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Methicillin-Resistant *Staphylococcus Aureus*: A Mini Review

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ABSTRACT

Methicillin-resistant Staphylococcus aureus (MRSA) which emerged in hospitals in 1961 is now a leading cause of associated healthcare infections. The MRSA which is a Staphylococcus infection remarkably developed resistance to methicillin which was used to treat it. This review covers the epidemiology, pathophysiology, clinical manifestations, diagnostic measures, and effective management of MRSA. Currently, MRSA infection is encountered in small community hospitals, which leads to community-acquired MRSA (CA-MRSA) when the patients are discharged and introduce the strain into the community. MRSA can lead to diverse infection such as skin and soft tissue infections, bone and joint infections, and acute bacterial endocarditis. MRSA incidence is increasing in the population, and therapeutic measures are few and accompanied by diverse side effects notably the ability to develop resistance by S. aureus. Therefore, a well-formulated strategy which will prevent the spread of the pathogen is always a priority for healthcare providers. It is noteworthy to state that Vancomycin is still the first line drug although a Vancomycin-resistant strain has been reported.

Keywords: Staphylococcal infections, Vancomycin resistance, Methicillin, Endocarditis, Bacterial, Health personnel

INTRODUCTION

Staphylococcus aureus is a gram-positive bacterium grouped with *Bacillus* spp. by ribosomal RNA sequences and grows in aerobic and anaerobic conditions, as grape-like clusters. In humans, its habitats include the nasal membranes and skin of warm-blooded animals, where it can cause a diverse range of infections from mild, such as skin infections and food poisoning, to life-threatening, such as pneumonia, sepsis, osteomyelitis, and infectious endocarditis [1]. The organism is toxigenic, and one of the effects of the toxin is reducing the efficacy of antibiotics. Methicillin resistance is seen in *Staphylococcus aureus*, and so many other antibiotics and including highly potent beta-lactam drugs. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been implicated as the main cause of nosocomial infection worldwide since the 1970s [1].

The strain MRSA is implicated as one of the organisms in the development of resistance to antibiotics [2]. The *Staphylococcus aureus* resistance to antimicrobials is a well-known fact today in medicine; the species has shown the ability to evolve and show resistance which has brought about challenges in its antibiotics treatment.

Evolution of MRSA into the Community

Staphylococcus aureus is a dynamic and versatile microscopic organism that has a momentous capacity to gain anti-infection protection rapidly. In the pre-anti-infection period, *Staphylococcus aureus* had for quite some time been related to high mortality. Penicillin, first presented in the mid-1940s, immediately brought down the death rates related to *Staphylococcus aureus* contaminations. That was short lived as strains resistant to penicillin were discovered in the in hospitals by mid-40s. *Staphylococcus aureus* resistance was commonplace for both community, and hospital strains demonstrated resistance to penicillin. The introduction of methicillin, a penicillinase-resistant semisynthetic penicillin, quickly solved the problem of penicillin-resistant *Staphylococcus aureus*. Again in 1961, less than a year later, MRSA was reported [3] showing the nature of this organisms to developing antibiotic resistance.

Methicillin-resistant *Staphylococcus aureus* (MRSA) diseases have as of late turned into the major concentration concern of healthcare professionals. MRSA has risen as a noteworthy medical issue that is never again restricted to just doctors and nurses. Reports of MRSA contaminations happening in group settings (for example daycares, institutions, sports groups) also resulting in deaths in children and grown-ups have made it a cause of concern in all fields and increased its global awareness, as they additionally put a vast monetary strain on our health care system. Therefore, necessitating the need for physicians and healthcare workers to know more about the transmission, prevalence, risk factors, clinical signs and symptoms, and treatment of MRSA.

The treatment of staph infection started in the 1940s, 60 years after the discovery of the organism. The overuse and misuse of the drugs, however, led to the adaptation (or resistance) to the penicillin drugs in the 1950s [4].

As time progressed, the use of methicillin and other related drugs became the drugs of choice to combat the penicillin resistant staphylococcal infections [5]. A new strain resistant to methicillin was discovered by British scientist in 1961 and in 1968 the US experienced its first case, as time progressed these strains of MRSA developed resistances to other penicillin-related antibiotics [6].

