



## Nosocomial Infections -A Review

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**ABSTRACT:** *Nosocomial infections are acquired, during or after being hospitalized. These infections are of high importance and are responsible to cause multiple issues during treatment making the treatment prolonged and economically burdensome. Some common HAI include those caused by Candida albicans, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Klebsiella pneumonia. These infection are serious and are caused due to multiple factors such as antibiotic resistance, intrinsic factors and the host –environment interaction during the presence of the pathogen. Pakistan being a developing country faces many issues while tackling with nosocomial infections, these not only cause socio-economic burden but also diminish the quality of life. There is no national approach to control and manage the nosocomial infections. This review not only highlights the hospital acquired infections as a serious threat but also clearly guide to adopt a “manageable approach” so such policies can be made and implemented in the health care system to resolve the problem through a systematic and coherent approach.*

**Keywords:** : *Nosocomial infections, health-care system, global concern, healthcare complications.*

## INTRODUCTION

Hospital acquired infections (HAIs) is one of the most serious public health problems of the 21st century.

Substantial data has been reported regarding the nosocomial infection and their adverse effect on the population, as these infections are a major global safety concern for both patients and health-care

professionals (Sharif et al., 2019). HAIs are complication causing infections usually faced in the hospital care facilities. World Health Organization (WHO) estimates that seven to twelve percent of the hospitalized patients are affected with HAIs, whereas about 1.4 million people are suffering from hospital acquired infections (WHO, 2002).

WHO defines “An infection acquired during 48 hours of hospitalization or after being discharge, which was not apparent earlier at the time patient arrived is regarded as a nosocomial infection”. The infections acquired by the workers and the staff during duty in the occupational environment are also included as the nosocomial infections.

These infections majorly affect hospitalized patients. These are of great consequence in veterinary medicine and have considerable adverse effects on the individual patient as well as on the veterinary hospital as a whole (Milton et al., 2015). The risk factors in veterinary hospitals are the same as compared to those in the human hospitals. A study by Mielke (2010) described that 1 to 4 % patients withstand one of any nosocomial infection.

The cases of nosocomial infections occurring in veterinary hospitals is not well established and is in its early stages of being comprehended (Milton et al., 2015). A number of outbreaks of having varied etiological agents has been documented in veterinary hospitals, a few significant agents include

*E. coli*, *S. aureus*, *C. diificile*, *S. typhimurium* and *Salmonella spp.* (Weese and Armstrong, 2003; Wright et al., 2005; Weese et al., 2006; Goehring et al., 2010; Steneroden et al., 2010).

Patient susceptible state largely effects the risk of development of various nosocomial infections. Senior individuals are at higher risk of developing HAIs because of immune senescence and decline in the immune system with increasing age (Eckenrode et al., 2014). Excessive cases of morbidity, mortality and other illnesses caused HAIs have been demonstrated by several studies (Al-Tawfiq et al., 2014). According to a study by Korotetskiy et al. (2019) of every 100 hospitalized patients, 7 (in developed), while 10 in developing countries can acquire or are at risk of acquiring an infection from the healthcare system.

### Causative agents of HAIs

Nosocomial infections can be caused by many microorganisms but a very few are chiefly responsible for causing hospital-acquired infections (Khan et al., 2015). Almost ninety percent of HAIs are caused by bacteria, while rest are caused by protozoans, viruses, fungi, and mycobacteria's.

Bacteria are notorious pathogens responsible for causing hospital-acquired infections. The origin of these organisms can either be endogenous or exogenous by nature. Some of these are a part of the naturally occurring microflora of the patient and can be a cause of infection, if

the immune system of the patient becomes compromised (Khan et al., 2017). Actinobacter is a pathogenic bacterial strain responsible for causing infections in ICUs and accounts for 80% of reported HAIs (Joshi and Litake, 2013). *Bacteroides fragilis* cause inflammation of colon and is transmitted through inappropriately cleaned hands (Chander, 2017).

