality rates in intensive care units e.g., *Acinetobacter baumannii*. Other agents which are notorious for multi-drug resistance are vancomycin-

resistant *Staphylococcus aureus* (VRSA), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-intermediate *Staphylococcus aureus.*

Many drugs are produced with an extended-spectrum but responsible pathogens had shown resistance from them like *Enterobacteriaceae* family shown resistance against carbapenems and cephalosporin drugs, *Enterococcus* showed resistance from vancomycin, *Pseudomonas aeruginosa,* and *Acinetobacter* species are multidrug-resistant (Sievert et al., 2015).

Antibiotic resistance by biofilm production

The major contribution of resistance from drugs occurs due to biofilm production. Biofilm- producing bacteria are notoriously impossible to eradicate because biofilm production plays the main role in resistance by decreasing susceptibility. The composition and structure of biofilm is a major barrier that stops the antibiotics from reaching the living cells of the human body and this barrier contains extracellular DNA and exopolysaccharides **(Figure 1A)**. For different antibiotics against different species, the effectiveness of the barrier varies. Larger drug molecules are unable to pass through it such as vancomycin but quinolones can move freely (Stewart et al., 2002).

Effect of cephalosporin antibiotic on bacterial biofilm

Cephalosporin is a beta-lactam antibiotic that acts against the gram +ve species and kills the bacteria by destroying the penicillin-binding proteins, which are the major component of the bacterial cell wall and help in the formation of peptidoglycan. Peptidoglycan makes up 50% of the bacterial cell wall. Peptidoglycan is made up of N-acetyl muramic acid and N-acetyl glucosamine along linear chains and β 1-4 linkages.

These linear chains form cross-linkage by oligopeptides. Cephalosporin destroys these cross- linkages byendopeptidases *D*-ala-*D*-ala trans and carboxyl. **(Figure 1B)** These catalyzed structures do not inhibit any intracellular synthesis of the bacterial cells, their main function is to only act on cross-linkage of peptidoglycan layer D-alanyl-D-alanine bond of peptidoglycan have similarity with structural analog (β-lactam) of cephalosporin.

The bacterial enzyme mistakenly takes the β-lactam which reduces the catalytic activity of the cell; this led to the killing of bacteria. But in the latest studies bacteria had shown resistance from cephalosporin, this resistance is due to the formation of biofilm. By using the plasmid DNA or chromosomal DNA bacteria produce a barrier outside of their wall which consists of two main components exopolysaccharides and extracellular DNA.

These components decide the two main strategies of the bacterial cell. One is what kind and amount of enzyme should be produced so that resistance occurs and second what will be the location of enzyme in cell, if gram +ve species then the location of enzyme will be extracellular and if the bacteria are gram-ve the location of enzyme will be in periplasmic. This leads to the formation of barriers. This barrier contains a matrix that acts as a diffusion barrier and the hostile environment under the matrix where the drug loses its efficacy and bacteria lead to survive with the

