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Nosocomial Infections in Saudi Arabia Caused by Methicillin Resistance *Staphylococcus aureus* (MRSA)

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Abstract

Nosocomial infections that are infections acquired in hospitals are becoming a serious concern globally due to the severe complications and outcomes caused by them. Methicillin resistant *Staphylococcus aureus* is one of the major causes of nosocomial infections worldwide, though there are other bacteria implicated in such infections. It is the strongest resistance faced during the last century and it still represents a serious threat to health in our present time. MRSA is dangerous because of bacterial genetic plasticity that allows them to acquire genetic materials that help them fight antibiotics, in the case of MRSA the genetic material being the SCC*mec*. SSC*mec* contains *mecA* gene that is known for its ability to provide resistance against beta-lactam antibiotics. MRSA has been detected in KSA since the 1990s, but still there are few and random studies concerning this issue compared to the rest of the world. Control and prevention measures must be strictly applied to avoid these infections from occurring and also there is an urgent need to upgrade to more sophisticated and targeted control measures to combat bacterial resistance that poses to be a major threat to mankind.

Keywords: Nosocomial infections; *Staphylococcus aureus*; MRSA; Antibiotic resistance KSA

Nosocomial Infections

Nosocomial infection is defined according to the National Nosocomial Infections Surveillance (NNIS) as "a localized or systemic condition that results from adverse reaction to the presence of an infectious agent(s) or its toxin(s) and that was not present or incubating at the time of admission to the hospital" [1]. The common definition of nosocomial infection is, an infection which occurs within 48 hours after hospitalization, or after 3 days from discharging, or 30 days from an operation. According to studies, the nosocomial infections are found mainly in intensive care units (ICU) compared other units of the hospital [2]. These infections affect healthcare quality and cause many problems and they were identified more than a century ago. They account for about 5 – 10% of the cases admitted to hospitals for emergency care in the developed countries. It is the result of a chain of events influenced by the microbe involved, the transmission method, and patient's adherence to physician's instructions. The rate of nosocomial infection increases with administration of many treatment methods such as hemodialysis, respirators, urinary catheters and intravenous catheters [1]. In industrialized counties such as USA, comprehensive studies were carried out on nosocomial infections because of their devastating effect of patient mortality rate and money consuming treatments yearly. On the other hand, there are only few reports from developing countries, and rare premature studies from the Middle East. As reported by the WHO on 2001, nosocomial infection has the highest percentage in South-East Asia, and the Eastern Mediterranean and one of the main reasons for this has been the inadvertent misuse of antibiotics leading to widespread resistance [3].

Bacteria Causing Nosocomial Infections

The bacteria which are commonly associated with nosocomial infection are *Staphylococci, Escherichia coli*, and *Pseudomonas*. Gram positive bacteria were categorized as the main cause of nosocomial infection, with *Staphylococcus aureus*; usually known as staph; in the center of these causes [4]. Staphylococci are opportunistic pathogens although they are normal cutaneous organisms present in the environment. They can invade human body and cause serious infections. There different types of this organism but the most common type involved with human infections is *Staphylococcus aureus* [5]. They are considered as the main reason for infections which are linked with severe illness and death [6]. The rate of bacteria which are becoming antibiotic resistant is increasing and especially in areas as ICU [7]. Staph is found in about 25-30% in the nose and skin of healthy people (i.e. asymptomatically), and sometimes they cause infections. These bacteria are the most common cause of skin infection in the USA [4]. *Staphylococcus aureus* has developed resistance over the past 20 years to many antimicrobial drugs which are used commonly in the USA [8].

