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Bacterial Infection in Diabetic Foot

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Abstract

Diabetes Mellitus (DM) is considered to be one of the most widespread chronic diseases, with almost 10% of the global adult population being diabetic or at risk of developing diabetes, characterized by high plasma glucose concentrations as a result of the inability of the body to adequately produce or use insulin effectively. Diabetes mellitus has been categorized into 3 main types; insulin-dependent diabetes mellitus, non-insulation-dependent, gestational diabetes mellitus. Several complications associated with diabetes. The long-term vascular problems of diabetes are the most damaging impact, "microvascular disorders", “neuropathy,” eye or “retinopathy,” and “nephropathy”. Diabetic Foot Infections (DFIs) are described as extensive soft tissue necrosis (ulcers) which are correlated with chronic infections (DFIs). Methicillin-Resistant Staphylococcus aureus (MRSA) oversaw hospital outbreaks. Diabetes people are exposed to both CA and HA-MRSA due to frequent ulceration and sores. The increase in MRSA soft tissue infections was mainly driven by more community-acquired infections rather than health-care-associated strains. MRSA can cause a variety of infections, such as; pneumonia, osteoarticular infections, toxic shock syndrome and bacteremia that might be progress to endocarditis or severe sepsis. DFIs treated surgically and or clinical therapy.

Keywords: Diabetes mellitus; Complications; Nephropathy; Diabetic foot ulcer; MRSA; *Staphylococcus aureus*

Introduction

Diabetes Mellitus (DM) is considered to be one of the most widespread chronic diseases, with almost 10% of the global adult population being diabetic or at risk of developing diabetes, characterized by high plasma glucose concentrations as a result of the inability of the body to adequately produce or use insulin effectively. The disease is diagnosed when there is impaired glucose tolerance and characterized by high plasma glucose concentrations [1-3].

Diabetes mellitus has been categorized into 3 main types [1]. Type 1 diabetes mellitus is an autoimmune disease that much of the time starts with individuals affected before they reach 40 and is classified as juvenile-onset or insulin-dependent diabetes mellitus. It is marked by self-destructing insulin, which produces beta cells in the pancreas by the body's immune system response. About 10-15 percent of all cases of diabetes mellitus Type 2 Diabetes Mellitus (T2DM) are stated to be a formerly named diabetes mellitus that was non-insulin-dependent that is often referred to as late-consumption diabetes. The peculiarity of this kind has its relative insulin deficiency and susceptibility to plasma glucose production which accounts for approximately 90% of all diabetes cases worldwide. The third type is Gestational Diabetes Mellitus (GDM), which is characterized by glucose intolerance which occurs first or has been first diagnosed after an oral glucose test throughout pregnancy [4].

Multiple problems relate to diabetes. Mortality-associated severe metabolic risks include excessive higher blood glucose (hyperglycemia) diabetic ketoacidosis and low blood glucose comas (hypoglycemia). The most devastating consequence of diabetes, its long-term vascular complications. These are wide-range risks and at least partially because of the chronic increase in blood glucose levels contributing to blood vessel damage [5].

Diabetic Foot Infections (DFIs) are described as extensive soft tissue necrosis (ulcers) which are correlated with chronic infections (DFIs). These ulcer infections are often too frequently accompanied by amputation since the ecology of such infections has little or no knowledge to management of eradication of chronic infection [6].

DFIs can be mono or poly microbial and may be caused by a large variety of pathogens aerobic gram-positive cocci like *Staphylococcus aureus*, gram-negative bacilli (*Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*), and anaerobes. The pathways behind the diabetes-bacterial infection relationship are little known [7-12].

Antimicrobial resistance is one of the big challenges worldwide in the management and mitigation of fast-growing pathogens and microbial outbreaks. Since the 1970s, MRSA has been the primary source of nosocomial infections around the globe. In particular the growing development of antibiotic resistance to methicillin and vancomycin [13].