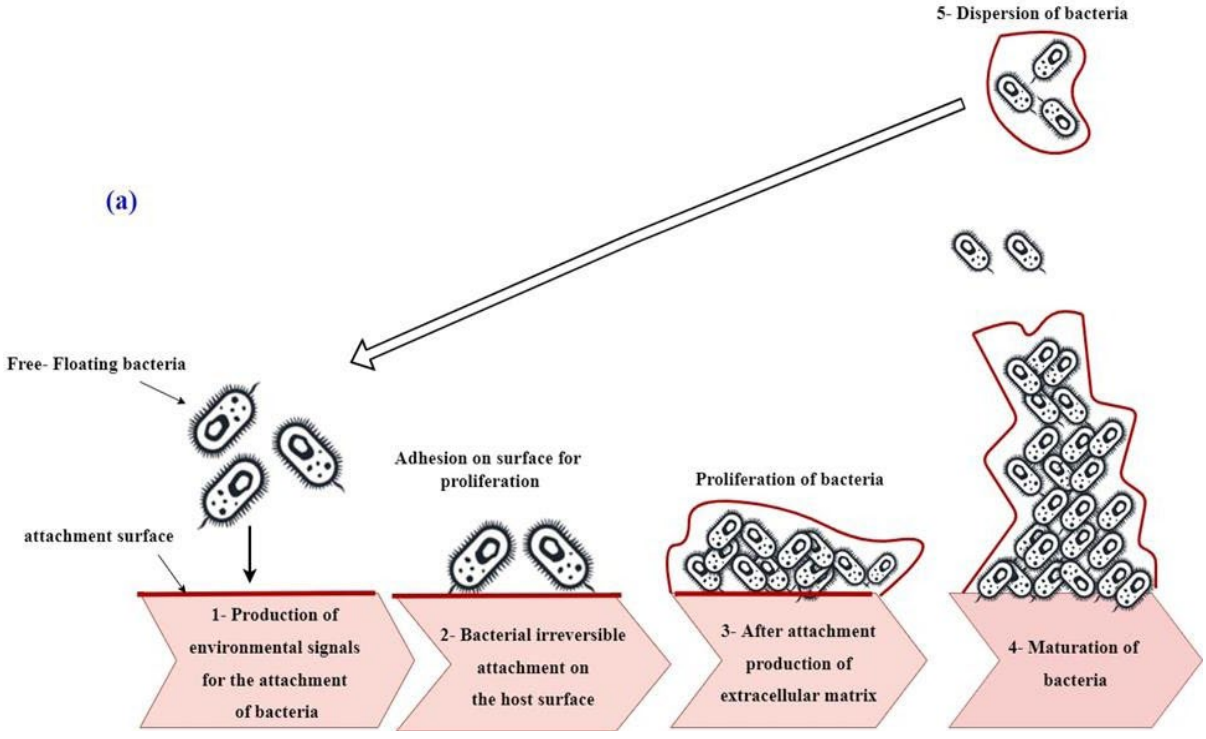

Figure 1(a). Production of biofilm by the bacteria on the cell surface of the host, its proliferationand dispersion.

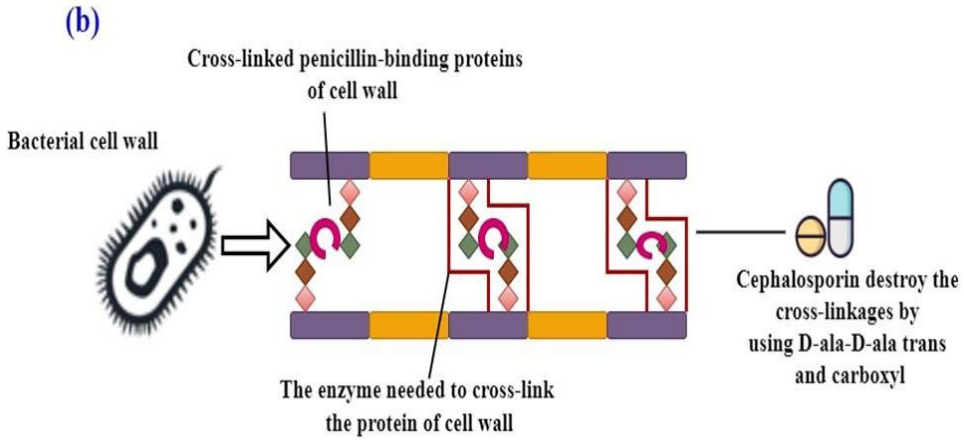

Figure 1(b). Cephalosporin destroy the cross-linkage of penicillin-binding-protein of peptidoglycan in the cell wall of bacteria.

occurrence of resistance (Kumar et al., 2021)

Viruses

Viruses account for only 5% of hospital-acquired infections. Virus nosocomial infections mostly occur in infants, children, and people who are immune compromised and have cardiac, chronic pulmonary and respiratory infections (Aitken & Jeffries, 2001). While unsafe needle practices in health care departments will lead to virus infections such as Human immunodeficiency virus (HIV), hepatitis B and these virus infections mostly occur in developing countries, and globally 5.4% of infections are HIV associated. Some other viruses which are related to HAIs but cause minor complications are influenza virus, herpes simplex virus, rhinovirus, rotavirus, and cytomegalovirus (Ganczak et al., 2008).

