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Nosocomial infections and their control strategies

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ABSTRACT

Nosocomial infections are also known as hospital-acquired/associated infections. National Healthcare Safety Network along with Centers for Disease Control for surveillance has classified nosocomial infection sites into 13 types with 50 infection sites, which are specific on the basis of biological and clinical criteria. The agents that are usually involved in hospital-acquired infections include *Streptococcus* spp., *Acinetobacter* spp., enterococci, *Pseudomonas aeruginosa*, coagulase-negative staphylococci, *Staphylococcus aureus*, *Bacillus cereus*, *Legionella* and Enterobacteriaceae family members, namely, *Proteus mirablis*, *Klebsiella pneumonia*, *Escherichia coli*, *Serratia marcescens*. Nosocomial pathogens can be transmitted through person to person, environment or contaminated water and food, infected individuals, contaminated healthcare personnel's skin or contact via shared items and surfaces. Mainly, multi-drug-resistant nosocomial organisms include methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*, whereas *Clostridium difficile* shows natural resistance. Excessive and improper use of broad-spectrum antibiotics, especially in healthcare settings, is elevating nosocomial infections, which not only becomes a big health care problem but also causes great economic and production loss in the community. Nosocomial infections can be controlled by measuring and comparing the infection rates within healthcare settings and sticking to the best healthcare practices. Centers for Disease Control and Prevention provides the methodology for surveillance of nosocomial infections along with investigation of major outbreaks. By means of this surveillance, hospitals can devise a strategy comprising of infection control practices.

1. Introduction

"Nosocomial" term is used for any disease acquired by patient under medical care [1]. It is an infection acquired by patient during hospital stay. Recently, a new term, "healthcare associated infections" is used for the type of infections caused by prolonged hospital stay and it accounts for a major risk factor for serious health issues leading to death [2]. About 75% of the burden of these infections is present in developing countries [3]. Asymptomatic patients may be considered infected if these pathogens are found in the body fluids or at a sterile body site, such as blood or cerebrospinal fluid [4]. Infections that are acquired by hospital staff, visitors or other healthcare personnel may also be considered as nosocomial [5].

The situations in which infections are not believed as nosocomial are: (1) The infections that were present at the time of admission and become complicated, nevertheless pathogens or symptoms change resulting to a new infection; (2) The infections that are acquired trans-placentally due to some diseases like toxoplasmosis, rubella, syphilis or cytomegalovirus and appear 48 h after birth [6].

Hospital-acquired infections appeared before the origination of hospitals and became a health problem during the miraculous antibiotic era. Due to these infections, not only the costs but also

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the use of antibiotics increased with an extended hospitalization. This resulted in elevated morbidity and mortality. Studies conducted in different parts of the world show that in North America and Europe 5%–10% of all hospitalizations result in nosocomial infections, while Latin America, Sub-Saharan Africa and Asia show more than 40% hospitalizations with nosocomial infections [7].

Nosocomial infections can be caused by any organisms but few organisms are particularly responsible for hospital-acquired infections. In this review article, a brief overview on different aspects of nosocomial infections, particularly sites of infections, common nosocomial bacterial agents, selected antibiotic-resistant pathogens along with their modes of transmission and control measures will be discussed.

2. Types of nosocomial infections

National Healthcare Safety Network with Center for Disease Control (CDC) for surveillance has classified nosocomial infection sites into 13 types, with 50 infection sites, which are specific on the basis of biological a nd clinical criteria. The sites which are common include urinary tract infections (UTI), surgical and soft tissue infections, gastroenteritis, meningitis and respiratory infections [8]. A change regarding nosocomial infection sites can be easily detected with time due to the elevated use of cancer chemotherapy, advancement in organ transplantation, immunotherapy and invasive techniques for diagnostic and therapeutic purposes. The perfect example of this can be seen in the case of pneumonia as prevalence of nosocomial pneumonia increased from 17% to 30% during five years [9].

3. Agents of nosocomial infections

Nosocomial infections are caused by many microbes and each one can cause infection in healthcare settings. Bacteria are responsible for about ninety percent infections, whereas protozoans, fungi, viruses and mycobacteria are less contributing compared to bacterial infections [10]. The agents that are usually involved in hospital-acquired infections include *Streptococcus* spp., *Acinetobacter* spp., enterococci, *Pseudomonas aeruginosa* (*P. aeruginosa*), coagulase-negative staphylococci, *Staphylococcus aureus* (*S. aureus*), *Bacillus cereus* (*B. cereus*), *Legionella* and Enterobacteriaceae family members including *Proteus mirablis*, *Klebsiella pneumonia* (*K. pneumonia*), *Escherichia coli* (*E. coli*), *Serratia marcescens*. Out of these enterococci, *P. aeruginosa*, *S. aureus* and *E. coli* have a major role [11]. UTI usually contain *E. coli*, while it is uncommon in other infection sites. Contrarily, *S. aureus* is frequent at other body sites and rarely causes UTI. In blood-borne infections, coagulase-negative *S. aureus* is the main causative agent. Surgical-site infections contain *Enterococcus* spp. which is less prevalent at respiratory tract. One tenth of all infections are caused by *P. aeruginosa*, which is evenly distributed to the entire body sites [4].

