International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

Nosocomial Infection and Role of Silver Nanoparticle in Controlling Nosocomial Infection

Mukul Kumar
[1,] *Student, Government Pharmacy Institute,Aryabhatta Knowledge University, Patna, Bihar*

Submitted: 05-05-2023 Accepted: 15-05-2023

ABSTRACT: Nosocomial infections, termed hospital-acquired infections (HAIs), are acquired from a healthcare or hospital setting. HAI is mainly caused by bacteria, such as Acinetobacter baumannii, Klebsiella pneumoniae, Escherichia coli, Enterococci spp., Methicillin-resistant Staphylococcus aureus (MRSA), and many more. Due to growing antibacterial resistance, nanotechnology has paved the way for more potent and sensitive methods of detecting and treating bacterial infections. Nanoparticles have been used with molecular beacons for identifying bactericidal activities, targeting drug delivery, and anti-fouling coatings, etc. This review addresses the looming threat of nosocomial infections, with a focus on the World scenario, and major initiatives taken by medical bodies and hospitals in spreading awareness and training. Further, this review focuses on the potential role nanotechnology can play in combating the spread of these infections.

KEYWORDS:

o.	LIST OF ABBREVIATIONS
SNP/AgNP	Silver Nanoparticles
NP	**Nanoparticles**
CDC	Centres for Disease Control and Prevention
HAI	**Hospital-acquired infection**
HCAI	Healthcare associated infections
MRSA	**Methicillin-resistant Staphylococcus aureus**
NI	Nosocomial infection
NHSN	**National Health Safety Network**
CLABSI	Central-line associated bloodstream infections
CRBSI	**Catheter-related bloodstream infections**
CAUTI	Catheter-associated urinary tract infections
VAP	**Ventilator-associated pneumonia**
SSI	Surgical site infections
UTI	**Urinary tract infection**
ICU	Intensive care units
EPIC	**European Prevalence of Infection in Intensive Care Study**
WHO	World health organisation
SARS	**Severe acute respiratory syndrome**
COVID	Coronavirus disease
CCU	**Critical care unit**
IDEAS	Interactive Data Entry and Analysis System
SENIC	**Study on the Efficacy of Nosocomial Infection Control**
NNIS	National Nosocomial Infections Surveillance
MIC	**Minimum Inhibitory Concentration**
MBC	Minimum Bactericidal Concentration
ROS	**Reactive oxygen species**
PAE	Post agent effect
NC	**Nanocomposites**
LMWG	Low molecular weight gelators
PG	**Polymer gelator**
TEM	Transmission electron microscope
SEM	**Scanning electron microscope**

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

I. INTRODUCTION

The term 'nosocomial' is derived from two Greek words, 'nosus' and 'komeion' that literally translate into 'disease', and 'take care of'. It was during the first half of the 18th century that the scientific study of nosocomial infection or hospital-acquired infection (HAI) started.[1]. Nosocomial infections, also called health-care-associated or hospital-acquired infections, are infections that occur in a patient while receiving care in a hospital or other health care facility. They are subset of infectious diseases acquired in a health-care facility. 'Nosocomial' or 'healthcare associated infections' (HCAI) appear in a patient under medical care in the hospital or other health care facility which was absent at the time of admission., it must develop at least 48 hours after admission These infections can occur during healthcare delivery for other diseases and even after the discharge of the patients.[7]. These infections can lead to serious problems like sepsis and even death.

The increasing tendency of microbial infections, the rapid emergence of drug-resistant strains to recent antibiotics, and their quick evolution through mutation necessitates the development toward alternative strategies of microbial control. These strategies need not only focus on the development of the new drug but also should involve in developing newer methods of prevention and control of microbial contamination [2]. In view of this, silver-based antimicrobial hydrogels were developed which could play a crucial role in combating infections.

After an infection is confirmed to be of nosocomial origin, the specific type of infection is categorized based on the systemic classification provided by the National Health Safety Network (NHSN) with the Centres for Disease Control and Prevention (CDC) which are specifically based on clinical and biological criteria. criteria. According to the NHSN and CDC criteria, HAIs have been classified into 14 different types. Out of these, the incidences of device associated HAIs (DA-HAI) are the most common in healthcare settings which include central-line associated bloodstream infections (CLABSI), catheter-related bloodstream infections (CRBSI), catheter-associated urinary tract infections (CAUTI), ventilator-associated pneumonia (VAP), and surgical.[1]

TYPES OF NOSOCOMIAL INFECTION

Invasive devices such as catheters and ventilators employed in modern health care are associated to these infections. [7] The most frequent types of infections include central line associated bloodstream infections, catheter-associated urinary tract infections, surgical site infections and ventilator-associated pneumonia. A brief detail of these is given below

Fig 1 - Types of nosocomial infection

Catheter associated urinary tract infections (CAUTI) -

CAUTI is the most usual type of nosocomial infection globally.

Urinary catheters

- A urinary catheter is a tube inserted into the bladder to collect urine into a closed collection system. Urinary catheters can help patients who have difficulty controlling or emptying their bladder. As patients under anaesthesia are unable to control their bladder, urinary catheters are typically placed during surgical procedures to keep the bladder empty.
- Pathogens spread through an individual's perineum or a contaminated urinary catheter can lead to **urinary tract infections**, which are the most common nosocomial infections.
- **Symptoms** of urinary tract infections include painful urination, flank pain, and fever.
- According to acute care hospital stats in 2011, UTIs account for more than 12% of reported infections. CAUTIs are caused by endogenous native microflora of the patients. Catheters placed inside serves as a conduit for entry of bacteria whereas the imperfect drainage from catheter retains some volume of urine in the bladder providing stability to bacterial residence.
- CAUTI can develop to complications such as, orchitis, epididymitis and prostatitis in males,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

and pyelonephritis, cystitis and meningitis in all patients.[7]

- About 40% of hospital acquired infections occur in the urinary tract and are usually associated with catheterisation and instrumentation of urethra, bladder or kidneys. Initial infection is caused by Esh. coli, Staph, epidermidis and Enterococcus, but later on invaded by Klebsiella, Proteus, Serratia, Pseudomonas and Providencia sp.

Surgical site infections (SSI)–

Surgical procedures

- Surgical site infections are the second most common type that can develop after surgery.
- Length of operation, surgical technique, and operating room sterility are all factors that can affect the incidence of surgical site nosocomial infections.
- **Symptoms** may include skin redness, tenderness, and drainage from surgical sites.
- Surgical site infections are **caused by pathogens already prevalent on the skin or by organisms shed from members of the operating room staff**, and often involve the skin, organs, or implanted materials
- SSIs are nosocomial infections be fall in 2%–5% of patients subjected to surgery. These are the second most common type of nosocomial infections mainly caused by Staphylococcus aureus resulting in prolonged hospitalization and risk of death. The pathogens causing SSI arise from endogenous microflora of the patient. The incidence may be as high as 20% depending upon procedure and surveillance criteria used.[7]

Central line-associated bloodstream infections (CLABSI) –

Central venous catheters

- A central venous catheter (also known as a central line) is a tube placed in a large vein in the neck, arm, chest, or groin and can remain in place indefinitely. Central venous catheters can be used to give intravenous therapies such as total parenteral nutrition (TPN), which provides nutrients and fluids to patients.
- **Bloodstream infections** can result from pathogens that may penetrate the skin during insertion of hubs of central lines. This is the third most common form of nosocomial infection and has the highest rate of mortality.
- **Symptoms** of infection may include skin redness, tenderness, and drainage at insertion sites.
- CLABSIs are deadly nosocomial infections with the death incidence rate of 12%–25%. Catheters are placed in central line to provide fluid and medicines but prolonged use can cause serious bloodstream infections resulting in compromised health and increase in care cost. Although there is a decrease of 46% in CLABSI from 2008 to 2013 in US hospitals yet an estimated 30,100 CLABSI still occur in ICU and acute facilities wards in US each year [7].

Ventilator associated pneumonia (VAP)–

Mechanical ventilation

- **Ventilator-associated pneumonia** is a respiratory infection caused by breathing in contaminated oropharyngeal flora during mechanical ventilation (machine-assisted breathing).
- Together with central-line bloodstream infections, it is the third most common nosocomial infection.
- Early-onset nosocomial pneumonia occurs within the first four days of admission and is commonly caused by community-acquired pathogens like Staphylococcus aureus, Streptococcus pneumoniae, and Haemophilus influenzae.
- Late-onset pneumonia is frequently caused by multi-drug resistant bacteria like MRSA, Pseudomonas aeruginosa, Klebsiella, and Acinetobacter.
- **Signs and symptoms** include fever, increased mucus production, increased white blood cell count, and abnormal chest X-ray findings.
- VAP is nosocomial pneumonia found in 9–27% of patients on mechanically assisted ventilator. It usually occurs within 48 h after tracheal incubation. 86% of nosocomial pneumonia is associated with ventilation. Fever, leukopenia, and bronchial sounds are common symptoms of VAP [7]
- Mostly Gram-negative bacilli organisms like Klebsiella, Enterobacter, Serratia, Proteus, Esch.coli, Ps. aeruginosa reach the lower respiratory tract by aspiration from the pharynx causing necrotising bronchopneumonia

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

	Relative percentage by site of infection				
	BSI	PNEUM	UTI	SSI	Others
Coagulase-negative staphylococci	39.3	2.5	3.1	13.5	15.5
Staphylococcus aureus	10.7	16.8	1.6	12.3	13.7
Pseudomonas aeruginosa	3.0	16.1	10.6	9.2	8.7
Enterococci spp.	10.3	1.9	13.8	14.5	5.9
Enterobacter spp.	4.2	10.7	5.7	8.8	6.8
Escherichia coli	2.9	4.4	18.2	7.1	4.0
Candida albicans	4.9	4.0	15.3	4.8	4.3
Klebsiella pneumoniae	2.9	6.5	6.1	3.5	37.7
Others	21.8	37.1	25.6	26	3.5

TABLE 1 - Common pathogens associated with nosocomial infections in ICU patients
National Nosocomial Infections Surveillance System January 1989–June 1998. [8]
(BSI = bloodstream infection; PNEUM = pneumonia; UTI = urinary tract infection; SSI = surgical site infection)

CAUSATIVE AGENTS

The common causative agents of such infections are Staphylococcus aureus, including antibiotic-resistant MRSA, Escherichia coli, Enterococcus spp., and Candida spp. [1] Pseudomonas aeruginosa, Escherichia coli, Klebsiella spp., Mycobacterium tuberculosis, and Candida albicans.[2].
Overall Bacteria are the most common causative agent followed by fungi and viruses.

BACTERIA –

Bacteria are the most common pathogens responsible for nosocomial infections. Some belong to natural flora of the patient and cause infection only when the immune system of the patient becomes prone to infections. Acinetobacter is the genre of pathogenic bacteria responsible for infections occurring in ICUs. It is embedded in soil and water and accounts for 80% of reported infections. Bacteroides fragilis is a commensal bacteria found in intestinal tract and colon. It causes infections when combined with other bacteria. Clostridium difficile cause inflammation of colon leading to antibiotic-associated diarrhoea and colitis, mainly due to elimination of beneficial bacteria with that of pathogenicC .difficileis transmitted from an infected patient to others through healthcare staff via improper cleansed hands. Enterobacteriaceae (carbapenem resistance) cause infections if travel to other body parts from gut; where it is usually found. Enterobacteriaceae constitute Klebsiella species and Escherichia coli. Their high resistance towards carbapenem causes the defence against them more difficult. Methicillin-resistant S. aureus (MRSA) transmit through direct contact, open wounds and contaminated hands. It causes sepsis, pneumonia and SSI by travelling from organs or bloodstream. It is highly resistant towards antibiotics called beta-lactams. [7]

FUNGI –

Fungal parasites act as opportunistic pathogens causing nosocomial infections in immune-compromised individuals. Aspergillus spp. can cause infections through environmental contamination. Candida albicans, Cryptococcus neoformans are also responsible for infection during hospital stay. Candida infections arise from patient's endogenous microflora while Aspergillus infections are caused by inhalation of fungal spores from contaminated air during construction or renovation of health care facility [7]

VIRUSES –

Besides bacteria, viruses are also an important cause of nosocomial infection. Usual monitoring revealed that 5% of all the nosocomial infections are because of viruses. They can be transmitted through hand-mouth, respiratory route and faecal-oral route. Hepatitis is the chronic disease caused by viruses. Healthcare delivery can transmit hepatitis viruses to both patients and workers. Hepatitis B and C are commonly transmitted through unsafe injection practices. Other viruses include influenza, HIV, rotavirus, and herpes-simplex virus [7]

WHO IS AT RISK FOR A NOSOCOMIAL INFECTION?

- Increasing age
- Greater length of hospitalization
- Excessive or improper use of broad-spectrum antibiotics

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

- Higher number of invasive devices and procedures (for instance: central venous catheters, urinary catheters, surgical procedures, and mechanical ventilation)
- Comorbid conditions
- Diabetes
- Chronic lung disease
- Renal insufficiency
- Malnutrition

Epidemiology Of Nosocomial Infections

Nosocomial infection affects huge number of patients globally, elevating mortality rate and financial losses significantly. According to estimate reported of **WHO**, approximately 15% of all hospitalized patients suffer from these infections. These infections are responsible for 4%–56% of all death causes in neonates, with incidence rate of 75% in South-East Asia and Sub-Saharan Africa. The incidence is high enough in high income countries i.e., between 3.5% and 12% whereas it varies between 5.7% and 19.1% in middle- and low-income countries. The frequency of overall infections in low-income countries is three times higher than in high income countries whereas this incidence is 3–20 times higher in neonates.[7].

Gram-positive bacteria are the commonest cause of nosocomial infections with Staphylococcus aureusbeing the predominant pathogen. There has been an increase in the rate of antibiotic resistant bacteria associated with nosocomial infections in ICU. Bacteria develop resistance when they acquire new genetic material.[18].

They affect 1 in 10 patients admitted to hospital. Annually, this results in 5000 deaths with a cost to the National Health Service of a billion pounds. On average, a patient with hospital acquired infection spent 2.5-times longer in hospital, incurring additional costs of Rs,2,88,736 more than an uninfected patient [8].