Viruses can also be a cause of hospital acquired infections. A study by Aitken and Jeffries (2001) deduced that five percent of all the nosocomial infections are caused by viruses. WHO (2002) determined that these infections are transmitted through fecal-oral, respiratory route or via the hand to mouth transmission (WHO, 2002). Hepatitis is one of the chronic disease transmitted as a nosocomial infection. Healthcare facility can serve as a source of delivery of the virus both patients and workers through unsafe injection practices (CDC, 2016). Some of other potential contributors of HAIs include influenza, HIV, rotavirus, and the herpes-simplex virus (Khan et al., 2017).

Fungal parasites such as *Aspergillus spp.*, *Candida albicans* and *Cryptococcus neoformans* (WHO, 2002) serve as pathogens capable of causing hospital-acquired infections. Bacteria like enterococci, *P. aeruginosa*, *S. aureus* and *E. coli* play a key role in causing HAIs (Horan et al., 2008).

## Host Susceptibility

Apart from the causative agent and the environmental factors, host susceptibility also play an important role in the occurrence of nosocomial infections. The host susceptibility factors that contribute to the nosocomial infectivity includes;

1. Age
2. Chronic diseases
3. Immune status
4. Diagnostic procedures
5. Therapeutic procedures
6. Environmental Factors

## Types of HAIs

HAIs are categorized into four important types (Khan et al., 2017).

1. Bloodstream related infections (CLABSI),
2. Urinary tract infections caused during usage of catheters (CAUTI),
3. Infections at the surgery site (SSI)
4. Ventilator-associated pneumonia (VAP)

Bloodstream related infections occurs when bacteria enters the central line of a patient where catheters are placed to supply medicines and fluid (WHO, 2012). CLABSI are lethal infections and their death incidence rate twelve to twenty-five percent (CDC, 2015).

UTIs account for more than twelve percent of reported infections and

can cause serious complications such as, orchitis, prostatitis, epididymitis, pyelonephritis, meningitis and cystitis (CDC, 2016).

SSI are infections opportunistic in nature and that have been acquired through a surgery wound. Surgical site infections involve tissues under the skin, organs, or implanted material (CDC, 2015). These are commonly caused by *S. aureus* and lead towards prolonged stay in hospitals and eventually death (Anderson, 2011).

VAP is usually experienced by a person on the ventilator. It is a lung infection that develops during the hospitalization (CDC, 2012). It usually occurs within 48 h after tracheal Intubation (Hunter, 2012). Some of the common symptoms of VAP are Fever, leucopenia, and bronchial sounds (Hijalmarson and Boethius, 2007).

### **Risk areas for the acquisition of nosocomial infections**

Many healthcare facilities serve as risk areas for acquisition of the causative agent. These includes;

1. Intensive Care Unit
2. Operation Theatres
3. Dialysis Unit
4. Burns Unit
5. Transfusion Service Unit
6. Food Handlers
7. Acute Surgical Wards
8. Orthopaedic Wards
9. General Wards
10. Drinking Water Areas

### **Epidemiology**

The prevalence of hospital acquired infections is estimated to be in range of 5-10% in developed countries while the percentage exceeds up to a range of 30% in resource-poor countries (Benenson, 1995). The range is observed to be around 10.1% in the middle income countries (Plowman et al., 1999). They are responsible for 4%–56% cases of mortality in neonates (Syndor and Perl, 2011). The incidence of HAIs is sufficiently raised in high income countries and whereas it varies in middle and lower income republics (Nejad et al., 2011).

### **HAIs in developed countries**

The European Centre for Diseases prevention and Control (ECDC) states that healthcare-associated infections (HAIs) and antimicrobial resistance (AMR) are the most serious public health problems of the 21st century, globally and in Europe. According to an estimate 10% of the European population is hospitalized each year because of HAIs (Dulon et al., 2011). Approximately 1.75 million patients are affected annually with hospital acquired infections in Europe and causes 175,000 deaths (ESF, 2005). Reports from United States indicate that nosocomial infections account for two million infections and ninety thousand deaths per year (Ecker and Carroll, 2005).

