METHICILIN RESISTANT *STAPHYLOCOCCUS AUREUS* SKIN, SOFT TISSUE INFECTION AMONG HIV INFECTED INDIVIDUALS ATTENDING HIV CARE AND TREATMENT CLINICS IN DAR ES SALAAM CITY, TANZANIA

By

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Medicine in Internal Medicine of the Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences (MUHAS)

October, 2011

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam, a dissertation entitled: **Methicilin - resistant *Staphylococcus aureus* skin, soft tissue infection among HIV infected individuals attending HIV care and treatment clinics in Dar es Salaam city, Tanzania** in partial fulfilment of the requirements for the degree of Master of Medicine in Internal Medicine of the Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam

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DECLARATION AND COPYRIGHT

I, **Honoratha F. Maucky,** declare that, this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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ACKNOWLEGEMENT

Glory and honor be to Almighty God who is; and was with me throughout this work and my studies at large. I am sincerely grateful to Dr. Mgonda Y. and Dr. Munseri P. for their untiring support, constructive criticism and encouragement during the preparation of this dissertation.

I would like to thank head of Department Prof Lutale and all other members of staff whose contributions and constructive criticisms have made this work much better.

Sincere thanks also should go to Dr. Makwaya and Prof. Hirji of the Department of Biostatistics for his statistical assistance.

I would like to thank Amana, Temeke, Mwananyamala and Muhimbili hospital staff, and Muhimbili National Hospital laboratory technician; Mrs Mary Nyange for her support and encouragement that allowed my work goes smoothly.

Special thanks to all of my colleagues for their co operation throughout my work.

My heartfelt gratitude should go to my Husband; Ayubu S.N. for his moral and material support and my children; Jaedon and Breena for their love and tolerance when I was overwhelmed with my dissertationwork.

Lastly, I acknowledge with gratitude the financial contribution from the Ministry of Health.

ABREVIATIONS

ARV	-	Antiretrol viral
CA- MRSA	-	Community Acquired Methicillin Resistance *Staphylococcus Aureus*
CDC	-	Centers for Disease Control and Prevention
CRF	-	Chronic renal failure
CTC	-	Care and Treatment Clinic
HIV	-	Human immunodeficiency virus
HCAMRSA	-	Health-care associated methicillin –resistant *Staphylococcus aureus*
KS	-	Kaposi's sarcoma
MRSA	-	Methicilin Resistance *Staphylococcus aureus*
MSSA	-	Methicillin Sensitive *Staphylococcus aureus*
MNH	-	Muhimbili National Hospital
PVL	-	Pantine Valentine Leucocidin
PTSAgs	-	Pyogenic toxin superantigens
SCCmec	-	Staphylococcus Cassete Chromosome
SPSS	-	Statistical package for the social sciences
SSSS	-	Staphylococcal Scalded-skin Syndrome
SSTI	–	Skin and/or soft tissue infection
TSS	-	Toxic Shock Syndrome
TX	-	Texas

DEFINITION OF TERM

MRSA – Staphylococcus aureus that is resistant to methicillin and cefoxitin.

TABLE OF CONTENTS

CERTIFICATION…… …….ii
DECLARATION AND COPYRIGHT…….iii
ACKNOWLEGEMENT ……iv
ABREVIATION S ……..v
TABLE OF CONTENTS……vi
ABSTRACT……ix

CHAPTER ONE……..1
1: INTRODUCTION AND LITERATURE REVIEW……...1
1.1 *STAPHYLOCOCCUS AUREUS*……....1
1.2 MICROBIOLOGY OF *STAPHYLOCOCCUS AUREUS*……2
1.3 VIRULENCE…….2
1.3.1 TOXINS……..2
1.3.2 PYROGENIC TOXIN SUPERANTIGENS……...2
1.3.3 EXFOLIATIVE TOXINS……...3
1.3.5 ROLE OF PIGMENT IN VIRULENCE……3
1.4 TREATMENT OF *STAPHYLOCOCCUS AUREUS* INFECTIONS…….3
1.5 METHICILLIN - RESISTANT *STAPHYLOCOCCUS AUREUS*…….5
1.6 METHICILLIN - RESISTANT *STAPHYLOCOCCUS AUREUS* AND DISEASES……...7
1.7 COMMUNITY-ACQUIRED METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS* AND SKIN INFECTION……8
1.8 MANAGEMENT OF COMMUNITY-ACQUIRED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* SKIN INFECTION……10
1.8.1 INCISION AND DRAINAGE…….10
1.8.2 ANTIBIOTICS…….11
1.8.3 TOPICAL TREATMENT……14

1.9 PREVENTION OF CUTANEOUS COMMUNITY-ACQUIRED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTION……14
1.9 METHICILLIN - RESISTANT *STAPHYLOCOCCUS AUREUS* AND OTHER SYSTEMIC INFECTIONS……...17
1.10 EPIDEMIOLOGY…….....18

CHAPTER TWO……..…….....23
2.0 PROBLEM STATEMENT……..23
3. 0 RATIONALE OF THE STUDY……24
4. 0 OBJECTIVES…….25
4.1 Broad objective……26
4.2 Specific objectives.……..26
5. 0 METHODOLOGY…….26
5.1 STUDY AREA.……...26
5.2 STUDY DESIGN..……...26
5.3 STUDY SETTING..…….27
5.4 TARGET POPULATION.……...27
5.5 STUDY POPULATION……..27
5.6 PERIOD OF THE STUDY……..28
5.7 INCLUSION CRITERIA…….28
5.8 EXCLUSION CRITERIA……...28
5.9 STUDY SAMPLE…….....28
5.10 SAMPLING TECHNIQUE……..29
5.11 DATA COLLECTION METHODS……..29
5.11.1 CLINICAL INTERVENTION……...29
5.11.2 SAMPLE COLLECTION AND PROCESSING……30
5.12 LABORATORY METHODS……30
5.12.1 LABORATORY PROCEDURES……..30
5.12.2 T- LYMPHOCYTE CD4 CELL COUNT……..31

5.13 DATA QUALITY CONTROL……..32
5.14 DATA PROCESSING AND ANALYSIS…….32
6.0 ETHICAL ISSUES……..32
7.0 PATIENTS DISPOSAL……...33

CHAPTER 3……..33
8.0 RESULTS……34
8.1 Characteristics of Patients with HIV and skin and/or soft tissue infection attending HIV CTCs in Dar es Salaam……..38
8.2 Prevalence of *S. aureus* SSTI among HIV patients attending HIV CTCs in Dar es Salaam……41
8.3 Antibiotic susceptibility pattern of the *S.aureus* isolated from SSTI of HIV patients……42

CHAPTER 4……..49
9.0 DISCUSION……49
9.1 Prevalence of skin and/or soft tissue infection among HIV infected patients in Dar es Salaam……49
9.2 Prevalence of *S. aureus* skin and/or soft tissue infection among HIV infected patients in Dar es Salaam……50
9.3 Antimicrobial susceptibility pattern of *S. aureus* isolated from, skin and/or soft tissue infection of HIV infected patients in Dar es Salaam…….50
9.4 Prevalence of MRSA skin and/or soft tissue infection among HIV patients in Dar es Salaam……....51
10.0 CONCLUSION…….54
11.0 STUDY LIMITATIONS…….....54
12.0 RECOMMENDATION…….55
13.0 REFERENCES……..56
14.0 APPENDICES……...67
14.1 Appendix I…….67
14.2 Appendix II……72

ABSTRACT

Back ground:

Methicilin Resistance *Staphylococcus aureus* (MRSA) is found worldwide. HIV infection is a known risk factor for the development of MRSA infections and HIV infection may also increase the risk of recurrent disease. HIV infection has been associated with an increased incident of *S. aureus* skin and/or soft infection and nasal colonization with *S. aureus* in most patients.

Objective

To determine the prevalence of MRSA skin, soft tissue infections and nasal carriage among HIV infected adults attending HIV care and treatment clinics in Dar es Salaam, Tanzania.

Methods:

Study design and settings:

A cross sectional study was conducted in all three district hospitals available in Dar; the HIV clinics at Amana hospital in Ilala district, Temeke hospital, in Temeke district, Mwananyamala hospital in Kinondoni district and Muhimbili National hospital, which is a tertiary care hospital located in Ilala Dar es Salaam. Patients were consecutively recruited into the study until the calculated sample size was achieved.

A standard questionnaire was used to collect demographic data, and other MRSA related risk factors that included prior use of co-trimoxazole, prior use of antibiotics other than co-trimoxazole, history of prior hospital admission, family history of skin infection, known cases of Diabetes mellitus, malignancy, chronic renal failure, on dialysis. Physical examination was performed that included inspection for soft tissue infections and nasal swabs were collected from all HIV infected patients included in the study. Additionally swabs or pus aspirate was collected from all patients with skin and or soft tissue infections for the examination of MRSA. Resistance testing was performed for *Staphylococcus aureus*, MRSA was defined as *Staphylococcus aures* resistant to methicillin and cefoxitin.

Results:

A total of 271 HIV infected patients were recruited into the study, 107 (39.5%) were males and 164 (60.5%) were females. The prevalence of MRSA skin and/or soft tissue infection among HIV patients was found to be 4/271(1.5%). High proportion of MRSA SSTI was found among females 3/16(18.8%) than males 1/14(7.1%), however the difference in prevalence between the sexes was not statistically significant. (p=0.351) Prevalence of MRSA skin and/ or soft tissue infection was high among the patients CD4 counts <200, 3 (60.0%) compared to patients with CD4 count of 200-500cells/µL 1 (5.0%) patients p=0.003. None of the patients with CD4 cell count of >500 was found to have the MRSA. MRSA was found in the following lesions: folliculitis 1/1(100%), Ulcer 2/3 (66.7%) and abscess 1/5 (20%). MRSA skin and/or soft tissue infection was more common among patients who were on co-trimoxazole; 4/8 (50.0%) than on those who were not on co-trimoxazole prophylaxis 0/22 (0.0) % p=0.003 MRSA SSTI was significantly more prevalent 3/7 (42.9%) among patients with a prior history of using antibiotics compared to patient with no prior history of using antibiotics 1/23 (4.3%), p=0.009. The duration of antibiotic use was not found to have any significant relationship with MRSA skin and/or soft tissue infection. Hospital admission prior recruitment to the study was significantly found to be associated with MRSA. Among HIV patients with MRSA SSTI who had prior history of hospital admission; 2/4(50.0%) subjects had MRSA SSTI while only 2/26 (7.7%) patients with no prior history of hospital admission had MRSA. P = 0.020

Conclusion and Recommendation:

MRSA in skin and/or soft tissue infection among HIV-infected patients is common and occurs mostly in HIV patients with low CD4 count, prior hospital admission, prior use of co-trimoxazole and other antibiotics. Early detection of patients with skin and/or soft tissue infection, prompt evaluation and proper treatment will minimize duration and transmission of infection. Preventive measures should be brought on including screening of the carriers, improving of personal hygiene, isolation of the potential infected patients to avoid spreading of the resistant strain of MRSA.

CHAPTER ONE

1: INTRODUCTION AND LITERATURE REVIEW

1.1 *STAPHYLOCOCCUS AUREUS*

The staphylococci are gram-positive spherical cells, usually arranged in grape-like irregular clusters. Some are members of the normal flora of the skin and mucous membranes of humans; others cause suppuration, abscess formation, a variety of pyogenic infections, and even fatal septicemia. The pathogenic staphylococci often hemolyze blood, coagulate plasma, and produce a variety of extracellular enzymes and toxins. The most common type of food poisoning is caused by a heat-stable staphylococcal enterotoxin.[1]The genus *Staphylococcus* has at least 35 species. The three main species of clinical importance are *Staphylococcus aureus, Staphylococcus epidermidis,* and *Staphylococcus saprophyticus. Staphylococcus aureus* is **coagulase-positive,** which differentiates it from the other species.

S. aureus is a major pathogen for humans. It was discovered in Aberdeen, Scotland in 1880 by the surgeon Sir Alexander Ogston in pus from surgical abscesses.

Almost every person will have some type of *S aureus* infection during a lifetime, ranging from minor skin infections, such as pimples, impetigo (may also be caused by *Streptococcus pyogenes*), boils (furuncles), cellulitis folliculitis, carbuncles, scalded skin syndrome and abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, toxic shock syndrome (TSS), and septicemia. *Staphylococci* can host phages, such as the Panton-Valentine leukocidin, that increase its virulence.[76]

S. aureus infections can be spread through contact with pus from an infected wound, skin-to-skin contact with an infected person by producing hyaluronidase that destroy tissues, and contact with objects such as towels, sheets, clothing, or athletic equipment used by an infected person. Deeply penetrating *S. aureus* infections can be severe. Prosthetic joints put a person at

particular risk for septic arthritis, and staphylococcal endocarditis (infection of the heart valves) and pneumonia, which may be rapidly spread.

1.2 MICROBIOLOGY OF *STAPHYLOCOCCUS AUREUS*

S. aureus is a facultatively anaerobic, Gram-positive coccus, spherical bacterium which appears as grape-like clusters when viewed through a microscope and has large, round, golden-yellow colonies, often with hemolysis, when grown on blood agar plates. The golden appearance is the etymological root of the bacteria's name; aureus means "golden" in Latin.

S. aureus is catalase positive and able to convert hydrogen peroxide (H_2O_2) to water and oxygen, which makes the catalase test useful to distinguish staphylococci from enterococci and streptococci. *S. aureus* is primarily coagulase-positive that causes clot formation while most other *Staphylococcus* species are coagulase-negative.[2] However, while the majority of *S. aureus* are coagulase-positive, some may be atypical in that they do not produce coagulase (the most common organism in patients with nosocomial bacteremia is coagulase-negative staphylococcus.

1.3 VIRULENCE

1.3.1 TOXINS

S. aureus is capable of secreting several toxins, which can be categorized into three groups. Many of these toxins are associated with specific diseases.