Each year Nosocomial infections causes 4.5-billion-dollar economic damage and due to these 90,000 individuals die and 2,000,000 health care workers are affected annually.

Incidence of nosocomial infection

The WHO data showed that in the world, 35 million health care workers are exposed to the risk of Nosocomial Infection. Based on result different study in the developed countries, incidence of nosocomial infection in regular wards and intensive care units (ICUs) ward reported to 5–15% and 50%, respectively. Reported WHO showed that amount incidence of nosocomial infection for hospitalized patients evaluated about 15% [18]

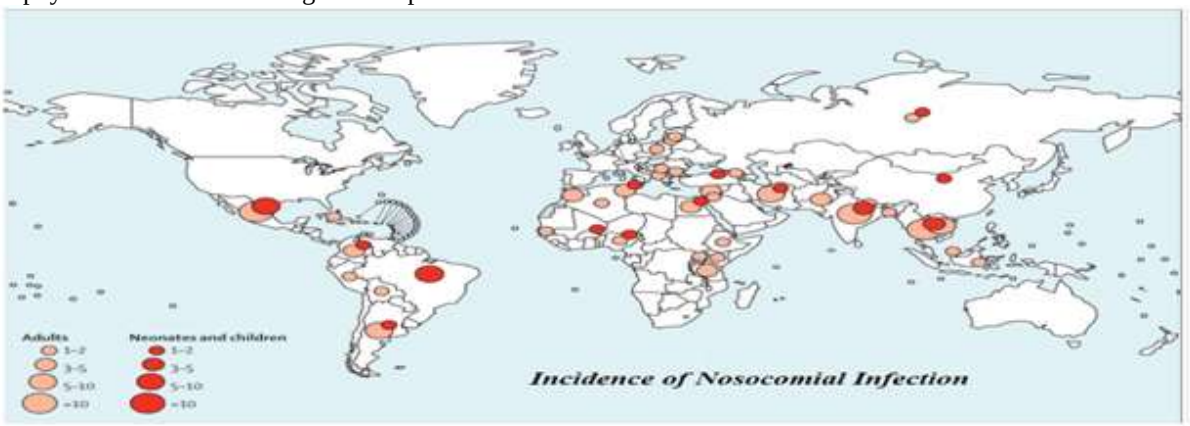

Fig 2 - Incidence of nosocomial infection

Risk Factors Determining Nosocomial Infections

Demographic patients (age and gender), type of catheter used (arteriovenous, urinary and blood syringe head), procalcitonin, white blood cell (WBC), and use of ventilator in ICU ward are the main **factors** attributed to nosocomial bacterial infection. One of the most important **Complications** NIs is increase recovery time and psychological and mental problems for the patient [18]

Nosocomial Infections also depends upon the environment in which care is delivered, the susceptibility and condition of the patient, and the lack of awareness of such prevailing infections among staff and health care providers.

Environment - Poor hygienic conditions and inadequate waste disposal from health care settings

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

Susceptibility- Immunosuppression in the patients, prolonged stay in intensive care unit, and prolonged use of antibiotics.
Unawareness - Improper use of injection techniques, poor knowledge of basic infection control measures, inappropriate use of invasive devices (catheters) and lack of control policies [25]. In low-income countries these risk factors are associated with poverty, lack of financial support, understaffed health care settings and inadequate supply of equipment's.[7]

Related to underlying health status	Related to acute disease process	Related to invasive procedures	Related to treatment
• **Advanced age** • **Malnutrition** • **Alcoholism** • **Heavy smoking** • **Chronic lung disease** • **Diabetes**	• Surgery • Trauma • Burns	• Endotracheal or nasal intubation • Central venous catheterisation* • Extracorporeal renal support • Surgical drains • Nasogastric tube • Tracheostomy • Urinary catheter	• Blood transfusion • Recent antimicrobial therapy • Immunosuppressive treatments • Stress-ulcer prophylaxis • Recumbent position • Parenteral nutrition • Length of stay

TABLE 2 -Factors that predispose to nosocomial infections. European Prevalence of Infection in Intensive Care Study (EPIC) study risk factors.[8]

EFFECT ON HUMAN HEALTH

Most human organs that are affected by the complications of nosocomial infections are lung, skin, bone, eye, throat, ear, and nose. Also, the main systems in human body that NIs has many side effects included central nervous systems, circulatory system, gastrointestinal tract, skin and soft-tissue, respiratory and cardiovascular systems. Based on result studies conducted in the United States, the incidences and prevalence pneumonia, SSI, gastrointestinal, UTI and BSI were 21.8%, 21.8%, 17.1%, 12.9% and 9.9%, respectively [18]

TRANSMISSION

The main reasons for the spread of such infections are attributed to the microbial cross contaminations arising from inadequate hygiene and healthcare practices. The droplet-sized body fluids carrying microorganisms during coughing, sneezing, conversation, suctioning, and bronchoscopy also most often contaminate the surrounding surfaces. Such droplets can successfully deposit directly on a host's mucosal surface (e.g., conjunctivae, mouth, or nose). When originated through cross contamination, the microbial pathogens most often develop biofilms on the mucosal and soft tissues of hospitalized patients, as well as on the surfaces of medical devices and instruments. Such microbes residing in the self-assembled hydrated layer are hard to kill by external stress.[2]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

Fig 3 -Routes of transmission nosocomial infection [18]

Microflora of patient –

- Bacteria belonging to the endogenous flora of the patient can cause infections if they are transferred to tissue wound or surgical site. Gram negative bacteria in the digestive tract cause SSI after abdominal surgery.[7]
- Improper implementation of medical waste management, non-use of appropriate disinfectants, and lack of proper air conditioning system [18]
- The use of non-sterile surgical and non-sterile dressing, needle sticking, non-observance of standard precautions during the patient's hospitalization and medical care. [18]

Patient and staff –

- Transmission of pathogens during the treatment through direct contacts with the patients (hands, saliva, other body fluids etc.) and by the staff through direct contact or other environmental sources (water, food, other body fluids).[7]
- Low level of knowledge of patients and treatment staff about the causes of nosocomial infections. [18]
- Failure to observe standard precautions in contact with the patient by the care staff. [18]

Environment –

- Pathogens living in the healthcare environment i.e., water, food, and equipment's can be a source of transmission. Transmission to another patient makes one more reservoir for uninfected patient.[7]
- Improper use and inadequate personal protective equipment, thin gloves, drawing blood, needle recapping, transit disposal needle, needles penetration to skin, non-standard safety boxes, resistance of antibiotics. [18]
- Failure to properly observe the principles of hand hygiene are the main common routes and reasons of transfer and enter infectious microorganisms into human body. [18]

HOW CAN NOSOCOMIAL INFECTIONS BE PREVENTED?

- Implementation of infection control protocols to reduce exogenous and endogenous transmission in health-care facilities.
- Administration of antibiotics and antiseptic therapy to the carrier staff or source patient to destroy the pathogenic microorganisms. Before administering therapy, the organism is to be isolated and antibiotic sensitivity test is to be done.
- The transmission route is to be controlled by regular hand washing, disinfection of equipment. Poor hand hygiene is responsible for 40% of infections transmitted in hospitals.[8]
- Increasing the level of awareness, especially of sensitive groups (patients and HCW), about the ways to prevent nosocomial infections [18]
- Proper sterilisation and disinfection of the inanimate objects in the hospital environment should be done. Thus, the source of infection can be controlled.
- Protective garments are necessary for health providers exposed to body fluids, for example sweat, oropharyngeal fluids, blood or urine. Gloves and aprons should be worn for handling body fluids. High efficiency particulate air (HEPA) filter masks are recommended for sputum smear positive patients with tuberculosis, particularly for cough-inducing procedures.[8]
- Disinfection of excreta and infected material is necessary to control the exit point of infection.
- Holding regular and periodic training workshops in connection with standard precautions and prevention of occurrence nosocomial infection.[18]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

- By vaccination e.g., tetanus, gas gangrene and Hepatitis B, the susceptible host can be protected
- Further research using more sophisticated methodology is warranted. [18]

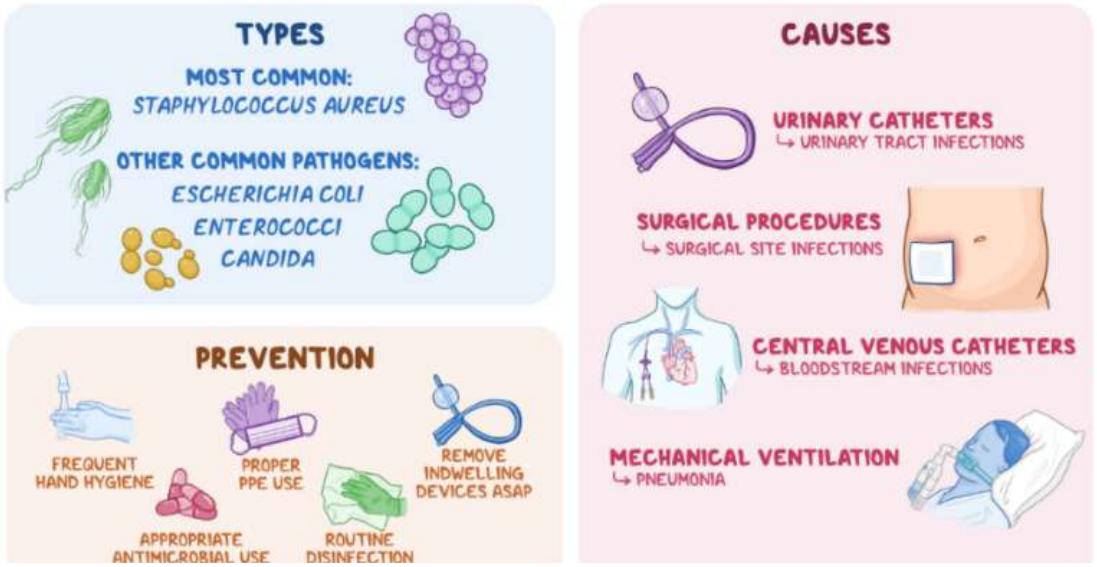

Fig 4 – Nosocomial infection types, causes and prevention

ADVERSE EFFECTS

Antimicrobial resistance

Pathogenic microbes that are used to fight antibiotics become resistant to these drugs by gene mutation, and new generations emerge that cannot be fought, called antibiotic resistance. Excessive use of antibiotics has provided the basis for drug resistance of available and common drugs and has increased the prescribing of new and more expensive drugs. One of the most important causes of this type of drug resistance is the arbitrary or excessive use of antibiotics. In the development of antibiotic resistance, underlying factors such as anomalies, abnormalities of the genitourinary system, genitals, bladder return to the ureter, recent use of antibiotics, recurrent urinary tract infections should be considered; Because some of these factors can cause irreparable problems. Based on reported different studies the highest antimicrobial resistance, with 8/10 resistant to methicillin, sulbactam-ampicillin, cefazolin, erythromycin, gentamicin, ciprofloxacin, ofloxacin in the strains of S. aureus.[18]

Length of hospital stay

Nosocomial infections are always one of the major health problems along with the expansion of hospitals and increase the incidence and death of these infections by increasing the length of hospital stay. As a result, it drastically increases hospital costs. Nosocomial infections alone cause 88,000 deaths per year in the United States and cost more than 6 billion $ a year in additional medical care. Increased hospitalization time due to nosocomial infection can lead to the cancellation of surgeries and adverse effects on the patient and companions, disruption of the operating room, waste of time, confusion and unemployment of staff, unnecessary occupation of hospital beds and increasing hospitalization time, increasing costs and increase the risk of nosocomial infections. Analysis of surveillance models in a German hospital showed that additional length of hospital stay (LOS) was sensitive to the location of acquisition and the type of HAI. The extra LOS due to all HAI was 12 days for all units but differed on the type of HAI such that CAUTI, SSI, and primary bloodstream infections were responsible for 3.3, 12.9, and 12.5 additional days, respectively. [18]

Associated costs

Increase in hospital costs and enhancement number of mortality and morbidity in patients admitted to medical centres is one of the most important side effects due to the creation nosocomial infections. Based on result different study nosocomial infections increase 8–10% of number hospitalized patients in all of world. Also,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

according to various reports and findings, the annual economic losses caused by the NIs are calculation at about $ 10 billion. in US healthcare system Based on reported to the Centres for Disease Control and Prevention (CDC) approximately annually estimate of the direct cost of nosocomial infections were between $28 billion to $45.[18]

RULES AND REGULATION

- In many countries, nosocomial infection regulations have been established nationally, in order to ensure routine infection control operation in healthcare settings. However, in healthcare settings where patients with emerging or unknown infectious diseases are diagnosed and treated, especially those operated by local governments, infection control methods against severe infectious diseases such as MERS are often imperfect.[20]
- Patients should be informed about the potential risk of developing HAI when receiving care. Healthcare workers should assess the patient's risk factors for developing a specific infection and identify and address ways to limit modifiable risk factors. [18]
- Equipment, facilities, supplies, and standards of operations need to be improved. More importantly, all personnel in healthcare settings, such as doctors, nurses, and administrative and other staff, have to develop their own awareness, essential knowledge, and skills in order to protect themselves against emerging infectious diseases. [20]
- Hygiene policies and performance standards for removing and placing syringe caps always provide the best and safest way for staff. [18]
- Proper control measures should be taken to ensure that nosocomial infections do not occur in designated healthcare settings that accommodate suspected cases suffering from emerging infectious diseases. To this end, a comprehensive and detailed evaluation of nosocomial infection control should be conducted in each designated healthcare setting.[20]
- Negative-pressure quarantine ICUs and wards should be built in accordance with the demand in the area.[20]
- Minimizing consecutive work ceilings should be included in the planning of universities' educational and medical centres. [18]
- Regulations, standards, procedures, and operational instructions on protection against infections from emerging respiratory, gastrointestinal, body fluid, and insect-borne infectious diseases should be established. [20]
- An infectious patient is to be isolated.
- Periodical regular trainings for the knowledge of prevention and control emerging or unknown infectious diseases, and emergency exercises regarding nosocomial infection events among medics can also help to strengthen the infection control system.[20]