In a study reported, the USA has a case fatality rate of CLABSI of up to 12.3%, VAP 14.4%, CAUTI 2.3%, while

of SSI is 8%. Hence, CLABSI and VAP are associated with the highest number of preventable deaths (Al-Tawfiq et al. 2014).

According to a study by Behzadnia et al. (2014) in Europe, the incidence of NIs in the general children ward is 1% and 23.6 % in the neonatal intensive care units. Nejad et al. (2011) reported that 5-15% of patients in regular wards and around 50% patients in intensive care units (ICUs), are affected by NIs in developed countries.

Doshi et al. (2009) demonstrated that the blood stream and urinary tract infections are caused by NIs and cause heavy death toll in USA. According to a study (Wenzel, 2007), there are 50,000 to 120,000 deaths annually in USA because of nosocomial infections. HAI also accounts for 37,000 deaths annually and, in addition, around 7 million Euros are spent annually on extra nursing care, treatment costs and secondary operations every year (WHO, 2011). This troublesome state of HAI makes it one of the major issues regarding patient safety in Europe.

### **HAIs in underdeveloped countries**

Not much attention has been given to the occurrence of nosocomial infections and only a few studies conducted in the developing countries, addressing the concerned issue. Health care associated infections are 4<sup>th</sup> leading cause of disease and are a major health hazard (Dulon et al. 2011) According to

studies by Nejad et al. (2011) and Allegranzi and Pittet (2009) the magnitude of the NIs is underrated in developing countries because their diagnosis is complex and surveillance studies require proficiency and resources.

Pittet et al. (2005) demonstrated that surveillance systems provide regular reports on national trends of endemic HAI and are thus helpful in evaluating and analyzing the incidence of these cases. National Healthcare Safety Network of the United States of America and German hospital infection surveillance system in the developed countries are such examples that have a surveillance system (Pittet et al. 2005). But the case is not the same when it comes to developing countries, as an aggravated economic burden is observed, due to deficiencies in the health-care (WHO, 2011).

### **HAIs in Pakistan**

Nosocomial Infections pose a serious health issue in public sector hospitals of developing countries such as Pakistan where there are no well-defined guidelines nor any controlled management collaboration for hospital infections and its prevention from further spread. It has been clearly stated that, multidimensional problems are being faced in the health-care facilities of rural and urban areas in Pakistan due to extensive nosocomial infections and presence of multi-drug- resistant bacteria. This can lead towards epidemics and economy loss (Menon, 2006).

In Pakistan, 1,170,561 cases of nosocomial infections are reported each year. Insufficient literature is available for hospital acquired infections in Pakistan and therefore, it is unclear to know about the actual number of cases occurring, and answers to related questions such as frequent occurrence of multi-resistant bacteria, and the financial loss and distress of individuals could not be given appropriately due to lack of evidence.

Generally hospitals of Pakistan, lack awareness and education related to hospital acquired infections. However, other social, ethical and economic factors also need to be considered in the control of these infections (Memon, 2006). According to a report by WHO, 2002 *Candida albicans*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Klebsiella pneumonia* attribute towards causing HAIs.

Apart from training the staff and health workers about the basic identification and transmission of microbes, other aspects are also essential and pivotal to be addressed e.g., how to provide a solution to the problem and to follow a proper standard operative protocol with its relevant preventive guidelines (Gastemeir et al. 1999); means and ways to keep the hospital environment clean and non-contaminated (Talon, 1999); to have quality circles (Forster et al. 2000); effective management of infections (Kelsey, 2000); providence of hygienic protocols in hospitals (Hirsch, 1999) and measurement of the index of microbial air

contamination (Pasquarella et al., 2000). All these are highly effective strategies in preparing personnel for any outbreak situations.

## **Transport of HAIs to the community**

A study claimed that poor hand washing practices by the hospital staff is vital cause of spread of HAIs, thus staff defiant to hygienic practices can transmit infections (Rao et al., 2012). Dirty clothes and filthy shoes carried by staff and visitors are also a source of infection (Mahmood and Aftab 2014). Hence, unhygienic environment is a contributing factor to HAI.