Fungi

Fungal infections mostly occur in those patients of the hospital who are using indwelling devices such as urinary or central line catheters. Immunocompromised and have respiratory problems (Spivak et al., 2018). Fungal species that cause HAIs are candida species such as *C.glabrata*, *C.auris*, *C.parapsilosis*, and *C.albicans* High mortality and morbidity rate of fungal infection is associated with *C.auris* because it is a globally multidrug-resistant organism and has a high rate of failure in treatment (Spivak et al., 2018). In areas, of healthcare constructions, *Aspergillus fumigatus* may cause contamination through airborne transmission, but the primary, the source can be hospitalized, patients (Park et al., 2019).

Transmission of microorganisms

Different responsible pathogens related to healthcare infection had different routes of transmission. They can be transmitted through direct contact and indirect contact such as air droplets. Microorganisms that are transmitted methicillin-resistant are methicillin-resistant Staphylococcus aureus (MRSA) in bacteria, C. difficile in fungi, and Rotavirus. Droplet transmission occurs through respiratory tract are less than five microns. Sample of such pathogens is Neisseria, Influenza virus, and Bordetella pertussis. While the airborne transmission less than five microns travel long distance such as measles, tuberculosis, and SARS-COV-2 and chickenpox virus.

In this **table** different responsible microorganisms cause different percentages of hospital-acquired infection in many healthcare settings (ICU) with resistance from different antibiotics and high mortality rates.

PATHOGENICITY OF MULTIDRUG-RESISTANT MICROBES

The emergences of drug-resistant microorganism's leads to limitations in conventional therapies of treatment.in treating patients' antibiotic-resistant infectious bacteria are a major risk and challenge in hospital settings. The diagnosis and treatment of these infectious bacterial diseases can be done by the establishment of proper diagnostic tests and characterization of a particular strain of microbe. The bacterial strains that are a threat to the new world are *Acinetobacter baumannii,* methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus,* and *Clostridium difficile.*

Infection of *Clostridium difficile*

Clostridium difficile is the only bacterial organism that causes antibiotic-associated colitis inflammation of the inner lining of the colon and diarrhea. This bacterium spread through the aerosols or the fecal-oral route of transmission. *C.difficile* causes tissue injury by producing the toxins that act on epithelial cells of the intestine and injure the tissues which result in diarrhea. The critical risk factors for *C. difficile* are environmental contamination and the use of antibiotics. Some other factors also include hospitalization, immunosuppression, increase of age, and different comorbidities (Dinleyici et al., 2019).

Infection of *Acinetobacter baumannii*

A. baumannii was first reported in 1911 and isolated from soil. It is gram-negative and coccobacillus in nature. It was

derived from the Greek word *akinetes* which means they are non-motile. This genus has many catabolic pathways due to which they contain different substrates and cause different types of infection. Species that have seventy percent DNA relatedness and homology in groups are known as genomic species. Nowadays 32 genomic species of Acinetobacter are known. While in medical and clinical *Acinetobacter baumannii* has more importance and is mostly isolated from the diagnostic tests of hospital-acquired infections. (Eliopoulos et al., 2008)

In 1970 it was declared as a nosocomial pathogen because it got resistant to those antibiotics that were used as the best treatment in that era such as sulphonamides and β lactam. This led to new outbreaks and resistance to these antibiotics. Introduction of new antibiotics takes place. In 1980 imipenem and aztreonam were introduced in 1990 ciprofloxacin was manufactured but *Acinetobacter baumannii* is still resistant to these antibiotics and is now known as multidrug- resistant, extensively drug-resistant, and pan drug-resistant microorganism. (Peleg et al., 2020)

Acinetobacter baumannii entered into the body of the host through intravascular, urinary catheters, wounds, mucous membrane, respiratory tracks, and burns. After the entrance into the host, they adhere to the epithelial cells and damage the tissues of the host by producing proteinases and gelatinases. In tissue, they colonize by making biofilm and cause infection. It causes infections such as Novtic shock, multiorgan failure, and bacteremia (Garnacho et al., 2010).

Infection of multidrug-resistant *Staphylococcus aureus*

Methicillin-resistant staphylococcus aureus (MRSA) causes surgical wound infection and bloodstream infection in patients who are admitted to hospitals more than 72 hours. Its association with these infections is related to 95% of the mortality rate. In 2008 its highest prevalence was observed in Portugal.

