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Research Article

Molecular Epidemiology of Methicillin Resistant Staphylococcus Aureus (MRSA)

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Abstract

Staphylococcus aureusis a gram-positive bacterium that can cause infections in almost anyone. The problem with the bacterium arises when S. aureus becomes resistant to methicillin. The bacterium's resistance to Methicillin and other beta-lactams is inherited from the mec.A gene located on the staphylococcal cassette chromosome mec (SCCmec), which serves a variety of functions in conferring its resistance to the drugs. It is important to understand the characteristics and components of infectious organisms, especially for epidemiological purposes. There are a variety of tests that can be conducted for the epidemiological and molecular study of MRSA which include plasma analysis, antibiogram typing, zerotyping, phage typing, bio typing, whole cell protein typing and zymotyping along with analysis restriction endonuclease. The two main DNA sequences analyzed when typing MRSA are MLST and SLST. MRSA can be classified as CA-MRSA (Community Acquired MRSA) and HA-MRSA (Hospital Acquired MRSA), based on the location where infection was contracted. Damage to skin and the mucous membrane gives a passage way for the bacteria to enter the individual. Diagnosis of MRSA can be made based on a samples obtained from an infected site on the patient and treatment is based on whether the infection is CA-MRSA or HA-MRSA. Worldwide, the infection rate of MRSA varies greatly, however, regardless of location, MRSA infection is a great concern. There are a variety of risk factors associated with infection of MRSA that have to be taken into consideration, especially when attempting to prevent the disease. This review looks into details of the molecular epidemiology of MRSA as well as the transmission, diagnosis and treatment options available.

Keywords: Molecular epidemiology; PVL; Staphylococcus Aureus; MRSA; SCCmec; Spa typing.

Introduction

Staphylococcus aureusis a gram-positive bacterium, which can cause a variety of infections including, but not limited to, superficial skin lesions (boils, styes), osteomyelitis, endocarditis, food poisoning and toxic shock syndrome [1]. S.aureusis also a major cause of hospital-acquired infections based on infection of surgical wounds in hospitalized patients. However, for the past few decades, S. auerushas been more and more difficult to treat due to its constant evolution and resistance to treatment with drugs such as Methicillin and Vancomycin [2]. Methicillin-resistant Staphylococcus aureus (MRSA) is considered a major health problem worldwide. For many years, MRSA has been considered the prototype for multi-resistant nosocomial pathogens, which causes infections in high-risk, hospitalized patients [3]. However, due to changes to the healthcare system along with the evolution of the microorganism, MRSA can now also be considered a major cause of community-acquired infections (CA-MRSA) [3]. CA-MRSA strains differ from nosocomial strains in that they infect a different group of patients, causes different signs and symptoms, differ in their susceptibility patterns and can spread rapidly in the healthy population, as opposed to high-risk, hospitalized patients [4]. The epidemiological studies performed throughout the years shows increase in the number of MRSA cases. The first outbreak of MRSA in a United States hospital was in 1968, in Boston MA [5]. From the 1960s to the 1990s, MRSA became an endemic pathogen in

the United States due to an increasing number of cases in university hospitals, especially in the intensive care units [5]. In 1975, the percentage of MRSA cases in hospitalized patients was 2.4%, which increased to 29% in 1991, and almost 50% in 2003 [5]. With the increase in number of cases and evolution of the various strains of S. aureus, it is important to determine what strain of MRSA the patient is infected with in order to determine an appropriate treatment regimen. Most, if not all, MRSA isolates are resistant to all available penicillin's and other Beta-lactam antimicrobial drugs, making treatment of MRSA extremely difficult [4].

Resistant Determinant

Staphylococcus aureus inherits its physiological Methicillin resistance characteristics and traits from the mecA gene located on the staphylococcal cassette chromosome mec (SCCmec). This gene codes for the 78-kDa penicillin binding protein 2a (PBP2'), which decreases the affinity of beta-lactam antibiotics from penetrating the bacterial cell wall. Currently, eleven SCCmec types have been identified. Six out of those eleven gene types have been linked with the direct cause of Staphylococcus aureus' ability to resist methicillin and other beta-lactam antibiotics. SCCmec types I, IV, V, and VI have been identified to specifically encode for the resistance of beta-lactams antibiotics. Where as, SCCmec types II and III have been identified as the determinants of carriers for various multi-resistance elements.SCCmec type III has been identified to carry plasmids that inhibit the proteins Kanamycin, Tobramycin, Bleomycin, and pI 258. These proteins code for resistance against penicillins by interfering with the bacteria's mRNA functions to promote bacterial protein synthesis. Additional plasmids such as pT181 are also altered to code for tetracycline resistance. The SCCmec gene also impacts transposon Tn554 gene that carries the ermA gene that is responsible for inducible macrolide, lincosamide, and streptogramin resistance [6]. MRSA is a highly evolved species because of its capability to modify its own genetic materials to adapt to the environment it seeks to thrive in. Its ability to modify self-genes to remain resistant to potent antibiotics makes it a difficult bacterium to control.