There are a wide variety of bacterial foot diabetic infection with different degree of foot infections and/or foot ulcers all of them could diagnosed, treated and prevented by several route of manipulations. Explain all the above in construed and fully detailed method is the main purpose of this review article which aim to identifying the definitions and types of diabetic mellitus, diabetic complications, diabetic foot infection and/ or ulcer. Different bacterial foot infection, MRSA (definition and types), treatment and prevention routes of diabetic foot infection.

Diabetes mellitus

Diabetes Mellitus (DM) is considered to be one of the most widespread chronic disease, with almost 10% of global adult population

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being diabetic or at risk of developing diabetes, characterized by high plasma glucose concentrations as a result of the inability of the body to adequately produce or use insulin effectively. The disease is diagnosed when there is impaired glucose tolerance and characterized by high plasma glucose concentrations [1-3].

In addition, guidelines are summarized for the specific diagnosis of biochemistry in fasting, oral glucose tolerance tests as well as the usage of Hemoglobin A1c (HbA1c). The rising incidence of diabetes calls for targeted screening of risk populations for diabetes and pre-diabetes. This provides the foundation for the early implementation of interventions to prevent and prolong the development of diabetes in these risk categories. [14].

Types of diabetes mellitus

Diabetes mellitus has been categorized into 3 main types [1]. Type 1 diabetes mellitus is an autoimmune disease that much of the time starts with individuals affected before they reach 40 and is classified as juvenile-onset or insulin-dependent diabetes mellitus. It is marked by self-destructing insulin, which produces beta cells in the pancreas by the body's immune system response. About 10-15 percent of all cases of diabetes mellitus Type 2 Diabetes Mellitus, (T2DM) are stated to be a formerly named diabetes mellitus that was non-insulation-dependent that is often referred to as late-consumption diabetes. The peculiarity of this kind is its relative insulin deficiency and susceptibility to plasma glucose production which accounts for approximately 90% of all diabetes cases worldwide. The third type is Gestational Diabetes Mellitus (GDM), which is defined by first or first diagnosed glucose sensitivity after an oral glucose test in pregnancies after an oral glucose tolerance test. Glucose resistance may be normal, but pregnant women with a family history of diabetes, elevated maternal age, obesity, and higher ethnicity can again be popular. These mothers' babies are expected to become obese and have a poor glucose tolerance [4,10].

Complications of diabetes

Several complications associated with diabetes. Acute metabolic complications to mortality include unusually elevated blood glucose (hyperglycemia) diabetic ketoacidosis and low blood glucose coma (hypoglycemia). The long-term vascular problems of diabetes are the most damaging impact. These problems are common and are at least partially triggered by the continual rise in blood glucose levels that contribute to blood vessel injury. In diabetes, the resultant conditions are categorized under "microvascular disorders" (because of disruption to tiny blood vessels). Microvascular complications involve neural damage or “neuropathy,” eye or “retinopathy,” and kidney disease termed “nephropathy” [5].

Macrovascular complications and microvascular complications: The principal macrovascular complications include accelerated cerebrovascular disease and accelerated cardiovascular disease resulting in myocardial infarction stroke. While underlying etiology tends to be controversial, myocardial disease with diabetes now seems to be at least partially atherosclerosis independent. Other chronic diabetic problems is depression dementia and sexual dysfunction [5,15,16].

Neuropathy

More than half of all diabetes patients experience neuropathy, with a chance of one or more lower limb amputations for life projected to be up to 15 percent in certain communities. Neuropathy can also develop and can be a significant cause of compromised wound healing, erectile dysfunction, and cardiovascular diabetes disease. The occurrence of vascular defects such as capillary membrane thickening and endothelial hyperplasia with a resulting reduction of oxygen stress and hypoxia have historically clinically characterized the progression of the condition of neuropathy. Advanced diabetic neuropathy attributable to nerve fiber degradation is marked by altered vibrational and thermal sensitivities that contribute to sensory loss of perception. Hyperalgesia, paresthesia, and allodynia are also recorded in 40-50% of patients with diabetic neuropathy with discomfort. Few diabetics often have discomfort without clinical proof of neuropathy (10-20 percent), which can significantly affect the quality of life [5,17,18].