Excessive and improper use of broad-spectrum antibiotics, especially in healthcare settings, are elevating nosocomial infections. Penicillin-resistant pneumococci, multi-drug-resistant tuberculosis, methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *S. aureus* are common examples of drug-resistant bacteria. The distribution of bacteria in nosocomial infections is changing over time. For example, *Proteus* spp., *Klebsiella* spp. and *Escherichia* spp. were responsible for nosocomial infections in the 1960s, but from 1975 to 1980s, *Acinetobacter* spp. with *P. aeruginosa* created clinical difficulties [12]. During the recent years, streptococci along with coagulase-negative staphylococci and coagulase-positive staphylococci reemerged and incidence level of *K. pneumonia* and *E. coli* declined from 7% to 5% and 23%–16%, respectively [13].

4. Bacteriology of commonly isolated nosocomial pathogens

A multicenter study was conducted in Japan to isolate bacteria from surgical infections during 2011–2012. About 785 strains including 31 of *Candida* spp. were isolated from 204 out of 259 surgical patients. About 523 strains were isolated from primary infections and 231 from surgical site infection. From primary infections, anaerobic Gram-negative bacteria were prevalent. *Enterococcus* spp. was the highest among Gram-positive aerobic bacteria followed by *Streptococcus* and *Staphylococcus* spp. *E. coli* was the predominant form among the Gram-negative aerobic bacteria followed by *K. pneumonia*, *P. aeruginosa* and *Enterobacter cloacae* [14].

4.1. S. aureus

Out of many species of *Staphylococcus* genus, *S. aureus* is considered one of the most important pathogens, responsible for nosocomial infections. It is Gram-positive cocci, non-spore forming, catalase- and coagulase-positive, immotile, facultatively anaerobe [15]. It is not only a disease-causing organism but also plays its role as commensal. It mainly colonizes in nasal passages. About 20% individuals have persistent colonization of *S. aureus*, whereas 30% are intermittent. Hospitalized patients with decreased immunity and immunocompetent people in community are more prone to *S. aureus* infections. *S. aureus* infects not only the superficial but also the deep tissues and local abscess lesion. Toxin-mediated diseases of *S. aureus* include food poisoning, due to ingestion of enterotoxins, while toxic shock syndrome toxin 1 is responsible for toxic shock syndrome [16] and exfoliative toxins cause staphylococcal scalded skin syndrome. Virulence mechanisms of *S. aureus* include toxins, enzymes and immune modulators [15].

4.2. E. coli

E. coli is an emerging nosocomial pathogen causing problems in health care settings [17]. *E. coli* is Gram-negative and oxidase-negative facultative anaerobe bacteria. It can colonize in gastrointestinal tract of human beings and other animals. *E. coli* is responsible for a number of diseases including UTI, septicemia, pneumonia, neonatal meningitis, peritonitis and gastroenteritis. Virulence factors meant for its pathogenicity are endotoxins, capsule, adhesions and type 3 secretion systems [18]. Specialized virulence factors are seen in case of UTI and gastroenteritis.

4.3. Vancomycin-resistant enterococci

Enterococci is the second leading cause of hospital acquired infections worldwide and the main leading cause in United States contributing 20%–30% of infections. These are facultative anaerobic Gram-positive enteric microbes [19]. They are a part of

normal microbiota in female genital tract and gastrointestinal tract as well. Enterococci are involved in the blood-borne infections; UTI and wound infections consort to surgical procedures [20]. Virulence factors include extracellular surface proteins, cytolysin, adhesions, hemolysins, gelatinase, extracellular superoxide and aggregation substances [21].

4.4. K. pneumonia

Three to seven percent of hospital-acquired bacterial infections are related to *K. pneumonia*, which is the eighth significant pathogen in healthcare settings. It is a Gram-positive bacillus and an opportunistic bacterium, which is a part of Enterobacteriaceae family. It usually colonizes gastrointestinal tract, pharynx and skin. It gets involved in diseases such as neonatal septicaemia, pneumonia, wound infections and septicemia. Its virulence factors include endotoxins, cell wall receptors and capsular polysaccharide [22].