The demographics of patients and hospital environmental factors are the main factors that contribute to its infection. MRSA is the main pathogen of hospital-acquired pneumonia along with ventilator-associated pneumonia. In hospitals, one-third of the infection is caused by methicillin- resistant coagulase-negative *Staphylococcus aureus* which mainly accounts for foreign body- associated infection (Vestergaard, 2021).

Cefazolin, oxacillin, and nafcillin are mainly recommended against *Staphylococcus aureus.* But vancomycin is suggested as the best antibiotic for treatment. But in the 21st-century vancomycin- resistant *staphylococcus aureus* is also found. The mucosal surface of the host triggers the virulent genes of bacteria. *S. aureus* got entrance into the body from an open wound and colonize on the mucosal surface of the gastrointestinal tract, nose, and vaginal wall. While the entrance of bacteria from the nose mucosal surface led to bacteremia because 20% of *S. aureus* colonize in the nose. It causes infection of the nasal carriage, mouth, ears, and throat **(Figure 2A)**.

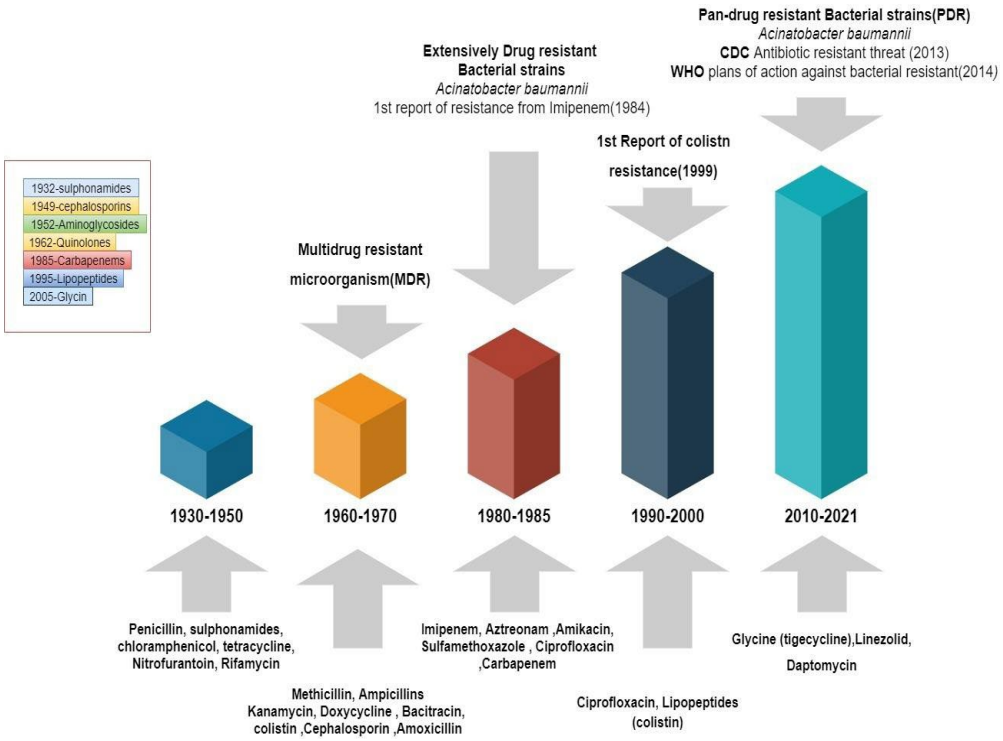

Figure 2 (a). History of increasing antibiotic resistance of Multidrug-resistant bacterial strain *Acinetobacter baumannii* from emerging antibiotics from 1930-2021. Arrows on the upside showthe resistance of multidrug, exclusive drug, and pan drug bacterial strains of methicillin-resistant Staphylococcus aureus and Acinetobacter baumannii. The Block with different colors shows the dates of introduction of mainly used and golden antibiotics.

