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Update on bacterial nosocomial infections

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Abstract. – With increasing use of antimicrobial agents and advance in lifesaving medical practices which expose the patients for invasive procedures, are associated with the ever increasing of nosocomial infections. Despite an effort in hospital infection control measures, health care associated infections are associated with significant morbidity and mortality adding additional health care expenditure which may leads to an economic crisis. The problem is further complicated with the emergence of difficult to treat multidrug resistant (MDR) microorganism in the hospital environment. Virtually every pathogen has the potential to cause infection in hospitalized patients but only limited number of both gram positive and gram negative bacteria are responsible for the majority of nosocomial infection. Among them *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and Enterococci takes the leading. Many intrinsic and extrinsic factors predispose hospitalized patients for these pathogens. Following simple hospital hygienic practices and strictly following standard medical procedures greatly reduces infection to a significant level although not all nosocomial infections are avoidable. The clinical spectrum caused by nosocomial pathogens depend on body site of infection, the involving pathogen and the patient's underlying condition. Structural and non structural virulence factors associated with the bacteria are responsible for the observed clinical manifestation. Bacteria isolation and characterization from appropriate clinical materials with antimicrobial susceptibility testing is the standard of laboratory diagnosis.

Key Words:
Nosocomial infections, Multiple drug resistance (MDR), Virulence factors, Risk factors.

Introduction

The term "nosocomial" applies to any disease contracted by a patient while under medical care[1]. More precisely, nosocomial infections (NI) [also known as hospital associated/acquired infections (HAI)] are those infections that develop in a patient during his/her stay in a hospital or other type of clinical facilities which were not present at the time of admission. It may become clinically apparent either during the hospitalization or after discharge[2]. Hence, pathogens that cause such infections are termed nosocomial pathogens. However, an asymptomatic patient may be considered infected if pathogenic microorganisms are found in a body fluid or at a body site that is normally sterile, such as the cerebrospinal fluid or blood[3]. Infections acquired by staff or visitors to the hospital or other health care setting and neonatal infection that result from passage through the birth canal may also be considered nosocomial infections[4].

In addition, there are two special situations in which an infection is not considered nosocomial: (1) infection that is associated with a complication or extension of infection already present on admission, unless a change in pathogen or symptoms strongly suggests the acquisition of a new infection, and (2) in an infant, an infection that is known or proved to have been acquired transplacentally (e.g., toxoplasmosis, rubella, cytomegalovirus, or syphilis) and becomes evident at or before 48 hours after birth[5].

Infections acquired in hospitals have existed since the very inception of hospitals themselves, and continue to be an important health problem even in the modern era of antibiotics. They result in high morbidity and mortality, extended hospitalization, greater use of antibiotics, and increased costs. Studies have indicated that nosocomial infections occurred in 5%-10% of all hospitalizations in Europe and North America and in more than 40% of hospitalizations in parts of Asia, Latin America, and sub-Saharan Africa[6].

Bacteriologically, almost any organism have the potential to cause nosocomial infection but only limited number of organisms are frequently

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responsible for diseases acquired in hospitals. In this review article, a brief overview on aspects of nosocomial types by site of infection, common nosocomial bacterial agents, selected antibiotic resistant nosocomial pathogens, and source, transmission, risk factor and prevention of hospital acquired infections will be discussed.

Types of Nosocomial Infections

Based on clinical and biological criteria, CDC and National Healthcare Safety Network (NHSN) categorize health care associated infection sites into 13 major types which contain approximately 50 potentially specific infection sites for surveillance purpose. The most common types of nosocomial infections that could occur in a hospital set up are: Surgical wound and other soft tissue infections, urinary tract infections (UTI), Respiratory infections, Gastroenteritis and Meningitis[7]. However, with increased use of invasive procedures for therapeutic and diagnostic purposes, cancer chemotherapy, immunotherapy and advances in organ transplants, it is possible to observe change in the distribution of nosocomial infection sites over time. For example, the incidence of nosocomial pneumonia was changed from 17% in early 1990s to 30% in 1995[8].

Agents of Nosocomial Infections

A large number of microorganisms are responsible for hospital infections and any microbe may have the capacity/ability to cause an infection in the hospitalized patients. Ninety percent of the NIs is caused by bacteria, whereas mycobacterial, viral, fungal or protozoal agents are less commonly involved[9]. The bacteria that commonly cause nosocomial infections include *Staphylococcus (S.) aureus*, *Streptococcus* spp., *Bacillus cereus*, *Acinetobacter* spp., coagulase negative staphylococci, enterococci, *Pseudomonas (P.) aeruginosa, Legionella* and members of the Enterobacteriaceae family such as *Escherichia (E.) coli*, *Proteus mirabilis*, *Salmonella* spp., *Serratia marcescens* and *Klebsiella pneumoniae*. But the most frequently reported nosocomial pathogens have been *E. coli*, *S. aureus*, enterococci and *P. aeruginosa*[10].