DIAGNOSIS

Methods diagnosis of nosocomial infections

- Laboratory, demographic, blood and urine cultures, serological equilibrium analysis, a chest x-ray, physical examination and the clinical observations, are used to confirm diagnoses of nosocomial infections. [18]
- Tests available for nosocomial infections diagnosis, is positive culture plates (including chocolate agar, blood agar, and blood culture plates) containing pathogens (agents of bacteria) isolated from patients. [18]
- The main characteristics of this method include have higher speed detect, genome detects, follow and the determination of agents the infection disease. [18]

PRECAUTIONS

1. Use caution when using sharp and winning medical devices, using useful safety boxes, proper use of safety boxes and preparation of standard safety boxes rigidity in all wards in hospital and medical centres. [18]
2. Avoiding hand-to-hand passing and needle recapping.
3. Increasing knowledge of health care worker.
4. Holding workshops and training courses in connection with about infections. [18]
5. Reduction of use of sharp devices, and direct contact with needles.
6. observance of standard precautions in the process of collecting, decontaminating and disposing of winning tools are the most important actions to reduce of the risk of nosocomial infections.[18]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

Agent	causative factor	Routes of Transmission	Adverse health effects
Nosocomial Infection	Bacteria (Gram-positive organisms include coagulase-negative Staphylococci, Staphylococcus aureus, Streptococcus species, Legionella species, and Aspergillus species, Enterococcus species, Gram-negative organisms include species of the Enterobacteriaceae family, including Klebsiella pneumoniae and Klebsiella oxytoca, Escherichia coli, Proteus mirabilis, and Enterobacter species; Pseudomonas aeruginosa, Acinetobacter baumanii, and Burkholderia cepacian), viruses (hepatitis B and C and human deficiency virus (HIV)), and fungi (Candida species, such as C. albicans, C. parapsilosis, C. glabrata), microorganisms,	Clostridioides difficile Infection (CDI), Pneumonia, Skin and Soft Tissue Infection (SSI), Central Line-Associated Blood Stream Infection (CLABSI), Catheter-Associated Urinary tract Infection (CAUTI), Intravenous catheterization, cytotoxic drugs, radiation therapy	Transmission of infectious diseases, antimicrobial resistance, develop hospitalized patients, not cost-effective,

TABLE 3 - Summary of the association between Nosocomial Infection, causative factor and adverse health effects. [18]

STAGES OF TESTING

- Samples were transferred to microbiology laboratory. In the next stage, the species of bacteria, genus of bacteria, and antibiotic susceptibility testing of the isolates should be determined. [18]
- Incubation the samples at 37 ◦C with and without CO2 for the duration 24–72 h, Gram staining and prepared microscopic slides are other steps of sample preparation. [18]
- Depending on the result of Gram staining, differential tests were performed according to the guidelines, standard protocols, and antibiotic susceptibility testing provided by the WHO and reference laboratories. [18]
- The Kirby-Bauer method is the standard method for determination and diagnosis the species and genus. The diameter of inhibition zone was measured and the sensitivity or resistance of isolates was determined based on standard tables. Antibiotic sensitivity test was performed using the same antibiotic disks used in the hospital laboratories. [18]

Antibiotics Use and its Resistance

The Centres for Disease Control and Prevention (CDC) estimates that each year about 100 million courses of antibiotics is prescribed by office-based physicians, while approximately 50% of those are unnecessary. The selection of antimicrobials should be based upon the patient's tolerance in addition to the nature of disease and pathogen. The aim of antimicrobial therapy is to use a drug that is selectively active against most likely pathogen and least likely to cause resistance and adverse effects.[7] Appropriate use of antibiotics is important. Up to 30% of ventilator associated pneumonias are treated inadequately. There is increasing evidence to suggest that the use of appropriate and early antibiotics improves morbidity and mortality. Appropriate antibiotic use requires a thorough knowledge of their mode of action.[8]

Antibiotic resistance is responsible for the death of a child every five minutes in South-East Asia region. Drugs that were used to treat deadly

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

diseases are now losing their impact due to emerging drug resistant microorganisms. This resistance threatens the effective control against bacteria that causes UTI, pneumonia and bloodstream infections. Highly resistant bacteria such as MRSA or multidrug-resistant Gram-negative bacteria are the cause of high incidence rates of nosocomial infections worldwide.[7]

Antibiotic control policy -The worldwide pandemic of antibiotic resistance shows that it is driven by overuse and misuse of antibiotics, which is a threat to prevent and cure the diseases The development of new diagnostics and other tools is required in healthcare institutes to stay ahead of evolving resistance. Pharmacists should play their role of prescribing the right antibiotic when truly needed and policymakers should foster cooperation and information among all stakeholders.[7]

Mode of action	Class of antibiotic	Examples	Clinical uses
Cell wall inhibitors	Penicillin	Penicillin V and G	Gram-positive
	Semi-synthetic penicillin	Ampicillin, Amoxicillin	Gram-positive and -negative bacteria, except penicillinase-producing bacteria, *e.g. S. aureus*
	Cephalosporins	Cefotaxime, cefradine, ceftazidime	Gram-negative organisms with later generation better with Gram-positive
	Monobactams	Aztreonam	Gram-negative organisms
	Carbapenems	Meropenem	Broad-spectrum
	β lactamase inhibitors	Clavulanate	
	Glycopeptides	Vancomycin	Gram-positive organisms (e.g. MRSA and enterococci)
Cell membrane inhibitors	Antifungal		
	Polyenes	Nystatin	Aspergillus, candida
	Imidazoles	Ketonazole	
	Triazoles	Fluconazole	
Protein synthesis inhibitors	Aminoglycoside	Gentamicin	
	Macrolides	Erythromycin	Gram-positive organisms
	Oxazolidinone	Linezolid	*H. influenza*
	Ketolides	Telithromycin	
	Streptogramins	Synercid	
Nucleic acids inhibitors	Fluoroquinonolones	Ciprofloxacin	Broad Gram-negative spectrum
	Nitro imidazoles	Metronidazole	*C. difficile*
	Rifampicin	Sulphonamides	
	Folate inhibitors		

TABLE 4 - Mode of action of common antibiotics [8]

STATISTICAL ANALYSIS

Nosocomial infections or healthcare associated infections occur in patients under medical care. These infections occur worldwide both in developed and developing countries. Nosocomial infections accounts for 7% in developed and 10% in developing countries. As these infections occur during hospital stay, they cause prolonged stay, disability, and economic burden.[7]

During hospitalization, patient is exposed to pathogens through different sources environment, healthcare staff, and other infected patients. Transmission of these infections should be restricted for prevention. Hospital waste serves as potential source of pathogens and about 20%–25% of hospital waste is termed as hazardous.[7]

Intensive care units (ICU) have the highest prevalence of hospital-acquired infections in the hospital setting. The European Prevalence of Infection in Intensive Care Study (EPIC), involving over 4500 patients, demonstrated that the nosocomial infection prevalence rate in ICU was 20.6%.1 ICU patients are particularly at risk from nosocomial infections as a result of mechanical ventilation, use of invasive procedures and their immunocompromised status [18]

Of every hundred hospitalized patients, seven in developed and ten in developing countries can acquire one of the healthcare associated infections These infections get noticed only when they become epidemic, yet there is no institution or a country that may claim to have resolved this endemic problem [7]

According to Extended Prevalence of Infection in Intensive Care (EPIC II) study, the proportion of infected patients within the ICU are often as high as 51%. Based on extensive studies in USA and Europe shows that HCAI incidence density ranged from 13.0 to 20.3 episodes per thousand patient-days.[7].

Globally, the incidence of HAI ranges from 3.6 to 19.1%. Out of these, high-income countries (HICs) account for 3.6–12%, whereas the low- and middle-income countries (LMICs) account for 5.7 to 19.1%. Studies state that the prevalence rate is up to 4.5% in the US and 5.7–7.1% in European countries, while this rate ranges

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

between 5.7% and 19.2% in low- and middle-income countries. Based on an extensive study conducted by the WHO in 2011, HAI incidence density ranged from 13.0 to 20.3 episodes per 1000 patient-days in the US and Europe, respectively. While more than 40% of hospitalizations with HAI were observed in Latin America, Sub-Saharan Africa, and Asia. The pooled cumulative incidence density of HAI (HAI/1000 patient-days (95%CI)) in HICs and LMICs are 17.0% (14.2–19.8%) and 42.7% (34.8–50.5%), respectively. As per an independent review by a UK committee, it is assessed that 10 million deaths will happen by 2050. Figure 1 shows the global distribution [1]

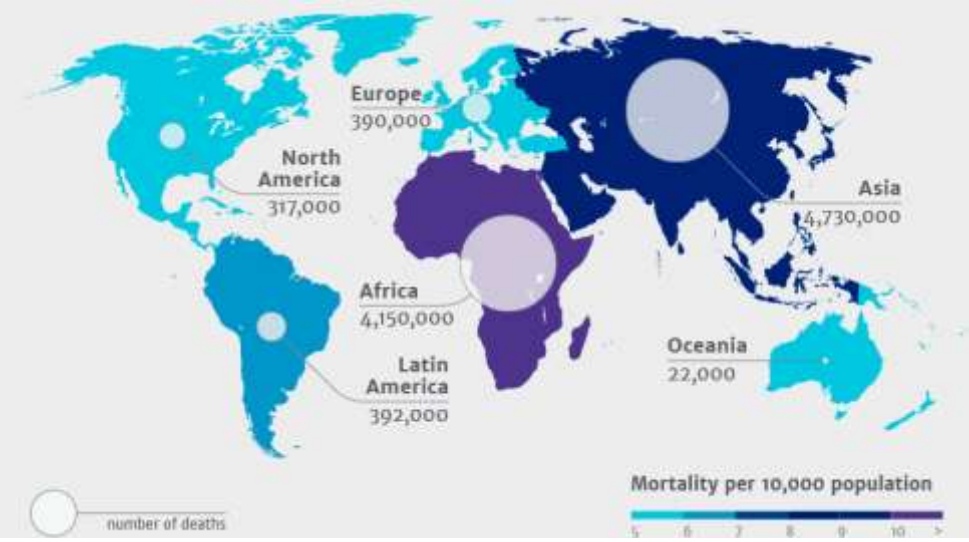

Fig 5. Global distribution of 10 million deaths expected by 2050 due to antimicrobial resistance [1]

RECENT TREND

COVID IMPACT ON NOSOCOMIAL INFECTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2- 2), first described in December 2019, causes coronavirus disease 2019 (COVID-19), and has been declared as a Public Health Emergency of International Concern by World Health Organization (WHO) on 30 January 2020.[9]The pandemic of SARS-CoV-2 infection at the beginning of 2020 has heavily hit most countries in the world, and one of the major challenges imposed by this infection has been the large numbers of patients in need for intensive care. Bacterial and fungal superinfection during intensive care unit (ICU) stay has been reported in other outbreaks of severe acute respiratory syndrome (SARS).[21]

The nosocomial infection rate in the ICU was noted to be higher among COVID-19 patients compared to non-COVID-19 patients; however, it was not statistically significant. COVID-19 patients seem to be more predisposed to catheter-associated urinary tract infection (CAUTI) potentially due to longer duration of indwelling urinary catheter-days despite a higher proportion of non-COVID-19 patients having urinary catheters. Nosocomial Infection in critically ill COVID-19 patients were known to have poor mortality, often requiring intensive care.[26]

During a study, 14.8% (10/71) developed nosocomial infections in COVID-19 patients and 2.7% (13/487) of non-COVID-19 patients developed nosocomial infections.[26]

Hospitals around the country continue to report a growing trend of mucormycosis cases in COVID-19 patients and this disease has been declared as an epidemic.[14]

MUCORMYCOSIS –

Mucormycosis (also called zygomycosis) is a serious but rare fungal infection caused by a group of molds called mucormycetes. Mucormycosis, or the deadly black fungus, is a life-threatening fungal infection caused by fungi that belongs to the subphylum Mucoromycotina and order Mucorales. Mucormycosis is a rare fungal infection caused by exposure to mucor mold commonly found in soil, manure, plants, decaying fruits and vegetables, air and even in the mucus of healthy people. It affects the sinus, brain and lungs

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

and can be life-threatening in diabetic or severely immunocompromised individuals.
A total of 45,432 cases of mucormycosis have been reported by states and UTs till July 15 of which 21,085 affected people are receiving treatment and 4,252 have died. India had recorded its highest number (6329) of mucormycosis cases.[14]

HISTORY

Mucormycosis was initially described in 1855, as this was the first authentic human case of this condition. In 1876, pulmonary mucormycosis was discovered by Furbringer in Germany in a cancer patient who presented with a haemorrhagic infarct in the right lung that consisted of fungal hyphae and spores. Mucormycosis was first seen in an autopsy in the year 1956.