MRSA Typing Methods

When looking at an infectious organism it is important to understand the characteristics that comprise it. Often, that organism displays components that lead to its' infectious nature; these traits are often of particular importance epidemiologically. Valuable pieces of information from these traits will lead to a better understanding of the organism's infectious and resistant nature. There are multiple tests that can be conducted to determine these specific qualities of genetic and phenotypic traits of methicillin resistant Staphylococcus aureus (MRSA). There is not an internationally agreed upon best testing method for typing MRSA, and none of the subsequent testing methods cover all criteria needed for adequate strain typing [7].

One of the first tests used for epidemiological and molecular study of MRSA was plasmid analysis (8). This evaluates the size and quantity of the plasmids; however, due to their mobility and ability to be readily gained or suddenly lost, this method of study is not considered remarkably useful [8].

For classification by phenotypic measures the following tests are available: antibiogram typing, serotyping, phage typing, biotyping, zymotyping, whole cell protein typing, and multilocus enzyme electrophoresis. Antibiogram typing is a screening process that exposes the organism in question to a panel of antibiotics and evaluates which substances they are susceptible to. This method of testing can be done quickly and at little cost [8].

Phage Typing has been helpful in recognizing epidemic strains in a midst of endemic strains [8]. Furthermore, it is also very useful in monitoring the dissemination and emergence of MRSA strains among hospitals and the general population [7]. This test is of particular importance for epidemiological study, and should be considered as a first measure analysis [8].

Serotyping can also be done to isolate specific qualities in a particular strain of MRSA; however, it is not widely used for epidemiologic studies due to its poor discriminatory power. Antigenic properties can be tested for such as: capsular polysaccharides, membrane proteins, and other cell surface markers. Many similar characteristics are commonly held between strains leading to unclear results [8].

Biotyping is an additional means of phenotypically classifying a particular strain of MRSA. This technique is achieved by observing metabolic characteristics such as urease production, and susceptibility to chemicals compounds. Although a good number of strains are typeable; like many other phenotypic tests the discriminatory power of the investigation is low [8].

In whole cell protein typing method, sodium dodecyl sulfate-polyacrylamide gel is used to separate proteins extracted from the whole cell and subjected to electrophoresis (SDS-PAGE). This process makes numerous bands, which are subjected to stain, and then compared to other known samples. Often these results are difficult to interpret for MRSA strains. Standard immune blotting and enzyme electrophoresis can be done as well, but do not yield much relevant information for typing [8].

Zymotyping is a more complex phenotypic test. The testing method utilizes electrophoresis on a polyacrylamide gel, and looks specifically at esterase enzyme profiles. There are three main esterase enzymes seen in MRSA strains; they are respectively deemed A, B, C. The distances each enzyme travels can be compared to known strains; however, it is of great difficulty to accurately reproduce findings [8].

A subsequent study is restriction endonuclease analysis

(REA) of Chromosomal DNA. The restriction endonuclease cuts a segment of DNA at a specific nucleotide sequence; the fragments are then run via electrophoresis through an agrose gel. Different strains of MRSA contain variations in the DNA chain. The unique sequences lead to unique REA profiles that are specific for that particular strain. These patterns can been visualized when stained with ethidium bromide and inspected under ultraviolet light [8].

There are several typing methods that use the southern blotting technology as a foundation for testing. Restriction Fragment Length Polymorphism (RFLP) is a southern blot analysis and is similar in method to REA. One difference is that the fragments are transferred to a nitrocellulose membrane; DNA labeled probes are used to detect certain fragment sequences of interest. RFLP is useful in telling strains apart, but is often difficult to understand. Genes that are most commonly targeted are the coagulase gene (coa) and spagene [8]. The spa gene is extremely useful in tracking epidemic isolates (9). Similarly, ribotyping blots restriction enzyme digestion of RNA and insertion sequences. Eco R1, a restriction enzyme has proven to be the best choice for this analysis method. In a similar fashion, binary typing utilizes a modified southern blot technique, which investigates the combinations of genetic loci. PCR is used to amplify the desired genes segments, which can then be identified by using known strain specific DNA probes. MRSA isolates are assigned a binary code based on the results of the reaction, and every strain of MRSA is typeable through this method [8].