Methicillin Resistant *Staphylococcus aureus* (MRSA)

It is a type of *Staphylococcus aureus* which gained resistance to common antibiotic used for Staphylococcus infections such as methicillin. Bacteria develop resistance when they acquire new genetic material that encodes for resistance and it is transferred to other strains. Methicillin Resistant *Staphylococcus aureus* (MRSA) causes up to 60% of nocosomial infection in ICU [2]. The antibiotic methicillin was first used clinically in the year 1960, and it is semi-synthetic penicillin which is poorly hydrolyzed by the bacterial enzyme penicillinase. Unfortunately, after being used for one year only, MRSA emerged in 1961 [9]. MRSA infection was described first in hospitalized patients and was subsequently recognized as an important nosocomial infection [10]. This infection started soon after methicillin was used as an antibiotic in 1961. The use of methicillin came as a

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result of penicillin resistant staphylococci, but it was only for a short period of time before MRSA was recognized as a human nosocomial infection [11]. MRSA was first detected in USA in the 1970s, and it was considered an endemic by the year of 1990 [8]. MRSA is also resistant to other antibiotics such as *B*-lactamase-resistant penicillin antibiotics such as cloxacillin, dicloxacillin, oxacillin, and nafcillin, as well as a closely related class of drugs known as cephalosporins (e.g., cephalexin). MRSA can be carried out in the nose and skin of about 1-2% of people, and some strains of MRSA can be very aggressive that regular staph infection. A major cause for these resistant strains development is the use of very powerful drugs for minor infections and the overuse of antibiotics [4]. MRSA strains prevalence rates were found to vary from one country to another, actually it also varies within the cities of the same country. However, worldwide the prevalence rate of MRSA has notably increased since the beginning of 1990. In the present decade, the rate of MRSA prevalence is reaching to alarming levels in a large number of countries; for example Italy (45%), United Kingdom (40%), and in France and Greece (35%). Also, the highest MRSA rates in bloodstream isolates in 2004 were reported from United Kingdom (44%), Greece (44%), and Ireland (41%) [6].

Mode of MRSA Dissemination

Usually patients become a victim to nosocomial infections either through infections with an endogenous microbe (normal flora of the body), or through cross contamination from healthcare workers or transferred between people through skin, and hands, or through use of contaminated equipments such as needles, razors, sports equipment, towels, or from an exogenous microbe (organisms from the environment) and environmental surfaces (e.g., athletic benches or mats), poor hygiene and sanitation conditions, and crowded living conditions also. The presence of cuts or abrasions in the skin allows easy transmission. MRSA is commonly transmitted in hospitals through the health care workers and in non-hospital facilities as dialysis center [1,4].

The Mechanism of Resistance in MRSA

The reason why bacteria can become resistant to antibiotic is their genetic plasticity and ability to evolve and adapt to environmental changes. This adaptation and evolvement resulted from the pressure of the use of antibiotic [12]. MRSA is the major cause of gram positive nosocomial infection because they have the ability to acquire a gene called *mec* A. Acquisition of a staphylococcal cassette chromosome mec (SCC*mec*), is the reason behind the change of strains of methicillin susceptible *Staphylococcus aureus* (MSSA) to strains of methicillin resistant *Staphylococcus aureus* (MRSA). This SSc*mec* carries a gene called *mecA* which in turn what gives MRSA its resistance. SSC*mec* is composed of two vital parts they are; first is the *ccr* gene complex which consists of *ccr* genes and open reading frames (ORFs) surrounding them, the second is the *mec* gene complex which consists of regulatory *mecA* gene with insertion sequences either upstream or downstream of the gene. The combination of different types of *mec* and *ccr* resulted in different types of SCC*mec* and consequently MRSA. Eight types of SCC*mec* were recognized some being more common than the others Table 1 shows the classification of the five most common types of SCC*mec* [9,11].

Usually, bacteria are damaged by the use of beta-lactam antibiotics such as (penicillins, cephalosporins) through the inactivation of important enzyme for the cell wall, leaving bacteria vulnerable for osmosis and lyses. Staphylococci have a protein that provides resistance to penicillin only, but the possession of *mec*A gene provides complete resistance to all beta-lactam antibiotics through producing an alternative protein to the one inactivated by the antibiotics [12] (Figures 1 and 2).