4.5. P. aeruginosa

P. aeruginosa contributes to 11% of all nosocomial infections, which result in high mortality and morbidity rates. It is non-fermenter Gram-negative organism causing diseases especially among immune-compromised people. The sites of colonization are kidney, urinary tract and upper respiratory tract. It is a cause of surgical and wound infections, UTI, pneumonia, cystic fibrosis and bacteremia. Some of important virulence factors are adhesions, hemolysins, exotoxins, proteases and siderophores [23].

4.6. Clostridium difficile (C. difficile)

C. difficile is an important nosocomial pathogen which mainly causes diarrhea. Several cases of *C. difficile* are reported in Europe, U.S. and Canada. It is a Gram-positive bacillus. It is anaerobic and spore-forming bacteria. It usually colonizes in intestinal tract and serves as part of normal microbiota [24]. Diseases caused by toxins produced by *C. difficile* are colitis and it is responsible for 15%–25% cases of diarrhea. Major virulence factors for *C. difficile* are toxins, fimbriae, capsule and hydrolytic enzymes [25].

5. Modes of transmission

5.1. S. aureus

Transmission of *S. aureus* is through infected individuals' skin or contact via shared items and surfaces like door handles, benches, towels and taps.

5.2. E. coli

E. coli can be transmitted through person to person, environment or contaminated water and food [17].

5.3. Vancomycin-resistant enterococci

Patients with diarrhea are common means of transmission. Their room items such as surfaces and equipments act as reservoirs. This bacterium can survive on theses surfaces for days or weeks and become a source of contamination for healthcare individuals and other patients [21].

5.4. K. pneumonia

In hospital settings, *K. pneumonia* can be transmitted by person-to-person contact and especially when healthcare professionals do not wash or clean hands after checking a contaminated patient. Respiratory machines, catheters or exposed wounds can be the source of its transmission. *K. pneumoniae* is reported to be transmitted through stool (77%), patients' hands (42%) and pharynx (19%) [22].

5.5. P. aeruginosa

Common reservoirs for its contamination include breast pumps, incubators [26], sinks and hands of hospital staff and hand soaps [27].

5.6. C. difficile

Spores of *C. difficile* can hold for months and become a problem for disinfectants and cleaning agents. Inanimate objects and infected intestinal patients are major sites acted as reservoirs. Hospital staff along with hospital settings are also playing their part to a greater extent [28].

6. Selected antibiotic-resistant nosocomial pathogens

Multi-drug-resistant nosocomial organisms include MRSA, vancomycin-resistant enterococci, *P. aeruginosa* and *K. pneumonia*, whereas *C. difficile* shows natural resistance. In the 1940s, the problem of drug resistance came into light and in the past few years, a rapid increase of multi-drug-resistant pathogens was seen.

Fifty to sixty percent of hospital-acquired infections are caused by resistant pathogens in the United States. Improper use of antibiotics is thought to be the major cause of this drug resistance.

6.1. MRSA

β-Lactamase antibiotics including penicillin along with other antimicrobials became resistant in the 1940s. Resistance of penicillin slowly prevails from hospitals to community due to its improper use. This resistance results are due to the Staphylococcal species having penicillinase enzyme which was later solved by the introduction of penicillinase-resistant antibiotics, cephalosporins. In the 1960s, methicillin-resistant species of *S. aureus* were reported. This resistance was due to the modification of penicillin-binding proteins. This modification made all β-lactam antibiotics along with their derivatives ineffective. Aminoglycosides resistance was another addition to methicillin resistance [29].

6.2. Vancomycin-resistant enterococci

Vancomycin resistance is seen in the enterococcal species due to the *vanA* and *vanB* genes. These genes are a part of plasmid and would spread resistance to other microbes as well. Enterococci are resistant to different classes of antibiotics which

include penicillin, ampicillin, aminoglycosides, tetracyclines, carbapenems, fluoroquinolones and macrolides [30].

6.3. P. aeruginosa

P. aeruginosa is becoming resistant due to different mechanisms working against antibiotics. These mechanisms include the restricted uptake of drug, drug modification and altered targets for antibiotics. Due to this increasing resistance, complications are seen in the treatment of *P. aeruginosa* infections. The drugs that are now ineffective due to increasing resistance include cephalosporins, trimethoprim, macrolides, chloramphenicol, tetracyclines and fluoroquinolones [23].

6.4. K. pneumonia

Resistance to β-lactam antibiotics is a major cause of complications in nosocomial infections. *K. pneumonia* is one of the microbes experiencing resistance of β-lactamase antibiotics along with *E. coli*. Cephalosporins of third and fourth generation show resistance for *K. pneumonia* [22].