Based on the data, *Escherichia coli* and *Staphylococcus aureus* were the most commonly isolated nosocomial pathogens. Although *E. coli* is found in a quarter of urinary tract infection (UTI) cases, it is isolated relatively infrequently from other infection sites. Conversely, *S. aureus* is rarely isolated from UTI but is common at other sites. In blood stream infection (BSI), coagulase-negative staphylococci are isolated almost twice as often as *S. aureus*. *Enterococcus (E.)* spp. is frequently isolated from surgical site infection (SSI), and BSI but rarely found in the respiratory tract. *Pseudomonas aeruginosa* is isolated from about 1/10 of all infections and appears to evenly affect all of the major sites except the blood stream, where it is found less often[11].

Large usage of broad spectrum antibiotics in hospital environment promoted emergence and reemergence of difficult-to-treat nosocomial infections in patients. Examples of bacteria possessing such drug resistance are methicillin-resistant *S. aureus*, penicillin-resistant pneumococci, vancomycin resistant enterococci, vancomycin resistant *S. aureus,* multi-drug resistant tuberculosis, *Acinetobacter baumanni*, *Stenotrophomonas maltophilia* and *Burkholderia cepacia*. Therefore, nosocomial pathogens are in dynamic changes and their distributions in body site are also changing over time. For example, in the early antibiotic era, hospital acquired infections were dominated by staphylococcal infections, well controlled initially by penicillin. Then, as Staphylococci became beta lactamase producers, beta lactamase stable compounds controlled them. Then, methicillin resistant *S. aureus* (MRSA) and gram negative bacilli emerged as agents responsible for NI. In the late 1960, resistant bacteria belonging to family enterobacteraceae (*Klebsiella* spp., *Escherichia* spp., *Proteus* spp.), became increasingly involved in NI and in the years 1975 to 1980, the emergence of multi resistant gram negative bacilli *Pseudomonas aeruginosa* and *Acinetobacter* spp was observed, presenting difficult therapeutic problems[12].

More recent surveys have indicated the reemergence of gram positive cocci including coagulase positive staphylococci, coagulase negative staphylococci and streptococci, whereas incidence of *Escherichia coli* and *Klebsiella pneumoniae* has decreased from 23 to 16% and from 7 to 5% respectively. In addition all surveys report the increasing or simultaneous persistence of *Pseudomonas aeruginosa, Acinetobacter* spp., and emergence of newer nosocomial gram negative organisms such as *Burkholderia cepacia* and *Stenotrophomonas maltophilia*[13].

Bacteriology of Commonly Isolated Nosocomial Pathogens

Staphylococcus aureus

The genus *Staphylococcus* is composed of several species of which *S. aureus* is by far the

most important nosocomial pathogen. It is non-motile, non spore forming, catalase positive, gram positive cocci, and facultative anaerobe arranged in cluster[14]. *S. aureus* is both commensal and pathogen. Approximately 20% of individuals are persistently nasally colonized with *S. aureus*, and 30% are intermittently colonized. S*taphylococcus aureus* is a leading cause of hospital-acquired infections. It is the primary cause of lower respiratory tract infections and surgical site infections and the second leading cause of nosocomial bacteremia, pneumonia, and cardiovascular infections. The armamentarium of virulence factors of *S. aureus* is extensive, with both structural and secreted products playing a role in the pathogenesis of infections.

Escherichia coli

It is Gram negative, facultative anaerobic, and oxidase negative. *E. coli* is one of the common organisms involved in gram negative sepsis and endotoxin-induced shock. Urinary track and wound infections, pneumonia in immunocompromised hospitalized patients, meningitis in neonates and *E. coli* associated diarrheal disease or gastroenteritis is other common infection caused by this organism. *E. coli* possesses a broad range of virulence factors some of which are shared by *Enterobacteriaceae* family (e.g. Endotoxin, capsule, antigenic phase variation, sequestration of growth factors, resistant to serum killing and antimicrobial resistant). But some strains responsible for disease such as UTIs and gastroenteritis possess specialized virulence factors[15].

Pseudomonas aeruginosa

P. aeruginosa is Gram-negative with mucoid polysaccharide capsule typically arranged in pairs. Identification is based on colonial characteristics and simple biochemical tests. It can transiently colonize the respiratory and gastrointestinal tracts of hospitalized patients, particularly those treated with broad spectrum antibiotics, exposed to respiratory therapy equipment, or hospitalized for extended period of time.