Neurons are also significant in scale. In diabetes, longer nerve fibers tend to be exhibiting an earlier lack of nerve conduction velocities with a lack of nerve terminals. Therefore, tingling and lack of feeling and reflexes are always found first in the feet and then rising to impact other places, particularly the hands. It is generally referred to as a delivery of "gloves and stocking," which entails numbness, dysesthesia (pins and needles), loss sensory, and nightly discomfort. Spatial knowledge of the limb position is often early influenced during the disorder. It often includes a sensation loss in reaction to trauma resulting in callous and other common foot injuries, which puts diabetic neuropathy patients at a high risk of foot and leg ulcers that eventually contribute to amputation. Some diabetics often suffer several fractures and grow a charcot joint that is degenerative in weight-bearing joints, marked by bone loss and subsequent deformation. Progressive motor weakness in diabetic neuropathy is also normal, which may contribute to the dorsal turning of hand and toes digits [5].

Diabetic foot infections

Extensive soft tissue necrosis (ulcers) that are correlated with chronic infections is known as Diabetic Foot Infections (DFIs). These ulcer infections are often too commonly accompanied by amputation since the ecology or regulation of this form of recurrent infection is little or no known and no understanding [6].

According to a prominent and usual lesion is the compromised diabetic foot mal perforin ulceration. Diabetic foot ulcers may also have physiological changes in the mechanisms of microcirculation, neuronal activity and growth factor activation [19]. Therefore, foot ulcer varies from that of non-diabetic cases of diabetic situations. In reality the presence of an ulcer raises the wound's vulnerability to bacterial infection. An aggressive infection grows with the adjoining expansion of deeper tissue from bacterial invasion to limb threatening infection above 2 cm of the ulcers. [10, 20-22].

Multi-Drug Resistant Species (MDROs) often infect diabetic foot ulcers due to poor care and inappropriate antibiotic treatment, chronic wound processing, frequent hospital admission, neuropathy, nephropathy and peripheral vascular diseases [22,23].

The disease severity progresses from ulceration and infection, to gangrene that results in hospitalization, which often precedes lower-extremity amputation. Purulent drainage or curetted materials from infected ulcers provide the best specimen for bacterial culture. For decades the only way to establish the cause pathogen(s) in the DFI was to culturing wound collections. As microorganisms on any skin wound are still present. DFIs can be mono- or poly-microbial and may be caused by a wide range of pathogens aerobic Gram-positive cocci like *Staphylococcus aureus*, Gram-negative bacilli (Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa), and anaerobes. The pathways behind the diabetes-bacterial infection relationship are poorly understood [7-12].

Micro-organisms comprise both skin ulcers. The clinical diagnosis of foot infection is based on purulent ulcers or classic inflammatory symptoms (e.g. erythema, discomfort, tenderness, warmth, or induration). The other main markers of DFI are foul odor, the occurrence of necrosis, and delay of wound healing, despite optimum treatment. However, signs can differ according to the disease's etiology. There is no similar trend of clinical signs in both patients. In some patients, local inflammatory changes may be less prominent or absent. Pressure and tenderness may be diminished or absent in neuropathic patients, whereas erythema in vascular patients can be absent. Many DFI patients have no systemic characteristics such as fever or chills. The lack of systemic indications or symptoms suggests a dangerous deep infection [12,15].

Variability of bacterial virulence factors and host susceptibility levels often must be taken into consideration. Indeed, the numerous species extracted from contaminated wounds have no comparable pathogenic influence, and an estimation of the intrinsic virulence ability of isolated bacteria to establish their true pathogens seems an excellent way to better classify the infection and differentiate between infections and colonization. Around 30% of the human population is colonized with *Staphylococcus aureus*. Imports involve a large variety of clinical diseases (e.g., bacteremia, endocarditis, skin and soft tissue, osteoarticular infections, respiratory infections and apparatus-related infections). The several factors of virulence and toxins produced by *Staphylococcus aureus* are well defined during infection. Any specific characteristics may therefore be found in DFI. The purpose of this analysis is to explain position. DFI aureus and its toxin role in the production of the infection [8, 9, 24-26].