One of the most reliable and commonly used genotypic study methods for MRSA is the use of Pulsed field Gel Electrophoresis (PFGE), it is considered by many to be the "gold standard" (10). This method is a variant of electrophoresis where the vector of electrical current is periodically shifted across an Agarose gel. The alterations to the electrical field allow for larger segments of DNA to separate out and avoid fragment overlap. With the use of this method all strains of MRSA are typeable. The Smaenzyme improves the banding pattern in the gel making significantly fewer bands, and leading to easier interpretation of the results. PFGE has been proven very effective in identifying outbreak strains of MRSA and use for recent epidemiological studies [8].

Arbitrarily primed polymerase chain reaction or random amplified polymorphic DNA (AP-PCR/RAPD) utilizes target DNA amplification via random amplification segments primed with indiscriminate sequences. AP-PCR/RAPD is a very rapid and simple technique that does not require the amplified segments to be digested. This method works well for rapid screening. Nearly all strains of MRSA are typeable by this method; however, this test is best utilized for outbreak strain analysis (8).

There are two main DNA sequence analysis based methods for typing MRSA, Multi Locus Sequence Typing (MLST) and Single-locus Sequence typing (SLST). MLST is a useful study to evaluate colonel evolution by evaluating seven housekeeping genes. This method also allows for evaluation of transmission across species [8]. If two or more different types of SCCmec are seen in the same sequence type it is indicative that MRSA clones have arisen on multiple occasions in the same genetic background by acquiring separate SCCmec into Methicillin-sensitive strains [11]. Each housekeeping gene is assigned its own allele which can be identified in various strains of MRSA. The alleles studied are arcC, aroE, glpF, gmk, pta, tp and yqiL. There are different sequences kept by each gene making them unique and able to type. In order to narrow the focus more precisely, single-locus sequence typing (SLST) is used. This study approach compares the variations in the sequence of one targeted gene via short sequence repeats (SSR) regions. This method has also been recommended for epidemiological study of domestic and international cases [8].

One genetic test for antibiotic resistance is the Staphylococcal cassette chromosome mectyping (SCCmec). There are relatively eight major types of SCCmec and multiple other subtypes. Each of the major type's code for resistance against different antibiotic therapies. In combination with MLST this study method shows reliable typing and evolution of MRSA strains. In conjunction with SCCmec, toxin gene profiles can be assessed; strains isolated from different regions of the world contain unique toxin gene characteristics. This evidence can serve of great value when assessing from which regions of the world a particular outbreak strain of MRSA transcended [8].

MRSA in Hospital Settings and in the Community

MRSA infections are classified according to where the infection was contracted: community-acquired MRSA or Hospital-Acquired MRSA (HA-MRSA). MRSA infections acquired by individuals with no past 1-year history of hospitalization or invasive medical procedures such as dialysis, surgery or catheter are known as CA-MRSA infections. CA-MRSA infections occur in overtly healthy individuals and manifest on the skin as pimples or boils. MRSA strains amongst the community are distinct from those present in the hospital. CA-MRSA strains are more virulent than HA-MRSA strains due to the production of many virulence factors such as Panton–Valentine Leukocidin (PVL), which can be associated with necrotizing pneumonia [7]. SCCmec types IV and V are mainly associated with CA-MRSA isolates but few reports have found SCCmec types I, II or III isolates. PVL is a S. aureus exotoxin and a genetic marker for CA-MRSA. Majority (40 to 90%) of MRSA strains that exhibit SCCmec type IV carry PVL and less than 5% of MRSA strains with SCCmec type I to III carry PVL [7]. Five PVL-positive CA-MRSA strains have been isolated worldwide; these are summarized in Table 1.

Clone	SCCmec Type	Spa typing	Location
ST1	IVa	t127, t128, t174, t176, t386, t558	Asia, Europe, USA
ST8	IV	t008, t024, t064, t190, t206, t211	Europe, USA
ST30	IV	t012, t018, t019, t021, t138, t268, t276, t318, t338, t391	Australia, Europe, South America
ST59	IV	t199, t216, t437, t444	Asia, USA
ST80	IVc	t044, t131	Asia, Europe, Middle-East

Table 1: Community acquired-MRSA phenotypes and their global distribution.

The USA300 MRSA variant has emerged globally, but it forms the genetic background of CA-MRSA in the United States [4]. Important characteristics of this strain include SCCmec type IV, PVL genes, and, in most strains, the ACME element [4]. Spa typing classifies USA300 as t008. USA300 achieved its dominant role in CA-MRSA infections in a brief period of time. By 2005, USA300 was responsible for 29% of MRSA infections in the United States [4]. Between 2004 and 2006 USA300 emerged in Canada and became accountable for 30% of MRSA reported cases [12]. More recently, it has been identified in the other parts of the world including Western Europe, Japan and Australia. Origin of CA-MRSA strains has widely been debated. Whether they are acquired from Methicillin-sensitive Staphylococcus aureus (MSSA) strains in the community or from HA-MRSA remain unclear since similarities between CA-MRSA and HA-MRSA strains have previously been discovered.

