ISSN: 2474-3658

Kest and Kaushik. J Infect Dis Epidemiol 2019, 5:093
DOI: 10.23937/2474-3658/1510093
Volume 5 | Issue 5
Open Access

Journal of
Infectious Diseases and Epidemiology

REVIEW ARTICLE

Vancomycin-Resistant *Staphylococcus aureus*: Formidable Threat or Silence before the Storm?

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Abstract

Globally, *Staphylococcus aureus* (*S. aureus*), notably methicillin-resistant *S. aureus*, is a leading cause of morbidity and mortality. Vancomycin is considered a drug of last resort for severe MRSA and other resistant Gram-positive infections. Vancomycin enjoyed a high level of success for decades following MRSA outbreaks until recent reports of increasing *S. aureus* MICs culminating in high-level vancomycin-resistant *S. aureus* (VRSA), first reported in 2002. Since then, there have been selected case reports of VRSA disease in the US and other countries. The resistance mechanism of VRSA is mediated by the *VanA* operon carried on the mobile genetic element Tn*1546* acquired from vancomycin-resistant *Enterococcus*; co-infections with VRE have occurred in all cases. There has been no documented person to person VRSA transmission. The prolonged interval between exposure to vancomycin and VRSA development and the limited number of cases are reassuring; whether this translates to the needed extended period of clinical quiescence before a global epidemic is unknown. According to the World Health Organization (WHO), *S. aureus* pathogenicity and resistance patterns pose a significant threat to human health worldwide; MRSA, vancomycin intermediate-resistant *S. aureus* (VISA) and VRSA are currently classified as bacteria of high priority with potential to cause significantly devastating worldwide mortality in the absence of effective containment and therapeutic solutions. There are limited choices of drugs that are effective against VRSA; several promising therapeutic options are in research and development phases. VISA and VRSA have also been isolated in animal husbandry from pigs, goats, and cattle.

We review VRSA history and evolution, clinical spectrum and management. We also speculate on future trends.

Keywords

Vancomycin-resistant *Staphylococcus aureus*, VRSA, Resistant *Staphylococcus aureus, S. aureus*, Antibiotic resistance

Introduction

S. aureus disease evolution

Staphylococcus aureus (*S. aureus*) is one of the world's most ubiquitous, yet sophisticated and fascinating bacteria due to its unique global epidemiology, disease spectrum and adaptation to every antibiotic used in its management including development of resistance before or immediately following extensive use. Table 1 summarizes the timeline of *S. aureus* antibiotic resistance.

S. aureus acquires genetic resistance against multiple classes of antibiotics through a variety of mechanisms - an existing gene undergoes mutation or changes in genetic configuration through the insertion of insertion sequences (IS), transposons and prophages [1].

A breakthrough in the management of previously universally fatal *S. aureus* infections followed the availability of penicillin in the 1940s. Penicillin's antibacterial effect is due to its core *β-lactam* ring that inhibits its bacterial cell wall biosynthesis. Indeed, *S. aureus'* fascinating nature in terms of resistance development was first described in clinical isolates pre-dating the

Citation: Kest H, Kaushik A (2019) Vancomycin-Resistant *Staphylococcus aureus*: Formidable Threat or Silence before the Storm?. J Infect Dis Epidemiol 5:093. doi.org/10.23937/2474-3658/1510093

Accepted: September 19, 2019: **Published:** September 21, 2019

Table 1: Timeline of *Staphylococcus aureus* antibiotic resistance [11].

Antibiotic	Year Antibiotic Introduced	Year Resistance Identified	Notes
Penicillin	1943	1940	Penicillinase, a highly potent plasmid-encoded *β-lactam* ring hydrolyzer, was extracted from naturally resistant strains of *S. aureus* samples, collected before its clinical use
Methicillin	1960	1962	Before widespread use, resistance to Celbenin (Methicillin) was noted in clinical isolates obtained from skin lesions and anterior nares of hospitalized patients with no previous exposure to the drug.
Linezolid	2000	2001	
Vancomycin	1972	2002	Resistance development evolved slowly over time with MIC creeps, therapeutic failures, VISA then VRSA
Ceftaroline	2010	2011	

use of penicillin that showed the presence of penicillinase, a highly potent plasmid-encoded *β-lactam* ring hydrolyzer [2].

