

BRIEF REVIEW ON MRSA AND VRSA**Deepak Bhatt*, Saugat Dahal, Rajindar Singh and Sushobhan Bhandari**

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560035.**ABSTRACT**

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacteria that is resistant to many antibiotics. Staph and MRSA can cause a variety of problems ranging from are skin infections and sepsis to pneumonia to bloodstream infections. Vancomycin-resistant *Staphylococcus aureus* (VRSA) is a rare, multidrug-resistant bacterium of public health concern that emerged few decade back. Appropriate antimicrobial prescribing by healthcare providers, adherence to recommended infection control guidelines, and, ultimately, the control of both MRSA and VRSA are necessary to prevent further emergence of VRSA strains. Increased frequency of *S. aureus* infections imposes a high and increasing burden on healthcare resources. Methicillin-resistant

staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE) cause nosocomial infections and are linked with increased rates of illness and death. Common preventive measures when used by health care professional and general public help to reduce infection chances. Appropriate use of right antibiotic lead to decrease chance of evolution of drugs resistance. As of now, all MRSA and VRSA isolates have been susceptible to several Food and Drug Administration (FDA) - approved drugs.

KEYWORDS: *Staphylococcus aureus*, MRSA and VRSA.**INTRODUCTION**

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an adaptable pathogen capable of causing a wide variety of human diseases. Increased frequency of *S. aureus* infections imposes a high and increasing burden on healthcare resources. In many countries, MRSA infections in hospitals are common. Data from the National Nosocomial Infections Surveillance system suggest that, in the United States. no more than a few drugs, such as

vancomycin (a glycopeptide), daptomycin (a lipopeptide), and linezolid (an oxazolidinone), have been approved for the treatment of serious infections caused by MRSA. Another drug, tigecycline (a glycylcycline), has shown good activity against MRSA strains *in vitro*.^[1]

Vancomycin-resistant *Staphylococcus aureus* (VRSA) is a rare, multidrug-resistant bacterium of public health concern that emerged few decade back. VRSA (*S. aureus* with vancomycin minimum inhibitory concentration [MIC] ≥ 16 $\mu\text{g/mL}$) arises when vancomycin resistance genes (e.g., the *vanA* operon, which codes for enzymes that result in alteration or elimination of the vancomycin binding site) from vancomycin-resistant enterococci (VRE) are transferred to *S. aureus*. To date, all VRSA strains have arisen from methicillin-resistant *S. aureus* (MRSA).^[2]

Methicillin-resistant *staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) cause nosocomial infections and are linked with increased rates of illness and death^[3-4] Both organisms are now endemic in many healthcare institutions, particularly in intensive care units (ICUs).^[3] Vancomycin is commonly used to treat infections caused by MRSA; however, the recent emergence of *S. aureus* infections with high-level resistance to vancomycin call into question the future effectiveness of vancomycin for these nosocomial infections.^[4] All known vancomycin-resistant *S. aureus* (VRSA) isolates reported thus far have possessed the *vanA* gene, which confers resistance to vancomycin and is believed to have been acquired when a MRSA isolate conjugated with a co-colonizing VRE isolate.^[5] Thus, patients concurrently co-colonized with MRSA and VRE are prone to the risk of colonization or infection by VRSA.

Public health considerations

The burden of MRSA is significant. In 2009, there were an estimated 463,017 (95% confidence interval: 441,595, 484,439) MRSA-related hospitalizations, or a rate of 11.74 (95% confidence interval: 11.20, 12.28) per 1,000 hospitalizations.^[97] Many of these infections are less serious, but the Centers for Disease Control and Prevention (CDC) estimates that there are 80,461 invasive MRSA infections and 11,285 deaths due to MRSA annually.^[16]

Mechanism of acquired resistance

Staphylococci have two primary mechanisms for resistance to β -lactam antibiotics: the expression of an enzyme (the PC1 β -lactamase) capable of hydrolyzing the β -lactam ring,

thus rendering the antibiotic inactive, and the acquisition of a gene encoding a modified penicillin-binding protein (PBP), known as PBP 2a, found in MRSA and coagulase-negative staphylococci. PBP 2a is intrinsically resistant to inhibition by β -lactams.^[6]

Mechanism of vancomycin resistance

Visa: Vancomycin binds with the D-alanyl-D-alanine C terminus of the bacterial cell precursors, thereby preventing cross-linking by transpeptidation resulting in inhibition of cell wall production by attacking sites responsible for cell wall production.