HA-MRSA infections are acquired in hospitals or other healthcare related facilities such as nursing homes or dialysis centers. These infections are severe and patients are at a higher risk of contracting HA-MRSA if they have a prolonged hospital stay, received broad-spectrum antibiotics, had recent surgery or invasive medical procedures including introduction of a tube into the body, such as a urinary catheter or a central line IV catheter. Failures in infection control measures (e.g. hand washing prior to patient contact) can further increase the transmission of HA-MRSA infections. HA-MRSA strains consist of SCCmec types I, II and III. These strains are larger in size, contain more antibiotic resistance genes and have fewer excision and reintegration sites [12]. HA-MRSA strains do not have PVL genes or the SCCmec IV element found in CA-MRSA [13]. A study conducted by Vandenesch and colleagues compared HA-MRSA isolated in France and USA and discovered that most HA-MRSA (95%) contain lukE-lukDleucocidin genes. Furthermore, they found that all U.S. HA-MRSA (31 of the 33 isolates) had SCCmectype II element, the remaining two isolates had type I element. Conversely, 23 of the 24 French HA-MRSA were of SCCmectype I and only 1 was of type II [13].

Colonization and Infection

Staphylococcus aureusis a gram-positive bacteria consisting of a thick peptidoglycan wall and forms spherical colonies. These bacteria live on the skin's surface and attach to epithelial cells on the outermost layer of skin. S. aureus is exceptionally good at beating out other bacteria and binding to the limited available spaces on epithelial cells. Colonization is common in healthy people, approximately 25% to 30% of the population is colonized with S. aureus; however, colonization does not mean that the person has an infection [14]. The most common site for colonization of S. aureus is the nasal passageway; however, the axilla, groin, and hands are also accepted as common sites for colonization [15]. If MRSA is found in one of these locations additional testing the other areas is necessary; it has been shown that with more colonization sites of S. aureus/MRSA there is subsequently a higher risk of developing infections [16].

In most cases, intact skin and mucous membranes are sufficient and effective as a barrier against transmission. If these barriers are damaged due to cuts, burns, or any other wounds, S. aureuscan gain access to the underlying tissues and vasculature allowing for colonization and subsequent infection with typical symptoms including redness, pain, and fever [17].

MRSA is easily transmittable through direct contact with an infected wound or via contact with shared items, such as a towel or razor, which has touched the infected wound. Transmission risk increases in certain populations, especially people who are frequently in crowded places such as school students, military personnel and athletes. Many MRSA infections occur in the hospital setting and are specifically known as healthcare acquired MRSA, or HA-MRSA [18].

Diagnosis

When a patient with a suspected infection regresses and does not improve with antibiotics MRSA may be suspected. A patient may also be tested for MRSA if they are being transferred to a hospital from another healthcare setting where MRSA is known to be present or if they have had a previous history of MRSA. A patient sample is obtained from the infected site or alternatively a nasal secretion sample or blood sample if the patient has pneumonia. Routine diagnosis of S. aureusinvolves a tube Coagulase tests or a latex agglutination test. When S. aureusis identified further

tests can be done to determine its likelihood of the bacteria being MRSA. The most recent gold standard test is the broth Micro dilution test. This involves numerous test plates of blood agar containing various mixtures of the antibiotic and the organism. These mixtures are then heated and incubated. Growth of the organism is then determined after a period of up to 48 hours. Latex methods detecting Penicillin Binding Protein 2a (PBP 2a) and/or Polymerase Chain Reaction (PCR) methods detecting the mecA gene can be used in conjunction [18] Other tests including the cefoxitin disk screen test or a plate containing 6 μg/mL of Oxacillin in Mueller-Hinton agar supplemented with 4% NaCl as alternative methods of testing for MRSA may also be used. Oxacillin and Cefoxitin are often tested with the isolated bacteria as Methicillin is no longer commercially available in the United States and theses antibiotics survive better in storage. Furthermore, they are more reliable in detecting resistant strains. Cefoxitin is also a better inducer of the mecA gene. This makes these antibiotics more accurate in detecting MRSA and is therefore preferred [19].

Treatment

MRSA infections can be categorized into 2 distinct groups based on the means by which the infection was acquired: hospital-acquired and community-acquired infections. HA-MRSA is multi-drug resistant, while CA-MRSA is susceptible to Clindamycin and Erythromycin [20].