According to a study contaminated stethoscopes can carry organisms like *Clostridium difficile* (Mahmood and Aftab, 2014), hence doctors should clean their stethoscopes to avoid transmission of germs and spread of HAIs.

HAIs can also be responsible for infections in neonates (Mahmood and Aftab, 2014). The infection tends to be caused during recurrent cannulation without applying Aseptic techniques. Since, neonates have very fragile and thin veins, the insertion is invasive for them. The mistaken pricks for the insertion into veins, increase the risk of acquisition of HAI. In addition to it, the “diseased health care provider” and “overcrowded ward environment” are some other contributory factors to HAIs (Talaat et al., 2003).

## **Antibiotic resistant bacteria**

Infectious diseases had a high fatality rate during 1900s. Then the field of medicine was revolutionized by discovery of microbial secondary metabolites known as wonder drugs. This marked the beginning of the “antibiotic era”, which has been of substantial importance for mankind ever since (Martens and Demain, 2017). Antibiotics are lower molecular weight compounds mostly produced by microorganisms or derived from natural organic products.

Some of the antibiotics are natural while others are synthesized. For example, sulfa drugs and oxazolidinones are synthetic products whereas fluoroquinolones are naturally derived products (Heeb et al., 2011; Fernanandes, 2006). The first quinolone was a compound derived from the distillation of quinine from the Cincona tree bark. These antibiotic products are used in majority for chemotherapy against pathogenic microbes (Martens and Demain, 2017).

1940-1960 is considered as “Golden era of antibiotics”, in terms of discovery, development and production of antibiotics at commercial level. Discovery

of new antibiotics continued in the years that followed but not as rapidly as in the early years. The classes of antibiotics that were produced and discovered at that time includes; the penicillins, cephalosporins, tetracyclines, aminoglycosides, chloramphenicol, macrolides and glycopeptides (Martens and Demain, 2017).

Antibiotics are a critical factor in increasing life expectancy (Lederberg, 2000). With effective antibiotics infections are cured easily and mortality rate is easily restrained. More than 90% of antibiotics originate from the actinomycetes. (Martens and Demain, 2017).

Infectious disease are the 2<sup>nd</sup> leading killer in the world, being in the top three in developed nations while at 4<sup>th</sup> position in the United States (Martens and Denim, 2017). Approximately, seventeen million people are imposed with death each year due to bacterial infections (Butler and Buss, 2006). Drug resistance induces more complications in the treatment (Table. 1). Drug-resistant bacteria kill 25000 people each year in Europe (Walsh and Fischbach, 2009).

**Table. 1: Mechanism of antibiotic resistance**

| Sr.No   | Genetic basis of antimicrobial resistance  | References  |
|---|--|---|
| 1.  | Modifications of the Antibiotic Molecule   | Ramirez and Tolmasky, 2010; Wilson, 2014  |
| 2.  | Destruction of the antibiotic molecule   | Crichlow et al. 1999; ; Bonnet, 2004; Lolans et al. 2006; Rice, 2006; Kapoor et al. 2017  |
| 3.  | Decreased Antibiotic Penetration and Efflux  | Martin and Arias, 2016  |
| 4.  | Changes, Protection and Modification of the target site  | Tenover, 2006   |
| 5.  | Horizontal Gene Transfer (HGT)   | Wasinger et al. 1995 ; Goldenfeld and Woese, 2007; Stricker et al. 2008   |
| Perhaps the antibiotic resistance is sole major public health threat nowadays (Laxminarayan, 2014). <i>Gonorrhea</i> , which was treated with penicillin in the 1970s, but now it has become resistant to ceftriaxone and cephalosporins (Martens and Demain, 2017). Some drug resistant strains include; |  | 8. Drug-resistant <i>Streptococcus pneumonia</i><br>9. Drug-resistant Tuberculosis (CDC, 2017)<br>10. <i>Escherichia coli</i> ( <i>E. coli</i> )<br>11. Erythromycin-resistant Group A Streptococcus<br>12. Extended spectrum <i>Enterobacteriaceae</i><br>13. Fluconazole-resistant <i>Candida</i><br>14. <i>Klebsiella pneumoniae</i> ,<br>15. Methicillin Resistant <i>Staphylococcus aureus</i> (MRSA)<br>16. Multidrug resistant <i>Pseudomonas aeruginosa</i><br>17. Multidrug-resistant <i>Acinetobacter</i><br>18. <i>Mycobacterium tuberculosis</i><br>19. <i>Mycoplasma genitalium</i> . (Kummerer, 2004) |
|   | 1. Carbapenem-resistant <i>Enterobacteriaceae</i><br>2. Clindamycin-resistant Group B Streptococcus<br>3. <i>Clostridium difficile</i><br>4. Drug-resistant <i>Campylobacter</i> ,<br>5. Drug-resistant non-Typhoidal <i>Salmonella</i><br>6. Drug-resistant <i>Salmonella</i> serotype typhi<br>7. Drug-resistant <i>Shigella</i> , |   |