Pathogenesis by this organism is initiated when the normal defense mechanism is impaired, e.g. when body barriers are disrupted by direct tissue damage like intravenous or urinary catheter; or when neutropenia is present, as in cancer chemotherapy. The bacterium attaches to and colonizes the mucus membrane or skin and, invades locally, and produces systemic disease. These processes are mediated by different virulent factors like pili, enzymes (elastases, proteases, phospholipase C), and toxins (exotoxin A). The clinical spectrum produce by *P. aeruginosa* includes: blue-green pus producing wound infections, meningitis, urinary tract infection, and necrotizing pneumonia[16].

Enterococcus spp.

Enterococci are Gram-positive cocci typically arranged in pairs and short chains. They are facultative anaerobic and grow optimally at 35°C on complex media requiring vitamin B, nucleic acid base, and carbon source such as glucose. Enriched sheep blood agar supports the growth with large, white colonies. Enterococci are considered part of the normal flora of the gastrointestinal and genitourinary tracts of humans and have emerged as one of the most important nosocomial pathogens. The majority of human enterococcal infections are caused by two species, *Enterococcus faecalis* and *E. faecium,* and other species are uncommon.

Enterococci are important hospital-acquired pathogens. Isolates of *Enterococcus faecalis* and *Enterococcus faecium* are the third- to fourth-most prevalent nosocomial pathogen worldwide. The most common nosocomial infection produced by these organisms are urinary tract infection (associated with instrumentation and antimicrobial administration) followed by intra-abdominal and pelvic infection. They also cause surgical wound infection, bacteremia, endocarditis, neonatal sepsis, and rarely meningitis. *E. faecalis* is the most common cause of infections (80-90%) followed by *E. faecium* (10-15%)[17].

Selected Antibiotic Resistant Nosocomial Pathogens

Most of the high profile nosocomial organisms are multi-drug resistant (MDR) either with acquired, e.g. methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum β-lactamase (ESBL) producers, or natural resistance (*Clostridium difficile*), Historically, antibiotic resistance has been a problem soon after the introduction of penicillin G and sulfonamides into general medical use in the 1940s.

The past few decades have seen an alarming increase in the prevalence of resistant antimicrobial pathogens in serious infections. In the USA, for instance, 50-60% of >2 million nosocomial infections are caused by antibiotic-resistant pathogens. The use of antibiotics has been identi-

fied as an important risk factor in the emergence of antibiotic resistance in both Gram-positive and Gram-negative bacteria, although mechanisms of antibiotic resistance vary between pathogens and often reflect the cellular structure of the pathogen[17].

Methicillin-resistant Staphylococcus aureus (MRSA)

Resistance to penicillin and newer narrow-spectrum β-lactamase–resistant penicillin antimicrobial drugs (e.g., methicillin, oxacillin) appeared soon after they were introduced into clinical practice in the 1940s and 1960s, respectively. Penicillin resistance was initially confined to a small number of hospitalized patients, but resistance spread as use of penicillin increased, first to other hospitals and then into the community. This problem caused by penicillinase producing *Staphylococcus* species is solved with the development of penicillinase-resistant penicillins, the cephalosporins, and several other groups of antibiotics active against *Staphylococcus species*. However, soon methicillin-resistant *Staphylococcus* spp. (MRSA) was reported within a year after the introduction of methicillin in 1959-1960. The first outbreak of a methicillin-resistant *S. aureus* (MRSA) infection was documented in 1968. Since then its incidence in the hospital setting has risen immensely. This time, resistance was mediated by modification of the penicillin binding proteins (PBP2a) which is encoded by the chromosomal mecA gene carried on a mobile genetic element, the staphylococcal cassette chromosome mec (SCCmec). This alteration in the target site confers resistance to all β-lactams and their derivatives (Figure 1). In addition, methicillin resistance is often combined with resistance to other types of antibiotics, e.g. aminoglicosides[18].

Vancomycin-resistant Enterococci

The first report of vancomycin-resistant enterococci (VRE) came in 1996. Four resistant phenotypes have been identified: VanA, VanB, VanC and VanD, with VanA being the most common type encountered. Resistance to vancomycin requires the expression of several genes (Figure 2) and, as a consequence, it does not arise spontaneously; rather, it does so by the acquisition of these genes from another organism. Vancomycin resistance in enterococci is often linked with ampicillin resistance, which sometimes arises because of genetic linkage[18].