MRSA is resistant to all b-lactam antibiotics (Penicillins, Cephalosporins and Carbapenems). Intravenous Vancomycin has been the primary means of treatment of MRSA for decades. Vancomycin inhibits cell wall synthesis via blocking glycopeptide polymerization by binding tightly to the D-alanyl-D-alanine portion of the cell wall precursor [21]. Newer agents, including Daptomycin, Linezolid and Quinupristin/Dalfopristin, appear to be as efficacious at treating serious MRSA infections as Vancomycin. Quinupristin/Dalfopristin inhibits bacterial protein synthesis by binding to various locations on the 50S ribosomal subunit [22]. Linezolid is a secondary treatment option because of its potential adverse effects, which most commonly include headache, diarrhea, decreased hemoglobin count, thrombocytopenia, and leukopenia [23]. Linezolid acts to inhibit the bacterial protein synthesis by binding to 23S ribosomal RNA of the 50S subunit, which prevents the formation of a functional 70S initiation complex [23]. In the case of life-threatening infections, Vancomycin is often used in combination with Rifampin and Gentamicin to provide a synergistic effect. Gentamicin binds to 30S and 50S ribosomal subunits to interfere with bacterial protein synthesis, leading to defects of the bacterial cell membrane [24]. Rifampin binds to the beta subunit of DNA-dependent RNA polymerase, blocking transcription and inhibiting RNA synthesis [25]. The combination of Vancomycin, Gentamicin and Rifampin demonstrate enhanced destruction of MRSA infections, and decreased antibiotic resistance.

Uncomplicated skin and soft-tissue infections, in which the patient shows no evidence of systemic infection, can be treated with oral antibiotics such as Trimethoprim/Sulfamethoxazole, a Tetracycline, or Clindamycin. Linezolid can also be used; however this is expensive and rarely clinically required. This should only be used in consultation with an infectious disease specialist. In the case of small abscesses (<5cm), incision and drainage may be sufficient treatment [26]. Although antibiotics are often not required in these cases, many physicians will still prescribe them. In the event there is a lack of response to oral antibiotics or in the case of a complicated infection (evidence of systemic disease), the patient must be hospitalized and placed on intravenous antibiotics (Vancomycin is first line treatment option) [26].

First line therapeutics for bacteremia and sepsis, as a result of MRSA infection, is intravenous antibiotics, specifically Vancomycin. Identification and removal of the source of infection (e.g. intravascular or urinary catheter) is essential in successfully treating the patient. Intravenous Vancomycin is also first line treatment for pneumonia caused by MRSA infection [26].

MRSA infection can be a cause of endocarditis in both prosthetic and native heart valves. Intravenous Vancomycin is generally the first line therapy for native heart valves; however, Daptomycin is commonly used in the case of native tricuspid valve endocarditis [26]. Daptomycin binds to the bacterial cell membrane causing rapid depolarization, inhibition DNA, RNA, and protein synthesis [27]. Prosthetic valve endocarditis is treated with an intravenous combination of Vancomycin, Gentamicin and oral Rifampicin [26-28]. Valve replacement is needed for heart failure, severe regurgitation, hemodynamic instability, or for abscess or fistula formation in both types of endocarditis.

In the case of septic arthritis, the joint should be aspirated and intravenous antibiotics and oral Rifampicin should be prescribed. Rifampicin should always be used in combination with other agents to reduce the risk of developing antibiotic resistance [26]. The first step in treating a catheterized patient presenting with a UTI of MRSA origin is removal of the urinary catheter. UTIs may be treated with oral or intravenous antibiotics, depending on the severity of the illness. Oral antibiotics can be used to treat patients with uncomplicated UTIs (dysuria and fever with no evidence of sepsis). Complicated UTIs (signs and symptoms or evidence on culture of resistant organisms) require intravenous antibiotics [20,26].

Research and development of new agents to treat MRSA is an ever-ongoing process. A drug that has recently hit the mark is a lipoglycopeptide called Dalbavancin. Dalbavancin is used in the treatment of adults presenting with acute bacterial and struc-

ture skin infections caused by Staphylococcus aureus (including MRSA), Streptococcus pyogenes, Streptococcus agalactiae, and Streptococcus anginosus. Dalbavancin acts by binding to the D-alanyl-D-alanine terminus, interfering with cell wall synthesis [29].

Epidemiological Determinants

The quality of infection control practices within a given facility can pose a significant impact on the number of incidences of MRSA infections. In fact, some acute care facilities have documented reductions up to 70% in MRSA infections [30]. Therefore, countries with decreased access to health care resources or poor infection control practices may have a much higher instance of MRSA infections.

Infections with CA-MRSA phenotypes are far more prevalent in the summer; whereas, infections with HA-MRSA phenotypes peak in the winter [31]. One possible explanation for the elevated incidence of CA-MRSA infections in the summer is that people may be more likely to spend time in community-based settings in the warmer summer months.