Pathophysiology of MRSA And Epidemiology Among Various Countries

Polymorphonuclear neutrophils are the main host defense against *Staphylococcus aureus*. When the organisms evade the innate barrier, and penetrate the skin, the phagocytes (neutrophils and macrophages) move to the site of infection to defense the host. The microorganism, however, evades hosts responses by various mechanisms which include blocking the migration of the phagocytes, inhibiting the action of host antibodies, using polysaccharide capsules or biofilms which are anti-phagocytic.

The factors that enable *Staphylococcus aureus* in its pathogenicity includes Panton-Valentine leukocidin (PVL), alpha-hemolysin (also called alpha-toxin), phenol-soluble modulins (PSMs), the arginine catabolic mobile element (ACME), and a regulatory locus referred to as *agr* [7].

Differential gene expression for proteins such as PVL, alpha-toxin, and PSMs appears to also contribute to the enhanced virulence of community acquired-MRSA (CA-MRSA). These elements are under the control of *agr*, a regulatory locus that controls the expression of *Staphylococcus aureus* toxins [7]. PVL is involved in the breakdown of human leucocytes.

The methicillin resistance gene (*mecA*) which is responsible for the resistance, encodes a methicillin-resistant penicillin-binding protein that is not present in susceptible strains and is believed to have been acquired from a distantly related species [8]. Methicillin resistance in *Staphylococci* is associated with the acquisition of a large transmissible element known as staphylococcal cassette chromosome mec (*SCCmec*), an event that occurred in *Staphylococcus aureus* before the isolation of the first methicillin-resistant *Staphylococcus aureus* (MRSA) strain in 1961 [9].

The *mecA* gene is carried in the mobile cassette of the staphylococcal cassette chromosome *mec* (*SCCmec*), of which four forms have been described that differ in size and genetic composition [10]. A variety of MRSA isolates are multi-resistant and are susceptible only to glycopeptide antibiotics like vancomycin and investigational drugs [11]. MRSA isolates that have decreased susceptibility to glycopeptide intermediately susceptible *Staphylococcus aureus* (GISA) which are known to be a cause of great public health concern [12].

Epidemiological confirmation has dependably proposed that MRSA emerged as a result of the presentation of methicillin into clinical practice [13]. One of the major challenges faced by MRSA in hospitals and globally is decreased susceptibility to other antibiotics including the beta-lactam drugs and spread of MRSA which are difficult to treat [14].

The MRSA was originally isolated in hospitals but has now rapidly spread to the entire community as well. Colonization rates have been identified to be increased in adolescents, children, hospitalized elderly patients, and young women [6]. Some ethnic groups such as Pacific Islanders, Alaskans, and Native Americans have been identified to have an increased risk of contracting MRSA [15]. Overcrowding, living in close quarters and sharing personal items coupled with poor hygiene could also facilitate the spread of the infection, and this is possibly the reason MRSA has a greater risk of being seen in military personnel, overpopulated areas and in intravenous drug abusers [16].

Types of MRSA

Over time, three major forms have been discovered across the globe. They include i) the healthcare-acquired MRSA

(HA-MRSA), ii) the community-associated MRSA (CA-MRSA) and iii) the livestock-associated MRSA (LA-MRSA) [17]. HA-MRSA occurs significantly in immunocompromised individuals, or patients with a risk factor for the disease, unlike CA-MRSA which occurs in otherwise healthy individuals [6].

As the name implies, the HA-MRSA is typically identified in hospitals or other healthcare institutions in patients who are hospitalized or have recently paid a visit to some form of healthcare. The prevalence of HA-MRSA is much greater in the Americas and East Asia compared to Europe. Data from different studies have shown prevalence rates of greater than 70% in South Korea, Sri Lanka, and Vietnam, and less than 50% in Portugal, Greece, and Italy [14]. The clonal complexes (CCs) CC5 and CC8 are most commonly seen globally [14]. CC45 is seen in the United States and Europe while CC22 is seen in Australia, Canada, and Indonesia [14].