20. *Neisseria gonorrhoeae*

21. *Neisseria gonorrhoeae*

22. *Salmonella spp.*

23. Vancomycin-resistant  
*Enterococcus*

24. Vancomycin-resistant *S. aureus*

Minimum inhibitory concentrations (MIC) of various antibiotics has been categorized for antimicrobial susceptibility testing (AST) in various studies and help in providing analysis requiring related to the compounds. It depends on divisions set by various international organizations (Lin et al., 2015). These divisions mark whether an antibiotic is reported as susceptible or not. The Clinical and Laboratory Standards Institute (CLSI) is the most widespread guidelines used globally (Kassim et al., 2016). These guidelines are based upon the MIC distributions, pharmacokinetic studies, pharmacodynamic (PK-PD) properties and their respective resistance mechanisms (Marchese et al., 2012). Whereas the implementation of antibiotic liability guidelines in the United States is synchronized by the Food and Drug Administration (FDA). In 1997 the European Committee on Antimicrobial Susceptibility Testing (EUCAST) was established to synchronize antibiotic interpretive breakpoints all over Europe, thus most of European countries have since swapped CLSI guidelines with EUCAST guidelines (Kahlmeter, 2015).

## Environmental factors and antibiotic resistance

The use, misuse and overuse of antibiotics have contaminated the virgin environments. There are several ways in which antibiotics enter the environment such as, hospital, agricultural and industrial waste, animal husbandry and sewage (Segura et al., 2009).

Hospitals are considered as a major source of environmental pollution by antibiotics due to extensive use of antibiotics. Different Studies demonstrated hospital effluent is a source of antibiotic pollution (Kummerer, 2004; Kummerer, 2009; Diwan et al., 2010 and Segura et al., 2009).

Antibiotics are used in agriculture as a growth promotor and are also sprayed on the infected plant parts (Khachatourians, 1998; Kummerer, 2009). Sometimes Antibiotic leaches out and contaminates the farm environment.

Sewage treatment plants (STP) and waste water treatment plants (WWTP) play a chief role in spread of antibiotic resistance in the urban areas (Kummerer, 2009; Segura et al., 2009; Szczepanowski et al., 2009). WWTPs contain Residual antibiotics and antibiotic resistant bacteria from domestic sewage, hospital waste and animal farming waste (Da Silva et al., 2005). Thus WWTP serve as an important source for polluting environments with antibiotics and antibiotic resistance genes.

## **Occurrence of Antibiotic resistant bacteria in hospital environment**

Antimicrobial resistance is a rising problem in several bacterial pathogens and is of particular concern for hospital-acquired infections (Gaynes and Monnet, 1997). Occurrence of antibiotic resistance bacteria in hospitals is because of huge number of patients, extensive usage of invasive procedures, and exceeding rates of antibiotic usage (Golkar et al., 2014). Golkar et al. (2014) surveyed that about two million Americans develop HAIs annually and thus results in 99,000 deaths, most of which are due to antibacterial resistant pathogens. In 2006, two common infections i.e. sepsis and pneumonia caused deaths of approximately fifty thousand American inhabitants (Golkar et al., 2014).

Antibiotic-resistant infections affect economy of a nation by adding considerable costs to health care system (CDC, 2013). Antibiotic-resistant infections increases the socioeconomic burden over families and community settings (Golkar et al. 2014).