1.3.2 PYROGENIC TOXIN SUPERANTIGENS

Pyogenic Toxin Superantigens have superantigen activities that induce TSS. This group includes the toxin TSST-1, which causes TSS associated with tampon use. The staphylococcal enterotoxins, that causes a form of food poisoning.

1.3.3 EXFOLIATIVE TOXINS

Exfoliative toxins are implicated in the disease *staphylococcal* scalded-skin syndrome (SSSS), which occurs most commonly in infants and young children. It also may occur as epidemics in hospital nurseries. The protease activity of the exfoliative toxins causes peeling of the skin observed with SSSS.

1.3.4 OTHER TOXINS

Staphylococcal toxins that act on cell membranes include alpha-toxin, beta-toxin, delta-toxin, and several bicomponent toxins. The bicomponent toxin Panton-Valentine leukocidin (PVL) is associated with severe necrotizing pneumonia in children. The genes encoding the components of PVL are encoded on a bacteriophage found in community-associated MRSA strains.

1.3.5 ROLE OF PIGMENT IN VIRULENCE

Some strains of *S. aureus* are capable of producing *staphyloxanthin* - a carotenoid pigment that acts as a virulence factor. It has an antioxidant action that helps the microbe to evade killing with reactive oxygen used by the host immune system. It is thought that staphyloxanthin is responsible for S. aureus' characteristic golden colour.[3]

1.4 TREATMENT OF *STAPHYLOCOCCUS AUREUS* INFECTIONS

The treatment of choice for *S. aureus* infection is penicillin; but in most countries, penicillin-resistance is extremely common.

Penicillin is a group of antibiotics derived from Penicillium fungi. [4] Penicillin antibiotics are historically significant because they were the first drugs that were effective against many previously serious diseases such as syphilis and *Staphylococcus* infections. Penicillins are still widely used today, though many types of bacteria are now resistant. All penicillins are Beta-lactam antibiotics and are used in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms.

In 1928, Sir Alexander Fleming observed that colonies of the bacterium *Staphylococcus aureus* could be destroyed by the mould Penicillium notatum, proving that there was an antibacterial agent there in principle. Alexander Fleming grew the mould in a pure culture and found that it produced a substance that killed a number of disease-causing bacteria. Naming the substance penicillin, Dr. Fleming in 1929 published the results of his investigations, noting that his discovery might have therapeutic value if it could be produced in quantity.

At the time, however, the importance of Alexander Fleming's discovery was not known. Use of penicillin did not begin until the 1940s when Howard Florey and Ernst Chain isolated the active ingredient and developed a powdery form of the medicine.

Four years after drug companies began mass-producing penicillin in 1943; microbes began appearing that could resist it. The first bug to battle penicillin was *Staphylococcus aureus*.[5]

Staphylococcus aureus is one of the major resistant pathogens. It is found on the mucous membranes and the skin of around a third of the population, it is extremely adaptable to antibiotic pressure. It was the first bacterium in which penicillin resistance was reported in 1947, just four years after the drug started to be produced massively. By the late 1960s, more than 80% of both community- and hospital-acquired staphylococcal isolates were resistant to penicillin. This pattern of resistance, first emerging in hospitals and then spreading to the community, is now a well-established pattern that recurs with each new wave of antimicrobial resistance [6]

Staphylococcal resistance to penicillin is mediated by penicillinase (a form of β-lactamase) production: an enzyme which breaks down the β-lactam ring of the penicillin orimolecule. Penicillinase-resistant penicillins such as methicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin and flucloxacillin are able to resist degradation by staphylococcal penicillinase.

Methicillin, a form of penicillin, was introduced to counter the increasing problem of penicillin-resistant *S. aureus*. Methicillin was one of most common types of antibiotics used to

treat *S. aureus* infections; but, in 1961, British scientists identified the first strains of *S. aureus* bacteria that resisted methicillin. This was the so-called birth of MRSA.[7]

Methicillin is a narrow spectrum beta-lactam antibiotic of the penicillin class. It was developed by Beecham in 1959. It was previously used to treat infections caused by susceptible Gram-positive bacteria, particularly beta-lactamase-producing organisms such as *Staphylococcus aureus* that would otherwise be resistant to most penicillins, but is no longer clinically used. Its role in therapy has been largely replaced by flucloxacillin and dicloxacillin, however the term methicillin-resistant *Staphylococcus aureus* continues to be used to describe *Staphylococcus aureus* strains resistant to all penicillins. Methicillin is no longer manufactured because the more stable and similar penicillins such as oxacillin (used for clinical antimicrobial susceptibility testing), flucloxacillin and dicloxacillin are used medically.

1.5 METHICILLIN - RESISTANT *STAPHYLOCOCCUS AUREUS*

Methicillin-resistant *Staphylococcus aureus* is a bacterium responsible for difficult-to-treat infections in humans. It may also be referred to as multidrug-resistant *Staphylococcus aureus* or oxacillin-resistant *Staphylococcus aureus*. MRSA is by definition a strain of Staphylococcus aureus that is resistant to a large group of antibiotics called the beta-lactams, which include the penicillins and the cephalosporins.
MRSA has evolved an ability to survive treatment with beta-lactam antibiotics, including methicillin, dicloxacillin, nafcillin, and oxacillin

The mechanism of resistance to methicillin is mediated via the *mec* operon, part of the staphylococcal cassette chromosome mec (SCC*mec*). Resistance is conferred by the mecA gene, which codes for an altered penicillin-binding protein (PBP2a or PBP2') that has a lower affinity for binding β-lactams (penicillins, cephalosporins and carbapenems). This allows for resistance to all β-lactam antibiotics and obviates their clinical use during MRSA infections. As such the glycopeptide, vancomycin, is often deployed against MRSA.[8]

MRSA was first detected in Britain in 1961 and is now "quite common" in hospitals. MRSA was responsible for 37% of fatal cases of blood poisoning in the UK in 1999, up from 4% in 1991. Half of all *S. aureus* infections in the US are resistant to penicillin, methicillin, tetracycline and erythromycin.

The increasing frequency of antimicrobial resistance among infectious organisms is of great concern to both medical providers and the general public. Of particular concern is the possibility of spread of multi-drug resistant germs in the community. Since the first reported episode of methicillin resistant *Staphylococcus aureus* (MRSA) infection in the United States in 1968[9], the proportion of *S. aureus* isolates resistant to methicillin causing infections in hospitalized patients has risen significantly from 2% in 1974[10] to about 40% 1997. Over the past 20 years, infections with MRSA have been limited primarily to patients in hospitals or long-term care facilities. However, recent reports of "community-acquired" MRSA infections raise concern.

These infections reportedly occur in otherwise healthy, non-hospitalized persons without contact with healthcare personnel or other colonized patients[11] .A report of MRSA infections leading to four deaths in previously healthy children demonstrated that MRSA infections can be community-acquired in persons with no exposure to the hospital system.[12] This raises serious concerns about the possibility of transmission of MRSA outside the healthcare system. If MRSA becomes the most common form of *Staphylococcus aureus* in a community, it will make treatment of common infections much more difficult.[13]

1.6 METHICILLIN - RESISTANT *STAPHYLOCOCCUS AUREUS* AND DISEASES

Methicillin Resistant Staphylococcus aureus is found worldwide. The most important reservoir is individuals who may be colonized with MRSA without evidence of infection. The usual sites of colonization with MRSA are the nostrils, groin, axilla, and wounds.

Most health professionals who are colonized with MRSA do not develop infection and many spontaneously clear the organism without treatment. Once colonization has been present for more than three months, it becomes much more difficult to clear.

MRSA can be categorized according to where the infection was acquired: hospital-acquired MRSA (HA-MRSA) or community –associated MRSA (CA-MRSA).

HA-MRSA is acquired in the hospital setting and is one of many hospital-acquired infections exhibiting increased antimicrobial resistance. HA-MRSA has increased during the past decade due to a number of factors including an increased number of immunocompromised and elderly patients, an increase in the number of invasive procedures e.g., advanced surgical operations and life support treatments, and failures in infection control measures such as hand washing prior to patient contact and removal of non-essential catheters.

CA-MRSA is caused by newly emerging strains unlike those responsible for HA-MRSA and can cause infections in otherwise healthy persons with no links to healthcare systems. CA-MRSA infections typically occur as skin or soft tissue infections, but can develop into more invasive, life-threatening infections. CA-MRSA is occurring with increasing frequency in the United States and around the world and tends to occur in conditions where people are in close physical contact, such as athletes involved in football and wrestling, soldiers kept in close quarters, inmates, childcare workers, and residents of long-term care facilities.

CA-MRSA has only been known since the 1990s. CA-MRSA is of great concern to public health professionals because of who it can affect. Unlike the hospital sources, which usually can be traced to a specific exposure, the origin of CA-MRSA infection can be elusive. CA-MRSA skin infections are known to spread in crowded settings; in situations where there is close skin-to-skin contact; when personal items such as towels, razors, and sporting equipment is shared; when personal hygiene is compromised; and when healthcare is limited.

Outbreaks of CA-MRSA have involved bacterial strains with specific microbiologic and genetic differences from traditional HA-MRSA strains, and these differences suggest that community strains might spread more easily from person to person than HA-MRSA.

While CA-MRSA is resistant to penicillin and methicillin, they can still be treated with other common-use antibiotics.

CA-MRSA most often enters the body through a cut or scrape and appears in the form of a skin or soft tissue infection, such as a boil or abscess. The involved site is red, swollen, and painful and is often mistaken for a spider bite. Though rare, CA-MRSA can develop into more serious invasive infections, such as bloodstream infections or pneumonia, leading to a variety of other symptoms including shortness of breath, fever, chills, and death. CA-MRSA can be particularly dangerous in children because their immune systems are not fully developed.

Attention should be paid to minor skin problems—pimples, insect bites, cuts, and scrapes. Researchers continue to study information about these cases in an attempt to determine why certain groups of people become ill when exposed to these strains. Researchers also continue to try to understand why high-incidence areas may appear.

1.7 COMMUNITY-ACQUIRED METHICILLIN RESISTANT *STAPHYLOCOCCUS AUREUS* AND SKIN INFECTION

CAMRSA skin lesions are pleomorphic. The most common presentations of CA-MRSA infection are abscess, cellulitis, or both. These infectious lesions are not uncommonly misinterpreted by the patient as spider bites or insect bites. Other manifestations of cutaneous CA-MRSA infection are impetigo, folliculitis, and paronychia.

The first report in the dermatologic literature describing the cutaneous manifestations of CA-MRSA skin infection was published in the February 2004 in American.[14] During a study period of 7 months, MRSA was cultured from skin lesions. The finding was that, 10 of 19

patients (53%) had *S. aureus* cutaneous infections. The CA-MRSA skin lesions were pleomorphic, most commonly presenting as an erythematous, abscess, cellulitis or both. [14]

Bullous impetigo is most common in hot, humid weather, presenting as very superficial blisters or erosions, most commonly seen in the groin or axilla. Because the blisters are flaccid, they are short-lived; often only erosions or yellow crusts are present. These lesions closely mimic cutaneous candidiasis. Impetigo has been described in six studies[15, 16].

The incidence of impetigo varied from 3% to 30%; [17] the other studies observed the incidence of CA-MRSA-associated impetigo to be either 10% to 25%.[15]

In addition, there have been several reports with either atopic dermatitis [27] or chronic skin conditions, [19] whose skin was superinfected or impetiginized with CA-MRSA.

Ecthyma is an eroded or superficially ulcerated lesion with an adherent crust. Under this crust is often a plane of purulent material teeming with staphylococci. Removal of this crust is necessary to treat the lesion topically. Infectious CA-MRSA skin lesions have been described as ulcers[18, 21] and infected [22] or open[23] wounds. CA-MRSA has also been cultureded from ear drainage in patients with otitis externa .[24]

Folliculitis due to *S. aureus* occurs most commonly in the hairy areas of the trunk, groin, axilla, or face, especially in men who shave. Follicular pustules are the primary lesion. Often the follicular lesions of the trunk are intensely pruritic and may be mistaken for other pruritic dermatoses, such as scabies. About 50% of HIV-infected persons with scabies have coexistent *S. aureus* folliculitis. Occasionally, follicular lesions extend more deeply, forming abscesses. Rarely, all follicles across several square centimeters are infected, forming a large, violaceous, hidradenitis-like plaque. The plaque may be studded with pustules and have deep tracts connecting infected follicles. These plaques may mimic KS, but overlying pustules are quite unusual in KS. Rarely, abscess of the muscle (pyomyositis) may occur.