DIAGNOSIS OF HOSPITAL ACQUIRED INFECTIONS (HAIs) ON BASIS OF INFECTION TYPE

The different types of hospital-acquired infection have different diagnoses based on infection time, symptoms, causes, laboratory tests, and infection type. The diagnosis on basis of symptoms gives a view that infection can be due to catheters, use of broad-spectrum antibiotics, and environmental factors. Time of infection shows that disease was before admitting into hospital or after taking admission into the hospital. The diagnostic laboratory tests confirm the infection type which included blood tests, complete blood tests, antibiotic sensitivity tests, inflammatory markers, etc. These diagnostic tests are helpful in the evaluation of infection. Hospital-acquired infections include the following diagnosis based on types of infection:

1. Diagnosis of catheter-associated urinary tract infection
2. Diagnosis of soft tissues infection
3. Diagnosis of catheter-associated bloodstream infection
4. Diagnosis of hospital-acquired pneumonia
5. Diagnosis of *C. difficile* infection

Diagnosis of catheter-associated urinary tract infection

The patients who are diagnosed with hospital-acquired infections such as urinary tract infection can have the following infections upper urinary tract infection, lower urinary tract infection, urethritis, acute cystitis, nephrolithiasis, and pyelonephritis (Hooton et al., 2010). For laboratory diagnosis, the urine sample is always taken after removal of catheters so that bacterial biofilm in catheters does not come with the sample. This gives a pure urine culture for urine analysis. In catheterized patients usually, bacteriuria is present, along with colonies of uropathogenic bacterial strains. This type of bacteriuria has no symptoms of urinary tract infection and it is called asymptomatic bacteriuria. And has no specific treatment. (Hooton et al., 2010).

Diagnosis of Soft Tissue Infections

Soft tissue infection occurs in atelectasis along with fever after the operation. The reaction of drugs, urinary tract infections, pneumonia, and side effects of the medicine are also associated with post-operation. The common infections of surgical sites are associated with herniation of wounds, gas gangrene tumors, burns, or cellulitis conditions. Infection of the surgical site can occur after thirty to ninety days of operation. The radiographic imaging, purulent drainage, and positive cultures are used for the diagnosis of surgical site infection. For the clinical presentation of infection, an antibiogram is performed by using drainage from the surgical wound, infected tissues, and purulent in a culture. For the deep surgical wounds, a swab sample is taken because microbes mostly colonize at superficial swabs. The whole diagnosis always depends upon the type of infection. (Madden et al., 2018)

Diagnosis of catheter-associated bloodstream infection

When localized infections are not present then blood is drawn for clinical presentation. For the blood to be cultured the sample is always taken from two areas one is from the peripheral vein (only present in legs, arms, feet, hands not in chest or abdomen) and the second is from the indwelling central venous catheter. If the sample drawn from the central venous catheter is positive then it gives surety of bacteria and other infections are ruled out. Bacteremia can occur due to the following conditions such as endocarditis, wound infection, and pneumonia. Based on blood culture testing, antibiotic therapy is started (Lutwick et al., 2019).

Diagnosis of hospital-acquired pneumonia

For diagnosis of hospital-acquired pneumonia following symptoms mimics pneumonia infection such as pulmonary emboli, edema, upper respiratory tract infection, and asthma. Hospital-acquired pneumonia shows its symptoms after forty-eight hours of ventilation or hospitalization. For further clinical presentation radiography and chest-x-ray are used. These techniques identify that leukopenia can also be present. In laboratory diagnosis, a sputum sample is taken by using the process of non-invasive sampling from brushing off the specimen, aspiration from endotracheal and bronchoalveolar lavage. For further diagnosis and checking the response of antibiotics from different generations sample is stained and then cultured with antibiotic susceptibility tests. For *Mycobacterium tuberculosis* and fungal sample, another culture medium is used. (Papazian et al., 2020)

Diagnosis of Clostridium difficile infection

Diarrhea is caused by two types of microorganisms' antibiotic-associated or noninfectious and infectious diarrhea. Infectious diarrhea is caused by viruses, fungi, and some pathogenic bacteria while noninfectious include *Klebsiella oxytoca, Salmonella, Clostridium preferences,* and *Staphylococcus aureus*. *Clostridium difficile* causes infectious diarrhea along with diseases related to the acute abdomen such as volvulus, ileus, and pseudo-obstruction. In some cases, hospital- acquired infectious diarrhea is also related to damage of the respiratory system, nervous system.