Vrsa: VRSA strains also have been found to have thicker cell walls than the sensitive strains. As with VISA strains, there is also increased peptidoglycan synthesis. It has been shown that vancomycin is only trapped in the outer layers and sequestered by the bacteria and not deactivated.^[7]

Prevention

Screening programs

Patient screening during hospital admission, with nasal cultures, prevents the cohabitation of MRSA carriers with non-carriers, and exposure to infected surfaces. The test used (whether a rapid molecular method or traditional culture) is not as important as the implementation of active screening.^[8]

Surface sanitizing

Alcohol has been proven to be an effective surface disinfectant against MRSA. Quaternary ammonium compounds can be used in conjunction with alcohol to extend the longevity of the sanitizing action. The prevention of nosocomial infections involves routine and terminal cleaning. Non-flammable alcohol vapor in carbon dioxide systems (NAV-CO₂) do not corrode metals or plastics used in medical environments and do not contribute to antibacterial resistance.

In healthcare environments, MRSA can survive on surfaces and fabrics, including privacy curtains or garments worn by care providers. Complete surface cleanliness is necessary to eradicate MRSA in areas where patients are recovering from invasive procedures. Testing patients for MRSA upon admission, isolating MRSA-positive patients, decolonization of MRSA-positive patients, and terminal cleaning of patients' rooms and all other clinical areas they occupy is the current best practice protocol for nosocomial MRSA.

Studies published from 2004-2007 reported hydrogen peroxide vapor could be used to fumigate busy hospital rooms, despite taking significantly longer than traditional cleaning. One study noted rapid recontamination by MRSA following the hydrogen peroxide application.^[9]

Research on copper alloys

In 2008, after evaluating a wide body of research mandated particularly by the United States Environmental Protection Agency (EPA), registration approvals were granted by EPA in 2008 granting that copper alloys kill more than 99.9% of MRSA within two hours.

Subsequent research conducted at the University of Southampton (UK) compared the antimicrobial efficacies of copper and several non-copper proprietary coating products to kill MRSA. At 20 °C, the drop-off in MRSA organisms on copper alloy C11000 is dramatic and almost complete (over 99.9% kill rate) within 75 minutes. However, neither a triclosan-based product nor two silver-containing based antimicrobial treatments (Ag-A and Ag-B) exhibited any meaningful efficacy against MRSA. Stainless steel did not exhibit any antimicrobial efficacy.^[10]

Hand washing

As with some other bacteria, MRSA is acquiring more resistance to some disinfectants and antiseptics. Although alcohol-based rubs remain somewhat effective, a more effective approach is to wash hands with running water and an antimicrobial cleanser with persistent killing action, such as chlorhexidine.^[11] In another study chlorhexidine (Hibiclens), *p*-chloro-*m*-xylenol (Acute-Kare), hexachlorophene (PhisoHex), and povidone - iodine (Betadine) were evaluated for their effectiveness. Of the four most commonly used antiseptics, povidone-iodine, when diluted 1:100, was the most rapidly bactericidal against both MRSA and methicillin-susceptible *S. Aureus*.^[12]

Proper disposal of hospital gowns

Used paper hospital gowns are associated with MRSA hospital infections, which could be avoided by appropriate disposal.^[13]

Isolation

Excluding medical facilities, current US guidance does not require workers with MRSA infections to be routinely excluded from the common workplace. Therefore, unless directed by a health care provider, exclusion from work should be reserved for those with wound

drainage that cannot be covered and contained with a clean, dry bandage and for those who cannot maintain good hygiene practices. Workers with active infections should be excluded from activities where skin-to-skin contact is likely to occur until their infections are healed. Health care workers should follow the Centers for Disease Control and Prevention's Guidelines for Infection Control in Health Care Personnel.^[14]

Restricting antibiotic use

Glycopeptides, cephalosporins, and, in particular, quinolones are associated with an increased risk of colonisation of MRSA. Reducing use of antibiotic classes that promote MRSA colonisation, especially fluoroquinolones, is recommended in current guidelines.^[15]

Decolonization

Care should be taken when trying to drain boils, as disruption of surrounding tissue can lead to larger infections, or even infection of the blood stream (often with fatal consequences). Any drainage should be disposed of very carefully. After the drainage of boils or other treatment for MRSA, patients can shower at home using chlorhexidine (Hibiclens) or hexachlorophene (PhisoHex) antiseptic soap (available over-the-counter at many pharmacies) from head to toe. Alternatively, a dilute bleach bath can be taken at a concentration of 2.5 µL/mL dilution of bleach (about 1/2 cup bleach per 1/4-full bathtub of water). Care should be taken to use a clean towel, and to ensure that nasal discharge doesn't infect the towel (see below).