What followed was the development of the first semisynthetic penicillin, methicillin. However, before its widespread use, methicillin-resistant *S. aureus* (MRSA) isolates were recovered from skin lesions and nares of hospitalized patients [3] with no previous exposure to the drug. This organism became the first epidemic clone of what became known as MRSA.

MRSA disease mostly occurred initially in hospitals and healthcare settings. In the early 1990s, a genetically different MRSA strain was isolated from infected and colonized Western Australian hospitalized patients with no prior health care exposure [4]. Later designated community-acquired *S. aureus* (CA-MRSA), this strain showed better antimicrobial susceptibility, different genotypic and SCC*mec* types and was more likely to encode Panton-Valentine leukocidin (PVL), a potent toxin that leads to white blood cell destruction and necrotizing skin and deep tissue lesions [5]. In addition to its virulence, PVL-positive CA-MRSA pose significant public health risks due to its rapid global spread and outbreaks in households and social groups [6]. Contrariwise, the Healthcare-acquired MRSA (HA-MRSA) is associated with multidrug class resistance as well as inducible macrolide, lincosamide and streptogramin resistance [5,6] due to its SCC*mec* types (II and III) that contain additional resistance determinant genes.

MRSA with increased minimum inhibitory concentration (MIC) to vancomycin, later designated vancomycin intermediate-resistant *S. aureus* (VISA) was first reported in Japan in 1997 [6,7]. Unlike the foreign SCC*mec* gene conferring resistance in MRSA, VISA's MIC values result from cumulative effects of novel mutations that appear over time during vancomycin therapy. Highly variable mutations in a large number of loci affecting regulatory and coding genes lead to increased vancomycin MIC of *S. aureus* strains [8]. The first reports of VRSA (with a vancomycin MIC ≥ 16 µg/ml) infection was reported in the US in 2002, decades following reports of similar European *S. aureus* strains that showed reduced susceptibility to teicoplanin, a glycopeptide antibiotic belonging to the same class [9,10].

Resistant-bacteria related diseases are a major global health threat that results in infections in an estimated 2 million people, causing 23,000 deaths each year in the United States alone [11]. Resistant *S. aureus* (MRSA) is responsible for about 50% of deaths [11,12]. Therefore, the global burden of a VRSA disease epidemic burden would be catastrophic. Additionally, the potentially devastating effect of global spread will likely lead to resource-related inequity in its containment creating a vicious cycle; with the globalization of travel and organisms' ability to adapt to changing environments, containment would be quite challenging if not impossible.

The estimated total economic burden caused by antibiotic-resistant infections in the US is about $20 billion in health care costs and $35 billion a year in lost productivity [12]; other indirect costs are likely to be significantly higher. Therefore, without effective control and new antibacterial agents, annual deaths could exceed 10 million by the year 2050 [13].

According to WHO, *S. aureus* pathogenicity and resistance patterns pose a great threat to global health; MRSA, VISA and VRSA are currently classified as bacteria of high priority with the potential to cause significantly devastating worldwide mortality if adequate solutions are not found [14].

VRSA History and Evolution

In 1953, vancomycin was first isolated from a strain of *Amycolatopsis orientalis* (formerly *Nocardia orientalis*) found in a soil sample [15]. The name vancomycin was derived from “vanquish” because of its ability to vanquish resistant *Staphylococcus*. It was first used clinically after the Food and Drug Administration (FDA) approval in 1955 to treat penicillin-resistant strains of *S. aureus* [16].