TRANSMISSION

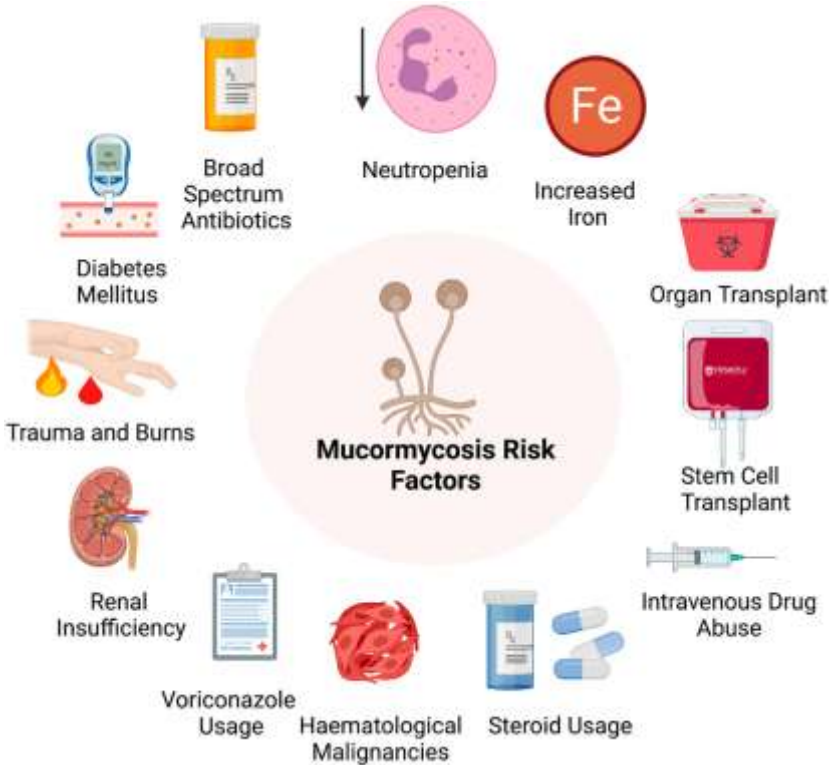

Fig 6 - Risk factors associated with the development of mucormycosis

The main mode of infection of mucormycosis is through the inhalation o spores, consumption of contaminated food and inoculation of the fungi into abrasions or cuts on the skin. In addition, outbreaks of mucormycosis have also been linked to contamination of medical devices, ventilation systems and hospital disposables like bandages, hospital linen etc. Mucormycosis mostly infects immunocompromised individuals whose immune system lacks the ability to mitigate the fungi.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

MECHANISM

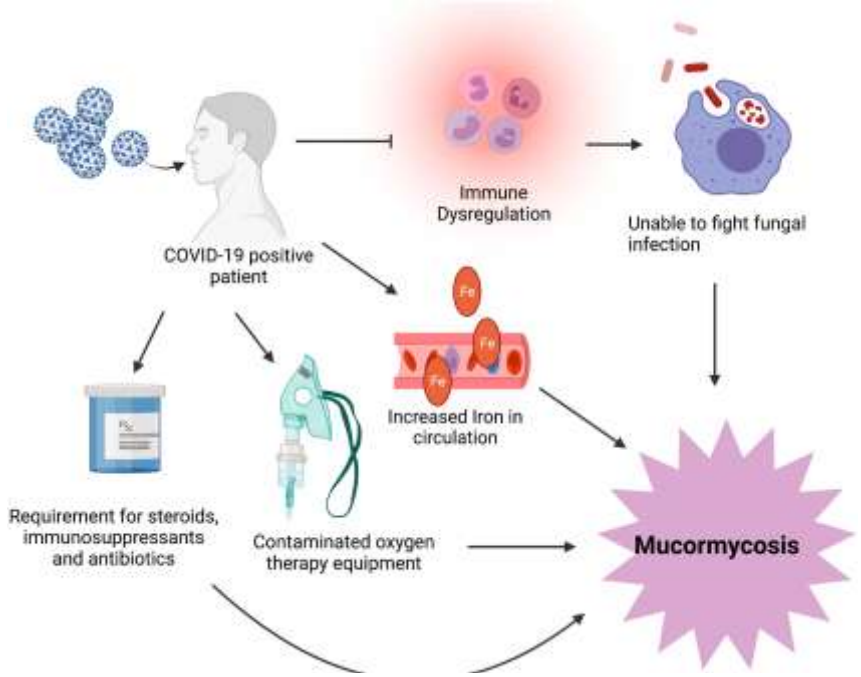

Fig 7 - Possible mechanism of mucormycosis in COVID-19 infected patients.[14]

Mucormycosis is becoming common among COVID-19 patients, especially due to physiological stressors such as high body temperature osmolarity, hypoxia which are common conditions when affected with SARS-CoV-2. Also, these patients undergo heavy intake of steroids, use oxygen masks and ventilators to combat SARS-CoV-2 infection, which turns as an entry pass to the body for the Mucorales fungus. Further, this fungal infection could impact the COVID-19 in two-way scenario:

1) when the COVID- 19 patients who have diabetes as co-morbidity, create an acidic environment that enables a unique environment for these fungi to grow. Also, due to hyperglycaemia, there is a decrease production of T-cells and immunosuppression, resulting in a cytokine storm.

2) heavy intake of steroids also releases a huge amount of sugar which helps in the rapid multiplication and growth of fungal hyphae. Also, steroids tend to inflammation the immune cells leading to cytokine storm and damage to cellular organs.

SYMPTOMS -

Mucormycosis has been associated with various underlying conditions that predispose an individual to the infection. Some of these factors include diabetes, neutropenia, organ or stem cell transplantation, trauma and burns, haematological disorders, steroidal use, metabolic acidosis, intravenous drug usage, renal insufficiency, broad-spectrum antibiotics, increase in iron in the system, malnutrition, usage of voriconazole

DIAGNOSIS –

It is mainly diagnosed by laboratory analysis of the biopsy isolated from the site of infection. In addition, other imaging tests like CT are also beneficial for diagnosis.

WORLD IMPACT

Majority of mucormycosis occurred in Europe (34%), followed by Asia (31%), North or South America (28%), Africa (3%), Australia and New Zealand (3%). The Leading International Fungal Education (LIFE) estimates 10,000 cases globally.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

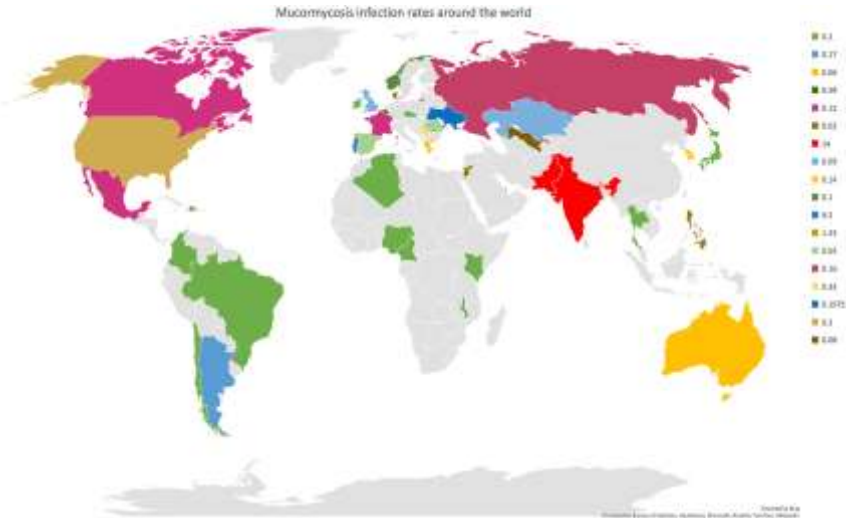

Fig 8. Mucormycosis infections around the world: The estimated rates of mucormycosis infection per 100 K individuals around the world is illustrated in this figure.[14]

CURE - Surgery and antifungal therapy

CASE STUDY

1. A study in Madrid from the initial days of Covid outbreak which saw a devastating impact patient admitted specially in ICU.[21]

	Patients ($N = 140$)	Nosocomial infection during ICU ($N = 57$)	No infection during ICU ($N = 83$)	p value
Age—year (IQR)	61 (57–67)	63 (60–68)	61 (54–66)	0.03
Sex—male	108 (77%)	47 (82%)	61 (73%)	0.21
Body mass index (IQR)	30.4 (26–32)	30.7 (26–32)	30 (26–31)	0.56
APACHE II (IQR)	14 (10–17)	15 (12–19)	13 (9–16)	0.02
Comorbidities				
Hypertension	60 (42%)	26 (45%)	38 (46%)	0.9
Chronic ischemic heart disease	20 (14%)	11 (19%)	9 (11%)	0.16
Chronic kidney disease	8 (6%)	5 (9%)	3 (4%)	0.2
Chronic obstructive pulmonary disease	10 (7%)	7 (12%)	6 (7%)	0.31
Diabetes	28 (20%)	16 (28%)	12 (14%)	0.048
PaO_2/FIO_2 ratio on first day of MV (IQR)	124 (69–156)	115 (60–143)	134 (71–210)	0.35
Treated with invasive mechanical ventilation	134 (96%)	56 (98%)	78 (94%)	0.22
Time from hospital to ICU admission—days (IQR)	4 (1–6)	4 (1–4)	4 (1–6)	0.8
ICU length of hospitalization—days (IQR)	14 (8–17)	20 (11–24)	11 (7–15)	< 0.001
Severe ARDS at ICU admission	83 (59%)	39 (68%)	44 (53%)	0.068
Ceftriaxone	120 (85%)	53 (92%)	67 (80%)	0.042
Azithromycin	118 (84%)	53 (92%)	65 (76%)	0.019
Other antibiotics	105 (75%)	47 (82%)	58 (69%)	0.091
Steroids	127 (90%)	56 (98%)	71 (85%)	0.01
Tocilizumab	96 (68%)	40 (70%)	56 (67%)	0.73
Mortality and causes of death				
ICU mortality	51 (36%)	31 (54%)	20 (24%)	< 0.001
Refractory respiratory failure	19 (37%)	9 (29%)	10 (50%)	0.52
Septic shock	17 (33%)	17 (55%)	0	< 0.001
Multiorgan failure	7 (14%)	1 (14%)	6 (86%)	0.14
Cardiac arrest	6 (12%)	3 (10%)	3 (15%)	0.63
Other causes	2 (4%)	1 (3%)	1 (5%)	0.78

TABLE 5 -Clinical characteristics of the study population and comparison between infected and non-infected patients.[21]

(IQR, interquartile range; ARDS, acute respiratory distress syndrome; ICU, intensive care unit)

Data are presented as number and %, unless otherwise indicated. The most commonly used steroid dose regimen was methylprednisolone 1 mg/kg/day for a median of 10 days

2. Nosocomial Infections in Patients Admitted in Intensive Care Unit (ICU) of a Tertiary Health Centre, India [28]

Case -Data were collected retrospectively from 130 patient's records presented with symptoms of nosocomial infection in MICU of a Tertiary Health Centre, Tumkur from August 2012 to May 2013.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

Result- Incidence of nosocomial infections in MICU patients was 17.7% (23/130). Of which 34.8% (8/130) was urinary tract infection (UTI) being the most frequent; followed by pneumonia 21.7% (5/130), 17.4% (4/130) surgical site infection, 13.0% (3/130) gastroenteritis, 13.0% (3/130) blood stream infection and meningitis. The nosocomial infection was seen more in the 40-60 year of age. The males were more prone to nosocomial infections than the female.

Nosocomial infections	Number of patients	Percentage
Urinary tract infections	8	34.78
Pneumonia	5	21.73
Soft tissue infections	4	17.39
Gastroenteritis	3	13.04
Blood stream infections	2	8.69
Meningitis	1	4.34
Total	23/130	17.69

TABLE 6 - Distribution of nosocomial infections among nosocomial positive patients.[28]

Type of infection	Type of device used	Infection with device (%)	Infection without device (%)
UTI (08)	Catheter	5 (62.5)	3 (37.5)
Pneumonia (05)	Ventilator support	3 (60)	2 (40)
Blood stream infections (02)	CVP catheter	2 (100)	-
Others (09)	-	-	09
Total (23)		9 (39.13)	14 (60.86)

UTI: Urinary tract infection, CVP: Central venous pressure

TABLE 7 - Devices related to nosocomial infections.[28]

3.Deaths from Nosocomial Infections died at Columbia-Presbyterian Medical Centre and Hackensack Hospital.[32]

Case - A Study was performed at the hospital course of 100 consecutive patients who died at Columbia- Presbyterian Medical Centre and 100 consecutive patients who died at Hackensack Hospital.

	Nosocomial Infection	
	Present	Absent
Group size		
Columbia	30	70
Hackensack	33	67
Age (yr) Mean (range)		
Columbia	67 (16–90)	54 (newborn-99)
Hackensack	69 (41–91)	70 (newborn-97)
Hospital stay (days) Mean (range)		
Columbia	43 (3–211)	10 (1–75)
Hackensack	31 (1–365)	10 (1–69)

TABLE 8 - Demographic Factors in Series of Consecutive Deaths at Columbia- Presbyterlan Medical Centre and Hackensack Hospital.[32]

Result - The epidemiologic patterns of infection were similar although the institutions provide care for different types of patients. There were 88 nosocomial infections in 63 patients. When the nosocomial infection was causally related or contributed to death, infection of the lower respiratory tract was predominant in 31 of 52 (60 per cent) instances. When the nosocomial infection was unrelated to death, urinary tract infection was predominant in 13 of 36 (36 per cent) infections. Among those who died with nosocomial infection, 42 of 63 (67 per cent) patients were terminal on admission and were typically in their 60's with metastatic carcinoma. The 21 patients who were not terminal on admission were typically in their late 70's and had complications of arteriosclerotic cardiovascular disease. Pneumonia was the most frequent nosocomial infection related to death.[32]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

Nosocomial infection	Total		Relation to Death: Causal		Contributed		None	
	No.	%	No.	%	No.	%	No.	%
Respiratory tract	35	40	13	59	18	60	4	11
Urinary tract	22	25	2	9	7	23	13	36
Primary bacteremia	8	9	5	23	2	7	1	3
Decubitus ulcers	5	6	–		–		5	14
Wound	5	6	–		1	3	4	11
Intraabdominal	3	3	–		2	7	1	3
Meningitis	2	2	2	9	–		–	
IV Site	3	3	–		–		3	8
Tracheostomy	4	5	–		–		4	11
Thrush	1	1	–		–		1	3
Total	88		22		30		36	

TABLE 9 - Relation Between Death and Type of Nosocomial Infection [32]

Underlying Disease	Nosocomial Infections: Present				Absent			
	Columbia		Hackensack		Columbia		Hackensack	
	No.	%	No.	%	No.	%	No.	%
Solid tumors	15	50	9	27	22	31	27	40
Arteriosclerotic cardiovascular	6	20	8	24	19	27	20	30
Central nervous system	5	17	6	18	10	14	4	6
Gastrointestinal	1	3	4	12	3	4	3	4
Renal	1	3	2	6	3	4	2	3
Multiple fractures	–		2	6	1	1	–	
Collagen-vascular	–		1	3	–		1	2
Hematologic malignancies	–		–		1	1	2	3
Pneumonia	–		–		1	1	5	7
Newborn disorders	–		–		9	13	1	2
Others	2	7	1	3	1	1	2	3
Total	30		33		70		67	

TABLE 10 - Relation of Underlying Host Disease to Nosocomial Infection [32]

SOME OTHER CASE STUDIES-

4.Nosocomial outbreaks of severe acute respiratory syndrome (SARS) among hospital wards in Guangzhou and Hong Kong, China. [31]

Case -A case–control study was conducted were hospital wards in which superspreading events of SARS occurred, and control wards were wards in which patients with SARS were admitted, but no subsequent nosocomial outbreaks occurred.