The Wagner system assesses ulcer depth and the presence of osteomyelitis or gangrene by using the following grades as shown in Figure 1: Grade 0 (pre-or post-ulcerative lesion), grade 1 (partial/full thickness ulcer), grade 2 (probing to tendon or capsule), grade 3 (deep with osteitis), grade 4 (partial foot gangrene), and grade 5 (whole foot gangrene) [27].

Some bacterial infection of diabetic foot

The Head of the Department of Infectious Diseases approved this retrospective study. To preserve patient confidentiality, no personal identifiers were used on the data collection form. All data collected was rendered anonymous prior to analysis.

Methicillin Resistant *Staphylococcus Aureus* (MRSA)

Antimicrobial resistance is one of the world's biggest health problems which hinders effective treatment and prevention of rapidly increasing infections and microbial outbreaks. Since the 1970s, MRSA has been the primary source of nosocomial infections in the world. Despite the availability of antibiotics for nearly 70 years, the increased advent of antibiotic resistance particularly to methicillin and vancomycin has rendered the treatment difficult for doctors. [12, 13].

Difference between *Staphylococcus aureus* and MRSA

Staphylococcus aureus is a gram-positive bacterium non-motile, coagulase positive Firmicutes phylum coccoid bacterium. While 52 species and 28 subspecies (list of prokaryotic names with standing in nomenclature) form the Staphylococcus genus and it is an optional anaerobic that is contained in the skin and in human nasal passages. It has been known for over 100 years as a significant cause of human illness. The bacteria are poisonous and decreases the potency of antibiotics as one of the consequences of this toxin. Methicillin, the first synthetic penicillin to cure *Staphylococcus aureus* infections was introduced in 1960. However, in Figure 2 methicillin-resistant strains were identified in the hospital shortly after and MRSA outbreaks contributing to serious disease and mortality were identified [12, 13, 28-31].

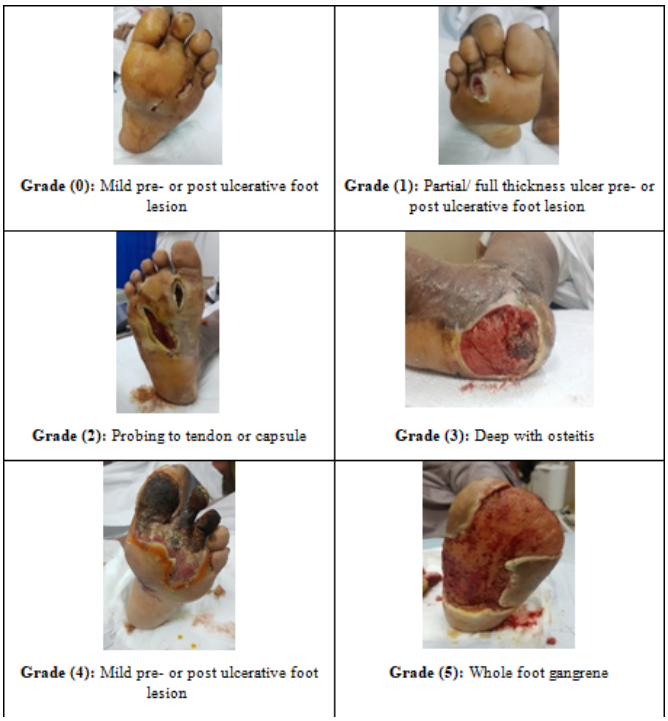

Figure 1: Infected diabetic foot wounds according to (Wagner's grade).