## **Occurrence of antibiotic resistance in health care system in Pakistan**

Antimicrobial resistance has established itself as health threat in almost all countries, including Pakistan. Increasing antibiotic consumption in humans and animals, particularly of broad-spectrum antibiotics, is one of the

major underlying factors contributing to antibiotic resistance globally. In Pakistan, indiscriminate and excessive use of antibiotics in farm animals and poultry for therapeutic, prophylactic and growth promotion has also added to AMR. Khan et al. (2011) demonstrated that growing rates of resistance in both human and veterinary medicine are the potential cause of serious health implications.

## **Effects of Nosocomial Infections**

Hospital acquired infections are responsible to cause multiple issues during treatment making the treatment prolonged and economically burdensome. The main significant effects are enlisted below:

1. Hospital acquired infections spread MDR, making treatments prolonged and cause chronicity of disease (Wenzel., 1995; Plowman et al., 1999).
2. It is a source of spread of endemic in the hospital and epidemic in the community (Tikhomirov, 1987).
3. These infections influence to cause a socio-economic burden (Ducel, 1995).
4. They increase the span of hospitalization (WHO, 2002).
5. They are responsible to increase the morbidity and mortality (Kirkland et al., 1999).

6. These infections cause complications in the recovery of the patient (Wakefield et al., 1988).
7. HAI are a source of distress and psychological suffering for the patient apart from the physical discomfort.
8. Additional surgical procedures have to be adopted sometimes.

## **Control and Prevention**

Hospital acquired infection create an imbalance between resource allocation and the primary/secondary healthcare, diverting the funds to manage these infections, making funds scarce for the management to work on major clinically important issues. Hence, prevention and control of these infection is highly essential (CDC, 2017).

As we know, the patient during its hospitalization is exposed to a number to risk areas and has to interact with the staff and faculty of the health care facility. Therefore, the patient is not only susceptible these infections, but also once on acquisition of such infection, can be a potential source of its spread as well. The crowded condition of the hospital and the frequent transfer of the patient from one area to the other, during treatment can easily be observed, serving as a chain for transmission of the infection (WHO, 2002).

Microbial flora of the patients can be transferred to the objects, devices,

materials which subsequently are source of infection and reinfection. These objects serve as an unidentified source of contamination. So, it is highly recommendable to have preventive measures to control and avoid the spread of the pathogen. Following are some measures and ways that can reduce the spread and transmission of infection within and outside the health-care facility.

1. The health authority should develop a control programme at regional and national level to support hospitals in reducing the risk of nosocomial infections.
2. Some programmes developed at regional and national level should have consistent objectives. The guideline for the surveillance and preventive practice should be provided.
3. The guidelines should be adopted and updated accordingly.
4. The health-care professionals should be provided with the proper training to tackle any serious urgency.
5. The programmes providing training and guidance should be harmonized and be continual in nature.
6. Surveillance of nosocomial infection, with proper reporting and having a proper database, can help evaluate and implement the control programme and can also highlight the major issues be faced during monitoring.

7. An agency should be designated by the government to investigate and evaluate the program.
8. Risk prevention awareness and promoting good healthcare practices can minimize the nosocomial infections.
9. Infection control committees can help play their part in collaborating and sharing information.
10. Infection control committee along with people from medical and non-medical profession can help improve hygiene standards in a facility.
11. Personal hygiene, proper sanitization, sterilization methods and disinfecting the surfaces can not only control but effectively inhibit the microbial growth. All the above mentioned measures can be effective and help in controlling nosocomial infections.

## CONCLUSION

Nosocomial infections are widespread globally and can affect all countries equally. These infections cause significant burden to both the patient and the healthcare workers and contribute to be a source of hazard for the public health. Functional disability and emotional stress are increased when patient suffers from nosocomial infections, increasing disability conditions leading to death of patients.

The patient not only suffers physically but also psychologically and has to bear high treatment costs as well. The hospitalization charges are one of the main contributors to the economic loss for the infected patient.

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