Studies on Nosocomial Infections and MRSA in KSA

A study done on MRSA in Jeddah over a period of three years (1990-1992) revealed that about 7.5% per annum of all isolated *S. aureus* were MRSA. About 71% of isolates came from wound sites [13]. A retrospective study in the year of 1998 for the review of MRSA clinical experience in two tertiary care hospitals in Jeddah resulted in

	SCC*mec* Type	*mec* Type	*ccr* Type
1	Type I	Class B	Type 1
2	Type II	Class A	Type 2
3	Type III	Class A	Type 3
4	Type IV	Class B	Type 2
5	Type V	Class C2	Type 5

Table 1: Major types of MRSA according to classes of SSC*mec* obtained.

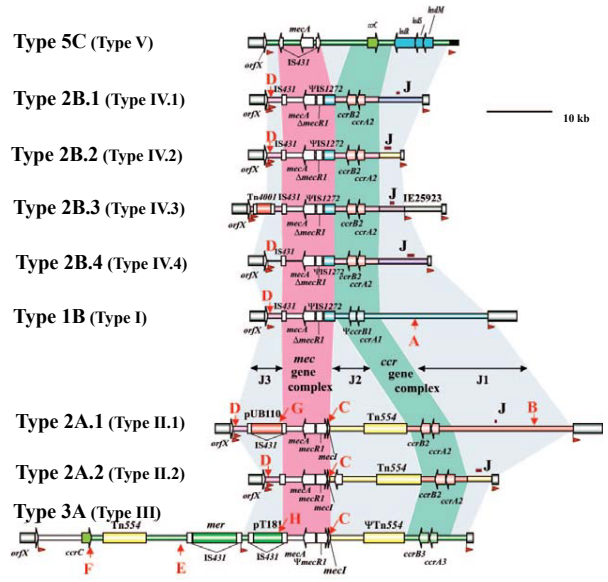

Figure 1: Structural comparison of *SCCmec* elements, which are based on nucleotides sequence [9].

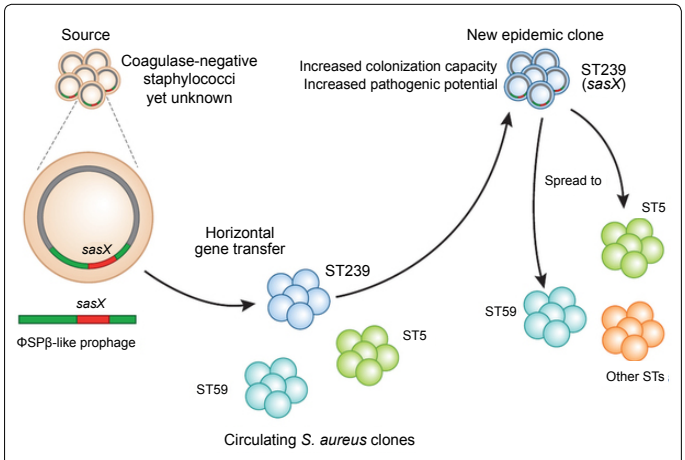

Figure 2: Mechanism of acquiring *mecA* gene and transferring from MSSA to MRSA.

MRSA being found in 222 cases out of 673 staph isolates. In 84.2% of the cases nosocomial infection occurred and it affected all age groups. Highest rates of MRSA were in intensive care units (26.6%), then comes the medical wards (24.8%), and 19.8% from the surgical wards. Isolates that caused infection were 73% of the cases while the remaining caused only colonization. The commonest sites of infection were as follow; surgical wounds (35.2%), chest (29%), and central venous catheters (13%). This study concluded that MRSA prevalence is high and it is quickly increasing in both two hospitals as well as the rest of the world. So, MRSA spread must be prevented through the implementation of control measures, hygiene precautions, and policies development for antibiotics use restrictions in hospitals [14].