5.Norovirus Infection Outbreak and its control in a tertiary care hospital

Case - A Norovirus (former Norwalk-like virus) infections outbreak and its control in a tertiary care hospital during February through May 2004 were studied.

6.Investigate the impact of COVID-19 outbreak on nosocomial infection rate in Iran. [29]

Case-This cross-sectional study was conducted in an educational hospital, southeast Iran. The nosocomial infection rates of critical/intensive care units (CCU/ICUs) and medical-surgical units were assessed during and before the COVID-19 outbreak.

CONTROL PROGRAMS

Approximately two million nosocomial infections occur annually in patients admitted to acute-care hospitals in the USA. The Study on the Efficacy of Nosocomial Infection Control (SENIC Project) indicated that 32 % of nosocomial infections which occur in the absence of an infection surveillance and control program could be prevented by a well-organized program. [12]

The Study of the Efficacy of Nosocomial Infection Control (SENIC) demonstrated that a third of nosocomial infections might be prevented with appropriate infection control measures. These comprise surveillance methods, prevention strategies and treatment programs.[8]

Factors that should be considered in setting national priorities for nosocomial infection prevention and control efforts include incidence, mortality, prolongation of stay, cost of treatment, and potential for prevention of infections at different sites. National nosocomial infection priorities in the USA cover infections caused by

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

emerging pathogens and infection at a particular site. [12]

The mechanism used to disseminate information on effective prevention strategies is the series of CDC 'Guidelines for the Prevention and Control of Nosocomial Infections'. These guidelines address prevention of nosocomial infections at the four major sites, handwashing and environmental control issues, infection control in personnel health, and isolation precautions. [12]

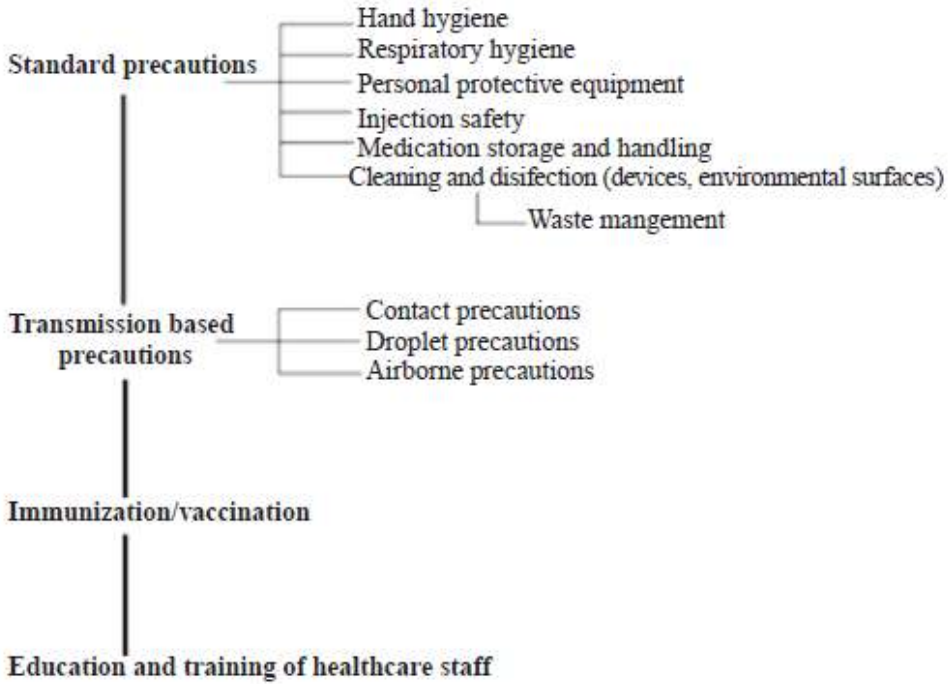

Fig 9- Infection control program.[7]

SURVEILLANCE

Surveillance is the ongoing, systematic collection, analysis and interpretation of information related to health. This is essential for the planning, implementation and evaluation of public health and also the timely dissemination of information.[8]. There were a lot of studies published which focused on optimizing surveillance measures and investigating the use of reference data for reducing infection rates. Only some studies estimating the impact of disease were found.[11]

In order to work cost effectively in the field of nosocomial infection prevention it is possible to either increase the preventive effect or to decrease the costs incurred by surveillance and infection control.[11]

Surveillance of nosocomial infections is one of the major activities of infection control personnel in US acute-care hospitals (8). In order for surveillance data to be useful to infection control personnel, the capacity must exist to analyse the data in an appropriate and timely manner. [12]

The best way for optimizing surveillance is by looking in Hospital databases to acquire the necessary information for assessing the situation and giving good feedback to the wards with the aim of stimulating effective infection-control activities. This would reduce surveillance working time.[11]

EXAMPLE– One such example is Interactive Data Entry and Analysis System (IDEAS), which has been developed for use in NNIS hospitals. In order to meaningfully analyse surveillance data over a period of time. It has become clear that there is a need for a practical approach to assessing different levels of patient risk for nosocomial infection. [12]

In order to convince policy makers and health-system administrators to spend money on infection prevention, reliable data on attributable mortality, prolongation of hospital stay and supplementary costs due to nosocomial infections are needed. At present there is a lack of such data. This lack of information is, however, only due to problems in the study designs and methods used to determine various outcomes.[11]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

NOTE-The National Nosocomial Infections Surveillance (NNIS) system at the Centres for Disease Control and Prevention (CDC) is a voluntary, confidential, hospital-based reporting system that has been influential in guiding infection-control efforts in hospitals across the USA and around the world.[11]

SILVER NANOPARTICLES

INTRODUCTION

With the increase in antibiotic resistance of nosocomial infections, nanoparticles, especially **silver nanoparticles**, provide a successful alternative due to their special properties including high stability. Nanoparticles increase the permeability of bacterial cell membranes, resulting in a higher uptake of antibiotics by bacterial cells [1]

The application of silver as an antimicrobial agent can be traced back to antiquity. Even silver was a preferred choice as an antimicrobial agent before the inception of antibiotics. In recent times, researchers are again inclining toward the use of silver due to its antimicrobial activity as well as the inability of microbes to become resistant to it. Silver also exhibits considerably lower toxicity to human cells compared to bacteria. Silver and its nanoparticles offer a broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria and even against multidrug-resistant pathogens [2].

Nanoparticles, by definition, are structures that have one dimension in the 1–100 nm range. Because of their widespread application, the commercial nanotechnology industry is predicted to increase significantly to $3 trillion by 2015.[5]

With increasing trends of resistance in these pathogens, there are limited antibiotics that can be used to treat these infections. In a few instances, the bacteria become resistant to all the available antibiotics, increasing the challenges to patient treatment and adding to the cost of management. Various technologies and other innovative strategies have been adopted and are under trial to combat and prevent infections from resistant organisms. **Nanotechnology** has gained interest amongst researchers due to its ability to improve existing therapeutics, by enhancing the physiochemical properties and stability of antibiotics, inhibiting or minimizing biofilm growth, target delivery at the infection site, and reducing side effects. It includes the use of nanoparticles of various elements to deal with the current HAI issues. For example, to combat nosocomial infections as drug delivery systems, molecular beacons, and to control biofilm formations. [1]

It is estimated that of all the nanoparticles in consumer products, **silver nanoparticle** (Ag NP) applications currently have **the highest degree of commercialization**.[5]

The method for the **synthesis and assembly** of silver nanoparticles in a biopolymer physical gel derived from **Abroma augusta** plant in imparting antimicrobial properties against nosocomial pathogens. Synthesized silver nanoparticles (diameter, 30 ± 10 nm) were uniformly distributed inside the hydrogel. Such synthesized hydrogel assembly of silver nanoparticles dispersed in the biopolymer matrix exhibited hemocompatibility and antimicrobial and antibiofilm characteristics against nosocomial pathogens. The developed hydrogel as a surface coating offers reduced hardness and modulus value, thereby minimizing the brittleness tendency of the gel in the dried state. Hence, we believe that the hierarchical assembly of our hydrogel owing to its functional activity, host toxicity, and stability could possibly be used as an antimicrobial ointment for bacterial infection control.[2]

Motivated by this, I focused my work on investigating the antimicrobial properties of a silver-based physical hydrogel system for controlling nosocomial infections. To the best of my knowledge

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

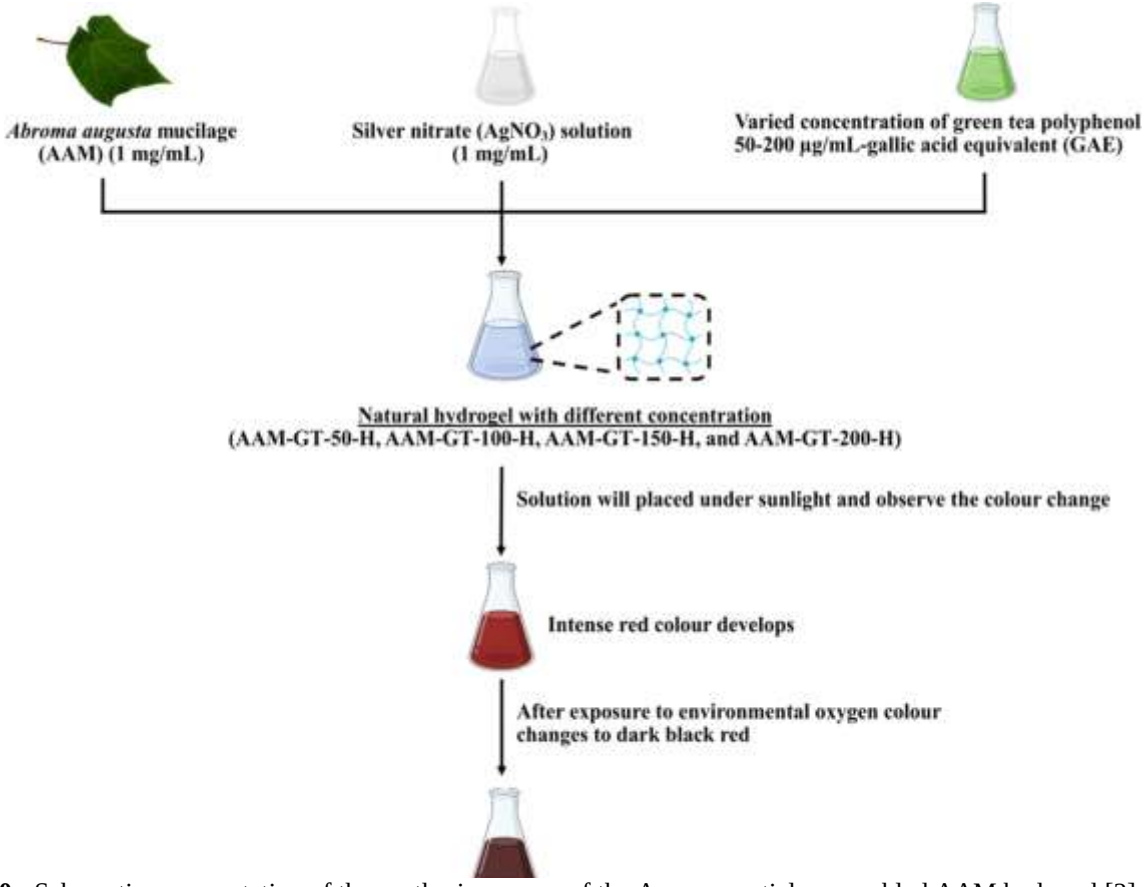

Fig 10 - Schematic representation of the synthesis process of the Ag nanoparticle-assembled AAM hydrogel.[2]

ADVANTAGES OF AGNP

1) The larger surface area of silver nanoparticles provides better contact and attachment with the microbial cell membranes. As a result, it attacks the microbes on multiple cellular targets and ensures lesser probabilities for a pathogen to develop resistance against it. This further leads to penetration and interaction with the building elements of the bacterial cell membrane and cause cell damage.[1]
2) Silver ions can also interact and denature DNA and RNA, inhibiting cell division and replication.[1]
3) SNP could provide a permissive environment that favours scar less wound repair.[4]
4) In medical applications, silver is used for the treatment of burn and chronic wounds, with new products containing nanosized silver being developed and introduced commercially. Silver nanoparticles have received considerable attention because of their attractive physicochemical properties when compared to different novel metal nanomaterials. [6]
5) The strong toxicity that silver exhibits in various chemical forms to a wide range of microorganisms is very well-known, and silver nanoparticles have recently been shown to be a promising antimicrobial material. [6]

DISADVANTAGES

Toxic effects of nanomaterials are very far and few between and no clear guidelines are available to quantify these effects. Even though nano silver - based wound dressings have received approval for clinical applications their possible dermal toxicity is reported to be a matter of concern.[4]

1) A large number of in vitro studies indicate that Ag NPs are toxic to the mammalian cells derived from skin, liver, lung, brain, vascular system and reproductive organs.[5]
2) Some studies have shown that this particle has the potential to induce genes associated with cell cycle progression, DNA damage and apoptosis in human cells at non-cytotoxic doses. [5]
3) Long-term exposure to silver ions could cause argyria, a permanent bluish grey pigmentation

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

of the skin. The cytotoxicity of silver particles increases dramatically as their size reduced to nanoscale.[3]

4) When used as a topical antimicrobial agent, SNPs with the diameter of 10 nm could destabilize the outer membrane, collapse the plasma membrane potential and deplete the levels of intracellular ATP in Escherichia coli cells.[3]
5) There is no comprehensive study currently which compares the cytotoxicity of silver ions and SNPs in human cells. Considering their potential applications in daily life, SNPs may enter human body through various routes such as the respiratory tract, gastrointestinal tract, skin and blood.[3]
6) Recent research has indicated that various tissues such as lung and liver might be important targets for SNPs.[3]
7) At **higher doses** of SNP, necrotic changes are seen. Therefore, at such doses SNP could elicit an inflammatory response which could adversely affect the wound healing process. [4]

SYNTHESIS OF NPs-

Polymeric nanocomposites are obtained by dispersing nanoparticles inside a polymeric network matrix. There are many ways to synthesize polymeric nanocomposites with metallic nanoparticles. One way involves the direct absorption of nanoparticles during the swelling of the polymeric matrix. Another is the absorption of a solution containing a precursor of the nanoparticles and then inducing a chemical or photoinduced reaction to obtain nanoparticles dispersed in the hydrogel.