According to recent studies, approximately one in three people carry staph in their nose, usually without any illness; whereas, two in 100 people carry MRSA [32]. Despite the dangers associated with MRSA infections, a study published in the Journal of the American Medical Association Internal Medicine showed a 54% decline in life-threatening HA-MRSA infections from 2005 to 2011. However, other population-based estimates are more conservative, suggesting a decline of 11%-17% in the United States from 2005 to 2011 [32].

The National Centre for Health Statistics released data from an MRSA surveillance program in 2012, involving 19,635,461 persons across the United States. The results showed a greater number of cases among Caucasians than other races. There is no definitive explanation for this finding; however, studies have shown that certain minority groups are far less likely to seek medical care [33]. Therefore, a Caucasian individual may be at greater risk of developing a hospital acquired MRSA infection, as he or she may be more likely to spend time in a hospital setting than an individual who is African American. Figure 1 illustrates the incidence of MRSA among various age groups. The findings suggest that the incidence of invasive MRSA infections is greatly increased among individuals aged 65 years or older. The chart also divides MRSA into three subcategories: hospital-onset (HO), community-acquired (CA), and healthcare associated community-onset (HACO). The third classification denotes individuals who tested positive for MRSA in a community setting, such as a walk in clinic, following a hospital admission.

Worldwide, the MRSA infection rates vary significantly; however, it still remains a global concern. Globally, highest rates of MRSA (>50%) are reported in North and South America, Asia and Malta while Intermediate rates (25–50%) are reported in China, Australia, Africa and some European countries [e.g. Portugal (49%), Greece (40%), Italy (37%) and Romania (34%)]. Recent studies has shown that, HA-MRSA prevalence declined in some European countries like France, Austria, Ireland, Greece and the United Kingdom while in other countries in Europe, it has remained stable. Although the rate of MRSA (HA) are much lower in India (22.6%) and the Philippines (38.1%), very high rates are reported in East Asia, mainly in ka (86.5%), South Korea (77.6%), Vietnam (74.1%), Taiwan (65.0%), Thailand (57.0%) and Hong Kong (56.8%) (34).

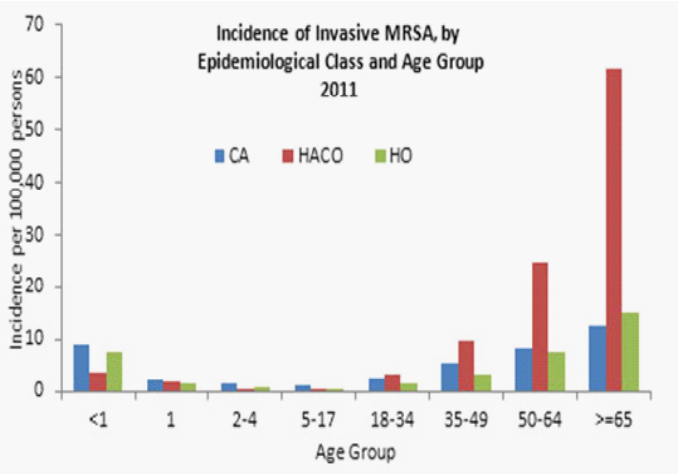

Figure 1: Age distribution of MRSA by epidemiological class(32).

Figure 2 illustrates the varying MRSA infection rates among 36 countries (35). The World Health Organization released a report in 2014 on the global surveillance of antimicrobial resistance, stating that this is a worldwide crisis. As microorganisms continue to develop resistance, common infections and minor injuries that have been treatable for years, may lead to death once again.

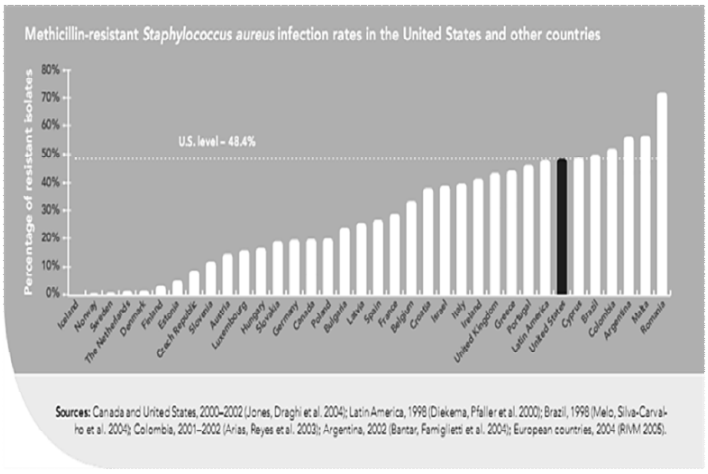

Figure 2: Global distribution of MRSA infection rates (35).