Vancomycin belongs to a class of glycopeptide anti-

biotics and is the conventional last resort antibiotic for serious or suspected infections due to MRSA, Enterococci, and penicillin-resistant *Streptococcus pneumoniae* in hospitalized patients, especially those with severe disease (pneumonias, severe skin/osteoarticular infections, deep tissue abscesses, and sepsis), immunocompromised and critically ill patients [17].

Despite its effectiveness for Gram-positive infections, vancomycin use was initially low due to its undesirable therapeutic window in the setting of less toxic and equally or more efficacious options. However, a dramatic increase in vancomycin use started gradually during the 1980s continuing exponentially with a > 100-fold increase by the 1990s [18,19].

Multiple events drove these uses that eventually led to significant expansion and current trends. First, vancomycin became the drug of choice for pseudomembranous enterocolitis due to its effectiveness against *Clostridium difficile* with the additional benefit of poor systemic absorption [20]. Secondly, there was an exponential increase in its use to treat resistant pathogens, due to epidemics and eventual global spread of severe resistant Gram-positive infections including MRSA diseases [21,22].

Over time, selective pressure led to complex MIC expressions in *S. aureus* strains, noted in selected patients showing suboptimal response to clinical therapy: strains showed MICs in susceptible range with subpopulations of vancomycin-intermediate daughter cells. With continued exposure, these heterogeneous vancomycin-intermediate *S. aureus* (*h*VISA) strains may have been precursors for the uniform population of vancomycin-intermediate clones [22-24]. MRSA isolates with vancomycin MICs 4-8 µg/mL, later designated vancomycin intermediate-resistant *S. aureus* (VISA), was first reported in Japan in 1997 [7]. VISA has been mostly described in Asia and Europe/America where prevalence in MRSA samples are reportedly at 3.42% and 2.75%, respectively [24].

The first vancomycin-resistant *S. aureus* (VRSA) strain (with a vancomycin MIC ≥ 16 µg/ml) was reported in the US in 2002, decades following reports of similar European isolates that showed reduced susceptibility to teicoplanin, a glycopeptide antibiotic belonging to the same class [9,10].

There have been 14 cases of VRSA infections reported in the US. Table 2 summarizes reporting year, case count, source, predisposing factors, and geographical location.

The resistance mechanism of VRSA is mediated by the *VanA* operon carried on the mobile genetic element Tn*1546* acquired from vancomycin-resistant *Enterococcus faecalis*. Co-infections with VRE have occurred in all cases [21,25]. There are only a few selected cases of other clinical *S. aureus* isolates with *vanA*-type resistance pattern reported in literature. In 2013, VRSA infection was reported in Europe in a 73-year-old with renal and cardiovascular disease [26]. The patient also harbored VRE. The strain showed similar genetic background to US VRSA strains. Other reports include *vanA*-positive ST239-*SCCmec* III/t037 from samples of hospitalized patients in Iran [27], and *vanA*-positive isolates from India and Pakistan [28]. Of real concern is the African study that showed a VRSA prevalence of 44.5% among samples from clinical isolates [29]. While many of these may represent differences in laboratory isolation methods, it is nonetheless concerning.

VISA and VRSA have also been isolated in animal husbandry from pigs, goats, and cattle. The clinical impact at this time is unknown [24,30,31].

According to the CDC, VRSA disease epidemiology demonstrates geographic clustering that is probably explained by the higher prevalence of precursor organisms in geographically related areas: eight of ten VRSA documented from 2002 to 2009 occurred in patients from Michigan, and all four VRSA infections since 2010 occurred in patients from Delaware. There has been no documented VRSA transmission to date.

Mechanisms of Resistance

The staphylococcal cell wall is a dynamic structure that is critical in host-pathogen interaction. In *S. aureus* cell wall synthesis, Penicillin-binding proteins (PBPs) are transpeptidases that incorporates new peptidoglycan precursors into pre-existing chains. *β-lactam* antibiotics are structural analogs of cell wall precursors that targets PBP, thereby inactivating and inhibiting the cross-bridge formation step with resultant cell lysis [32].

MRSA produces PBP2A, which bypasses *β-lactam*

Table 2: Historical US VRSA case count and geographical information [25,31].