If *Clostridium difficile* infection is suspected in patient stool testing and is preferred for diagnosis. A stool test is done against clostridium toxin genes or only clostridium toxins. For a more sensitive diagnosis, a liquid stool sample is taken. If a patient is suspected of ileus, then a rectal swab is taken. Radiography is recommended for severe illness or for toxins that are suspected. Nucleic acid amplification test (NAAT)

can be helpful but it leads to overdiagnosis (Polage et al., 2015).

ANTIMICROBIAL THERAPY AGAINST MULTIDRUG- RESISTANT MICROORGANISMS IN HOSPITALS

The emergence of multidrug-resistant microorganisms leads to the replacement of new antibiotics for the proper treatment and diagnosis of infectious diseases. Low efficacy level of drugs by efflux pumps, low drug accumulations in the body, and enzymatic degradation leads to the production of new generation antibiotics which are now used to control the infection but at a minimum level. A versatile tool has been introduced recently in the 21st century to treat bacterial infections at the Nano level. This Nano-level treatment improves access for intracellular transport of drugs, and drug delivery. There are following two ways of treatment of hospital-acquired infection caused by multidrug-resistant microorganisms:

-Treatment using silver nanoparticles

-Treatment using Antibiotics

Treatment using silver nanoparticles

The misuse of antibiotics and genetic mutations has led to resistance and multiple infections. In the United States, every year 2.8 million hospital patients are affected due to antibiotic-resistant infections. Nowadays the applications of nanoparticles against microorganisms are proven very useful. These small size particles (10-100nm) are very effective for biomedical applications. These nanoparticles attack pathogens in many physical ways such as disruption of a microbial cell, intracellular targeting's such as destroying the organelles of microbes and their walls.

Silver nanoparticles have wide applications in the treatment of infections by delivery of targeted drugs to their target. Antibiotics are the primary and conventional treatment for infections but due to their high dosage along with resistance is a problem. Silver nanoparticles help in the delivery of drugs without dissolving them into the body fluids and protecting them from resistant microbes (Rai et al., 2012).

Antibiotics and different peptides are loaded on silver nanoparticles that protect the drug from toxicity and solubility. By using the linker molecules drugs and peptides are attached to the nanoparticles so that they will go to their target point without any hurdle. Such as the covalent interaction of vancomycin antibiotics. This treatment nanotechnology has helped against many infectious diseases such as cancer and tuberculosis. Due to their biocompatibility and bioresorbable power, many diseases such as bloodstream infections, neuronal and respiratory infections are treatable. This treatment technology is also effective against multidrug-resistant microorganisms such as *Enterobacteriaceae* (resistant from carbapenem) *Clostridium difficile Acinetobacter baumannii* and Methicillin-resistant *Staphylococcus aureus* **(Figure 2B)**.

TREATMENT BY USING ANTIMICROBIAL THERAPY

Treatment using antibiotics

In hospitals catheter-associated infection depends on the organism that is cultured therefore sometimes removal of the catheter is a choice of treatment. Because catheters are infected with different species of microorganisms along with biofilm-like pseudomonads*, C. difficile, S. aureus,* etc. Depending on the severity of infections antimicrobial therapy is recommended, but for a proper treatment