A study over a six month period on nosocomial infection incidence and antibiotic misuse prevalence in a community hospital with 174 beds was done on 2002. The study included 2445 admitted patient, out of which 8.5% had nosocomial infection. The highest incidence rates were observed in; nursery (35.8%), intensive care (19.8%), gynaecological (16.2%) and surgical (11.7%) patients. The types of infections found were urinary tract (31.3%), wound (27.1%) and blood (14.9%) which accounted for more than 70% of the infections. *Staphylococcus aureus* (23%) and Pseudomonas aeruginosa (11%), caused more than 90% of the infections. Most of the bacteria found were multi-drug resistant (79%). About 80% of the patients were given either prophylactic or therapeutic antibiotics, 53% of them had multi-antibiotics at the same time while 72% of these used antibiotics were considered to be misused. Thus, the study concludes that more effective measures must be implemented for the high infection rate and the misuse of multiple antibiotics, and there must be a valid antibiotic use policies as well as an effective infection control committee in each hospital for monitoring these infections [15].

A study was done by Madani (2002) in King Abdulaziz University Hospital in Jeddah, Saudi Arabia to investigate MRSA prevalence during the year of 1998. *Staphylococcus aureus* was identified isolates from patients in about 292 samples; out of them 111 samples were MRSA (38%). About 74.8% of these isolates were from nosocomial infections cases. Moreover, from all the hospital areas, the highest was the medical ward (27%), then 20.7% was for both medical ans surgical wards for pediatrics. Then, other areas were as follow; 18% for outpatient department, 17.1% for adult surgical ward, 17.1% intensive care units. The previous results suggest that MRSA infection is increasing in the hospital as the remaining world, so the need for control measures for MRSA spread prevention must be established and implemented [16].

A prospective study done in Taif, Saudi Arabia during the year of 2004, at the Al Hada Armed Forces Hospital which examined all hospital patients; showed that the number of patients who developed infections in the hospital was 1382 patient. Nosocomial infection accounted for 668 of the cases with a percentage of 48.3%, while the remaining cases 714 (51.7%) accounted for community acquired infection. So, the rate of nosocomial infections was about 4.98%. MRSA was found to have the highest percentage (31.8%), suggesting it as the commonest nosocomial pathogen [1]. Another cohort study done in the intensive care unit of neonates in Abha General Hospital in 2010 focused in measuring nosocomial infection occurrence and the risk factors. From the 401 neonates which remained in the unit for 48 hours, 77 neonates developed infections. The main three infections were; pneumonia (50.0%), primary bloodstream (40.9%) and skin and soft tissues (6.5%). Nosocomial infection increased the risk of neonates dying 3 times than neonates free on infection [17].

Hamid et al. performed a study in Aseer Region in KSA in the year 2011, to investigate prevalence of infections causing bacterial pathogens located in the region, particularly *Staphylococcus aureus*. For this study, 9831 samples were investigated and 24.9% were caused by bacterial pathogens most commonly; *Escherichia coli, Klebsiella pneumoniae, Enterococcus* spp. and *S. aureus*. Most of the *S. aureus* isolates were from wounds and abscesses 77/210 (38.5%), and 53 (26.5%) were from vaginal discharges. MRSA were identified in 45% of all the 210 cases of *S. aureus*. So, the study concluded that wounds and abscesses were the mains source of *S. aureus*, and MRSA rates were actually high [18].