The incidence of CA-MRSA presenting as folliculitis is variable, and ranges from 2% to 100%.[25, 26]Some studies have observed the incidence of CA-MRSA-related folliculitis to be 7%, 10%, 15%and 20%.[27] One report described two patients whose cutaneous CA-MRSA infections lesions were characterized by a superficial folliculitis that initially appeared in the periumbilical region; in addition the folliculocentric pustules noted in some of the individuals with CA-MRSA-related folliculitis were located in areas of the body such as the chest, flanks and scrotum that are not usually affected by methicillin-sensitive *S.aureus*.[26] CA-MRSA-associated acute paronychia has been described in at least five patients. [28]

The infectious lesions occurred on the nail fold and adjacent soft tissue of a toe or finger among three individuals. [29]

Severe manifestations secondary to CA-MRSA infection have also been reported. A CA-MRSA infection initially began as a pustule on the right nares and progressed to bilateral orbital cellulitis, pansinusitis, and cavernous sinus thrombosis with subsequent permanent bilateral vision loss.[30] Necrotizing fasciitis, necrotizing myositis, or both were unexpected intraoperative findings in eight patients with CA-MRSA-associated abscess that was originally interpreted to be restricted to the skin and underlying soft tissue.[31]

1.8 MANAGEMENT OF COMMUNITY-ACQUIRED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* SKIN INFECTION

1.8.1 INCISION AND DRAINAGE

An important component of therapy especially when cutaneous CA-MRSA infection presents as an abscess, is incision and drainage.[32,33] Indeed, CA-MRSA skin infection may persist, even when the patient is being treated with systemic antimicrobial therapy to which the bacterial strain is susceptible, if the contents of the infectious, abscess are not released either by surgical intervention or spontaneous rupture. [29] One prospective study, which involved children who presented to the children's Medical Center, Dallas, TX for the management of skin and soft tissue abscesses caused by culture- proven CA-MRSA, concluded that incision and drainage without adjunctive antibiotic therapy was effective management of CA-MRSA skin and soft

tissue abscesses with diameter of less than 5cm in immunocompetent children. However, 4 of the 62 patients (6.5%) initially treated with an ineffective antibiotic were subsequently admitted to the hospital on follow-up.[34 35]

1.8.2 ANTIBIOTICS

In contrast with the findings noted in the study from Dallas, [34]other investigators have observed that some of their patients who developed severe manifestations of CA-MRSA infection originally presented with simple skin and soft tissue infections, some which were incised and drained, that were also initially managed with outpatient antibiotics.[35] In addition, CA-MRSA skin and soft tissue infections have been observed to persist, worsen and /or recur despite incision and drainage, especially when either additional systemic antimicrobial therapy is withheld or concurrent treatment is initiated with an antibiotic to which the bacterium is not susceptible**.** [46]Indeed, even the authors of the study performed in Dallas, who recommended withholding antibiotics after incision and drainage of CA-MRSA abscesses, subsequently noted that three(4.3%)of their patients had recurrent CA-MRSA skin infection. [37]

Lastly, as CA-MRSA infection is contagious and often associated with infection appearing within other family members and close contacts, antibiotic therapy, in addition to appropriate surgical intervention, may be helpful to limit the spread of infection. Therefore, after incision and drainage of suspected or confirmed CA-MRSA skin abscesses, initiation of empirical or culture-guided therapy with a systematic antimicrobial agent is an appropriate conservative therapeutic approach. [32]The duration of oral antibiotic therapy depends on the severity of the infection, the therapeutic response and the host factors; although a minimum of 10-14 days of therapy is usually necessary, treatment of 2 or 3 weeks may be needed in severe cases, in patients who are slow to respond, and in vulnerable hosts. [29, 32]

In geographic areas with high rates of outpatient MRSA infections, several investigators have suggested that orally administered non-B-lactam antibiotics, to which most strains of MRSA

are susceptible (such as trimethoprim-sulfamethoxazole, clindamycin,or a tetracycline), should initially be used for empirical treatment of uncomplicated skin and soft tissue infections.[32,40,41,42] Therefore, subsequent changes in antimicrobial therapy, if necessary, should be based on the bacterial isolate and antibiotic sensitivities observed on culture, optimally taken from the skin lesion prior to the initiating empirical antibiotics and the clinical response of the patient to empirical treatment. [43, 44]

Trimethoprim-sulfamethoxazole (one double-strength tablet (160mg/800mg) every 12h in adults, with appropriately adjusted dose for patients with renal insufficiency) has been recommended as either monotherapy, or in combination with rifampin (600mg daily in adults), to treat presumptive or confirmed cutaneous CA-MRSA infection.[42,43,44] In particular, when the rate of inducible clindamycin resistance is high in the community, trimethoprim-sulfamethoxazole may be the preferred empirical treatment for CA-MRSA. Clindamycin (300-450mg every 6hour in adults), as either monotherapy or in combination with rifampin (600mg daily in adults) also is useful to treat presumptive or confirmed cutaneous CA-MRSA infection.[44] In addition, increasing clindamycin resistance amongst CA-MRSA has been reported recently.[43]

CA-MRSA strains that are erythromycin resistant through the erythromycin ribosome methylase gene (*erm gene*) and are initially susceptible to clindamycin can potentially develop resistance to clindamycin during therapy. [40]The rate of inducible clindamycin resistance in CA-MRSA isolates varies widely, e.g from 2-8% (in Houston, TX) to 94% (in Chicago, IL). [47] Many laboratories are now performing the double disc diffusion test (D-test) to determine whether the clindamycin-susceptible CAMRSA stain harbors inducible resistance. [40]Whether inducible clindamycin resistance is clinically relevant in patients who are treated with clindamycin following incision and drainage of their CA-MRSA-associated abscess remains to be determined.

CA-MRSA isolates may also be susceptible to tetracycline.[50] Minocycline (100mg every 12h in adults) and doxycycline (100mg every 12 h in adults) are expensive, well-tolerated, long –

acting tetracycline that have excellent oral bioavailability and possess great ant-staphylococcal properties than tetracycline.[44] Similar to trimethoprim-sulfamethoxazole, the tetracyclines do not show activity against B-hemolytic streptococci. [40] In addition, they are contraindicated in children of 8years of age or younger. [42] Prospective studies are necessary to further evaluate the efficacy and potential role of minocycline and doxycline for the treatment of CA-MRSA as either monotherapy or in combination with other agents. [44]

The susceptibility of CA-MRSA to fluoroquinolones is available; however, MRSA strains readily develop resistance when the older fluoroquinolones (such as ciprofloxacin and levofloxacin) are used as monotherapy. [44, 48] In addition fluoroquinolones are not licenced for use in children.Yet, the newer fluoroquinolones (such as moxifloxacin and gatifloxacin), especially if used in combination with other antibiotics, may not be as susceptible to the development of resistance by CA-MRSA[51]

For patients who are critically ill with severe skin or soft tissue infection suspected to be caused by CA-MRSA, intravenous vancomycin is recommended,[48, 54]however, subsequent culture confirmation of MRSA is suggested as B-lactams (such as cefazolin)and semisynthetic penicillins (such as oxacillin and nafcillin) are more rapidly bacteriocidal and more efficacious than vancomycin against MSSA.[32]Several new anti-staphylococcal agents have recently been developed that provide additional therapeutic alternatives for patients with severe CA-MRSA infections such as linezolid ,daptomycin, quinupristin-dalfopristin, teicoplanin and tigecycline**;** [52] in addition, emerging agents that are currently being evaluated and may be useful for treating CA-MRSA i

nclude ceftobiprole, dalbavancin, oritavancin and telavancin.[44, 53]

1.8.3 TOPICAL TREATMENT

Topical treatment of infectious lesions and of potential sites of bacterial colonization (such as the nares) should be included in the management of cutaneous CA-MRSA infection.[32]The most effective approach for the decolonization of intranasal CA-MRSA is the application of

mupirocin 2% ointment at that location.[19, 29] In addition, for the treatment of patients who are colonized and/or infected with MRSA, bathing with an antimicrobial agent, often in conjunction with intranasal mupirocin application, has been shown to be effective; antimicrobial agents include povidone-iodine liquid soap (at either 10% or 7.5% concentration), 4%chlorhexide gluconate liquid detergent, and triclosan-containing preparations (at either 2%or 0.3% concentration) [55]

One protocol describes bathing with topical antibacterial liquid soap (either 7.5% or 10.0% povidine iodine) or detergent (4% chlorhexidine gluconate) daily, with special attention given to the affected body area, whilst receiving systemic antimicrobial therapy. The frequency of bathing was decreased to three times each week (every other day) for 2weeks and subsequently to twice each week (every third or fourth day) for additional 2weeks, before discontinuing the topical antibacterial agents. [29, 32]

Recently a small study evaluating the clearing of MRSA from superficial skin sites and wounds demonstrated that both 10% tea tree cream and 5% tea tree body wash were each more effective than chlorhexidine gluconate 4% soap or silver sulfadiazine 2% cream.[56] Moreover, bathing twice a week for 15min in water to which regular strength bleach (such as Clorox, one teaspoon per gallon of water) has been added appears to be helpful for preventing recurrent CA-MRSA skin infections.[42]

1.9 PREVENTION OF CUTANEOUS COMMUNITY-ACQUIRED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTION

Dermatologists and other healthcare providers need to be aware of the epidemiology, clinical features, management, and prevention of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection. Currently, infection caused by CA-MRSA is considered to represent a worldwide epidemic and infectious skin lesions are a frequent occurrence. Athletes, certain ethnic populations, children, homeless persons, homosexual men, household members of infected people, HIV-infected patients, intravenous drug abusers, military personnel, newborns, pregnant and postpartum women, tattoo recipients, and urban

dwellers of lower socio-economic status in crowded living conditions are individuals at increased risk of developing CA-MRSA infection. [73]

Risk factors have been identified for the acquisition and transmission of CA-MRSA. They include transmission of CA-MRSA secondary to skin -to-skin contact, which can potentially occur during several situations. For example, contact between an infected individual and another person can be an incidental event during routine social interactions or can result from the physical interaction between athletes participating in competitive sports, or following either hand-to-hand combat training , life saving procedures, or team skill-building exercises amongst military personnel.

The cutaneous entry of bacterial pathogens can be facilitated when the bacterium comes into contact with non intact epithelium. Therefore, abrasions and lacerations which result in damage to the skin's surface potentially promote the acquisition and transmission of CA-MRSA. The interaction between athletes who participate in competitive contact sports and the physical nature of military recruit training frequently result in these types of superficial injury to the skin. [29]

Finally, a vehicle for the transmission of bacteria is provided when infected individuals share personal items, such as razors, clothing, and sports equipment. The likelihood of transmitting CA-MRSA is greater if the contaminated items have not been cleaned or laundered between users. [23, 29]

Humid environments have also been postulated to result in an increased growth and transmission of CA-MRSA. For example, increased numbers of patients infected with CA-MRSA have been observed during the warmer months, particularly in military recruits.

The spread of CA-MRSA infection can potentially be prevented by initiating personal, environmental, and healthcare measures.[40]Improvement in the personal hygiene of patients and healthcare professionals is essential. Indeed, the single most effective behavior in preventing transmission of CA-MRSA is hand washing; soap and warm water or antibacterial

hand sanitizers and/or sanitation gels should be used. Individuals in group facilities and members of athletic teams should regularly shower, with soap and warm to hot water, in particular, sports participants should shower as soon as possible after the completion of practices and competitions. Soap bars should not be shared and individuals should consider using liquid soap when outbreaks occur. In addition, towels, clothing, razors and other personal items should not be shared.[75]

Screening and monitoring of CA-MRSA skin infections is important.[59] Performing bacterial cultures of potential infectious lesion can also be helpful. When abrasions and cuts are detected, they should be treated promptly. They should be covered with dry, clean dressings after they have been cleaned with soap and water. [40]

An individual with potentially infectious lesion should be isolated in an appropriate manner in order to prevent contact with non infected individuals, especially if the wound cannot be covered adequately. Similarly non infected sports participants should avoid skin-to-skin contact with other athletes who have draining skin lesions. [323 40, 57]If a cutaneous wound is draining, athletes should be kept from participating in practice and competition. They can be permitted to interact with other individuals once an accurate diagnosis has been established, appropriate treatment has been employed for an adequate duration, and the lesion has either healed sufficiently or can be covered adequately.

Environmental measure can be incorporated to decrease the transmission of CA-MRSA infection. For example, in athletes, these measures focus predominantly on establishing a routine schedule for appropriate cleaning and disinfection of the equipment that they either use or contact.[29,] Prior to and following each individual use and team practice, items such as wrestling mats, [49, 55] bench presses, [29, 36] whirl pools and wooden saunas should ideally be cleaned. Commercially bleach in 100 parts water [57] which is equivalent to one teaspoon of bleach in one quart of water. In addition after each use, uniforms, towels, and other clothing should be washed in hot water with detergent or bleach.[40]

Healthcare-initiated measures to limit the acquisition and transmission of CA-MRSA skin infections begin with education .The individuals for whom this teaching should be focused include potential patients (such as athletes and military recruits) family friends, coaches and superior officers. The content for instruction should include both the presentation of cutaneous CA-MRSA infections and the first aid measures that should be performed for skin wounds that are potentially infected.

Improved access to healthcare workers is also important in limiting and resolving cutaeous CA-MRSA infections. [41] The duration and transmission of CA-MRSA skin infection can be minimized by early recognition of potentially infectious skin lesions, followed by prompt evaluation, culture and appropriate treatment.[29,40]

1.9 METHICILLIN - RESISTANT *STAPHYLOCOCCUS AUREUS* AND OTHER SYSTEMIC INFECTIONS

MRSA can cause a wide range of infections/ diseases. Almost all systems can be infected by MRSA bacteria. MRSA has emerged as the predominant cause of skin and soft-tissue infections in many communities. Concurrent with the emergence of CA-MRSA, there have been increasing numbers of reports of community-acquired necrotising pneumonia in young patients and others without the classic health-care-associated risk factors. Community-onset necrotising pneumonia due to CA-MRSA is now recognised as an emerging clinical entity with distinctive clinical features and substantial morbidity and mortality. A viral prodrome (eg, influenza or influenza-like illness) followed by acute onset of shortness of breath, sepsis, and haemoptysis is the most frequent clinical presentation.[60]

The study done in Ireland showed the deaths from necrotizing pneumonia of four young children without underlying health care-associated (HCA) risk factors that brought CA-MRSA to worldwide prominence in the late 1990s .

Clinically, CA-MRSA usually causes skin and soft tissue infection, often with abscess and furuncle formation. However, it can cause serious life-threatening conditions, which in

addition to necrotizing pneumonia include necrotizing fasciitis, bloodstream infection, and septic shock.

The skin was the most common site of infection for both groups of patients: CA-MRSA, 80%; CA-MSSA, 93%. Other infection sites included the respiratory tract (13% for CA-MRSA-infected patients and 6% for CA-MSSA-infected patients), blood (4% for CA-MRSA-infected patients and 1% for CA-MSSA-infected patients), and urine (3% for CA-MRSA-infected patients) [61]

1.10 EPIDEMIOLOGY

Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections are well described among the general population, but little is known regarding the incidence of and predictors for recurrent CA-MRSA infections among HIV-infected persons.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is well recognized as a major cause of nosocomial infection worldwide. Due to the diffusion of MRSA strains in both hospital and community settings, prevention and control strategies are receiving increased attention. Approximately 25% to 30% of the population is colonized with *S. aureus* and 0.2% to 7% with MRSA.