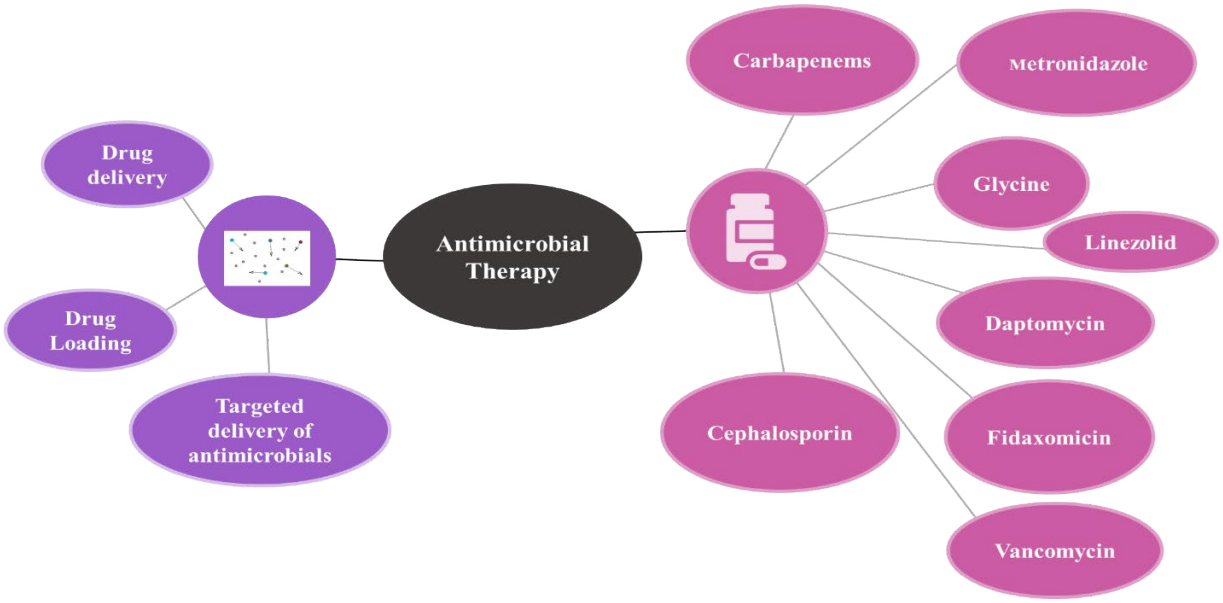

Figure 2(b). Antimicrobial therapy by using nanotechnology and recently introduced antibiotics against different multidrug-resistant microorganisms.

duration of antibiotics, dosage, and generation matter. For protection from hospital-acquired infections, the good hygienic practice should be done in operation theaters, disinfection of skin by using chlorhexidine and aNovtic procedures should be adopted.

Against *Clostridium difficile* infections metronidazole, oral vancomycin and fidaxomicin are effective. Cephalosporins and carbapenems are effective against *Enterobacteriaceae.*

DISCUSSION

The occurrence of hospital-acquired infections is 32% out of the other hospital infections. The highest number of infections is found in patients that are in intensive care units using different catheters. The involvement of different microbes leads to the production of multidrug-resistant microorganisms, due to which the use of antibiotics is limited. Emerging therapy by using high efficacy antibiotics and nanoparticles can be helpful against these resistant microorganisms.