The number of Ag-NPs obtained inside each hydrogel was determined as the Ag-NPs mg per g of dry hydrogel after 8 h of irradiation

The number of Ag-NPs obtained depends on the Ag+ ion concentration able to enter the hydrogel and the reducing capacity of the matrix.[17]

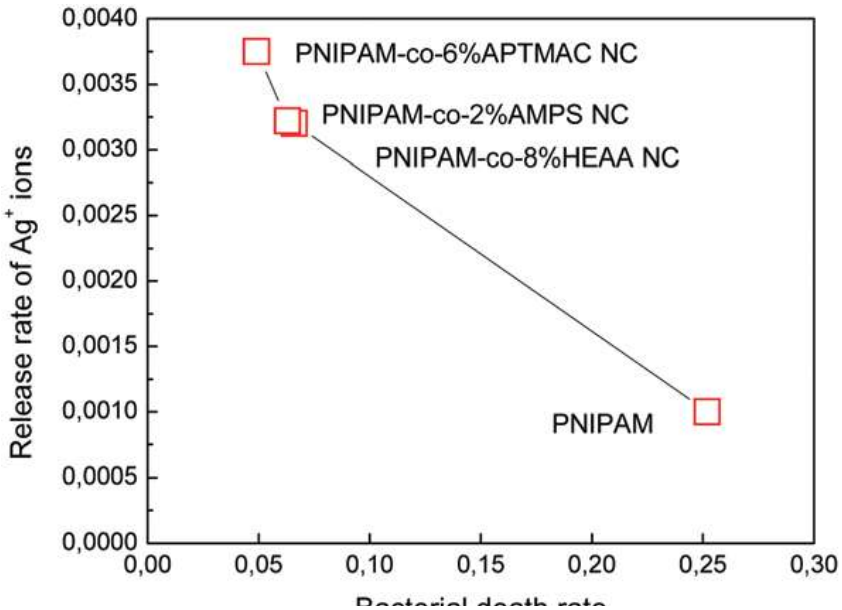

Fig 11. The relation between the release rate of Ag+ ions in solution and bacterial death rate at t50 and 37 1C for each type of NC.[17]

MECHANISM

These NPs offer many interaction mechanisms between nanomaterials and cell walls, such as changing the membrane permeability by penetration, blocking oxidative phosphorylation, or by generating free radicals leading to damage of the cell membrane, and in turn cell death, thus increasing the oxidative stress and destroying DNA. Additionally, the ionic activity of nanoparticles can modulate the bacterial signal transduction leading to the inhibition of bacterial growth or inactivating the enzymes by interacting with them. There are physical interaction mechanisms too, which include bacterial wrapping to induce surface stresses and penetration through sharp edges that causes physical damage and adverse chemical effects. Similarly, helpful is the creation of anti-adhesion surfaces that inhibit biofilm formation. In the present review, an attempt was made to highlight the potential novel solutions

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

provided by nanotechnology in the diagnosis, treatment, and control of MDR strains and its potential use in combat against nosocomial.

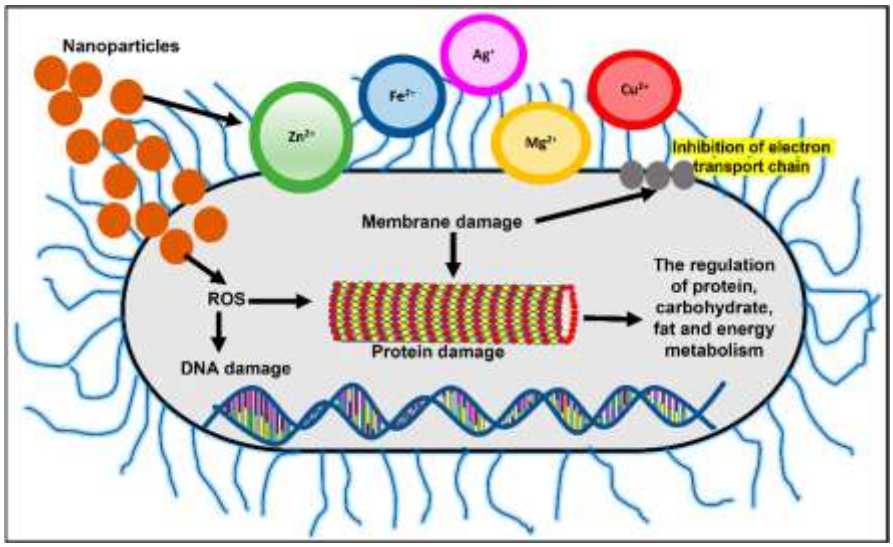

Fig 12: Mechanisms of nanoparticle action in bacterial cells include changing membrane permeability

and the generation of free radicals leading to DNA and protein damage. [1]

Nanoparticles can be used as molecular beacons to identify relevant bacterial strains in minimal time. This is especially important in emergency cases or in an ICU where immediate results are required to continue medical procedures. Molecular beacons are the most promising method for qualitative and quantitative biological detection of bacteria. In a recent study, molecular beacons loaded with nanoparticles have been used for the rapid detection of bacteria.

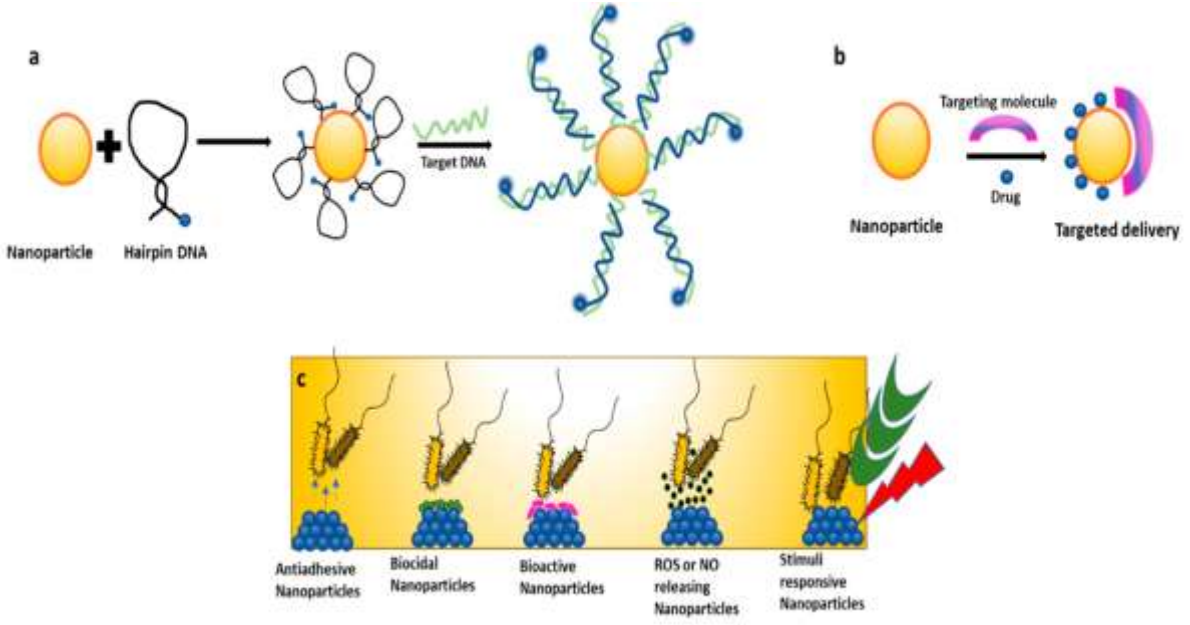

Figure 13. Mechanisms of nanoparticles combating nosocomial infections: (**a**) nanoparticles as molecular beacons, (**b**) nanoparticles for targeted drug delivery of antibiotics, and (**c**) types of nanoparticles preventing biofilm-associated nosocomial infections. [1]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

organisms used	SNP (μg/mL)		
	MIC_{50}[a]	MIC_{90}[b]	$MBC_{99.9}$[c]
Pseudomonas aeruginosa ATCC 9027	3.12	6.25	12.5
Salmonella abony NCTC 6017	3.12	6.25	12.5
Salmonella typhimurium ATCC 23564	3.12	6.25	12.5
Klebsiella aerogenes ATCC 1950	1.56	6.25	12.5
Proteus vulgaris NCIB 4157	3.12	6.25	12.5
Bacillus subtilis ATCC 6633	3.12	6.25	12.5
Staphylococcus aureus ATCC 6538	6.25	12.5	ND
Staphylococcus epidermidis ATCC 12228	3.12	6.25	12.5
Escherichia coli ATCC 117	1.56	6.25	12.5

Table 10. Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) of SNP against Different Organisms.[15]

organism	*D* at MIC[a] (h)	*D** at MBC[b] (h)
Pseudomonas aeruginosa ATCC 9027	3.5	4.7
Escherichia coli ATCC 117	4.4	6
Klebsiella aerogenes ATCC 1950	6.7	9
Salmonella abony NCTC 6017	6.4	9
Salmonella typhimurium ATCC 23564	5.4	7
Proteus vulgaris NCI B 4157	10	8
Bacillus subtilis ATCC 6633	7.17	12
Staphylococcus epidermidis ATCC 12228	7.3	12
Staphylococcus aureus ATCC 6538	18.9	>24
Pseudomans sp. # MDR 1	5.6	4.5
Staphylococcus sp. # MDR 1	>24	>24

Table 11. Microbicidal Activity of SNP at MIC and MBC against Different Bacterial Strains.[15]

Because Ag NP release silver ions (Ag+) in the aqueous state, it is necessary to distinguish between the toxic effects of Ag NP and dissolved Ag+. Ag NP might act as a "Trojan horse", bypassing typical barriers and then releasing Ag+ ions that damage cell machinery. Cytotoxic, apoptosis and induction of stress are produced by both Ag NP and Ag+ ions.

Ag NP were more toxic than Ag+ ions. Interestingly, a higher concentration of cysteine was required to eliminate Ag+ ion toxicity. These findings suggest that interactions between algae and nanoparticles may enhance the release of Ag+ ions, i.e., nanoparticles acted as an effective delivery vehicle for Ag+ ions. also suggest that both "nanosized particle of Ag" as well as "ionic Ag+" contribute to the toxic effects of Ag NP. further elaborated that these two silver forms have distinguishable toxicologic fingerprints. While Ag NP led to cellular and DNA damage, as well as carcinogenic and oxidative stresses, genes related with metal detoxification/metabolism regulation and radical scavenging action were also induced. In contrast, the Ag+ led to an induction of inflammatory response and metallic detoxification processes, but resulted in a lower overall stress response when compared to Ag NP.

In contrast, a study says that Ag NP induced toxicity independent of free Ag+ ions. compared Ag+ ions and Ag NP on the prevalence of phenotypic defects in zebrafish. None of the phenotypic defects observed in Ag NP treatment were observed in Ag+ ion treated embryos. These preliminary studies appear to indicate that Ag NP-mediated toxicity is independent of Ag+ ions.[5]

NOTE –

- SNP could not inhibit SOD activity by any direct mechanism.[4]
- The generation or external addition of ROS can cause cell death by two distinct pathways, viz. apoptosis or necrosis. ROS are known to trigger the apoptotic cascade, via

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

caspases, which are considered as the executioners of apoptosis.[4]

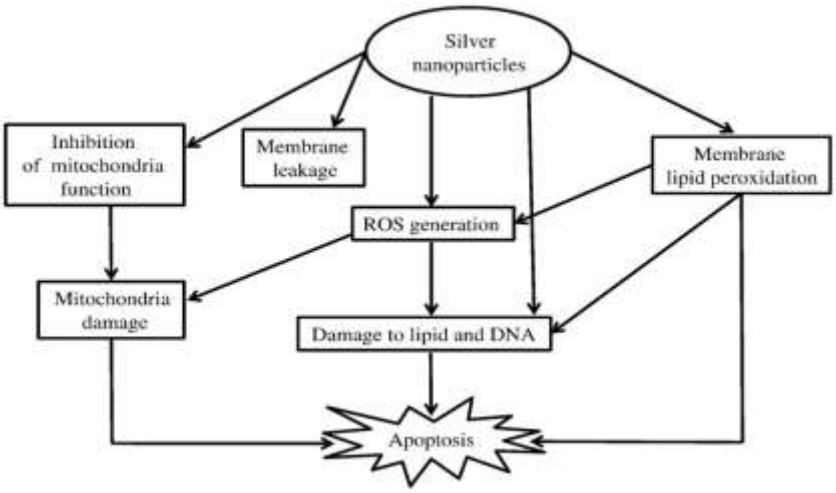

Fig 14 - Possible mechanism for silver nanoparticles induced toxicity.[5]

APPLICATION OF SILVER NP

- Various NPs are employed in life science to accurately detect a bacterial strain.[1]
- Intravenous injection of Ag NP has recently been evaluated for drug delivery and targeting applications. For example, Ag NPs have been shown to interact with the HIV-1 virus and inhibit its ability to bind host cells in vitro.[5]
- Observed that hybridizing molecular beacons with nanoparticles improved the bacterial.[1]
- Their unique plasmon-resonance optical scattering properties allow Ag NP use in bio-sensing and imaging applications.[5]
- NPs, playing important roles in the restoration of antibiotic activity.[1]
- Wide range of Ag NP applications has emerged in consumer products ranging from disinfecting medical devices and home appliances to water treatment.[5]
- Antibiotics conjugated with NPs give the advantage of lower sample consumption and higher sensitivity.[1]
- More importantly is the potential for the application of Ag NP in the treatment of diseases that require maintenance of circulating drug concentration or targeting of specific cells or organs.[5]
- Drugs with poor solubility and absorption ability can be delivered via nanoparticles for target-specific drug delivery.[1]
- Silver nanoparticles (Ag NP) are used in electronics, biosensing, clothing, food industry, paints, sunscreens, cosmetics and medical devices.[5]