Although, the types of MRSA strains present in many countries has been identified, no data regarding strains' types related to the Middle East or Arab countries were found. Strains causing hospital acquired MRSA which are reported within the region, KSA being one of the countries in this region is the pandemic strain ST239-III, while another pandemic strain found in Kuwait and Abu Dhabi is CC22-IV (UK-EMRSA-15). In 2011, King Fahad Medical City (KFMC) in Riyadh investigated MRSA prevalence rate within patients and they found the percentage to be 50.4%, so probably other hospitals have similar rates to KFMC. So, a study done by Monecke (2012) in Riyadh, Saudi Arabia aimed to identify MRSA strains which existed in the kingdom. In the study, 107 MRSA isolates obtained from KFMC were genotyped by using Microarray based assay. The study found 5 major MRSA strains; they are: CC8/ST239-III (20.75%), PVL-positive as well as -negative CC22-IV (18.87% and 9.43%, respectively), PVL-positive CC30-IV (12.26%) and PVL-positive CC80-IV (17.92%). Other strains found in lesser amount about 3% each include; CC1-IV/SCCfus, PVL-positive CC1/ST772-V, PVL-positive as well as-negative CC5-IV, CC5-IV/SCCfus, CC5-V, CC6-IV, CC45-IV, PVL-negative CC80-IV, PVL-positive CC88-IV, CC97-V and a CC9/ST834-MRSA strain. This shows the wide diversity of MRSA strains present in Riyadh, and the high prevalence of the gene encoding for the Panton-Valentine leukocidin which accounted for (54.21%) [19].

The nasal carriage of MRSA among the health care workers still represents an issue that must be dealt with and addressed. The most endemic areas inside the hospitals include; nursery, maternity, pediatric, medical, surgery, intensive care units. Studies are done to investigate the percentage of nasal carriage among the health care workers in hospitals and from patients' wounds and burns since 1990 up till now. A study done in 2007 at a specialized hospital revealed that the percentage of *S. aureus* isolates was 31.8% (112/352). From these positive 112 cases, 103 cases (92%) were methicillin sensitive *S. aureus* (MSSA), and 9 cases (8%) were methicillin resistant *S. aureus* (MRSA). The gender ratio was 23% male to 46% female, and the ratio between medical workers and administrative personnel was 35.5% to 2.6%, respectively. The carriage percentage was higher with people less than 35 years old (30.1-33.4%) compared to (6.8-15.7%) with people older than 35 years. The MRSA isolates were found resistant to many drugs, but both MRSA and MSSA isolates were sensitive to treatment with vancomycin [20].

A study published in 2013 which had collected data of MRSA in Saudi Arabia from 2002 up to 2012 (Figure 3) that covered five regions and included 26 published research article, and performed meta-analysis and statistical analysis. This study revealed that MRSA had a prevalence rate of 35.6% (95% CI, 0.28-0.42; P<0.01) out of the 22,793 strains of *S. aureus*. Among the major five regions of Saudi Arabia, MRSA prevalence rates varied dramatically. It ranged from 5.97% in Dahran to 94.59% in Riyadh. So, MRSA prevalence distribution average was the highest in Assir and Riyadh (40%-60%, respectively), while Makkah region showed intermediary result (25%-40%), with Al Gouf being the lowest with <15%. Despite the fact that the reasons for

Figure 3: Proportions Variation of MRSA in Saudi Arabia, 2002-2012 [21].

this geographic variation are unknown, a study by Van Belkum et al., confirmed that a single clone of MRSA is responsible for 93% of the isolates tested. So, this might indicate environmental or host factors as reasons for variation incidence. Comparing Saudi Arabia regarding results from this study with other regional countries, it appears that it has a higher MRSA prevalence rate compared to Lebanon, Bahrain, and Kuwait. Whereas, Saudi Arabia had a lower rate than the rate reported for Jordan, Oman, Egypt, and Iran which was >50%. With international scale, MRSA incidence was 29.2% in Spain which is lower than Saudi Arabia, while China was over 50% and Shanghai was over 80% which are higher than Saudi Arabia [21].