The emergence of MRSA as a cause of infection in the community in patients who have never been hospitalized and who have no other known risk factors for MRSA infection is a significant concern. Infections caused by these organisms have been described in earlier studies as having distinctive strain, virulence, and epidemiologic properties.[8, 34, 62]
Community-associated MRSA strains differ from health care-associated *S. aureus* strains in that they are more frequently recovered from skin and soft tissue sources, with at least two clones, designated USA300 and USA400, that are widely and geographically disseminated having been described; these clones contain staphylococcal chromosome cassette *mec* (SCC*mec*) type IVa and produce the virulence factor Panton-Valentine leucocidin [8, 63]

In Atlanta, Georgia, a study to determine epidemiology of community-acquired MRSA among persons with community-onset *S. aureus* skin and soft-tissue infections was done. Community-onset skin and soft-tissue infection due to *S. aureus* was identified in 389 episodes, with MRSA accounting for 72% .Among all *S. aureus* isolates, 63% (244 of 389 isolates) were community-acquired MRSA. Among MRSA isolates, 87% (244 of 279 isolates) were community-acquired MRSA. When analysis was restricted only to MRSA isolates that were available for pulsed-field gel electrophoresis, 91% (159 of 175 isolates) had a pulsed-field type consistent with community-acquired MRSA; of these, 99% (157 of 159 isolates) were the MRSA USA 300 clone. Inadequate initial antibiotic therapy was statistically significantly more common among those with community-acquired MRSA (65%) than among those with methicillin-susceptible *S. aureus* skin and soft-tissue infection (1%). The community-acquired MRSA USA 300 clones was the predominant cause of community-onset *S. aureus* skin and soft-tissue infection. Empirical use of agents active against community-acquired MRSA is warranted for patients presenting with serious skin and soft-tissue infections.

In Minnesota, America a study to compare community-acquired MRSA versus HA-MRSA found that of 1100 MRSA infections, 131 (12%) were community-associated and 937 (85%) were health care–associated; 32 (3%) could not be classified due to lack of information. Skin and soft tissue infections were more common among community-associated cases (75%) than among health care–associated cases (37%). Although community-associated MRSA isolates were more likely to be susceptible to 4 antimicrobial classes, most community-associated infections were initially treated with antimicrobials to which the isolate was nonsusceptible. Community-associated isolates typically possessed different exotoxin gene profiles (eg, Panton Valentine leukocidin genes) compared with health care–associated isolates.

In surveillance study conducted simultaneously at three centres across India revealed that, overall rate of methicillin-resistance among large hospitals in India with S aureus is nearly 32%. Similar data reported in other studies over the world in tertiary care centres.

In the study done in America showed that, the most common sites of infection in the CA-MRSA and CA-MSSA infections are skin/soft tissue (80 and 93%, respectively), respiratory tract (13 and 6%, respectively), and blood (4 and 1%, respectively).

In the same study, 14% of patients had CA-MRSA infections and 3% of patients with CA-MSSA infections had household contacts with similar infections.

In the community setting, the molecular characteristics of the *S.aureus* strains were found to be heterogeneous. It was found that, CA-MRSA isolates was more associated with USA300 (49%) and USA100 (13%) clones , and that 71% of the isolates were staphylococcal chromosome cassette *mec* (SCC*mec*) type IV, 29% were SCC*mec* type II, and 54% had the Panton-Valentine leucocidin (PVL) gene, that make it distinct from CA-MSSA.

Hospital admission is more needed in patients with CA-MRSA skin/soft tissue infections compared to those with CA-MSSA infections. Recurrences were more common in the CA-MRSA patients CA-MRSA was an independent predictor of clinical failure.
In a study done in Maryland, USA found that HIV-infected persons have a high incidence of CA-MRSA skin/soft tissue infections and a high rate of recurrence. The prevalence of patients with HIV who had wound culture-proven CA-MRSA SSTIs was 6.8% .Male had high prevalence 97% compared to female 58%. [65]

In a national survey which was conducted to determine the prevalence, risk factors and molecular epidemiology of MRSA carriage among nursing home (NH) residents in Belgium showed that 19.9% of the subjects were MRSA carriers. Risk factors included hospital contact, antibiotic exposure, impaired mobility and skin lesions at the resident level, and lack of MRSA surveillance, lack of antibiotic therapeutic formulary and the combination of less-developed infection control activities and a high ratio of physicians to residents at the institution level. MRSA isolates showed eight major types, three of which were predominant:

B2-ST45-SCCmec IV (49%; where ST stands for sequence type); A21-ST8-SCCmec IV (13%); and A20-ST8-SCCmec IV (10%). [111]

Outbreaks of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) have been noted in multiple sites in the United States. In retrospective clinic-based cohort study done in Califonia, among HIV infected adults of 126 potential events, 94 were clinically significant. Their primary sources were 83% skin or soft tissue, 10% blood, 6% respiratory, and 1.0% other sites. Among these, 60% were CA and 40% were nosocomial. Of antibiotics tested, only co-trimoxazole resistance was associated with nosocomial acquisition. In multivariate analysis, independent predictors of CA-MRSA infection included HIV transmission by men who have sex with men or by injection drug use, CD4 count <50 cells/μL, log10 HIV plasma viral load, and absence of co-trimoxazole prophylaxis. **[67]** Over the study period, the prevalence of MRSA among community-associated *S. aureus* infections was 26.7%. **[64]** Another study done in Spain, showed that the prevalence of MRSA to be 29.2%. **[72]** In the prospective study conducted in Russia August 2006 to April 2007, the prevalence of MRSA was found to be 48%.

Using Local Surveillance study of 2001 – 2002 done in South Africa, MRSA prevalence in general population was found to be 33.3%. A more recent survey of patients with *S. aureus* bacteraemia at two academic hospitals in Johannesburg identified a MRSA rate of 23%.

In the study done at Mugalo National Referral Hospital, Uganda showed that *S. aureus* is highly (28.7%) prevalent in surgical site infections. MRSA is highly (31.5%) prevalent among populations of *S. aureus* isolated from surgical site infections in Mulago National Referral Hospital, Kampala Uganda.

In the study done at Muhimbili National Hospital in the year 1997/1998, showed that, among the *S. aureus* strains isolated, 97.3%, 68.1%, 37.3%, and 6.5% were sensitive to cefuroxime,

erythromycin, tetracycline and penicillin G respectively. While 0.4% *S. aureus* isolate was resistant to methicillin using both the E test and presence of mec A gene. [74]

CHAPTER 2

2.0 PROBLEM STATEMENT

MRSA is found worldwide, predominantly in hospital. Recently, however new strains have emerged in the community that is capable of causing severe infections in otherwise healthy individuals without established risk factors.

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections are well described among the general population, but little is known regarding the prevalence of and predictors for recurrent CA-MRSA infections among HIV-infected persons.

Studies have shown that CA-MRSA causes *S. aureus* skin and soft-tissue infection in selected populations. HIV infection is a known risk factor for the development of MRSA infections; 7this report suggests that HIV infection may also increase the risk of recurrent disease. HIV infection has been associated with an increased incidence of nasal colonization with *S. aureus* in most [68] but not all studies [69]HIV-infected patients are also at risk for invasive infections with *S. aureus*. Results from a prospective study of SSTIs in HIV-infected out-patients done in USA, found a high rate of MRSA causing SSTI in community-dwelling patients. The majority of isolates were positive for PVL and SCCmec IV, which is typical of community-associated MRSA isolates causing SSTIs in the general population. The initial site of infection resolved in most cases but subsequent MRSA infection was relatively common. Among HIV-infected persons, risk factors for MRSA infection include injection drug use, low CD4 cell count, high HIV viral load, sex partners with skin infections, absence of trimethoprim/sulfamethoxazole prophylaxis, and recent receipt of a beta-lactam antibiotic.

The objective of this cross sectional study was to describe the prevalence of
CA-MRSA infections among HIV infected individuals attending CTC in Dar es Salaam city, Tanzania.

The current study described the prevalence of CA-MRSA skin and soft tissue infections among HIV infected individuals attending CTC in Dar es Salaam city, Tanzania.

3. 0 RATIONALE OF THE STUDY

Until recently, most methicillin-resistant *Staphylococcus aureus* (MRSA) infections were limited to the hospital setting. Several studies have documented the increasing prevalence of MRSA as a cause of community-onset infections and it is reported as a pandemic outbreak.

The diseases caused by MRSA ranges from mild skin infections to severe form of skin infections. Apart from skin infections, MRSA can cause disease to almost all systems which are difficult to cure without anti-MRSA.

The worldwide emergence of community-acquired methicillin-resistant *Staphylococcus aureus* has also led to discussion of this pathogen in recent revisions of the international community acquired pneumonia (CAP) guidelines. This pathogen is important because of its resistance to antibiotics commonly recommended for the empirical treatment of CAP and the association with rapidly fatal form of pneumonia characterized by tissue necrosis, pulmonary hemorrhage, and rapid progression to respiratory failure.[71]

HIV-infected persons commonly have cutaneous abnormalities; the prevalence approaches 100%. [61, 70] and often have several simultaneous or sequential cutaneous conditions with a progressively more intransigent clinical course, a key to suspecting underlying HIV infection.

Studies have shown that, approximately 50% of HIV-infected persons are nasal carriers of *S. aureus,* explaining in part the high rate of infection. Therefore, people with weakened immune systems, which include some patients with HIV infection, may be at risk for more severe illness if they get infected with MRSA. MRSA strains are showing resistance to more antimicrobial classes, and β-lactams antibiotics can no longer be considered first-line therapy for community-acquired SSTIs. For more serious infections, there are several new antimicrobial options with good MRSA coverage, including linezolid, daptomycin, and tigecycline. Several agents are currently under clinical investigation or are being considered

for approval by the US Food and Drug Administration, including ceftobiprole, dalbavancin, iclaprim, oritavancin, and telavancin.[77]

People with HIV should follow the same prevention measures as those without HIV to prevent staph infections, including practice good hygiene, cover wounds (e.g., cuts or abrasions) with clean dry bandages, avoid sharing personal items such as towels and razors, and contact their doctor if they think they have an infection.

Despite all that knowledge, the prevalence of CA-MRSA infection is largely unknown among HIV positive patients and in the general Tanzanian population.

It is therefore justifiable to have this study, which will describe the prevalence of CAMRSA infections in HIV infected individuals in Dar es Salaam City that would help in designing the appropriate control and treatment measures of MRSA infections, so as to reduce morbidity and transmission of MRSA infections.

4. 0 OBJECTIVES

4.1 Broad objective

To determine the prevalence of MRSA skin, soft tissue infections among HIV infected adults attending HIV care and treatment clinics in Dar es Salaam, Tanzania.

4.2 Specific objectives

1. To determine the prevalence of skin and soft tissue infection among HIV infected individuals attending HIV care and treatment clinics

2. To determine prevalence of *S. aureus* skin and/or soft tissue infection among HIV infected individuals attending HIV care and treatment clinics in Dar es Salaam
3. To determine the antimicrobial susceptibility pattern of *S. aureus* isolated from, skin and/or soft tissue infection among HIV infected individuals attending HIV care and treatment clinics in Dar es Salaam

4. To determine the prevalence of MRSA skin and/or soft tissue infection among HIV individuals attending HIV care and treatment clinics.

5. To describe the relationship between CD4 cell count with MRSA skin and/or soft tissue infection among HIV individuals attending HIV care and treatment clinics in Dar es Salaam.

6. To describe the relationship between co-trimoxazole use with MRSA skin and soft tissue infection among HIV individuals attending HIV care and treatment clinics.

5. 0 METHODOLOGY

5.1 STUDY AREA:

Dar es Salaam city, in Tanzania.

5.2 STUDY DESIGN:

It is a cross-sectional study.

5.3 STUDY SETTING:

The study was conducted in HIV CTCs from four different hospitals in Dar es Salaam. Dar es Salaam city has got three district; Kinondoni, Temeke and Ilala. Each district has got one hospital; Mwananyamala, Temeke, and Amana respectively. In addition, it has got Muhimbili

National Hospital; the largest tertiary referral hospital in the country. It receives referral cases from all district hospitals, together with private hospitals around the city. Moreover, Muhimbili National Hospital is a teaching hospital for Muhimbili University of Health and Allied sciences (MUHAS), the largest medical school in the country. Dar es Salaam is the commercial city of Tanzania with an estimated population of about 3.5 million people (2002 census).

5.4 TARGET POPULATION:

HIV infected individuals attending HIV care and treatment clinics.

5.5 STUDY POPULATION:

HIV infected individuals attending HIV care and treatment clinics in Dar es Salaam. A representative sample was taken from HIV CTCs from all three district hospitals and from MNH in Dar es Salaam. Each involved hospital had equal chance of contributing the subject to meet the required sample size; done as explained later. The number of HIV patients registered at each respective CTC was: 6,417 at MNH, 12,379 at Temeke, 16,200 at Amana and 15,350 at Mwananyala. The total number of HIV patients (50,346) register at the four CTCs was obtained. The ratio of the number of HIV patients at the specific CTC and the total number of HIV patients registered at the four CTCs was obtained. The sampling fraction was in turn multiplied by the total sample size required which was already calculated. Therefore, the number of HIV patients recruited from each CTC to meet the required sample size of 271 subjects was 34 from MNH, 67 from Temeke, 87 from Amana and 83 from Mwananyamala.

5.6 PERIOD OF THE STUDY:

September 2010 – May 2011

5.7 INCLUSION CRITERIA

- All known HIV infected individuals attending HIV care and treatment clinics in Dar es salaam
- Above or equivalent to eighteen years
- Consent to participate into the study

5.8 EXCLUSION CRITERIA

- Patients who were mentally disabled.
- Justification for exclusion:
    - They were excluded because mentally disabled cannot give some information like socio-demographic and risk factors that were searched from each subject that was included.