PREVENTION

Toxicity of Ag NP was reduced due to the coating which inhibited direct contact of particle surface with cellular components. [5]

MARKETED PRODUCTS

- ❖ Silver nanoparticles are also invariably used in a large number of consumer commodities due to their remarkable physical/chemical/biological properties and antibacterial effect. For example, multiple silver-containing preparations are invariably used in healthcare to prevent infections originating from burns, traumatic wounds, and diabetic ulcers. In addition, urinary and vascular catheters and other devices are sometimes impregnated with silver compounds to reduce the risk of infection.[2]
- ❖ Since ages, silver has been known to possess excellent antibacterial properties and it was used mainly because its toxicity to human cells is considerably lower as compared to bacteria. [4]
- ❖ Silver-based antimicrobial creams are commercially available today. Recently, researchers are trying to enhance the antimicrobial activity of silver for surface disinfection and germicidal coating and antimicrobial hydrogel.[2]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

- In 1990s, silver was introduced as a colloidal form (i.e., silver nanoparticles) in ointments that could be applied to open wounds to kill bacteria very effectively. Nanoparticulate silver containing bandages, wound dressings and ointments are readily available today.[4]
- A hydrogel-based antimicrobial delivery system consisting of physical, chemical/cross-linked gel, binding a large mass fraction of water in its swollen state, could be a preferred option for controlling nosocomial infections.[2]
- Monovalent silver compounds especially silver nitrate is used as chemoprophylactic agents in the treatment of burns to prevent bacterial infections, but their use is associated with a cosmetic disorder, viz., 'Argyria'. [4]
- Silver nanoparticles are also invariably used in a large number of consumer commodities due to their remarkable physical/chemical/biological properties and antibacterial effect. For example, multiple silver-containing preparations are invariably used in healthcare to prevent infections originating from burns, traumatic wounds, and diabetic ulcers. In addition, urinary and vascular catheters and other devices are sometimes impregnated with silver compounds to reduce the risk of infection.[2]
- The application of topical agents containing compounds such as silver sulfadiazine as a principal component, have been found to prevent bacterial infections but retard wound healing process, which is mediated by fibroblasts.[4]

Fig 15 - SNP containing formulation (S-gel) and its antimicrobial activity. S-gel with SNP concentration of 0.02 mg/g (i) and 0.1 mg/g (ii) and typical packaged product (iii). Zones of inhibition shown by 1% silver sulfadiazine (a), control gel without SNP (b) and S-gel with SNP concentration of 0.02 mg/g (c) and 0.1 mg/g (d).[15]

CASE STUDY

Study conducted on the antibacterial activity of silver nanoparticles (AgNPs) against nosocomial infection at AIIMS, India

Case- A study conducted on the antibacterial activity of silver nanoparticles (AgNPs) against nosocomial A. baumannii AIIMS 7 in biofilm mode.

Result -Nanoparticles exhibited significant biofilm disruption activity at a minimum inhibitory concentration of 2 mg/mL. The eradication of the biofilm was improved on combined exposure to AgNPs and antibiotics. These nanoparticles inhibited bacterial growth through intracellular oxidative stress and interact with thiol-groups in cellular proteins resulting in denaturation.[1]

HYDROGEL

Hydrogels are three-dimensional network of polymers that absorb and store large amounts of water [1]. Due to their high-water content, porosity and soft consistency, they can closely simulate natural living tissue, much more than any other class of synthetic biomaterials.[17]

Hydrogels can be used in biomedical areas for drug delivery, tissue engineering, biosensing and as antimicrobial materials etc. If the hydrogel is given antibacterial function, it can protect the wound from infection and promote wound healing. To promote wound healing, the hydrogels need to be able to absorb wound exudate, regulate the moist as well as chemical environment for the wound, allow permeate and exchange of oxygen and water vapour. In biomedical applications,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

hydrogels are suitable templates for the preparation of nanoparticles.[23]

When hydrogels are in a viscose medium like agar, there is an ability to absorb water and so 3D hydrogels tend to collapse due to lack of water. However, when the hydrogel contains ionic functional groups that have more swelling capacity than neutral hydrogels this could favour the release of active species.[17]

The data on Post agent effect (PAE) indicated that dose regimen of the silver nanoparticle (SNP) formulation should ensure sustained release of the drug, and hence a formulation (S-gel) containing SNP for topical application was developed. At higher concentration of silver (0.1 mg/g) in S-gel, a significantly wider zone of inhibition was observed than that with the S-gel containing less silver, indicating a dose-dependent activity. When a standard commercial preparation, 1% silver sulfadiazine (SSD), was tested against P. aeruginosa, the inhibition zone was 23 mm, which was similar to S-gel (0.1 mg/g), indicating that S-gel formulation showed antibacterial activity, comparable to silver sulfadiazine albeit at 30-fold less silver concentration.[15]

A. augusta mucilage (AAM) polysaccharide is an example of physical gel. Although the potential application area of this matrix is in the form of composite coating, rheological studies of the AAM matrix after the assembly of silver nanoparticles may be of immense help in providing an idea about the gelling stability.[2]

Hydrogels self-assembled from low-molecular-weight gelators (LMWGs) have seen intensive development in recent years for different types of biological applications including cell culture, tissue engineering, drug delivery, antimicrobial therapy and wound healing. These materials are obtained from the self-assembly of small molecules in water, which interact through noncovalent interactions to form complex entangled fibrillar networks.[6] One of the most interesting properties of such gel networks is their tunability and responsiveness to external stimuli such as pH, temperature and light.[16]

ADVATAGES

The combination of low molecular- weight gelator (LMWG) and polymer gelator (PG) enables:

- Excellent control over AgNP size (because of the LMWG),
- Improved mechanical properties (because of the PG),
- Ability to shape the active LMWG into a core-shell bead format (because of the PG).
- These gel beads are very easy to handle and manipulate.
- They have antimicrobial properties against drug resistant bacteria.
- They may be promising materials for orthopaedic applications or wound healing, particularly given that antibacterial bead-shaped constructs are already in widespread clinical use in this setting.[16]

DISADVANTAGE

Since such gels are assembled via non-covalent interactions, they are often mechanically very weak, and can be difficult to manipulate. When designing high-tech programmable material.

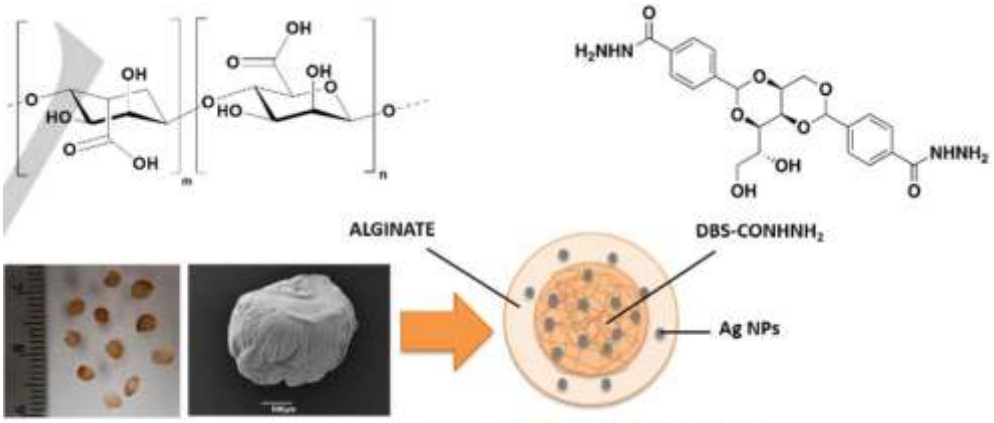

Fig 16. Structures of alginic acid and DBS-CONHNH2, photograph (left) and SEM image (right) of hybrid DBS-CONHNH2/alginate gel beads incorporating Ag NPs and schematic diagram of an AgNP-loaded core-shell gel bead.[16]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

Silver Nanoparticles are known to prevent biofilm formation and have antimicrobial properties against multiple drug-resistant bacterial strains. Ag can have an osteogenic effect on stem cells, promoting bone formation.

PREPERATION

Ag NPs are an effective low toxicity antibacterial agent that has been widely used. In recent years, researchers have loaded Ag NPs into hydrogels to obtain hydrogels with antibacterial properties.

There are two methods currently used to prepare hydrogels loaded with Ag NPs.

1) The Ag NPs are pre-synthesized and added into the hydrogel
2) The Ag NPs are in situ reduced within the hydrogel.

For example, hydrogel-silver nanocomposites were synthesized in which Ag NPs were distributed with diameter around 24–30 nm. The hydrogel displays excellent antibacterial effect against Escherichia coli. Xia et al. synthesized tapioca dialdehyde starch-chitosan hydrogels in which Ag ions were reduced to Ag NPs by the reductive aldehyde groups.[23]

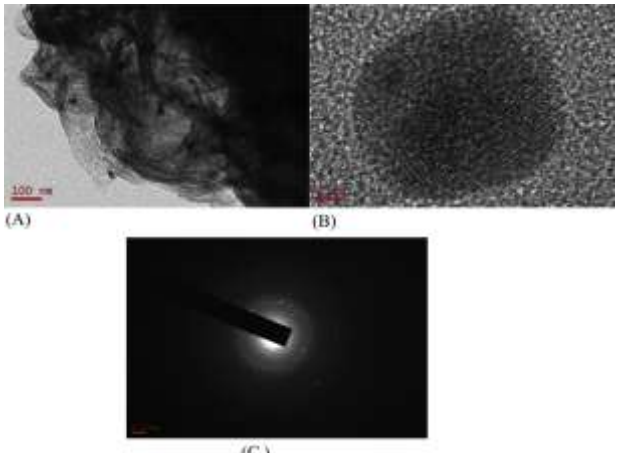

Fig 17. (A) TEM image of Ag NPs embedded hydrogel, (B) high resolution TEM image of Ag NPs and (C) TEM electron diffraction pattern of Ag NPs.[23]

The antibacterial effect of Ag NPs embedded hydrogel is significantly better than that of hydrogel without Ag NPs, due to the combination of lignin and Ag NPs that enhanced the antibacterial effect of the hydrogel.

The two networks could be spatially organised in two different ways forming, depending on the preparation method.

(1) Extended interpenetrating networks were obtained by combining an aqueous suspension (1 mL final volume) of DBS-CONHNH2 (0.3% wt./vol) with alginate (0.5% wt./vol). Heating ensured the complete dissolution of the LMWG and gelation was triggered on cooling. Once the DBS-CONHNH2 gel had formed, an aqueous solution of CaCl2 (5% wt./vol – 1 mL) was added on top of the gel to cross-link the alginate by diffusion of calcium ions.

(2) Core-shell structured gel beads were prepared by combining the same quantities of DBS-CONHNH2 and alginate, but after heating, the resulting hot solution was added dropwise (20 mL drops) to an aqueous solution of CaCl2 (5% wt./vol) to give small gel beads (ca. 3 mm diameter) on cross-linking of the alginate with self-assembly of the DBS-CONHNH2 occurring simultaneously as the system cooled.

Single-component gels based on DBS-CONHNH2 (in vials) or calcium alginate (in vials and as beads) were also prepared as control materials.[16]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

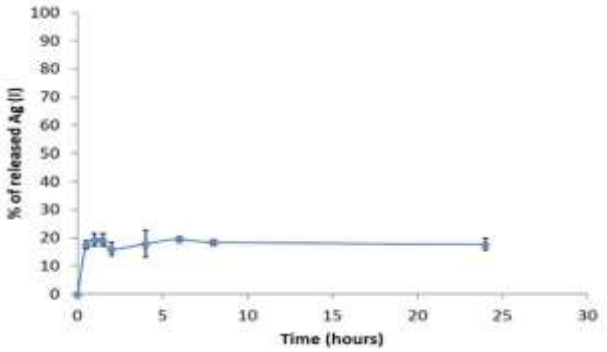

Fig 18. Release over time of Ag(I) ions from the DBS-CONHNH2/alginate hybrid gel beads.[16]

HYDROGEL SYNTHESIS

The NCs were synthesized by the absorption of AgNO3 solution into a hydrogel matrix, followed by UV light irradiation, without using additional toxic reactants. The hydrogels used as matrixes are based on N-isopropylacrylamide (NIPAM) and copolymers with different functional groups: 2-acrylamide-2-methylpropanesulfonic acid (AMPS), N hydroxyethyl acrylamide (HEAA) and (3-acrylamidepropil) trimethylammonium chloride (APTMAC). Neutral, anionic and cationic groups were added to the matrixes in order to study their effects on the release of antibacterial species. The NCs were characterized by UV-visible spectroscopy and transmission electronic microscopy. The kinetics of the release of Ag+ ions from the NCs were followed by UV-visible spectroscopy at 300 nm.[17]

After that they were purified through successive washing, and were swollen in AgNO3 solution to be irradiated with a UV lamp. Hydrogels began to adopt a brown-orange colour, which indicated that Ag nanoparticles (Ag-NPs) were formed inside the hydrogel mass. This was also verified by UV-Visible spectroscopy and TEM images.[17]

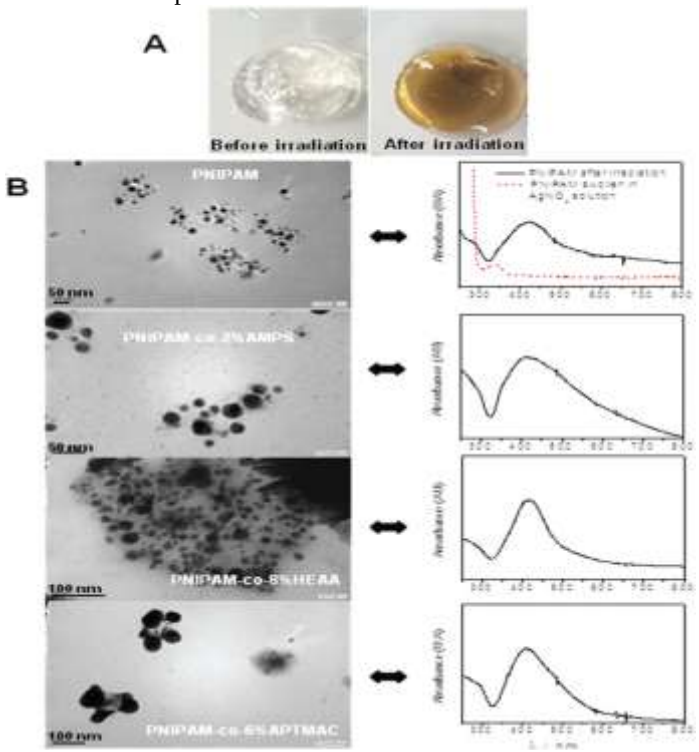

Fig 19. A- Photographs of the hydrogel matrix and nanocomposites based on PNIPAM (PNIPAM NC) are shown**. B** - TEM images show the spherical morphology of the Ag-NPs in all synthesized nanocomposites [17]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

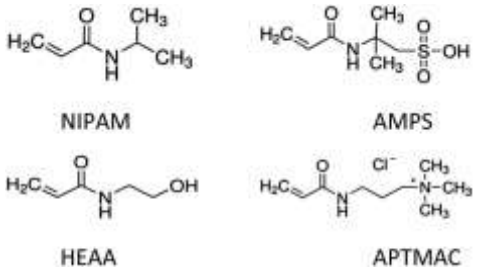

Fig 20 - Chemical structures of the monomers used.[17]

PROPERTIES

- **Thermal reversibility -** The hydrogel pre-solution is cooled to room temperature to form a hydrogel. When the formed hydrogel was heated at a temperature of 95 °C for 30 min, the hydrogel can become a free-flowing liquid. After cooling the solution again, hydrogel can still form, which indicates the hydrogel is thermal reversible.