All infectious lesions should be kept covered with a dressing. Mupirocin (Bactroban) 2% ointment can be effective at reducing the size of lesions. A secondary covering of clothing is preferred. As shown in an animal study with diabetic mice, the topical application of a mixture of sugar (70%) and 3% povidone-iodine paste is an effective agent for the treatment of diabetic ulcers with MRSA infection.^[17-20]

Community settings

The CDC offers suggestions for preventing the contraction and spread MRSA infection which are applicable to those in community settings, including incarcerated populations, childcare center employees, and athletes. To prevent MRSA infection, individuals should regularly wash hands using soap and water or an alcohol-based sanitizer, keep wounds clean and covered, avoid contact with other people's wounds, avoid sharing personal items such as razors or towels, shower after exercising at athletic facilities (including gyms, weight rooms,

and school facilities), shower before using swimming pools or whirlpools, and maintain a clean environment.^[21]

Treatment

For Mrsa

Vancomycin has been regarded as the first-line drug for treatment of MRSA. Unfortunately there has been an increase in the use of this antibiotic for other infections, such as pseudomembranous colitis due to *Clostridium difficile* and coagulase-negative staphylococcal infections in hospitalized patients. Both CA-MRSA and HA-MRSA are resistant to traditional anti-staphylococcal beta-lactam antibiotics, such as cephalexin. CA-MRSA has a greater spectrum of antimicrobial susceptibility, including to sulfa drugs (like co-trimoxazole (trimethoprim / sulfamethoxazole)), tetracyclines (like doxycycline and minocycline) and clindamycin (for osteomyelitis), but the drug of choice for treating CA-MRSA is now believed to be **vancomycin**. Newer drugs, such as **linezolid** (belonging to the newer oxazolidinones class) and **daptomycin**, are effective against both CA-MRSA and HA-MRSA. The Infectious Disease Society of America recommends **vancomycin, linezolid, or clindamycin** (if susceptible) for treating patients with MRSA pneumonia. Ceftaroline, a fifth-generation cephalosporin, is the first beta-lactam antibiotic approved in the US to treat MRSA infections (skin and soft tissue or community acquired pneumonia only).

Vancomycin and teicoplanin are glycopeptide antibiotics used to treat MRSA infections. Teicoplanin is a structural congener of vancomycin that has a similar activity spectrum but a longer half-life.

Because the oral absorption of vancomycin and teicoplanin is very low, these agents must be administered intravenously to control systemic infections. Treatment of MRSA infection with vancomycin can be complicated, due to its inconvenient route of administration. Moreover, many clinicians believe that the efficacy of vancomycin against MRSA is inferior to that of anti-staphylococcal beta-lactam antibiotics against methicillin-susceptible *Staphylococcus aureus* (MSSA).

Several newly discovered strains of MRSA show antibiotic resistance even to vancomycin and teicoplanin. These new evolutions of the MRSA bacterium have been dubbed vancomycin intermediate-resistant *Staphylococcus aureus* (VISA).

Linezolid, quinupristin/dalfopristin, daptomycin, ceftaroline, and tigecycline are used to treat more severe infections that do not respond to glycopeptides such as vancomycin. Current guidelines recommend daptomycin for VISA blood stream infections and endocarditis.^[22-31]

For VRSA treatment: For isolates with a Vancomycin MIC > 2 µg/mL, an alternative to Vancomycin should be used. The approach is to treat with at least one agent to which VISA/VRSA is known to be susceptible by *invitro* testing. The agents that are used include **daptomycin, linezolid, telavancin, ceftaroline, quinupristin–dalfopristin**. For patients with MRSA bacteremia in the setting of vancomycin failure the IDSA recommends high-dose daptomycin (10 mg/kg/day), if the isolate is susceptible, in combination with another agent (e.g. gentamicin 1 mg/kg IV every 8 h, rifampin 600 mg PO/IV daily or 300–450 mg PO/IV twice daily, linezolid 600 mg PO/IV BID, TMP-SMX 5 mg/kg IV twice daily, or a beta-lactam antibiotic).^[32]

Some medical causes of antibiotic resistance

So how does a physician decide if antibiotic treatment is necessary for a patient. If a doctor isn't really sure of the source of infection, but thinks it's bacterial, they often prescribe a broad-spectrum antibiotic. However, studies suggest that these **super antibiotics are best used for critically ill patients** - the ones who need treatment immediately.