5.9 STUDY SAMPLE:

Sample size of 271 subjects was obtained based on the following formula:

$$n = \frac{z^2\, p\,(100-p)}{\varepsilon^2}$$

n = Minimum sample size

z = point on SND curve corresponding to significance level of 5% (=1.96)

p= estimated prevalence of CA-MRSA SSTI among HIV infected individuals. (Put at 6.8%) [65]

ε = margin of error on p (set at 3%)

5.10 SAMPLING TECHNIQUE:

- Recruitment was done first from two CTCs, Amana and Temeke for the first month then done to the rest two CTCs; Mwanyamala and MNH in the following month. The CTC was attended thrice a week; Monday, Tuesday afternoon, and Wednesday morning due to convenience. The subjects who attended clinics morning hours are generally similar to those who attend afternoon hours as there was no specific time was

set for a certain group of patients for instance newly diagnosed versus follow up HIV cases.

- All eligible subjects, who consented, were recruited consecutively until the calculated sample size was achieved.

5.11 DATA COLLECTION METHODS:

5.11.1 CLINICAL INTERVENTION

All consenting subjects were interviewed for socio – demographic information, use of ARVs, factors related to the study; history of hospital admission, use of co–trimoxazole prophylaxis, family history of skin and/or soft tissue infection, and other related medical conditions such as; Diabetes mellitus, chronic renal failure, history of being on dialysis, organ transplantation, and malignancy. The HIV care and treatment card of each patient was also used to gather information that included: the type of ARV used, and use of antibiotics including cotrimoxazole. Thorough clinical dermatological evaluation was performed to each patient in bright/good light and under fully exposed skin and its appendages. Skin and/or soft tissue infection was identified. In patients with skin and/or soft tissue lesions, the distribution, pattern, morphological features of the lesions, and duration since onset were recorded into the questionnaire. The lesions were described according to the nomenclature committee of the International League of Dermatological Societies (ILDS). Diagnoses of skin and/or soft tissue infection was mainly based on clinical features.The investigator consulted a Dermatologist when in doubt of making a diagnosis of a lesion.

5.11.2 SAMPLE COLLECTION AND PROCESSING

Skin and Soft tissue sample collection

A sterile swab was used to collect pus from skin and or soft tissues of patients with infection. Pus/fluid aspiration was performed in patients with pus/fluid collecting lesions such as abscess. The aspirate were placed into an empty sterile tube, and the swabs were placed in Stuart transport medium The swab and the aspirate specimens were sent to the Central

Pathology laboratory at MNH for processing within 2 hours of collection. Venopuncture and 4mls of blood was collected for CD4 count determination.

5.12 LABORATORY METHODS:

5.12.1 LABORATORY PROCEDURES

All specimens (pus swabs/aspirates) were inoculated on chocolate agar, sheep blood agar and MacConkey agar plates. The plates were incubated aerobically at 37°c for 18 - 24 hours. After incubation time, plates were examined for evidence of bacterial growth. Evidence of bacterial growth was based on colony morphologies and gram stain reaction.
Identification of *S. aureus* was done based on colony morphology on 5% sheep blood agar. Cream to golden yellow colonies with or without haemolysis, Gram stain appearance and catalase test; followed by staphylase and DNAse test.

Other bacterial isolates (in case of mixed infection or bacterial growth other than S. aureus) were identified by their colonial morphology, gram staining appearance and biochemical tests.

Antimicrobial sensitivity pattern was performed using Kirby-Bauer disc diffusion Method according to Clinical and Laboratory Standards Institute Guidelines (CLSI). Sensitivity pattern for the isolated *Staphylococcus aureus* was tested using the following discs: tetracycline (30µg), penicillin G (10µg), oxacillin (1µg), erythromycin (15µg), gentamycin (10µg), ampicillin (10µg), cephalothin (30µg), vancomycin (30µg), imepenem (10µ), chloramphenicol (30µg), cefotaxime (30µg) and cefoxitin (30µg). Plates were incubated at temperature of 35^0 C. Interpretation of the diameters of inhibition zone was as follows: tetracycline >19mm, penicillin G > 29mm, oxacillin >13mm, erythromycin> 23mm, gentamycin>15mm, ampicillin >29mm, cephalothin >18mm, vancomycin >15mm, imepenem> 16mm, chloramphenicol >18mm, cefotaxine >23mm, and cefoxitin >18mm. The S. aureus was considered resistant to the respective specific antibiotic if the inhibition zone in millimeter was less than the mentioned diameter.

Detection of MRSA was done using cefoxitin, oxacillin discs (Oxoid uk) and oxacillin screen agar (5% NaCl, 6ug/ml oxacillin). Bacterial colonies was suspended in saline to a turbidity of 0.5 McFarland standards and inoculated on a Muller Hinton agar plate (Oxoid uk). Plates were incubated at 35^{0} C for cefoxitin disc and at 33^{0} C for oxacillin disc and oxacillin agar. All isolates resistant to cefoxitin and oxacillin were considered as MRSA. [85]

5.12.2 T- LYMPHOCYTE CD4 CELL COUNT

CD4 cell count was performed using BD FACS Count Machine. Whole blood was collected in the morning time before noon, (4ml) in EDTA collection tubes) by standard venopuncture procedures. The collected samples were kept at room temperature 18-25^{0} C and were processed within 30 hours. The BD FACS count reagent was drawn and put in a test tube. Blood which was in a purple colored stopper tube was taken and put in a test tube and mixed properly to avoid clotting. Using a pipette, 50µl of blood was drawn from a test tube and mixed with BD FACS count reagent in a test tube and closed with a cap then the mixture was put in a dark place, at room temperature for 60 to 120 minutes. After about 1 to 2 hours 50µl of fixative solution was drawn and mixed with an incubated blood then vortexed for 5 seconds. Fixative solution is used to stop reaction and protect the cells from damage. The mixed solution was put in the FACS count machine for analysis.

5.13 DATA QUALITY CONTROL:

- The principal investigator performed the interview and physical examination
- The principal investigator collected blood samples, pus/fluid discharge swab/aspirate from those who had skin and/soft tissue infection.
- Laboratory technicians performed microbiology and immunological analysis of the pus/fluid discharge contents and serum respectively.

5.14 DATA PROCESSING AND ANALYSIS:

- Entry of data and analysis was done using SPSS version 13.0
    - Descriptive statistics was performed
    - t - test was used to determine association of quantitative variables
    - χ^2 was used to determine association between categorical variables
    - $P < 0.05$ (i.e significance level of 5% was adopted)

6.0 ETHICAL ISSUES:

- Ethical clearance was sought from ethical clearance board of the Muhimbili University of Health and Allied Science
- Permission to conduct study was sought from all four hospitals
- Information about the study and consent form was given to interviewee prior to the interview
- Those who agree to participate in the study signed written informed consent

7.0 PATIENTS DISPOSAL:

- Subjects with skin or soft tissue infections were treated with antibiotics empirically.
- Patients were scheduled to revisit the HIV care and treatment clinics for their laboratory results
- Their medications were changed according to the susceptibility pattern.
- Subjects who were not on ARV treatment who were found to have low T-lymphocyte CD4 cell count or fulfilled the criteria for commencement of ARVs were, started on ARV treatment according to the Tanzanian National guideline for care and treatment of HIV-infected patients.

CHAPTER 3

8.0 RESULTS

A total of 271 HIV- infected patients were recruited into the study. Of these, 107 (39.5%) were males and 164 (60.5%) were females. Socio–demographic characteristics of the study population are shown in table 1**.**The age ranged from between 18-78 years among the study population.

Of all recruited patients, 4 (1.5%) patients had household history of skin and/or soft tissue infection, 6 (2.2%) were known patients with Diabetes mellitus, 5 (1.8%) were known to have Chronic renal failure. Subjects that were known to have malignacies were 7(2.6%) that included Chronic Myeloid Leukemia, Multiple myeloma, carcinoma of the stomach and Kaposi's sarcoma. More patients were on ARVs (67.5%), and on co-trimoxazole prophylaxis (53.1%) and 31.0% of all subjects had prior history of antimicrobial use other than co-trimoxazole. (Table 2)

Table1: Socio–demographic characteristics of the HIV infected patients attending HIV care and treatment clinics in Dar es Salaam.

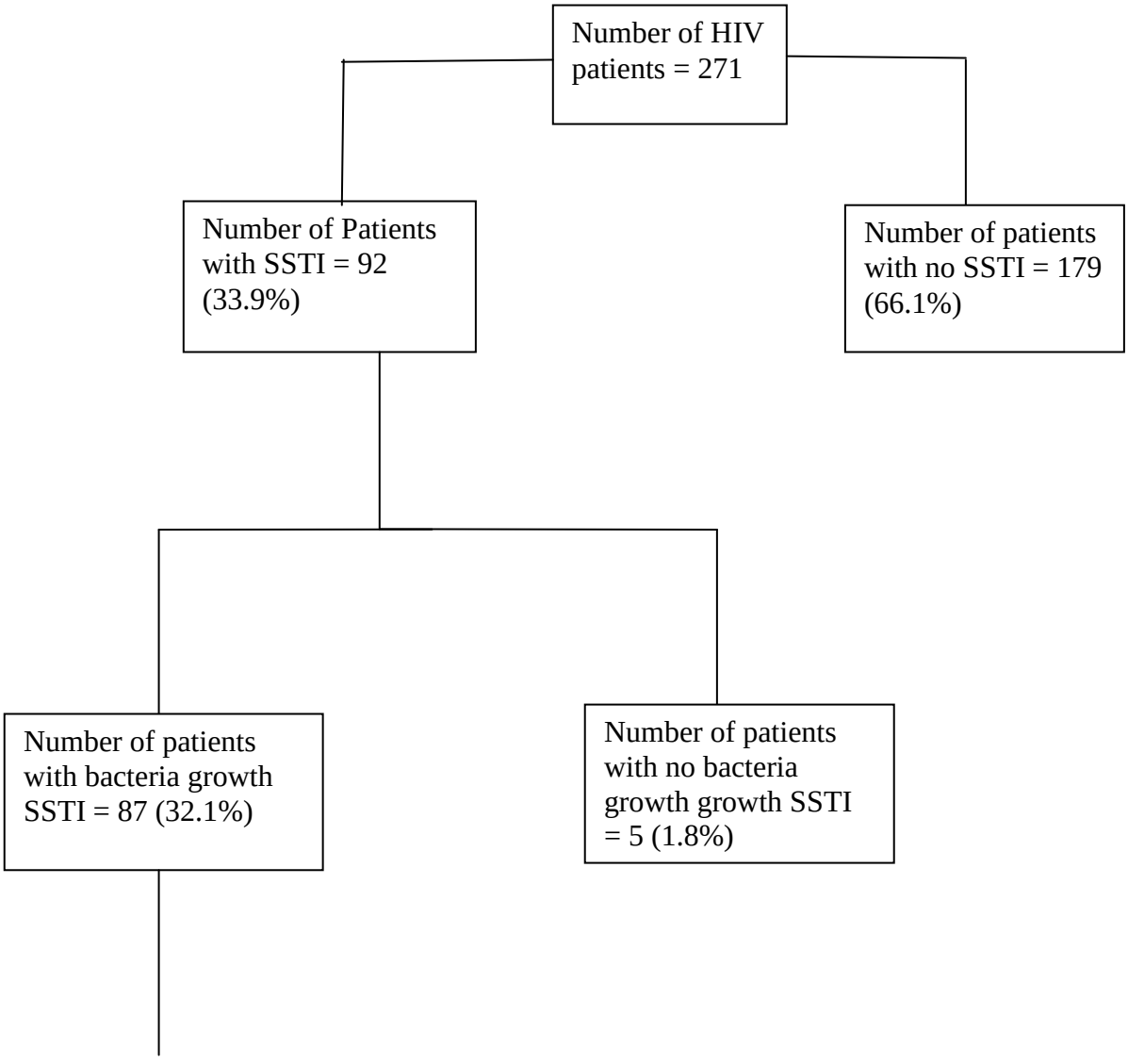
Socio-demographic characteristics	Male (%)	Female (%)	P - value
	Total=107 (39.5)	Total= 164 (60.5)	
Age (yrs)			
18–29	18 (16.8)	23 (14.0)	
30–39	30(28.0)	55 (33.5)	
40-49	38 (35.5)	62(37.8)	
≥ 50	21 (19.6)	24 (14.6)	0.568
Marital status			
Single	22 (20.6)	37 (22.6)	
Cohabiting	4 (3.7)	6 (3.7)	
Married	61 (57.0)	66 (40.2)	
Divorced	10(9.3)	20(12.2)	
Widowed	10(9.3)	35 (21.3)	
Education level			
Primary	63 (58.9)	102 (62.2)	
Secondary	27 (25.2)	43 (26.2)	
High education	9 (8.4)	5 (3.0)	
No formal education	8 (7.5)	14 (8.5)	0.280

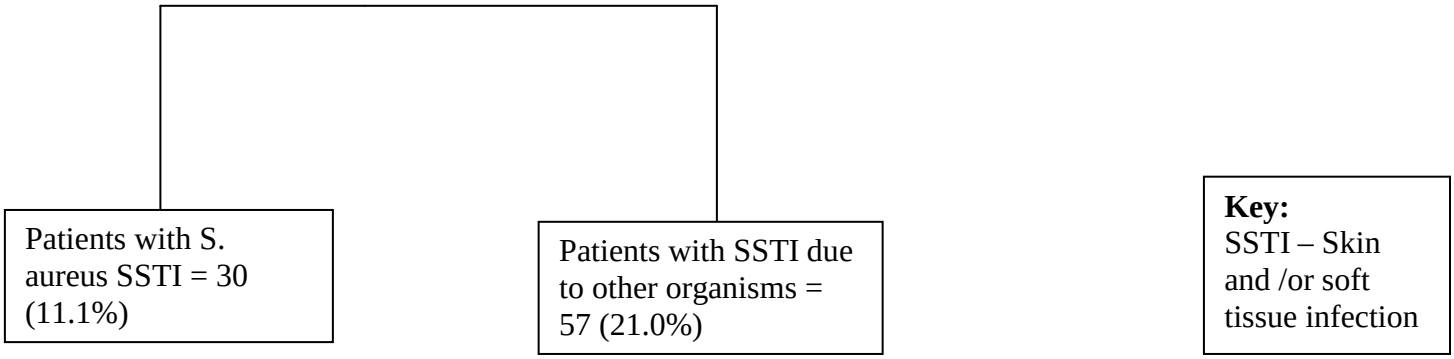
Occupation			
Employed	51(47.7)	73 (44.5)	
Not employed	56 (52.3)	91(55.5)	0.611