Fig 21. Thermal reversible property of the hydrogel. (A) the hydrogel was heated, (B) the hydrogel was cooled to room temperature.[23]

- The **Mechanical properties** of the Ag-loaded gels are studied by oscillatory rheology using a parallel plate geometry.

MECHANSIM OF HYDROGEL

In the presence of molecular oxygen, AgNPs are converted into Ag+ and contribute to the intracellular reactive oxygen species (ROS) formation. It leads to the damage of the proteins, DNA/RNA, lipid bilayer, and cofactor and eventually to cell death.[2]

The AAM polysaccharide acts as a carrier for silver nanoparticles, which provide antimicrobial action. From the nosocomial infections. The designed hydrogel also exhibited the ability to remove the bioburden from the contaminated blade surface and actively grown biofilm from the glass surface. AAM-H provides mesh networks for nanoparticle deposition, which provided a lesser influence on natural hydrogel structures. Successful assembly of silver nanoparticles did not hamper the original gel state of the natural biopolymer but reduces the hardness and modulus of the gel at the dry state, which vice versa minimizes the brittleness tendency of the gel after drying at the application surface. The developed silver-based hydrogel is hemo compatible in nature and offered nominal DNA degradation ability, indicating a less toxic nature. In summary, such a self-assembled silver hydrogel could be very successfully used as an alternative to antibiotics, preventing microbial cross contaminations, retarding colonization of nosocomial infections, and deterring biofilm growth. The biopolymer-silver hydrogel developed via photoreduction in our work could be used as a safe and effective antimicrobial ointment for bacterial infection control.[2]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

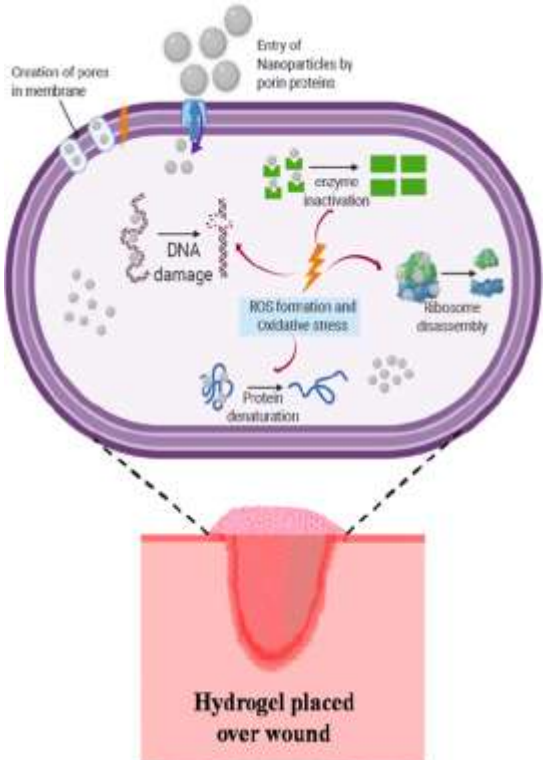

Fig 22 -Schematic representation of the mode of action of the synthesized hydrogel.[2]

II. CONCLUSION

Nosocomial infections are associated with a great deal of sorrow, loss of life and increased financial burden. Poor hygiene conditions are major risk factor for the emergence of antibiotic resistant bacteria. Gram-positive bacteria have overtaken Gram-negative organisms as the predominant cause of nosocomial infections. Infection control measures are important for the effective control, prevention and treatment of infection. Hand washing is the single most important measure to prevent nosocomial infections. Gloves must not be used as a substitute for hand washing; they must be washed on glove removal. Proper training and well skilled staff members are needed to attend those patients suffering from this infection. With increased burden of nosocomial infections and antimicrobial resistance, it has become difficult for healthcare administrations and infection control committees to reach the goal for elimination of intervals. However, by practicing sound and healthy ways for care delivery designed by infection control committees controlling transmission of these infections using appropriate methods for antimicrobial use, the resistance in emerging pathogens against antimicrobials can be reduced easily. An efficient surveillance method guided by WHO can help healthcare institutes to devise infection control programs. Proper training of hospital staff for biosafety, proper waste management and healthcare reforms and making general public aware of these endemic infections can also help in reduction of nosocomial infections. A self-assembled silver hydrogel could be very successfully used as an alternative to antibiotics, preventing microbial cross contaminations, retarding colonization of nosocomial infections, deterring biofilm growth and controlling nosocomial infection.

SOME OF THE ADVANTAGES FROM THE ABOVE RESULTS

a) It can be noted that the hydrogel itself does not exhibit any antimicrobial action.[2]
b) Antimicrobial performance can be achieved by the shaped hybrid gel system, the AgNP hybrid hydrogel beads have antibacterial properties against both Gram-positive and Gram-negative drug-resistant bacteria. [16]
c) Synthesized silver nanoparticles are more effective against the tested pathogenic strains compared to commercial antibiotic [2]

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

d) Initial screening of the AgNP-loaded gels showed very good antimicrobial properties against drug-resistant bacteria, in particular, VRE (vancomycin-resistant enterococci) and P. aeruginosa.[16]
e) The antimicrobial activity of silver nanoparticles is dependent on their shape and size.[2]
f) From the delivery point of view, entrapment of active drugs inside the polymer matrix and its release in the application area are important.
g) The synthesized silver hydrogel is relatively less toxic in nature compared to the standard silver nanoparticles toward healthy cells up to the concentration of 50 µg/mL [2]
h) Silver nanoparticles with haemolysis less than 5% are regarded as hem compatible.

REFERENCES

[1]. Ananda T., Nosocomial Infections and Role of Nanotechnology, Bioengineering, 2022,51(9), 1-13.
[2]. Roy A., Srivastava S.K., Hierarchical Assembly of Nanodimensional Silver−Silver Oxide Physical Gels Controlling Nosocomial Infections, ACS Omega, 2020, 5, 32617−32631
[3]. Liu W., Wu Y, Wang C., Hong C. L., Wang T., Chun Y. L, Cui L, Zhou Q.F., & Gui B. J., Impact of silver nanoparticles on human cells: Effect of particle size, Nanotoxicology, 2010; 4(3): 319–330
[4]. Paknikar K.M., Cellular responses induced by silver nanoparticles: In vitro studies, Toxicology Letters, 2008, 179, 93–100
[5]. Ahamed M., Silver nanoparticle applications and human health, ClinicaChimica Acta,411 ,2010, 1841-1848
[6]. Hussain S.M., Unique Cellular Interaction of Silver Nanoparticles: Size-Dependent Generation of Reactive Oxygen Species, J. Phys. Chem. B 2008, 112, 13608–13619
[7]. Khan A.H., Nosocomial infections: Epidemiology, prevention, control and surveillance, Asian Pac J Trop Biomed 2017; 7(5): 478–482
[8]. Inweregbu K., Dave J., Pittard A., Nosocomial infections, Continuing Education in Anaesthesia, Critical Care & Pain 2005,1(5), 17
[9]. Abbas M., Martischang R., Pittet I.D. Nosocomial transmission and outbreaks of coronavirus disease 2019: the need to protect both patients and healthcare workers, Abbas et al. Antimicrob Resist Infect Control (2021) 10:7
[10]. McDermott JH, Newman WG, Utilising Point of Care Diagnostics to Minimise Nosocomial Infection in the 2019 Novel Coronavirus (SARS-CoV-2) Pandemic, manuscriptcentral,2020,3
[11]. Gastmeier P., Nosocomial infection surveillance and control policies, Current Opinion in Infectious Diseases, 2004, 17:295–301
[12]. Hughes J.M., Setting Priorities: Nationwide Nosocomial Infection Prevention and Control Programs in the USA, Eur. J. CIin. Microbiol.1987, 348-351
[13]. Gaba S., Comparison of efficacy of silver-nanoparticle gel, nano-silver-foam and collagen dressings in treatment of partial thickness burn wounds, ScienceDirect, (2019),7
[14]. Mahalaxmi I., KaavyaJayaramayya, Venkatesan D., Subramaniam M.D., Renu K, Padmavathi, Mucormycosis: An opportunistic pathogen during COVID-19, Environmental Research,201,2021,111643
[15]. Omray P., Khandelwal S., and Paknikar K.M., Silver Nanoparticles in Therapeutics: Development of an Antimicrobial Gel Formulation for Topical Use, Molecular Pharmaceutics, 2009, 5(6), 1388–1401
[16]. Piras C.C., Mahon C.S., and Smith D.K., Self-assembled supramolecular hybrid hydrogel beads loaded with silver nanoparticles for antimicrobial application, Chem. Eur. J. 2010.1002
[17]. Rivarola C.R., highly effective antimicrobial nanocomposites based on hydrogel matrix and silver nanoparticles: long-lasting bactericidal and bacteriostatic effects, Soft Matter, 2019, 15, 8059
[18]. Suksatan W., Jasim S.A., Assessment effects and risk of nosocomial infection and needle sticks injuries among patents and health care worker, Toxicology Reports,9,2022,284-292
[19]. Taylor E., Reducing infections through nanotechnology and nanoparticles, international journal of nanomedicine,2011,6,1463-1473

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 598-629 www.ijprajournal.com ISSN: 2249-7781

[20]. Fu C., Nosocomial infection control in healthcare settings: Protection against emerging infectious diseases, Fu and Wang Infectious Diseases of Poverty, 2016, 5:30
[21]. Bardi T., Nosocomial infections associated to COVID-19 in the intensive care unit: clinical characteristics and outcome, European Journal of Clinical Microbiology & Infectious Diseases ,2021, 40:495–502
[22]. Murphy O.M. and Gould F. K., Prevention of nosocomial infection in solid organ transplantation, Journal of Hospital Infection ,1999, 42: 177–183
[23]. Li M., in situ reduction of silver nanoparticles in the lignin-based hydrogel for enhanced antibacterial application, Colloids and Surfaces B: Biointerfaces, 2019, 117,370-376
[24]. Sikhora A., Zahra F., Nosocomial Infection, National library of medicine, 2022,17
[25]. Weinstein R.A., Nosocomial Infection update, Centres for disease control and prevention,1998,5
[26]. Ong C.C.H., Nosocomial Infections among COVID-19 Patients: Analysis of intensive care unit surveillance data, antimicrobial resistance And Infection Control,2022,14
[27]. Johnston C.P., Outbreak Management and Implications of a Nosocomial Norovirus Outbreak, Clinical Infectious Diseases 2007, 45,534–40
[28]. Mythri H., Kashinath K.R., Nosocomial infection in patients admitted in intensive care unit of a tertiary health centre in India, Annals of medical and health sciences research,2014,4(5r),738-741
[29]. Maazaalaahi M., The impact of COVID 19 outbreak on nosocomial infection rate: A case of Iran, 2021,8
[30]. Lee N.Y., Ko W.C., Nanoparticles in the treatment of infections caused by multidrug resistant organisms, frontiers,2021,1-18
[31]. Gastmeiera P. and Vonberg R.P., Outbreaks of nosocomial infections: lessons learned and perspectives, Current Opinion in Infectious Diseases 2008, 21:357–361
[32]. Gross P.A., Nelj H.C., Deaths from Nosocomial Infections: Experience in A University Hospital and A Community Hospital, The American Journal of Medicine, February 1980, (68), 219-223
[33]. Managuli V., Nosocomial infections and role of nanotechnology, Health care sciences and services, 2022, 323
[34]. Bloukh S.H., Edis Z., Antimicrobial Properties of Lepidium sativum L. Facilitated Silver Nanoparticles, Pharmaceutics 2021, 13, 1352.
[35]. Ahamed M., Silver nanoparticle applications and human health, ClinicaChimica Acta 411 ,2010, 1841–1848
[36]. Arora S., Paknikar K.M., Cellular responses induced by silver nanoparticles: In vitro studies, Toxicology Letters 179, 2008, 93–100
[37]. AshaRani P. V., Cytotoxicity and Genotoxicity of Silver Nanoparticles in Human Cells, Acs Nano, 2008, 2(3), 279–290
[38]. Landelle C, and Pittet D., Definition epidemiology and general management of nosocomial infection, oxford university press, 2016, 283, 1-9
[39]. Ramasamy D. and Lee J., Recent Nanotechnology Approaches for Prevention and Treatment of Biofilm-Associated Infections on Medical Devices, BioMed Research International V 2016,9
[40]. Reyes H.A. and Moreno S., Evaluation of silver nanoparticles for the prevention of SARS-CoV-2 infection in health workers: in vitro and in vivo, plos one, 2022, 16(8), 3