The down side to this "broad" treatment is that while it targets the susceptible as well as resistant bacteria as well. In light of this, physicians are encouraged to use the most "specific" antibiotic they can. But, in order to do this, cultures must be obtained and tested to identify the source. Many times these cultures and tests are not performed due to time constraints, difficulty in obtaining a culture, expense, etc.

The US Center for Disease Control and Prevention (CDC) estimates that about one-third of the 150 million outpatient antibiotic prescriptions written each year are unnecessary. A majority of these patients suffer from colds and upper respiratory tract infections and other ailments often caused by viruses.

Increasing public awareness of the hazards associated with the misuse of antibiotics is one of the most important methods currently being utilized by organizations like the American Medical Association and many other concerned groups. This educational campaign has

focused on raising physician awareness on the dangers of inappropriate antibiotic over prescribing and encouraged to share this information with their patients.

Some basic guidelines for antibiotic use

- With cold and flu season officially here, clinics will be filled with patients looking for some relief. But **antibiotics do not work against colds or flu**. They are caused by viruses. Do not request antibiotics from your doctor unless there a specific bacterial infection.
- Most **sore throats** are also caused by viruses. One exception is strep throat, which is caused by bacteria. A throat culture can diagnose strep and antibiotic treatment is needed.
- Viruses are almost always the culprit behind most **coughs and bronchitis**. However, if **symptoms last for more than two weeks** or if the patient has a respiratory condition, they need to see a doctor to determine if an antibiotic is needed.
- **Sinus infections** are one of the most common complaints seen by physicians. These can be caused by bacteria or viruses. One common misconception is that if the symptoms include yellow or green mucus, it's a bacterial infection. Not necessarily. A virus could be the cause. However, antibiotics should **only be used for a SEVERE infection**, or one that **lasts more than two weeks** because that one is probably being caused by bacteria.
- When an antibiotic is prescribed, it is extremely important to **take ALL of the doses as directed**. Too many people quit taking their prescription when they begin to feel better. Some then decide to save the remaining meds for the "next" time that they get sick. However, **if the full round of medication is not taken, the "remaining" bacteria could bring the infection back worse than ever**. The best defense against an infection is to take the prescribed number of doses on the prescribed schedule. (However, one problem that should be noted here is that in a recent survey of patients who have been subscribed antibiotics, many say they were never told the importance of finishing the medication.).
- Use **regular soap and water** for washing. Avoid products with antibiotic ingredients on the labels.
- Eat **live culture yogurt or probiotics** containing acidophilus bacteria after finishing a course of antibiotic treatment. These products will help build up the healthy bacteria in your body.

- You can buy **meat and eggs** from animals that weren't fed antibiotics. This reduces farm use, and promotes farming that relies on clean living conditions for the animals.^[33]

CONCLUSUION

Use of appropriate infection control practices (such as wearing gloves before and after contact with infectious body substances and adherence to hand hygiene) by healthcare personnel can reduce the spread of MRSA and VRSA infection.

Vancomycin is the standard treatment for MRSA. Unfortunately, we are now seeing more incidents of VRSA (vancomycin resistant staph). The accepted procedure for MRSA is treatment with vancomycin; tigecycline and linezolid have been recently introduced).

Currently, there are two antibiotics that could be used against VRSA: tigecycline and linezolid. While tigecycline can be used to treat some infections (skin and abdomindal), it is not used to treat bloodstream infections. Tigecycline also must be administered intravenously, requiring a hospital stay during the course of therapy (usually several days).

Linezolid can also be used against VRSA, but it is not approved for use in children under 18, and can have serious side effects; linezolid resistance, As of now, all VISA and VRSA isolates have been susceptible to several Food and Drug Administration (FDA)-approved drugs.

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