Table 2: Medication at baseline

Variables	**Number of patients**	**(%)**
Patients who were using ARVs	183	67.5
Patients who were using co-trimoxazole	144	53.1
Patients with history of using antimicrobial other than co-trimoxazole	84	31.0

Figure 1: Dermatological finding and culture results





8.1 Characteristics of Patients with HIV and skin and/or soft tissue infection attending HIV CTCs in Dar es Salaam.

Of 271 HIV patients, 92 (33.9%) subjects had skin and/or soft tissue infection. Culture results among the subjects that had SSTI showed that, 87(32.1%) subjects had bacterial growth while 5 (1.8%) subjects had SSTI with no bacteria growth upon culture results. (Fig. 1)

Skin and/or soft tissue infection was more common among married (57.6%) couples, while it was less found among those who were single (17.4%), cohabiting (4.3%), divorced (12.0%) and widowed (8.7%). The finding was statistically significant with p-value 0.038

Skin and/or soft tissue infection was more found among those who were employed that accounted for 48.4%, than those who were not employed (21.8%). P-value <0.001

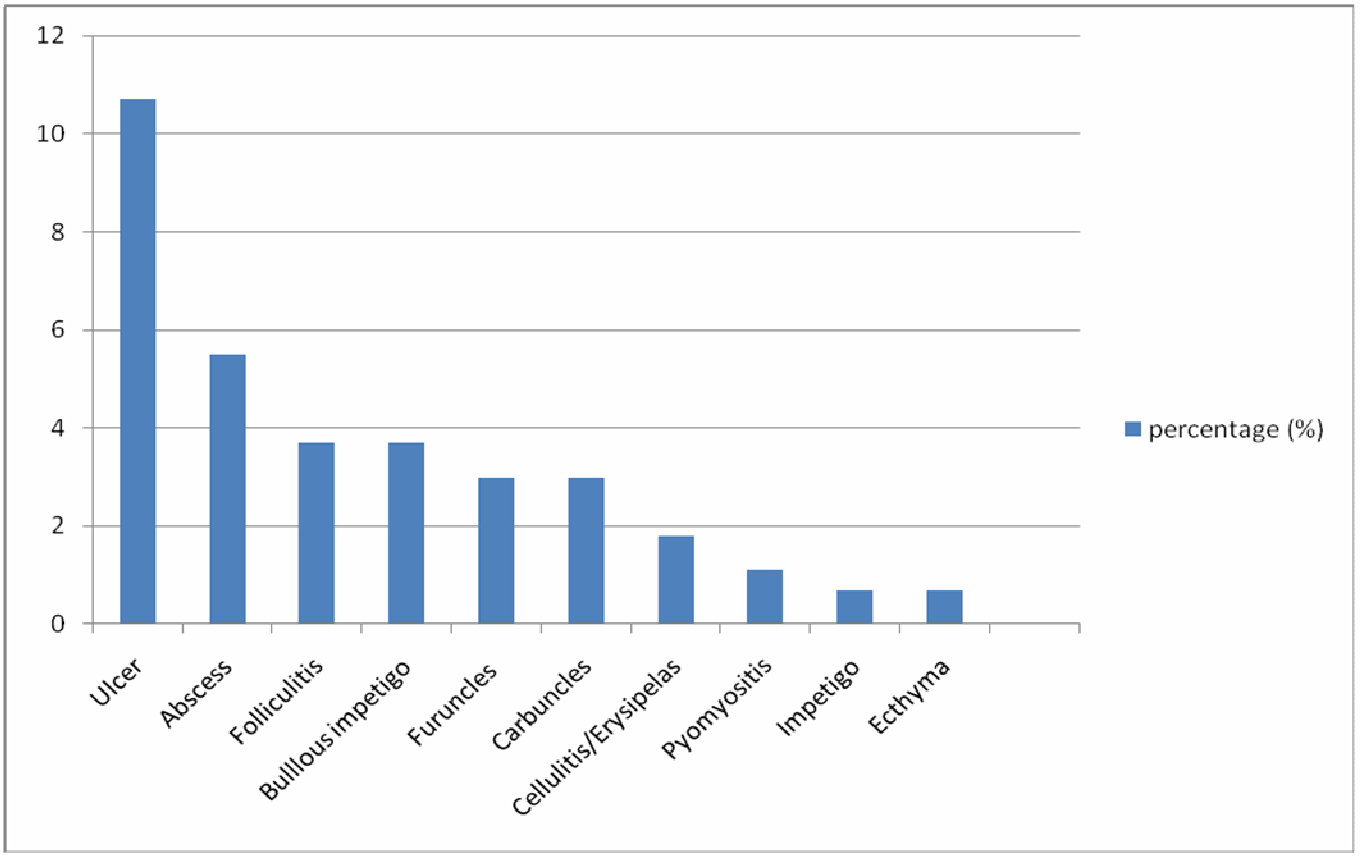
The most type of skin and/soft tissue infection that were found during physical examination were ulcers (10.7%), abscess (5.5%), folliculitis (3.7%) and bullous impetigo (3.7%). (Figure. 2)

Table: 3 Distribution of SSTI by socio-demographic characteristics

Variable	Total HIV patients (N= 271)	Patients with skin and/or soft tissue infection (33.9%)	P-value
Age			
18 – 29	41	16 (17.4.4)	
30– 39	85	30 (32.6)	
40 – 49	100	28 (30.4)	
>50	45	18 (19.6)	0.415
Sex			
Male	107	43 (46.7)	
Female	164	49 (53.3)	0.080
Marital status			
Single	59	16 (17.4)	
Cohabiting	10	4 (4.3)	
Married	127	53 (57.6)	
Divorced	30	11 (12.0)	
Widowed	45	8 (8.7)	0.038

Education level			
Primary	165	61 (66.3)	
Secondary	70	20 (21.7)	
High education	14	5 (5.4)	
No formal education	22	6 (6.5)	0.566
Occupation			
Employed	124	60 (65.2)	
Not employed	147	32 (34.8)	0.091

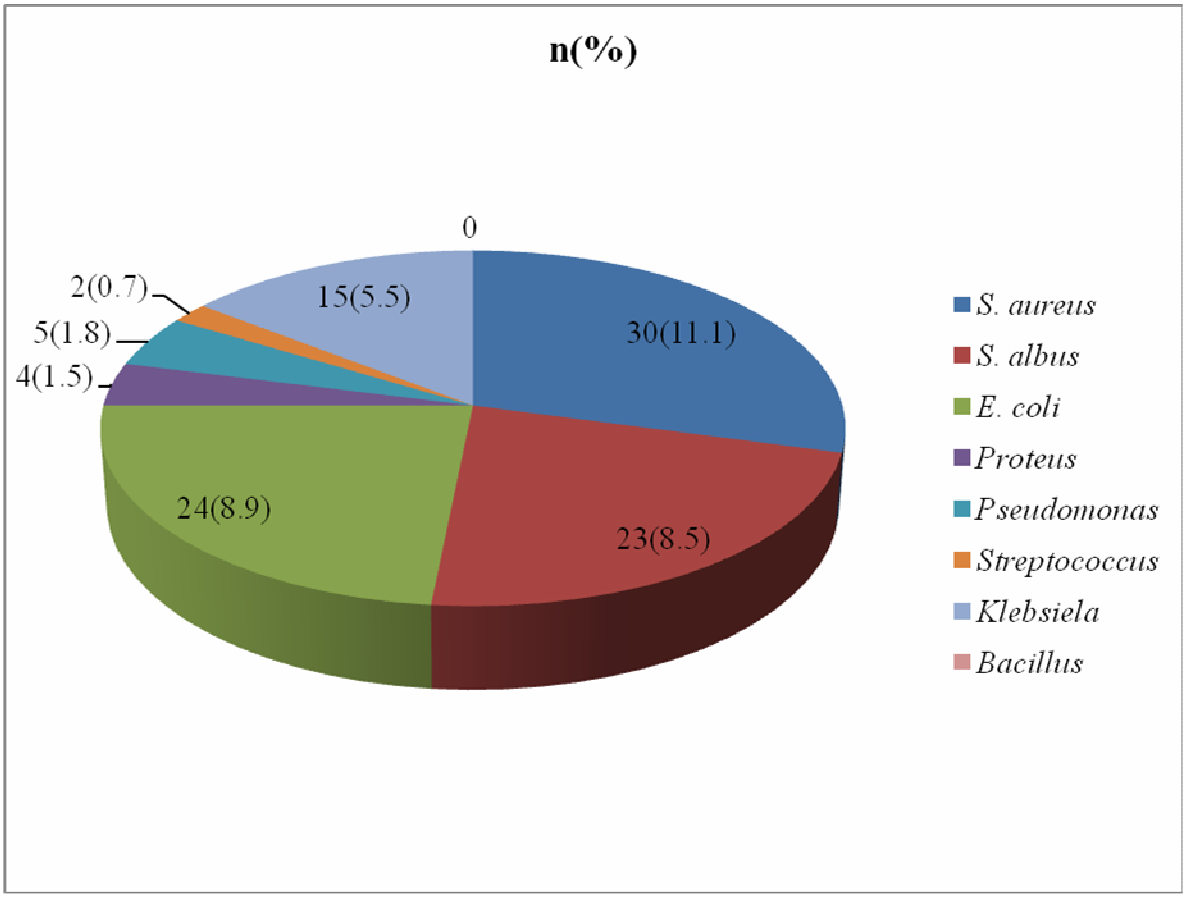
Figure 2: Type of lesions that were found on patients with HIV and skin and/or soft tissue infection attending HIV CTCs in Dar es Salaam.



8.2 Prevalence of *S. aureus* SSTI among HIV patients attending HIV CTCs in Dar es Salaam.

Among the 271 HIV patients, 30(11.1%) had *S. aureus* SSTI while 57(21.0%) had SSTI due to other organism as shown in figure 3. Fourteen (5.2%) patients had mixed bacteria SSTI. There was no significant difference in *S. aureus* SSTI distribution in terms of age, sex, marital status education or occupation.

Figure 3: Proportion of HIV patients with SSTI and the type of bacteria isolated



8.3 Antibiotic susceptibility pattern of the *S. aureus* isolated from SSTI of HIV patients

About 90.0% of all isolated *S. aureus* was sensitive to vancomycin while only 10.0% was found to be resistant. The antibiotics that were found to be more resistant to *S.aureus* were Ampicillin (96.7%), Erythromycin (86.7%), Penicillin G (90.0%), Tetracyline (73.3%), and Co-trimoxazole (63.3%). (Figure 4).

Among all 271 HIV patients, 4 (1.5%) had methicillin – resistant *S. aureus* skin and/or soft tissue infection. Of all *S. aureus,* 5(16.7%) were resistan to Methicillin. Among those which were resistant of Methicillin a significant number; 4(80.0%) met the definition of MRSA. S.aureus that were resistant to vancomycin were 3(10.0%) and 2(66.7%) were also resistant to other antimicrobial that met the criteria for MRSA. While 7(23.3%) of S.aureus were resistant cefoxitin and 4(57.1%) of them were also MRSA. The finding was statistically significant with p – value of <0.001, 0.004 and <0.001 respectively. (Table 4)

The type of lesion most frequently affected by MRSA SSTI was folliculitis (100%), ulcers (66.7%) and abscesses. None of the furuncles, carbuncles, impetigo, bullous impetigo and pyomyositis type of lesions was either found to have MRSA. These findings were statistically significant P = 0.027. (Table 5)

The location of the skin and/ soft tissue infection lesion was found to have any relationship with MRSA.

There was no significant difference in MRSA SSTI distribution according to age, sex, education, marital status or occupation. However higher (18.8%) proportion was found among females than males (7.1%) P=0.351

Patients, who had history antibiotic use, had higher 3(75.0%) proportion of MRSA SSTI than 1(33.3%) that had not prior used antibiotics. And the finding was statistically significant. P=<0.001

The time of antibiotic used was either not significantly related to MRSA SSTI.