MRSA Risk Factors

According to the Centers for Disease Control and Prevention, cases of disease caused by MRSA can be classified into one of three epidemiological classifications. The first is hospital-onset (HO) if the MRSA culture is obtained on or after the fourth day of hospital admission; second is healthcare-associated community-onset (HACO) if the culture is obtained in an outpatient setting or before the fourth day of hospitalization including one or more of the following conditions: 1) history of hospitalization, surgery, dialysis, or residence in a long term care facility in the previous year, or 2) the presence of a central vascular catheter (CVC) within 2 days prior to MRSA culture; and finally the last classification is community-associated (CA) if none of the previously mentioned criteria are met [32]. From these three classifications, you can infer the most common risk factors associated with MRSA infection. MRSA is usually spread by direct contact with an infected wound or by contaminated hands of healthcare providers. Those who are carriers for MRSA but do not have signs of infection can spread the bacteria to others and potentially cause infection [36].

The following risk factors for community acquired MRSA infection are shown in Table 2. The rapid spread of community-associated MRSA has been characterized by outbreaks of cutaneous infection in normally healthy people. The organism has moved into the healthcare setting, containing new virulence factors and causing necrotizing, frequently lethal pneumonia especially following influenza infection [37].

HIV infection constitutes a highly vulnerable population for MRSA colonization, and prior exposures to hospital or incarceration are significant factors. One study looked at the prevalence of MRSA infection in HIV patients who are MRSA carriers. This study found that 6.9% of individuals with HIV infection are MRSA carriers. History of hospitalization during the previous 12 months was associated with a 3.1 times higher risk of MRSA colonization. Previous or current incarceration was also associated with a higher risk for carriage. Current antiretroviral therapy, current use of TMP-SMX, or illicit drug use was not observed to be associated with increased risk of MRSA colonization. Extranasal screening increased the detection of MRSA colonization by at least 31.6%, meaning that nasal screening alone will underestimate the rate of colonization by at least one-third. The added yield from groin screening was 19.3%, from perirectal screening 18.5%, and from throat cultures 17.5%. Data for colonized and non-colonized individuals with history of incarceration found that individuals with history of incarceration are 77% more likely to be MRSA colonized compared with patients without. This study also found strong evidence that MRSA colonization is mainly related to previous exposure to settings with high prevalence of MRSA, such as hospitals, jails, and prisons and weaker evidence regarding the association with high-risk sexual behaviors [38].

Risk Group or Factor
Children <2 years old
Athletes (mainly participants in contact sports)
Injection drug users
Men who have sex with men
Military personnel
Persons living in correctional facilities, residential homes, or shelters
Veterinarians, pet owners, and pig farmers
Adults aged ≥ 65 years
Blacks
Recent influenza-like illness and/or severe pneumonia
Concurrent skin and soft-tissue infection
History of colonization or recent infection with a community-associated MRSA strain
Known close contact (in same household) with a person colonized and/or infected with MRSA

Table 2: Epidemiological risk factors for infection with community-associated MRSA [37].

Close contact with a person who is a carrier of or infected by MRSA, is another risk factor in contracting MRSA [39]. One study looking at Staphylococcus aureus colonization among household contacts of patients with skin infections found that from 1162 persons enrolled in the study (350 index patients and 812 household members) the most common infection isolate characteristic was ST8/SCCmec IV, PVL1 MRSA (USA300) (53%). S. aureus colonized 40% (137/350) of index patients and 50% (405/812) of household contacts. A nares-only survey would have missed 48% of S. aureus and 51% of MRSA colonized persons. Factors independently associated ($P < 0.05$) with the index strain type colonizing household contacts were recent skin infection, recent cephalexin use, and USA300 genetic background. They concluded that USA300 MRSA appeared more transmissible among household members compared to other S. aureus genetic backgrounds.

MRSA has become common and widespread within hospitals and intensive care units. According to the National Nosocomial Infections Surveillance (NNIS) System Report, between 1992 and 2004, MRSA accounted for >60% of S. aureus isolates in US hospital ICUs [40]. Between 1999 and 2000, an estimated 125,969 hospitalizations with a diagnosis of MRSA infection occurred annually, including 31,440 for septicemia, 29,823 for pneumonia, and 64,706 for other infections, accounting for 3.95 per 1,000 hospital discharges [42]. Hospital acquired MRSA infections are likely due to advances in patient care and also of the pathogen's ability to adapt to a changing environment. This includes increasing medical interventions, devices, older population and additional

comorbidities, as well as antibiotic use/overuse contributing to its resistance [37,42]. In a recent study of 298 patients with prosthetic devices (orthopedic, cardiovascular and long term catheters), more patients were infected with Methicillin-resistant (158/298, 53%) than Methicillin-susceptible S. aureusstrains. The average length of stay was 16 (±14) days for patients with community-acquired S. aureus bacteremia and 33 (±28) days for patients with hospital-acquired S. aureusbacteremia [43].