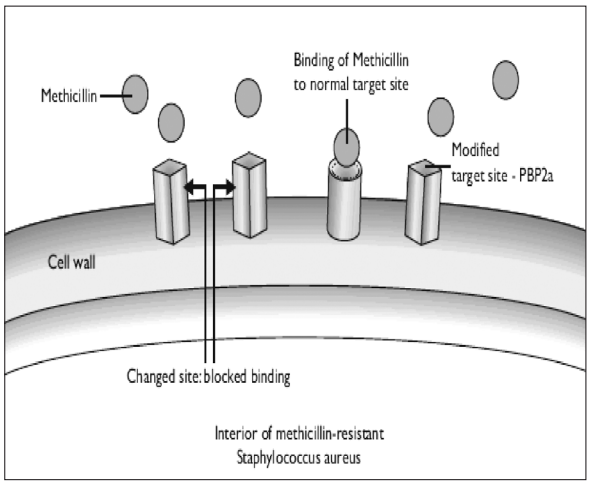

Figure 1. Methicillin resistance in *Staphylococcus aureus* is achieved by a structural modification to the methicillin target site.

Sources and Transmission of Nosocomial Infections

The nosocomial pathogens that cause infections can come either from endogenous or exogenous sources. Animate and inanimate sources of exogenous infections include hospital staff, other patients, visitors, food, water, fomites, urinary catheter, intravenous devices, respiratory equipment and other prostheses.

The most important means of transmission of nosocomial infections is by contact, usually directly but sometimes indirectly by means of secretions from the body. Air can also be a route of transmission of air borne-nosocomial pathogens (e.g., in droplet nuclei and aerosols)

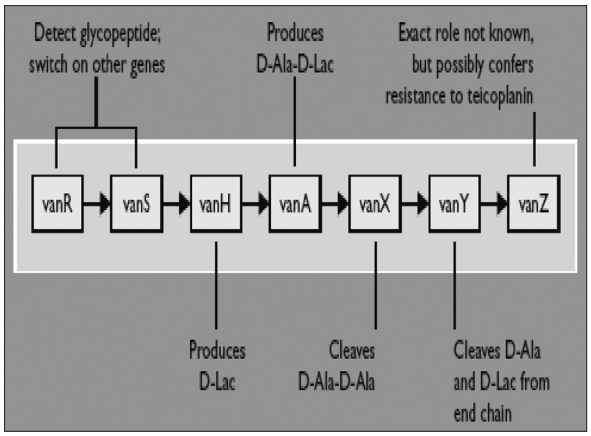

Figure 2. Expression of several genes, including vanR, vanS, vanH, vanA, vanX, vanY and vanZ, results in resistance to vancomycin in enterococci and *Staphylococcus aureus*.

that infect the respiratory tract. The faeco-oral route is a portal of entry for food-borne and water-borne infections. The most common reservoirs for nosocomial colonisers are the oropharynx, the gastrointestinal tract and the urinary tract[19].

Risk Factors for Nosocomial Infections

Hospitalized patients are at unusually high risk of infection for various reasons. The risks are roughly divided into two categories, intrinsic and extrinsic factors. Intrinsic risk factors are those that are inherent in the patient because of underlying disease conditions. Extrinsic risk factors may reside in the patient care staff (practices of an individual caregiver) or the institution (practices in an entire hospital). While many extrinsic factors contribute to nosocomial infections, the factors that have been most frequently implicated and studied are certain high-risk medical interventions, such as surgical operations and the use of invasive devices[20].

Some of general predisposing factors that make patients susceptible to nosocomial infections include concurrent infections, prosthetic devices, surgery, immunosuppressive agents, administration of broad-spectrum antibiotics, and emergence of multidrug resistant pathogens. Other risk factors include age of patient, duration of hospitalization, underlying diseases like diabetes, tumors or overcrowding in the hospital wards. Among the numerous risk factors for acquiring a nosocomial infection, the length of hospital stay remains the most important[20].

Prevention of Nosocomial Infection

Prevention of nosocomial infections is the responsibility of all individuals and services providing health care. And everyone must work cooperatively involve to reduce the risk of infection for patients and staff. Although, not all hospital infections are avoidable, a lot of infection can be prevented. Surveillance of NIs is an essential part of infection control and has been widely accepted throughout the world as a primary step towards prevention. However, reducing healthcare-associated infection rates depends on a variety of factors. Recently, much emphasis has been placed on staff related procedures, particularly hand hygiene. In addition, there has been increased recognition that environmental measures should form a crucial component of the overall strategy of prevention of healthcare-associated infections[21].

Frequent hand washing remains the single most important intervention in infection control. Gloves, gowns, and masks have a role in preventing infections, but are often used inappropriately, increasing service costs unnecessarily. Many are visibly upset when their poor hygiene practices are exposed and are offended when it is suggested that they may be potential vectors of disease and are spreading virulent microorganisms among their patients, putting some difficulties in infection control[21].

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