Fifty percent (50.0%) of patients with MRSA SSTI had prior history of hospital admission, P=0.020

There was no significant relationship between MRSA and chronic renal failure or malignancies. (Table 8)

Figure 4: *Staphylococcus aureus* and antibiotic susceptibility pattern

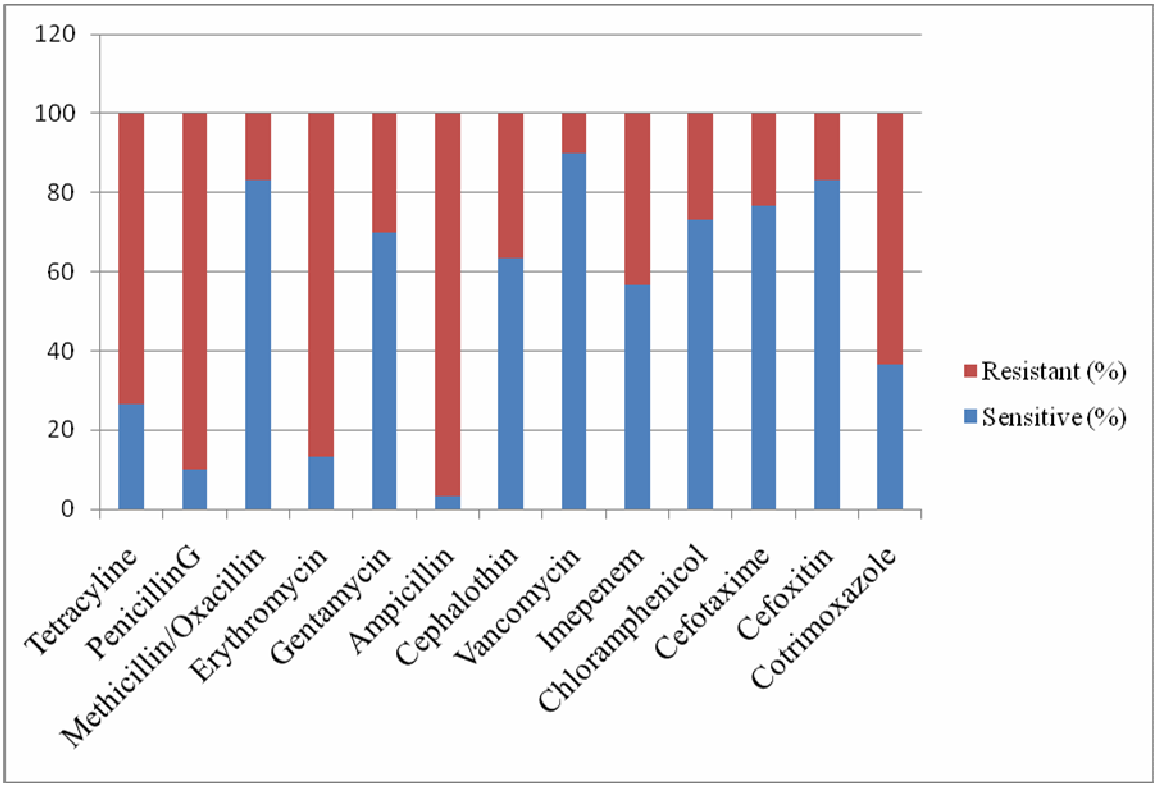


Table 4: Single drug resistant *S. aureus* versus MRSA

Antibiotic	**Number of Resistant *S.aureus* to individual drug 30 (%)**	**Number of MRSA 4(%)**	**P - value**
Tetracyline	22 (73.3)	4 (18.2)	0.195
Penicillin G	27 (90.0)	4 (4.8)	0.474
Methicillin/Oxacillin	5 (16.7)	4 (80.0)	<0.001
Erythromycin	26 (86.7)	4 (15.4)	0.399
Gentamycin	9 (30.0)	1 (11.1)	0.815
Ampicillin	29 (96.7)	4 (13.8)	0.690
Cephalothin	11 (36.7)	2 (18.2)	0.552
Vancomycin	3 (10.0)	2 (66.7)	0.004
Imepenem	13 43.3)	2 (15.4)	0.773
Chloramphenicol	8 (26.7)	3 (37.5)	0.019
Cefotaxime	7 (20.0)	1 (14.3)	0.933
Cefoxitin	7 (23.3)	4 (57.1)	<0.001
Cotrimoxazole	19 (63.3)	2 (10.5)	0.552

Table 5: MRSA and type of Skin and/or soft tissue infection in HIV patients

Type of SSTI lesion	Number of patient found to have S.aureus SSTI (n=30)	Number patients found to have MRSA SSTI: (n=4)
Folliculitis	1	1
Furuncles	5	0
Carbuncles	5	0
Impetigo	2	0
Bullous imptetigo	6	0
Ulcer	3	2
Abscess	5	1
Pyomyositis	1	0
Cellulitis/Erysipelas	2	0

Low CD4 cell count was found to be related to MRSA SSTI in HIV patients, in which 3 (60.0%) patients with MRSA SSTI had CD4 count less than 200cells/µL, while only 1 (5.0%) patients with MRSA SSTI had CD4 count of 200-500cells/µL, and no single patient who had >500cells/µL was found to have MRSA SSTI. P = 0.003 (Table 6)

Co-trimoxazole use was also related to MRSA SSTI among HIV patients. Of all 30 patients who were found to have *S. aureus* SSTI, 8 were using co-trimoxazole prophylaxis and 22 patients were not using prophylaxis. All (4) subjects who were found to have MRSA SSTI, were also using co-trimoxazole; and none of the case of MRSA was found among the 22 patients who were not on co-trimoxazole. And the finding was significant with P-value 0.003. (Table 7)

Table 6: Distribution of MRSA SSTI in relation to CD4 cell classification.

CD4-cell classification	Patients with *S. aureus* SSTI N=30	MRSA SSTI N=4	P - value
<200	5	3 (60.0%)	
200 – 500	20	1 (5.0%)	
>500	5	0 (0.0%)	0.003

Table 7: Distribution of MRSA SSTI in relation to co-trimoxazole use

Co-trimoxazole prophylaxis use	Patients with *S. aureus* SSTI N=30	MRSA SSTI N=4	P - value
Yes	8	4(50.0)	
No	22	0(0.0)	<0.001

Table: 8 MRSA skin and/or soft tissue infection and some associated factors in HIV patients attending CTCs in Dar es Salaam

Variables	HIV patients with S.aureus SSTI 30	MRSA SSTI % (N=4)	P - value
Other antibiotic use			
Yes	7	3 (75.0)	
No	23	1 (25.0)	0.009
Time of antibiotic use			
≤6 months	4	2 (66.7)	
>6months	3	1 (33.3)	0.659
History of hospital admission			
Yes	4	2 (50.0)	
No	26	2 (50.0)	0.020
Time of hospital admission			
Within 2 months	4	2 (50.0)	
Over 2 months	0	0 (0.0)	NA
Other medical condition			
CRF	2	0 (0.0)	
Malignancy	1	0 (0.0)	
Patients with no other associated medical condition	27	4 (14.8)	0.774

CHAPTER 4

9.0 DISCUSION

9.1 Prevalence of skin and/or soft tissue infection among HIV infected patients in Dar es Salaam.

The cross sectional study was conducted aiming to establish prevalence of MRSA skin and/or soft tissue infection among HIV patients. A total of 271 HIV infected patients were recruited into the study. Of these, 39.5% were males and 60.5% were females. The reason for having more females was due to the fact that there were more females registered in HIV care and treatment clinics in Dar es Salaam. Of 271 HIV patients recruited, prevalence of skin and/or soft tissue infection was found to be high that accounted for 33.9%.

A wide range of opportunistic dermatological disorders in HIV infected patients have being reported to decline with the use of potent antiretroviral therapy.[78] Yet some dermatological condition like, Acne vulgaris, staphylococcal infections and Erythema nodosum have being reported to have an association with immune reconstitution. [78, 79] ·Therefore skin and/or soft tissue infection among HIV patients may occur at any CD4 count. In this study, distribution of skin and/ soft tissue infection showed no significant difference in terms of CD4 cell group.

Skin and/or soft tissue infection was more common among married (57.6%) couples. While it was less found among those who were single (17.4%), divorced (12.0%) and widowed (8.7%). The finding could be explained by the nature of transmission of the skin and/or soft tissue infection; the direct contact and sharing of items like towels, bed sheet. Married individuals could be more prone to close contact than single and widowed, and probably they are more likely having tendency of sharing items which are implicated to transmit the disease.

It was found that, most of the type of skin and/soft tissue infection affecting HIV patients in Dar es Salaam were ulcers (10.7%), abscess (5.5%), folliculitis (3.7%) and bullous impetigo (3.7%). The same finding has being described in other similar studies whereby bullous

impetigo, ecthyma and folliculitis are the most common found bacterial infection among HIV. Bullous impetigo was reported to be common in hot humid weather, presenting as very superficial blisters or erosions, most commonly seen in the groin or axilla. [80] and therefore regarding the humid environment of Dar es Salaam, it was justifiable to find impetigo on the studied patients.

9.2 Prevalence of *S. aureus* skin and/or soft tissue infection among HIV infected patients in Dar es Salaam.

The major causative organism of skin and soft tissue infection is *S. aureus*. The study found high proportion of *S. aureus* SSTI 30/92 (33%) among HIV patients who had a clinical diagnosis of SSTI. The majority of patients who had bacteriological confirmed skin and/or soft tissue infection, had infection due to *S. aureus* than other infective bacteria. And the overall prevalence of *S. aureus* skin and/or soft tissue infection among HIV patients in Dar es Salaam was found to be 11.1%. About 52% of the patients had mixed infection. The study that was done in Mwanza region in non HIV patients found that 160/600 (26.6%) of patients with surgical wound had *S. aureus* wound infection. [87]

The study found that there was no significant difference in *S. aureus* SSTI distribution in terms of age, sex, marital status education or occupation.

9.3 Antimicrobial susceptibility pattern of *S. aureus* isolated from, skin and/or soft tissue infection of HIV infected patients in Dar es Salaam.

The study found that, about 90.0% of all isolated *S. aureus* was sensitive to vancomycin while only 10.0% was found to be resistant. And about 66.7% of the resistant *S. aureus* to vancomycin were also resistant to multiple drugs (MRSA). In the study done in general population among patients with surgical wound infection, found that all (160/600) isolated *S. aureus* were sensitive to vancomycin and therefore vancomycin could be considered for treatment of *S. aureus* infection. [86] The finding may highlight the emerging of resistant *S.aureus* strain to multiple drugs affecting HIV patients than general population. Another

study that was done in HIV infected patients reported to have found *S.aureus* strain that were 100% sensitive to Vancomycin [83.] It may mean that there is emerging of *S. aureus* that is resistant to the drugs that were previously known to be sensitive to.

The antibiotics that were found to be more resistant to *S.aureus* in this study were Ampicillin (96.7%), Erythromycin (86.7%), Penicillin G (90.0%), Tetracyline (73.3%), and Co-trimoxazole (63.3%). High (92%) rates of resistance to co-trimoxazole among MRSA has also been reported in another study that was done among patients with surgical wound infection in Mwanza region Tanzania, irrespective of their HIV status. [86] Use of co-trimoxazole, clindamycin and tetracycline has been recommended as empirical treatment for MRSA infection in areas with high rates of MRSA. This study and others reported high proportion of S. aureus that was resistant co-trimoxazole and the finding may affect the choice of antibiotics for the treatment of MRSA skin and/or soft tissue infection. However some studies reported isolation of MRSA that were mostly sensitive to co-trimoxazole.[87]

S. aureus that were resistant to Methicillin (80.0%), vancomycin (66.7%) and chloramphenicol, (37.5%) were also MRSA. This may challenge doctors in the treatment of infection caused by MRSA.

9.4 Prevalence of MRSA skin and/or soft tissue infection among HIV patients in Dar es Salaam.

This study explored the existence of MRSA skin and/or soft tissue infection among HIV patients in Dar es Salaam. The overall methicillin-resistant *S. aureus* skin and/or soft tissue infection was found to be 1.5%. The existence of MRSA colonization even in few patients may be a significant source for wide spreading of the resistant strain. Similar study that was conducted on men who had sex with men population reported almost similar prevalence of MRSA which was found to be 1.6%. [91]

The prevalence of MRSA in this study was higher (1.5%) than the reported prevalence of MRSA surgical wound infection that was found in general population at Muhimbili National Hospital that accounted for 0.4%.[74] HIV infection has been reported to be a risk factors for MRSA probably due to impaired immune function, frequent visit to health facilities or regular use of antibiotics as a result of recurrent bacterial infection. The high prevalence of MRSA among HIV infected patients in this study may suggest that MRSA is more prevalent in HIV patients than in non HIV patients.

The proportion of MRSA among the isolated *S. aureus* in this study was found to be low (13.3%) likewise in some other studies, one being the one that was done in Nigeria where by 12.5% of the isolated *S. aureus* was MRSA while the study done in Mwanza region in Tanzania found that 26/160(16.3%) of the *S. aureus* were MRSA.

Prevalence of MRSA varies among countries and health institutions.[88, 89] The study has found that of the 92 HIV patients with clinical diagnosis of SSTI, 4/92 (43.5%) had MRSA which is lower than (93.2%) the proportion of MRSA that was obtained in similar study done in Texas, USA. Another similar study [65] that was done at Maryland, USA on community acquired methicillin resistant *S. aureus* among HIV patients reported the prevalence of MRSA to be 6.8%. [87] While another study [64] done at California on CA- MRSA SSTI among HIV reported high proportion (26.7%) of MRSA among HIV patients with skin and/or soft tissue infection in which skin infection accounted 83% of all type of infection. MRSA is reported world widely and the prevalence varies such that a wide coverage research may be needed to explore the condition at various populations and set up so as to fight and prevent the spread of the resistant S.aureus.

Individuals who had prior history of hospital admission, were significantly more (50.0%) found to have MRSA SSTI than (7.7%) that had no prior history of hospital admission. The same finding was revealed in the study done at KCMC on nasal carriage MRSA among HIV patients in which 82.2% of MRSA carrier had prior hospital admission while 60% of MRSA

carrier had no history of admission. [91] The finding may reflect the, the resistant *S. aureus* strain could be acquired during hospital admission. HIV patients are more prone to some of disease conditions than non HIV patients that necessitate their frequent hospital visits and admissions. The gene analysis of the isolated MRSA would enable distinction between the hospital acquired and community acquired MRSA.