CA-MRSA is seen in the community in general and not nosocomial. It has been more commonly identified in younger persons, and most strains carry the gene that codes for Panton-Valentine Leukocidin (PVL) toxin that causes damage to white blood cells and subsequently tissues necrosis [16]. This form of MRSA is susceptible to drugs like tetracyclines, clindamycin, and fluoroquinolones [16].

LA-MRSA is the most recent form of MRSA to be discovered and is characteristic in farm animals such as cattle and pigs [14]. LA-MRSA may be seen in animal rearers, people who slaughter animals and who work in close contact with farm animals [14]. The CC398 has been commonly identified mostly in Europe in countries such as Austria, Denmark, and Belgium [14].

Clinical Manifestation and Laboratory Diagnostic Measures of MRSA

The most widely recognized clinical manifestation of MRSA includes surgical wound contamination, primary and secondary bacteremia, intra-abdominal/pelvic abscesses, osteomyelitis, prosthetic joint diseases and, occasionally, nosocomial pneumonia [17]. Infections caused by MRSA was thought to be different from methicillin-sensitive *Staphylococcus aureus* (MSSA) because it did not respond to antibiotics, but it is now shown that the difference is just their response to antibiotic therapies.

Common MRSA clinical infections involve the skin and soft tissues, and mostly not beyond the upper layer of the dermis, for example, cellulitis, impetigo, however in some cases may involve deeper structures like soft tissue abscess [17].

Endocarditis due to strains of MRSA was shown by studies to be nosocomial or seen in patients who had renal insufficiency, and those on hemodialysis and these patients also have MRSA endocarditis were seen to be older presumably showing the prevalence of nosocomial infection [7].

For different diagnosis, the method has been devised for earlier detection of MRSA in samples in the last ten years. The use of multiplex PCR primers to detect genes that identify strains of *Staphylococcus aureus* and *mecA* have been the major method used [18].

The main medium used for the screening and growth of MRSA is mannitol salt agar (MSA). Enrichment broths have also been utilized, and this increases the sensitivity, as it permits small numbers of MRSA to grow overnight in incubation before using a screening agar medium [18].

A Quick Overview of Effective Therapy and Protocols in Managing MRSA

MRSA has always been a significant problem to the treatment of *Staphylococcus* infections. Community acquired-MRSA (CA-MRSA) can be treated effectively by clindamycin therapy, although the possibility of acquired clindamycin resistance exists and patients with suspicions of MRSA are given vancomycin before microbiology culture results are received [19-25].

Another effective drug like vancomycin is linezolid, and is well tolerated in children with MRSA infections, and may be administered orally [21]. However, the drug linezolid is expensive, not readily available, has a lot of life-threatening adverse effect, for example, bone marrow suppression including thrombocytopenia). And also, there is a possibility of developing resistance in *Staphylococcus aureus* with its use [26].

Beta-lactams, such as cephalosporins and carbapenem, have been known to have *in vitro* effect against methicillin-resistant *Staphylococci* and other resistant Gram-positive cocci [22]. A clinical trial with ceftobiprole medocaril has shown evidence of success as a useful therapy against MRSA [20].

Incision and drainage are usually effective in less severe cases of community-associated MRSA skin or soft-tissue

infections [22,23]. Also use of oral trimethoprim/sulfamethoxazole, minocycline, doxycycline, or clindamycin is usually recommended [22]. Injuries should be managed properly to prevent transmission. However, should there be a case of complicated MRSA skin and soft-tissue infection resulting in hospitalization, intravenous vancomycin has been shown to be effective [21].

Another line of drug that is used for community-associated MRSA is rifampin. However, rifampin should not be used alone because of increasing resistance to rifampin due to mutation. It can be used in combination with trimethoprim-sulfamethoxazole or doxycycline for treatment of skin or soft tissue infections caused by CA-MRSA [25]. Also, trimethoprim-sulfamethoxazole or tetracyclines are not recommended as sole empirical therapy for a nonpurulent cellulitis because of resistance of group A *Streptococci* to these agents [27].

Fluoroquinolones are not being utilized in the management of skin and soft-tissue infections caused by community-associated MRSA because of the rapid development of resistance to them, which is widely prevalent.