Another study done in 2011 in Riyadh and it included a total of 740 subjects to investigate the nasal carriage of both the community acquired as well as the hospital acquired MRSA. From the 740 subjects, 550 subjects were residents and students from the community, while the remaining 190 subjects were collected from healthcare related locations such as; workers, nursing homes, hemodialysis units, and acute care wards. The study showed that *S. aureus* were found within 538 patients out of 740 (24.1%), and the rate of *S. aureus* colonization within the community *S. aureus* is significantly higher than the hospital related subjects 3.5 and 6.9%, respectively, but the reverse is true with the rate of MRSA colonization where it is significantly (P=0.002) lower for community subjects compared to hospital related subjects 3.5 and 6.9%, respectively. Students showed significantly higher rate of *S. aureus* carriage than other community subjects, but the MRSA colonization rate within community subjects was significantly lower among the student than other subjects (P=0.003). MRSA colonization within hospital related subjects had an average rate of 6.9% (5-11%), and the highest rate was found among chronic care subjects (11%). There was no significant difference in the rates of *S. aureus* and MRSA carriage between patients of different hospital related areas. However, the MRSA colonization rate was higher in the patients with *S. aureus* carriage compared to health care workers (P=0.042). All MRSA isolates were positive for the SCC*mec* gene. The study identified 7 types of the gene, five which are already known and two new variants were identified as well. For community related subjects, SCC*mec* type IV was the most common (87.5%), while type III group (type III, type IIIA and type III variants) (51.85%) and SCC*mec* type IV (40.7%) were found to be the most common within the health care related subjects. All clinical isolates had the type III group except for one sample; some of them had new type III variants [22].

A recent study by Iyer et al., 2014 compared the incidence of MRSA in nosocomial infections in health care workers from various units of hospitals in Jeddah. A group of students non-exposed to MRSA were used as a control and compared with health care workers from units of hospitals such as burn unit, ICU, and outpatient unit. For isolation, nasal swabs were taken from the volunteers and cultured on mannitol salt agar media selective for *S. aureus*. Suspected colonies were confirmed by PCR using specific primers for the coagulase and *mec*A gene. Typing of the coagulase-positive strains was done using restriction fragment length polymorphism (RFLP). The results indicated an incidence rate of 76% among healthcare workers. This is in comparison with students who served as control and were negative for MRSA. Using RFLP, four different types of MRSA were confirmed. The results of this study showed an alarming rate of incidence in burn unit. Effective control measures must be formulated and implemented to avoid indiscriminate use of antimicrobials and the spread of these infectious agents in the region [23].

Control Measures and Prevention Protocols

Protection and prevention against nosocomial infections start with continuous surveillance [1]. There is a real problem which is faced everywhere and the need for effective solutions is increasing to ensure the effectiveness of current antibiotics regime. Some of the proposed solutions include; development of new antibiotics effective against the resistant organisms, or vaccination against infection, and careful use of antibiotics to avoid resistance development. All physicians must be cautious when prescribing antibiotics to avoid the development of resistant strains [12].

There are steps to prevent all nosocomial infections including MRSA, these steps are as follow; 1)-Wounds must be covered with clean and dry bandages to avoid infection from draining pus which could contain staph. 2)-Hands must be clean all the time through washing them with soap and warm water, or by using alcohol based sanitizers. 3)-Avoid personal items sharing such as towels, razors, clothing, washcloths, and uniforms. 4)-Dirty sheets, clothes, and towels must be cleaned with warm/hot water and detergent, and drying them in hot

dryer instead of air dry to kill all bacteria on the fabrics [4]. 5)-Health care worker must be screened for MRSA carriage and treated if found positive. 6)-Patients with high risk for MRSA must be screened upon admission and isolated if found carriers. 7)-Hospital environmental cleaning and disinfection is recommended along with MRSA-infected patient isolation precautions. 8)-Increase the national surveillance and implementation of risk adjusting infection rates between hospitals to increase awareness. 9)-Development of less invasive infection resistant devices. 10)-Better implementation of existing control measures from both hospitals and health care workers [24].

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