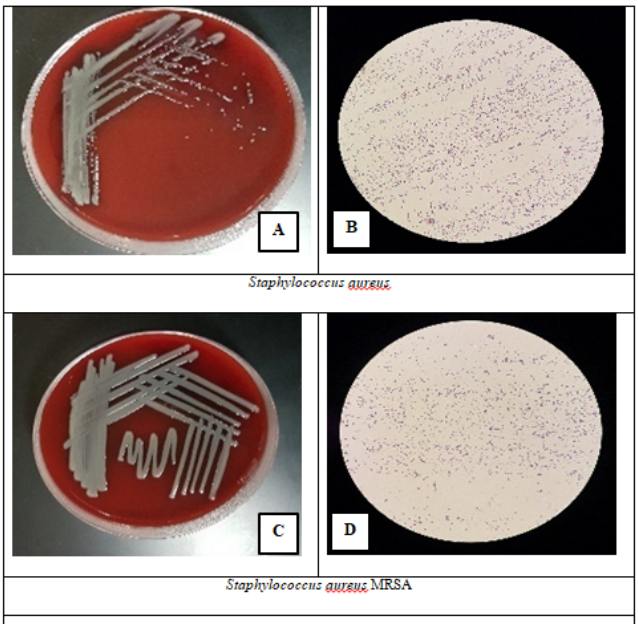

Figure 2: Macroscopic and microscopic difference between *Staphylococcus aureus* and MRSA.

MRSA categories

There are three main categories of methicillin-resistant *Staphylococcus aureus*. In the decade after its initial description, MRSA oversaw hospital outbreaks (health-care-associated MRSA (HA-MRSA)) in many parts of the world. The MRSA epidemiology was dramatically altered when individuals with no prior association with health-care (referred to as Community-Associated MRSA (CA-MRSA)) were observed, especially in Australia in the 1980s, and, in the 1990s, in the United States and non-healthy people, including infants. It has also been associated with livestock exposure since the mid-2000s (Livestock-Associated MRSA (LA-MRSA) [13,31-35].

Diabetes people are exposed to both CA and HA-MRSA due to frequent ulceration and sores. The additional Penicillin-Binding Protein 2a (PBP2a) provided by MRSA, which has low binding affinities for most penicillin and cephemic antibiotics. The resistance to methicillin is induced by the existence of the mec chromosome cassette element [12,36-39].

The most common causative agent in DFIs is *Staphylococcus aureus* and of these 23.7% were reported in a study as Methicillin-Resistant *Staphylococcus aureus* (MRSA). DFIs are soft tissue or bone infections below the malleoli. They typically start as skin ulceration where it extends from the skin into deeper subcutaneous tissues and/or bones contiguously in ~25 percent of instances. The affected foot ulcer normally precedes a total of 60% of amputations that may be mild or severe [12,19,40,41].

Reports from diabetic foot centers in the late 1990s showed that 15 percent of all isolates were MRSA. Studies in the early 2000s found that proportions of MRSA isolates were dramatically higher than in 1990, up to 30%. The increase in MRSA soft tissue infections was mainly driven by more community-acquired infections rather than health-care-associated strains [12,39,42-45].

In recent years, the strains of *Staphylococcus aureus* have grown to be more immune to multiple antibiotic forms, including first-line antibiotics including penicillin or oxacillin. Although vancomycin is the main therapeutic agent for MRSA infections over the last 50 years, its effectiveness in the face of increased Minimum Inhibitory Concentrations (MICs) is becoming increasingly concerned [12,46].

MRSA antibiotics resistance

In some reports, some patient has five times the chance of mortality by hospitalization with different forms of MRSA infection relative to equivalent patients without MRSA infection. In addition, a growing literature has shown that a strong Minimum Inhibitory Concentration of vancomycin (MIC) of MRSA strains damages bacteremia recovery or localized osteo-articular infections. These problems have contributed to new anti-MRSA agents, including linezolid, daptomycin, tigecyclin, ceftaroline, oritavancin, telavancin and dalbavancin being developed and more commonly used. Gram negative species developing β-lactamases-(ESBLs) in the wide range or carbapenemases are more interested as these show tolerances to most antibiotics. In the last decade, the risk of DFI isolating MDROs has risen. Many facets of wound microbiology are responsible for developing DFIs. DFIs are polymicrobial in nature (more than 1 form of bacterium), including microbial load, the variety of microbial profiles of Staphylococcus and Streptococcus being most frequently culprits [12, 47-53].