6.5. C. difficile

Increased use of broad-spectrum antibiotics against *C. difficile*-associated diseases makes it resistant. Cephalosporins, fluoroquinolones, clindamycins and ampicillins are those antimicrobials that are usually employed for *C. difficile*-associated diseases. Recent studies reported that the improper antibiotic use was the cause of increasing infections of *C. difficile* [28].

7. Control of nosocomial infections

There is a lack of actual statistics regarding the causes and antimicrobial susceptibility in developing countries. Pathogens with resistant organisms make it extremely difficult to devise a proper plan and its implementation for control [3].

7.1. Measurement and comparison of infection rates

It is difficult to measure the infection rates in different healthcare settings. For the measurement of infection rates, it is important to know the types of microorganism involved and its correct location inside the body of individual. Infectious organisms are heterogeneous in nature, which makes them different from one another. It is possible that in a hospital, the rates of infection show similarity while the location and heterogeneity of organisms greatly differ.

To compare the infection rates, one must know the type of healthcare settings, which may be public or private, because the infection rates vary in both types of hospitals. In addition, in these hospitals, the management of infections differs greatly. The types of services that a hospital provides to patients must be taken into account (Figure 1).

7.2. Development of infection control programs

Guidelines for the sterilization and disinfection of invasive devices and medical instruments used for surgeries were developed as the infection rates tend to raise [31,32]. Moreover, guidelines for the prevention of catheter-associated UTI were

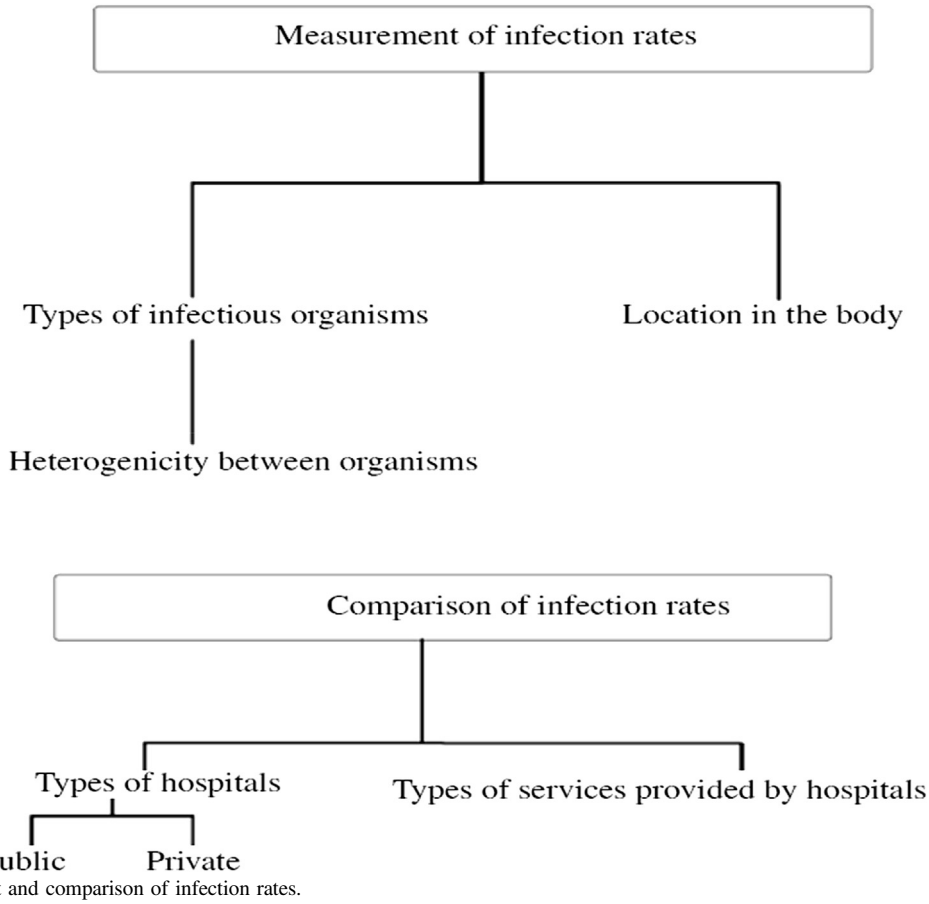

Figure 1. Measurement and comparison of infection rates.