In this study type of lesion affected by MRSA SSTI were folliculitis, ulcers, and abscesses.The finding is supported by other studies done previously.[25, 26]

The study revealed the low CD4 cell count to be significantly related to MRSA SSTI in HIV patients. The patients with low CD4 count are at higher chance of suffering opportunistic infection that may necessitate health facility visit, regular use of antibiotic; the things that may increase the chance of acquiring MRSA skin and/or soft tissue infection. Similar observation was found in the other similar study done previously, **[84]** A study done on nasal carriage MRSA also reported high proportion of MRSA carriage among the patients who had low CD4 count.**[85]** While studies reported that the low CD4 count is related to increased proportion of MRSA, othe**r** study reported that MRSA was not found to be related with low CD4 count.**[83]**

Prior history of co-trimoxazole use was found to be significantly related to MRSA SSTI among HIV patients. Similar significant relationship has being reported in the study done on nasal carriage MRSA among HIV patients in which 89.66% of the patients who were using co-trimoxazole were found to be MRSA nasal carriers.[91] Although some other study showed that current use of co-trimoxazole was protective of MRSA nasal carriage.[85] Co-trimoxazole is known to be sensitive to *S.aureus* and has been used to treat skin and/or soft tissue infection. And also is used as a prophylaxis for opportunistic infection among some HIV infected patients. Its use has been shown to have a significant relationship with MRSA infections. Probably its effects of being sensitive to *S. aureus,* clears out the organisms at the carrier sites like groin, nasal cavity, which may give chance to the resistant *S .aureus* strain prevailing around the world as it has been reported by some studies to colonize those areas hence become

source of infection. And many studies have shown that nasal carriage MRSA is significantly associated with infection due to MRSA.

10.0 CONCLUSION

MRSA in skin and/or soft tissue infection among HIV-infected patients is common and occurs mostly in HIV patients with low CD4 count, prior hospital admission, prior use of co-trimoxazole and other antibiotics. *S. aureus* was found to be resistant to commonly used antibiotics for the treatment of infection due to *S.aureus* that are used to treat infection due to *S. aureus,* affecting the drugs that are thought to be effective for the treatment of methicillin-resistant Staph; vancomycin. MRSA had a significant relationship with:

1. Low CD4 count (< 200cells/µL).
2. Prior use of co-trimoxazole and other antibiotics.
3. Prior hospital admission.

However large studies would be of greater benefit to have more details on the subject.

11.0 STUDY LIMITATIONS

One of the finding of the study is that, there were more MRSA SSTI among patients who had prior hospital admission than those with no prior history of hospital admission, but it was difficult to ascertain whether the resistant strain was acquired during hospital admission or at the community. Genetic description of the MRSA could reveal the strain that, however due to financial constrains, this study could not identify the presence of mecA gene and describe the genotype of the MRSA staphylococcal chromosomal cassette *mec* (SCC*mec* that could give a distinction between community acquired versus hospital acquired MRSA.

Also due to the same reason, the study could not be extended to identify the areas that were more colonized by the MRSA that could help in planning of the preventive measures.

12.0 RECOMMENDATION

1. Doctors should be aware of the existence of MRSA SSTI in HIV patients attending CTCs in Dar es Salaam

2. Patients should be aware of the MRSA SSTI and practice preventive measures

3. Screen at risk groups for MRSA colonization from the sites that have been reported for possible decolonization so as to prevent the spread of such a difficult to treat S.aureus resistant strain.

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14.0 APPENDICES

14.1 Appendix I : Questionnaire **QIN____**

Prevalence Of Community Acquired Methicilin Resistant *Staphylococcus aureus* Skin And Soft Tissue Infection Among HIV Infected Individuals Attending Care And Treatment Clinics In Dar Es Salaam City, Tanzania

PART I –Patient information

1. Name of CTC _____
2. Registration no: _____
3. Date of interview: ____/____/_____ (dd /mm/yyyy)
4. Name of interviewer: _____
5. Age _____
6. Sex:
    a. Male
    b. Female
7. Marital status:
    a. Single
    b. Cohabiting
    c. Married
    d. Divorced
    e. Widowed
    f. Separated
8. Highest level of education achieved:
    a. Primary school
    b. Secondary school
    c. High education (college or university)
    d. No formal education

9. Occupation

   a.
   b. Employed
   c. Not employed

.

12. Is there anyone in the household who has skin/soft tissue infection?

   d. Yes ☐
   e. No ☐
   f. Do not know ☐

13. Apart from HIV infection, do you have history of other medical (underlying) condition?

   a. DM
   b. CRF
   c. On dialysis
   d. Organ transplant
   e. Malignacy
   f. Others _____

14. Use of ARV drug:

   a. Yes ☐
   b. No ☐

15. Type of ARV drug used:

   a. First line drugs
   b. Second line drugs

16. Use of Co-trimoxazole prophylaxis:
    a. Yes ☐
    b. No ☐
17. Any other antibiotic used
    a. Yes ☐
    b. No ☐
18. If yes when was it?
    a. within 6 months
    b. over 6 months
19. History of hospital admission
    a. Yes
    b. No
20. If yes, when was it?
    a. Within two months
    b. Over two months

PART III – Dermatological examination on review

21. Infected skin lesion found
    a. Yes
    b. No

22. Duration of the dermatological lession
    a. days
    b. week
    c. Two weeks
    d. Three weeks
    e. Month(s)…..
    f. Year(s)….
    g. don’t know

26. Location of the skin lesion (s)

a. Scalp

b. Face

h. Mouth

i. Neck

j. Trunk

k. Genitalia

l. Extremities

m. Generalized

n. Others _____

27. Type of lesion/Diagnosis

a. Folliculitis

b. furuncles

c. carbuncles

d. Impetigo

e. Bullous impetigo

f. Ecthyma

g. Ulcer

h. Cellulitis/ Erysipelas

I Abscess

i. Pyomyositis

j. Others

PART III – Investigation results form

23. Swab/aspirate culture results

	Bacteria growth	No bacteria growth
Skin/soft tissue lesion		

24. Organism(s) isolated from Skin/soft tissue infected lesion_____

25. Sensitivity pattern of *Staphylococcus aureus* isolated from skin/soft tissue infected lesion

Drug	Resistant	Sensitive
Tetracycline		
Penicillin G		
Methicillin/Oxacillin		
Erythromycin		
Gentamycin		
Ampicillin		
Cephalothin		
Vancomycin		
Imepenem		
Chloramphenicol		
Cefotaxim		
Cefoxitin		
Co-trimoxazole		

26. The most recent CD4 count _____

14.2 Appendix II

Consent Form For Participation In The Study On "Prevalence Of Community Acquired Methicilin Resistant *Staphylococcal aureus* Skin And Soft Tissue Infections Among HIV Infected Individuals Attending HIV Care And Treatment Clinics At Dar Es Salaam City Tanzania.

ID-No.

English version

Greetings!

My name is Dr. Honoratha Francis Maucky, MD. I am a Resident Doctor in the department of Internal Medicine at MUHAS. I conducting a research with the objective of determining the prevalence of community-acquired methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections among HIV infected individuals attending HIV care and treatment clinics in Dar es salaam City, Tanzania.

Purpose of the study

The study is conducted in partial fulfillment of the requirements for the degree of Master of Medicine in Internal Medicine. I hope to learn the magnitude of community acquired methicillin resistant *Staphylococcus aureus* skin infections among HIV infected individuals attending HIV care and treatment clinics. You were recruited conveniently as a possible participant in this study because you reside in this area. About 271 HIV infected subjects will take part in this study.

What Participation Involves

If you decide to participate, we will ask you some questions about any

previous medical history, including history of recent hospital admissions and antibiotic use, use of septrine prophylaxis, family history of skin infection , and do physical examination to see if you have infected skin lesions. Also swab/aspirate for culture and sensitivity will be taken from nasal cavity and from the infected skin/soft tissue. Blood will be drawn (about

4mls) for CD4 count level. Empirical treatment will be given till the results for culture and sensitivity was ready.

Confidentiality

I assure you that any information that is obtained in connection with you in this study and that can be identified with you will remain confidential, however, the final report will be sent to the Muhimbili University of Health and Allied Sciences without disclosing your identity. To achieve this, your name will not be written on any questionnaire or in any report/documents that might let someone identify you. Your name will not be linked with the research information in any way. All information's collected on forms will be entered into computers with only the study identification number. Confidentiality will be observed and unauthorized persons will have no access to the data collected.

Risks

Despite pain that you might experience during drawing of blood and inconveniences in your time (about 40 minutes) there are no other risks to being in this study.

Right to Withdraw and Alternatives

Taking part in this study is completely voluntary. You can stop participating in this study at any time, even if you have already given your consent. Refusal to participate or withdrawal from the study will not involve penalty.

Benefits

We hope that the results of this study will help us understand the magnitude of community-acquired methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections among HIV infected individuals attending HIV care and treatment clinics. This can therefore help in providing useful guidelines in the treatment and control skin infections among HIV.

Who to Contact

If you ever have questions about this study, you should contact the Principal Investigator, Dr Honoratha Francis Maucky of Muhimbili University of Health and Allied Sciences, P. O. Box 65001, Dar es Salaam. If you ever have questions about your rights as a participant, you may contact Prof. Abud, Chairperson of the Senate Research and Publications Committee, P. O. Box 65001, Telephone : 255 22 2152489 Dar es Salaam and/or Dr. Y. Mgonda who is the supervisor of this study (mobile phone no. 0754 277 554)

.

Signature:

Do you agree?

Participant agrees …….. Participant does NOT agree …….

I ……. have read the contents in this form. My questions have been answered. I agree to participate in this study.

Signature of participant ……

Signature of PI or designee…….

Date of signed consent …….

Appendix II: Informed Consent Form (Kiswahili version)

CHUO KIKUU CHA SAYANSI ZA AFYA MUHIMBILI

KURUGENZI YA TAFITI NA UCHAPISHAJI

14.3 FOMU YA RIDHAA

Namba ya utambulisho:

Ridhaa ya kushiriki kwenye utafiti

Hujambo! Ninaitwa Dr. Honoratha Francisl Maucky, MD nashughulika kwenye utafiti huu wenye lengo la kutathimini ukubwa wa maambukizi ya ugonjwa wa ngozi usababishwao na bacteria wajulikanao kama *Staphylococcus aureus*, Utafiti huu utahusisha watu walioathirika kwa virusi vya ukimwi wahudhuriao kliniki za waathirika katika mkoa wa Dar es Salaam.

Madhumuni ya Utafiti

Utafiti huu unafanyika ili kutimiza sehemu ya matakwa ya shahada ya uzamili ya tiba ya Chuo Kikuu cha Afya na Sayansi ya Tiba Muhimbili. Utafiti unalenga kuchunguza ukubwa wa tatizo la ugonjwa wa ngozi usababishwao na bacteria waitwao *Staphylococcus aureus* walio sugu kutibiwa kwa dawa iitwayo methicillin, kwa waathirika wa virusi vya ukimwi wanaoshiriki kliniki za UKIMWI mjini Dar es Salaam. Tafadhali kuwa mkweli na muwazi kwa vile matokeo ya utafiti huu yanaweza yakatoa maamuzi na mapendekezo ya baadaye.

Nini kinahitajika ili kushiriki

Kama umeamua kushiriki, tutakuuliza maswali kuhusu afya, ikihusisha matibabu yoyote yaliyohusisha dawa kama antibiotic, mazingira yanayoweza kuchangia maambukizi ya ugonjwa huu wa ngozi, kama kuna mtu mwenye ugonjwa wa ngozi katika nyumba, habari ya kulazwa hospitali, matumizi ya dawa kama septrine. Pia nitakutoa damu mara moja kiasi cha mililita 4 sawa na kijiko kimoja cha chakula na tutaitumia kupima kiwango cha CD4, wingi wa damu. Pia utachukuliwa usaha au majimaji kutoka sehemu iliyoathirika na ugonjwa wa ngozi pale inapostahili kwa ajili ya kutambua ni bacteria gani wanahusika na kujua ni dawa zipi zitakazoweza kuwaua ili kukwepa matumizi ya dawa zile zisizoweza kuwaua

Usiri

Taarifa zozote zile zitakazopatikana katika utafiti huu ambazo zinaweza zikakutambulisha zitabaki kuwa siri, lakini taarifa ya mwisho ya utafiti huu itapelekwa chuo kikuu cha Muhimbili pasipo kutambulisha jina lako.

Hatari

Ukiachia maumivu madogo unayoweza ukayapata unapotolewa damu na kupoteza muda wako (kama nusu saa) hakuna hatari zozote za kushiriki katika utafiti huu.

Haki ya kujitoa au vinginevyo

Ushiriki katika utafiti huu ni wa hiari. Unaweza kuacha kushiriki katika utafiti huu muda wowote hata kama ulikwishatoa idhini yako. Kukataa kushiriki au kujitoa kutoka kwenye utafiti hakutahusisha adhabu yoyote.

Faida

Matokeo ya utafiti huu yataweza kutusaidia kuwa na ufahamu wa ukumbwa wa maambukizi ya ugonjwa wa ngozi usababishwao na bacteria aitwae *Staphylococcus aureus* mwenye sifa ya kutotibika kwa dawa iitwayo methicillin ambaye ameoneshwa kuongeza kwa watu wenye tatizo la VVU na hivyo itasaidia katika kutengeneza sera za kinga na tiba ya ugonjwa huo.

Endapo utapata madhara

Hutegemewi kupata madhara yoyote kutokana na ushiriki wako katika utafiti huu.

Nani wa kuwasiliana naye

Kama una maswali kuhusiana na utafiti huu, wasiliana na Mtafiti mkuu wa utafiti huu, Dr Honoratha F. Maucky wa Chuo Kikuu cha Afya na Sayansi ya Tiba Muhimbili, S. L. P. 65001, Dar es Salaam. Kama una swali kuhusu stahili zako kama mshiriki unaweza kuwasiliana na Prof. Abud, Mwenyekiti wa kamati ya Utafiti na

Uchapishaji, S.L.P 65001, Simu: 255 22 2152489 Dar es Salaam, au Dr. Y. Mgonda, kwa namba ya simu 0754 277 554.

Je umekubali?

Mshiriki amekubali ……..... Mshiriki hajakubali

…….....

Mimi ..... nimesoma maelezo ya fomu hii.

Maswali yangu yamejibiwa. Nakubali kushiriki katika utafiti huu.

Sahihi ya mshiriki……

Sahihi ya mtafiti mkuu au mwakilishi……

Tarehe ya kutia sahihi ya idhini ya kushiriki……..