Swab culture performance showed 100% susceptibility, negative infection predictability, and pathogens identification, whereas specificities were lower (20% to 40%). So, the diagnostic use of swab appears mainly to be the exclusion of a micro-organism as a real pathogen and not the confirmation of its role and the presence of infection. The cultivation method thus plays a role in identifying microorganisms [54,55].

Staphylococcus aureus initiation of infection

Staphylococcus aureus is normally triggered by bacterial transfer from the main reservoir of the nose to open microlesions and wounds on the skin (probably by hand contact). S. aureus surface proteins Fibronectin-Binding Protein B (FnBPB), Clumping factor A (ClfA), ClfB, Collagen adhesine (Cna), for example bind to extracellular matrix protectors and enable bacteria to connect and multiply on injured tissue. *Staphylococcus aureus* adheres to biofilms (i.e. sticky

agglomerations in an extracellular matrix of micro-organisms; Biofilms promote mechanical intrusion tolerance, host protection and treatment of antibiotics on artificial plastic or metal structures, allow it *Staphylococcus aureus* is a common cause of catheter-related or joint-replacement-related infections or ventilator-associated pneumonia. *Staphylococcus aureus* is used to manipulate the resulting influx of Poly-Morpho-Nuclear leukocytes (PMNs). *Staphylococcus aureus* that forms local inflammation [56-59].

Bacteria that are phagocytized, many produce pore-forming peptides (Phenol Soluble Modulins (PSMs)) and protein toxins (α-toxin, known as α-haemolysin) and several bi-component leukocides such as Panton-Valentine Leucocidin (PVL)), which are species-specific hosts and bind to host leukocyte membranes, leading to pore formation and causing lytic cell death, subsequently raising bacterial virulence. Massive inflammation increased by *Staphylococcus aureus* superantigen toxins, which bind to the Major Histocompatibility Complex (MHC) of antigen presenting, cells and activate a large percentage of non-specific T cells, leading to systemic hyper inflammation known as cytokine storms [31,60-65].

Staphylococcus aureus abscess formation: It's the *Staphylococcus aureus* coagulase proteins which produce fibrin pseudo capsules surrounding bacteria and infiltrated, preventing further leukocyte influx. *Staphylococcus aureus* can inhibit opsonization, for example, the formation of a polysaccharide microcapsule and prevention of the complement cascade. However, the microcapsule is missing from important MRSA clones [66-68].

Systemic infection: Abscesses may be interrupted later, releasing pus and live bacteria to the surface of the skin, either to facilitate pathogen dissemination or to induce bacteremia to the bloodstream. *Staphylococcus aureus* endovascular can bind to endothelial surfaces and platelets, and this adhesion can cause endocarditis, facilitate metastatic abscesses or trigger bacterial abscess in endothelial cells where, the bacteria are difficult to reach by antibiotics and host defense molecules. The agglutinating function of coagulases is meant to lead to systemic blood clotting, and the massive release of molecular trends connected to microorganisms along with superantigen toxin-induced cytokine storms contributes to fulminant systemic inflammation, sepsis and multi-organ dysfunction when bacterial endovascular dissemination cannot be contained [31,69-72].

Regulation and adaptation: Most of *Staphylococcus aureus* virulence factors are differentially regulated by the Accessory gene regulator (Agr). Quorum sensing system and other regulatory networks, which reported that there are many toxins have a high capability to cause invasive infections even in healthy people. Diagnosis, screening and prevention of MRSA can cause a variety of infections, such as pneumonia, osteo-articular infections, toxic shock syndrome, and bacteremia that might be progress to endocarditis or severe sepsis [31,73].

Microbiological diagnosis

Microbiological specimens from which MRSA can be isolated can be widely categorized into clinical and screening samples. Clinical samples (e.g. purulent discharge specimens, sputum, deep tissue and blood) are taken from people with complaints or signs to investigate active infection, while screening samples (e.g. nasal, perineal, and throat swab) are acquired for diagnosis of asymptomatic colonizing. To diagnose MRSA directly from clinical or screening samples or to classify MRSA from presumptive staphylococcal colonies derived from clinical samples, an array of phenotypic and non-phenotypic approaches may be used. For clinical diagnostics, phenotypic methods are normally preferred [31].