It was also found that MRSA rates for septicemia, pneumonia, and other infections increased with patient age, with the most diagnoses occurring in persons >65 years of age. Patients <14 and 15-44 years of age had lower MRSA hospitalization rates compared with patients 45-64 and >65 years of age [41].

Geographic variation in the United States has been observed, with more MRSA infections seen in the South, followed by the Midwest, Northeast, and West [41]. Similarly, in Europe, considerable variation exists in the incidence of MRSA, with only 0.5% in Iceland but 44% in Greece from 1999 to 2002. MRSA proportions significantly increased in Belgium, Germany, Ireland, the Netherlands, and the United Kingdom, and decreased in Slovenia [44].

Prevention and Control

The prevention of MRSA predominantly involves proper cleaning, disinfection, and handling of infected items or surfaces. In the case of a MRSA skin infection occurring in a facility setting, cleaning and disinfection should be performed on all surfaces that may have come in contact with the infection. Surfaces that may have come into contact with MRSA infection can be fully decontaminated by the usage of Environmental Protection Agency (EPA) registered disinfectants (45). Proper disinfection of surfaces with possible presence of MRSA should involve focus on areas that may come into contact with bare skin on a daily basis such as clinical examination tables, benches in a weight room, and even keyboards or other electronic devices [46].

Anyone can use a number of simple precautionary measures to avoid infection such as cleaning one's hands regularly, cleaning and covering any cuts or scrapes until fully healed, and using a towel or clothing to create a barrier between one's skin and the occupied surface. In a medical setting the prevention of spread of MRSA can be achieved by adequate hand washing and hand hygiene, wearing gloves, utilizing mouth, nose, and eye protection, gowning, executing appropriate handling of medical devices and equipment, as well as appropriate handling and transport of medical facility laundry [47,48].

An effective approach regarding the prevention and control of MRSA is early detection of the infection so suitable precautions and procedures can be implemented to avoid further infections. Screening for MRSA is commonly utilized technique that is used for patients who may be at risk of contracting the infection [49]. People at risk may include those who have been previously positive for the infection and are being re-admitted to a hospital setting, patients with non-intact skin including wounds and ulcers, patients who have recently been discharged from a facility where an outbreak or cluster has recently occurred, and patients who have been successfully decolonized should continue to undergo screening while still in a hospital setting [50].

Although there have been intense efforts to control MRSA infection and transmission within hospital settings, there remains an increase in incidence of MRSA. There are various studies aimed toward eradicating MRSA, therefore finding the best method by which to control further infection. Because of the drug resistant character of MRSA, topical antibacterial agents and germicides such as Mupirocin have become one of the favored approaches for MRSA outbreak prevention. Unfortunately, complete eradication of MRSA carriage or colonization has not shown to be assured or permanent [51].

Decolonization involving the use of Mupirocin in conjunction with other therapies such as Chlorhexidine baths has proven to be effective. A nursing home conducted a controlled trial of decolonization involving its residents yielded promising results. 61% of the residents remained decolonized for up to 90 days, with a trend of up to 6 months following topical Mupirocin within the nostrils [52].

Conclusion

In summation, MRSA remains one of the most difficult infections to treat due to its constant adaptation and resistance to antibiotics. It is notorious for, but not limited to, causing infection in those with compromised, or weakened immune systems, and among those confined to hospitals, or community health settings. Two in every 100 individuals are known to be infected. The majority of MRSA infections manifest as skin infections transmitted by human contact, or in contact with an object harboring the bacterium. Once infected, the skin develops cutaneous abscesses, pustules, or boils in areas of an open cut or wound; appearing red, swollen and often painful to the patient. Often, these abscesses must be drained. In severe cases, the heart, lungs, bones and joints may also become affected and pose health complications. Individuals at the highest risk of contracting HA-MRSA strain are those in nosocomial settings, nursing homes, and those with invasive medical devices, such as a catheter. Athletes, and individuals participating in contact sports, are most susceptible to developing CA-MRSA strain infection. Physicians are highly encouraged to educate their patients of the preventative measures that must be taken in order to avoid contracting infection. These include practicing proper hygiene; washing hands, covering any open wounds, sanitizing linens, avoiding contact with those infected, disinfecting any and all potentially contaminated surfaces, and wearing protective garments in a health setting. Extensive research is being con-

ducted to develop an effective treatment in combating MRSA, but at this point in time, practicing the appropriate measures to prevent the spread of infection is the most effective method of prevention.

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