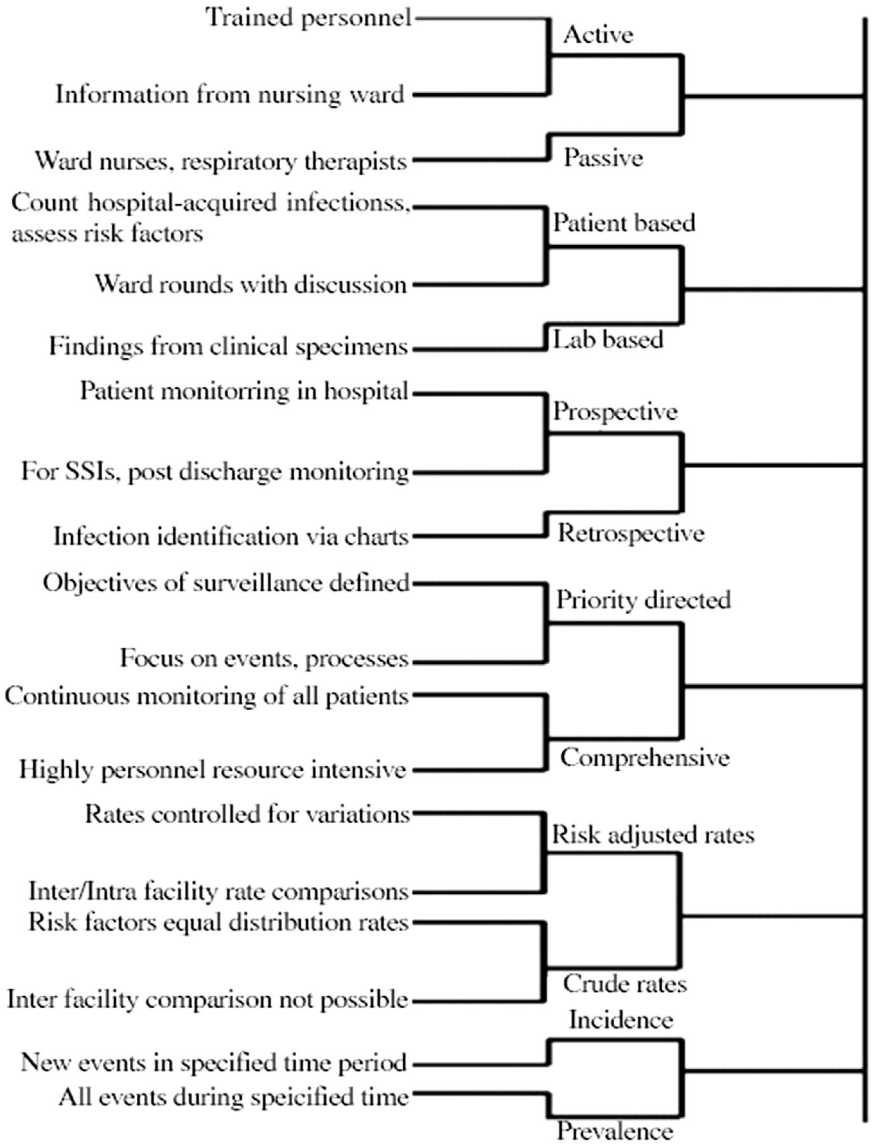

Figure 2. Suggested integrated team work for surveillance of nosocomial infections in any hospital.

also devised in 2009 [33]. Lack of compliance with the guidelines, leads to the transmission of nosocomial infections. CDC provides the methodology for surveillance of nosocomial infections along with investigation of major outbreaks. Infection prevention and control guidelines have been developed but the implementation is not yet much known [34]. Training of healthcare professionals, especially nurses, is extremely important for the control and prevention of infection [2,35]. A large gap is present between the existence of guidelines and their actual implementation [36].

7.3. Surveillance of nosocomial infections

Surveillance can be interpreted as "the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know" [37]. As a part of infection control program, surveillance obliges the data related to infected individuals with their infection sites. Hospitals can work on this data to control the infections by evaluating the efficacy of treatment. By means of this surveillance (Figure 2), hospitals can devise a strategy comprising of infection control practices [29].

8. Conclusions

In the age of antibiotics, nosocomial infections are still uncontrollable. The control of organisms responsible for nosocomial infections is much needed as they cause great economic as well as production loss. The transmission of these infections in the hospital settings through healthcare workers can be avoided by the use of infection control practices. Improper and frequent use of antibiotics is an important cause of drug-resistant organisms that are difficult to treat. Hospitals should devise the infection control programs through which infection rates can be compared and controlled. A well-managed surveillance methodology is required in the light of CDC guidelines. In addition, there is also great need that the best practice should be shared among hospitals to stop the spread of nosocomial infections.

Conflict of interest

We declare no conflict of interest.

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