It should be noted that the first line drug of choice in patients with invasive *Staphylococcus aureus* infection is vancomycin, however in cases where laboratory studies reveal susceptibility to rapidly acting beta-lactam drugs then a switch can be made to use drugs like oxacillin [25].

Proper hygiene protocols have proved to be ideal for minimizing community-acquired outbreaks and should be highly encouraged and taught in the various communities just as it is implemented in a hospital setting [21]. Furthermore, patients with CA-MRSA infections of soft tissue should be educated on the advantages of proper hand hygiene, use of personal items without sharing with others and proper handling of the wound [21]. Maintenance of proper hygiene among healthcare workers is also important (Table 1).

Table 1 Anti-staphylococcal antibiotics (adapted from [24])

Pharmacologic Agents	Mechanism of Action
Beta-Lactams (Penicillins and Cephalosporins)	Inhibitors of Cell Wall Synthesis
Glycopeptides	
Bacitracin	
Macrolides, lincosamides, Streptogramins	Inhibitors of Protein Synthesis
Tetracyclines	
Aminoglycosides	
Fusidic Acid	
Ansamycin	Inhibitors of Nucleic Acid Synthesis
Fluoroquinolones	
Sulfamides and diaminopyridines	Metabolic Inhibitors
Anti-MRSA b-lactams [cephalosporins (ceftobiprole, ceftaroline)]	Inhibitors of Cell Wall Synthesis
Ketolides (telithromycin)	Inhibitors of Protein Synthesis
Oxazolidinones	
Glycylcyclines (tigecycline)	
New diaminopyridines (iclaprim)	Metabolic inhibitors
FabI inhibitors	
Peptide deformylase inhibitors	
Ceragenins	Membrane-Active Agents
Lipopeptides (daptomycin)	
Friulimicins and amphomycins	
Lipoglycopeptides	
Glycodepsipeptides	

Reflection on the Screening Programs

MRSA is widely spreading globally, and treatment options are few with many having a diverse noxious effect. To treat this multi-resistant organism, well strategized clinical protocols must put in place to treat as the cost of treatment for HA-MRSA, for example, are not easily affordable. The prevalence of HA-MRSA can be reduced, and screening individuals can certainly help with this in regions where MRSA is endemic. Selective screening involves high-risk patients, especially those in hospital intensive care units and those positive for MRSA. This is cheaper and likely enforceable.

Although, an expanding prevalence of MRSA in Germany was reported stating that the screening program did not

lessen the general recurrence of all MRSA patients; without a doubt, this recurrence constantly expanded amid the whole investigation period [28]. The recurrence was attributed to the fact that screening and decolonization measures were not entirely adhered to in the clear majority of the health centers in the district as they were in the study centers. Hence, numerous patients were susceptible to the MRSA pathogen in different health facilities.

To relieve the recurrence of MRSA, an exceptionally strict adherence to the 'pursuit and devastate technique,' as utilized as a part of The Netherlands and Denmark in all healing facilities of a district with an MRSA issue, is required. Another probability found is that the dynamic hunt methodology amid the screening program brought about the discovery of more MRSA patients at healing facility affirmation than amid the control period. Nevertheless, there was a consistent increment in the recurrence of MRSA from the earliest starting point of the control period, however the presentation of the screening program saw a drop in the incidence afterwards [29].

Overall, on the off chance that doctor's facilities present such a program, they ought not to be frustrated if there seems to be no abatement in the general recurrence of segregation of MRSA.

CONCLUSION

The progressive increase in multidrug-resistant *Staphylococcus aureus* has revealed the need for a comprehensive and systematic integration of healthcare management systems. Adherence to strict recommendations regarding prevention and control guidelines must be aggressively encouraged and facilitated. Conduction of periodic surveillance to detect the emergence of these organisms and ensuring vigorous antibacterial administration by health care providers must be promoted. Also, proper hygiene by both patient and healthcare providers with use of safety precautions (gloves) and will improve quality of health in patients and reduce the cost of treatment and management of MRSA.

DECLARATIONS

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Conflict of Interest

The authors declare no conflict of interest.

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