Phenotypic methods: Pure *Staphylococcus aureus* cultivations and collected by putting clinical samples on the corresponding culture media may be screened using a disk diffusion system for methicillin resistance with applying a cefoxitin disk on supplementing Mueller-Hinton agar or Mueller-Hinton agar with 6 μg/ml Oxacillin and 4% NaCl (Clinical and Laboratory Standards Institute (CLSI) recommendations). Firstly, Oxacillin was administrated to detect MRSA; however, now Cefoxitin has a better inducer than Oxacillin and results in a clear identifiable phenotype. The disk-diffusion method need strict adherence time (reading after 24 hours) at temperature (35°c) to prevent false negative results [74].

The susceptibility test guidelines described above enable the slow rising MRSA subpopulation to exceed measurable levels in a hetero resistant population. MRSA may rarely be susceptible to Cefoxitin and Oxacillin and need an overnight exhibition of tolerance to low Cefoxitin concentrations. [31,75]

Methicillin tolerance may also be observed by an antigen–antibody based latex agglutination test that detects Penicillin-Binding Protein 2a (PBP2a) by using an anti-PBP2a antibody in *Staphylococcus aureus* colonies and cultures. Several automatic methods for detection and Staphylococci antimicrobial resistance monitoring have also shown high sensitivities and unique characteristics for the MRSA strains studied [31,76].

Prevention of MRSA infection

MRSA management interventions through healthcare services have been extensively applied. These strategies seek to reduce the occurrence of MRSA by the diligent application of antimicrobial agents (including introducing restrictions on their prescription), monitor the carrier reservoir, prevent MRSA transmission among patients and prevent the development of infection in carriers. Several methods are typically required to avoid transmission and MRSA infection successfully. The management segment addresses decolonization, an significant control action for which increasing evidence is accessible [31,77].

Hand hygiene: Health workers can gain MRSA in their hands by contacting patients with MRSA colonization and handling equipment contaminated with MRSA and MRSA can therefore be transmitted between the patients. Hand hygiene aims at reducing MRSA spread through this route with alcohol-based hand rubbing or soap and water. Indeed, the WHO has recognized hand hygiene as an essential factor in healthy patient treatment and has given specific guidance on the proper practices of hand hygiene for health workers [78,79].

The quality of enhancing the conformity of MRSA healthcare staff with hand hygiene was demonstrated at both national and local levels. For example, a decline in the occurrence of MRSA bacteremia from 1.88 to 0.91 per 10.000 patient bedding days was related to a national hand hygiene initiative in England and Wales at the end of 2004. While the hand hygiene program was carried out alongside other national infection prevention programs, improved alcohol rub procurement during the program was separately related to a decline in the rate of MRSA bacteremia after changes for all other measures [31,80,81].

Prevention of MRSA infection

Surgically

1. Consult a surgical consultant in selected mild and severe cases of DFIs.

2. In most situations, immediate surgical intervention is required abscesses, separation syndrome and nearly all deep tissue necrotizing infections.

3. In cases of osteomyelitis followed by soft tissue inflammation, it is normally advisable to suggest surgical operation, soft tissue envelope damaged, x-ray bone destruction incremental, or ulcer bone [6].

Antimicrobial therapy

1. Almost diabetic foot injuries are responsive to antimicrobial therapy, do not treat diabetic foot injuries clinically contaminated with antimicrobial therapy.

2. Choose antibiotic agents for care based on probable or confirmed causative pathogens, antibiotic resistance, clinical seriousness, DFI effectiveness and costs.

3. For most soft-tissue DFIs, antibiotic treatment lasts 1-2 weeks is generally acceptable.

4. Initially offer parenteral medication with most critical and some minor infections, then turn to oral care when the infection reacts [31,82-85].

Conclusion

The strategies seek to reduce the occurrence of MRSA by the diligent application of antimicrobial agents (including introducing restrictions on their prescription), monitor the carrier reservoir, prevent MRSA transmission among patients and prevent the development of infection in carriers. Several methods are typically required to avoid transmission and MRSA infection successfully.

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