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REFERENCES

1. Inweregbu K, Dave J, Pittard A (2005). Nosocomial infections. Cont Edu Anaesthesia Critical Care Pain. 5: 14-17.
2. Sikora A, Zahra F (2021). Nosocomial infections. StatPearls [Internet].
3. Storr J, Twyman A, Zingg W, Damani N, Kilpatrick C, et al (2017). Core components for effective infection prevention and control programs: new WHO evidence-based recommendations. Antimicrobial Resistance & Infection Control. 6: 1-18.
4. Frieri M, Kumar K, Boutin A (2017). Antibiotic resistance. Journal of infection and public health. 10: 369-378.
5. Khan HA, Ahmad A, Mehboob R (2015). Nosocomial infections and their control strategies. Asian Pac J Tropical Biomed. 5: 509-514.
6. Letica-Kriegel AS, Salmasian H, Vawdrey DK, Youngerman BE, Green RA, et al (2019). Identifying the risk factors for catheter-associated urinary tract infections: a large cross-sectional study of six hospitals. BMJ Open. 9: e022137.
7. Magill SS, O'Leary E, Janelle SJ, Thompson DL, Dumyati G, et al (2018). Changes in prevalence of healthcare-associated infections in US hospitals. New England J Med. 379: 1732-1744.
8. Ewan VC, Witham MD, Kiernan MA, Simpson AJ (2017). Hospital-acquired pneumonia surveillance-an unmet need. Lancet Respirat Med. 5: 771-772.
9. Mukagendaneza MJ, Munyaneza E, Muhawenayo E, Nyirasebura D, Abahuje E, et al (2019). Incidence, root causes, and outcomes of surgical site infections in a tertiary care hospital in Rwanda: a prospective observational cohort study. Patient safety in surgery. 13: 1-8.
10. Klompas M, Branson R, Eichenwald EC, Greene LR, Howell MD, et al (2014). Strategies to prevent ventilator-associated pneumonia in acute care hospitals: 2014 update. Infect Control Hospital Epidemiol. 35: S133-S154.
11. Baier C, Linke L, Eder M, Schwab F, Chaberny IF, et al (2020). Incidence, risk factors and healthcare costs of central line-associated nosocomial bloodstream infections in hematologic and oncologic patients. PloS one. 15: e0227772.
12. Tasbakan MI, Durusoy R, Pullukcu H, Sipahi OR, Ulusoy S (2013). Hospital- acquired urinary tract infection point prevalence in Turkey: differences in risk factors among patient groups. Ann Clin Microbiol Antimicrob. 12: 1-8.
13. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, et al (2013). Antimicrobial-resistant pathogens associated with healthcare-associated infections summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infection Control & Hospital Epidemiology. 34: 1-14.
14. Stewart PS (2002). Mechanisms of antibiotic resistance in bacterial biofilms. International journal of medical microbiology. 292: 107-113.
15. Kumar L, Brenner N, Brice J, Klein-Seetharaman J, Sarkar SK (2021). Cephalosporins Interfere With Quorum Sensing and Improve the Ability of Caenorhabditis elegans to Survive Pseudomonas aeruginosa Infection. Front microbiol. 12: 70.
16. Ganczak M, Barss P (2008). Nosocomial HIV infection: epidemiology and prevention— a global perspective. AIDS Rev, 10: 47-61.
17. Spivak ES, Hanson KE (2018). Candida Auris: an emerging fungal pathogen. J Clin Microbiol. 56: e01588-e01617.
18. Park JH, Ryu SH, Lee JY, Kim HJ, Kwak SH, et al (2019). Airborne fungal spores and invasive aspergillosis in hematologic units in a tertiary hospital during construction: a prospective cohort study. Antimicro Resist Infect Control. 8: 1-8.
19. Dinleyici M, Vandenplas Y (2019). Clostridium difficile colitis prevention and treatment. Probiotics and Child Gastrointestinal Health. pp 139-146.
20. Eliopoulos GM, Maragakis LL, Perl TM (2008). Acinetobacter baumannii: epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis. 46: 1254-1263.
21. Peleg AY, Seifert H, Paterson DL (2008). Acinetobacter baumannii: the emergence of a successful pathogen. Clin Microbiol Rev. 21: 538-582.
22. Garnacho-Montero J, Amaya-Villar R (2010). Multiresistant Acinetobacter baumannii infections: epidemiology and management. Curr Opin Infect Dis. 23: 332- 339.
23. Vestergaard M, Frees D, Ingmer H (2019). Antibiotic resistance and the MRSA problem. Microbiol Spectr. 7: 7-2.
24. Hooton TM, Bradley SF, Cardenas DD, Colgan R, Geerlings SE, et al (2010). Diagnosis, prevention, and treatment of catheter-

associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis. 50: 625-663.

25. Madden GR, Poulter MD, Sifri CD (2018). Diagnostic stewardship and the 2017 update of the IDSA-SHEA clinical practice guidelines for Clostridium difficile infection. Diagnosis. 5: 119-125.
26. Lutwick L, Al-Maani AS, Mehtar S, Memish Z, Rosenthal VD, et al (2019). Managing and preventing vascular catheter infections: a position paper of the international society for infectious diseases. International Journal of Infectious Diseases. 84: 22-29.
27. Papazian L, Klompas M, Luyt CE (2020). Ventilator-associated pneumonia in adults: a narrative review. Intensive Care Med. 46: 888-906.
28. Polage CR, Gyorke CE, Kennedy MA, Leslie JL, Chin DL, et al (2015). Overdiagnosis of Clostridium difficile infection in the molecular test era. JAMA Intern Med. 175: 1792-1801.
29. Rai MK, Deshmukh SD, Ingle AP, Gade AK (2012). Silver nanoparticles: the powerful nano weapon against multidrug-resistant bacteria. J Appl Microbiol. 112: 841-852.