Cases (Number)	Year	Age range	Source Diagnosis	Underlying conditions
Michigan (8)	2002 to 2009	40-78	Skin and skin structure infections	Obesity, diabetes, renal disease, rheumatologic diseases, skin disease
Pennsylvania (1)	2002	70	Osteomyelitis	Obesity
New York (1)	2004	63	Colonization	Diabetes, renal disease, rheumatologic disorder
Delaware (4)	2010 to 2015	64-83	Skin and skin structure infections, prosthetic device infection	Diabetes, renal disease, GI mucosal barrier infection

antibiotics. PBP2A is encoded by the *mecA* gene located on a mobile genomic island, the staphylococcal cassette chromosome mec (SCC*mec*) that carries the central determinant for broad-spectrum *β-lactam* resistance. Table 1 shows the timeline for *S. aureus* resistance to various antibiotics.

Glycopeptides like vancomycin's bactericidal activity occurs through inhibition of peptidoglycan synthesis by binding to the *D-ala-D-ala* terminus of the peptidoglycan precursor Lipid II [18,23,33]. Additionally, the *D-Ala-D-Ala* terminus is highly conserved in Gram-positive bacteria including *S. aureus* making vancomycin an active drug against a broad spectrum of gram-positive pathogens [23].

Specific operons that consist of genetic regulatory systems coding for multiple antibiotic resistance determinants occur in VRSA and *enterococci*; six resistance patterns (designated "*VanA*" through "*VanG*") have been reported [21]. Resistance is conferred to vancomycin through alteration in binding sites; in vancomycin-resistant organisms, the cell wall dipeptide precursors are altered to molecules with reduced affinity to vancomycin including D-alanyl-D-lactate (*VanA*, *VanB*, and *VanD*) or D-alanyl-D-serine (*VanC*, *VanE*, and *VanG*) [18,34]. The resistance mechanism of VRSA is mediated by the *VanA* operon carried on the mobile genetic element Tn*1546* acquired from vancomycin-resistant *Enterococcus faecalis*. Co-infections with VRE have occurred in all cases [21,25].

VanA is carried on the mobile genetic element Tn*1546*. Tn*1546*-based antibiotic resistance produces alteration of the dipeptide residue from *D-ala-D-ala* to d-alanyl-d-lactate (*D-ala-D-lac*), a dipeptide with substantially lower affinity for vancomycin [18,33]. Most VRSA strains carry plasmid-borne copies of Tn*1546* acquired from vancomycin-resistant *Enterococcus faecalis* [35]. Horizontal spread of resistance genes can occur efficiently through bacterial conjugation. Inc18 incompatibility conjugative plasmids occur naturally in *Enterococcus but not* in naturally occurring staphylococci with pSK41-like multi-resistant conjugative plasmids [36]. This pSK41-like plasmid has been shown to facilitate the transfer of Inc18-like *vanA* plasmid from *E. faecalis* to *S. aureus*, possibly via other molecules produced by pSK41-carrying isolates [36-38]. VRSA plasmids contain Tn*1546*: each strain contains both enterococcal and staphylococcal plasmids. Polymicrobial infections with VRE and MRSA strains in the health care setting have been an essential factor in VRSA infections [25,35].

13 out of 14 characterized US VRSA strains belong to the *S. aureus* clonal complex 5 (CC5) phylogenetic lineage; PGFE typing showed USA100/800/novel types [25,31,38]. The 13th US isolate belonged to the *S. aureus* (CC30) phylogenetic lineage. PGFE and *spa* typing showed USA1100/t019, a pattern typically seen in community-acquired infections [31]; the clinical significance of this variance is unknown. While VRSA isolates arise from lineages that are widespread and pathogenic, efficient person to person transfer has not been documented [25].

CC5 strains possess various traits that promote adaptation and growth optimized for its environment; additionally, they modulate host immunity through an arsenal of superantigens and lipoproteins. CC5 strains were identified in earlier MRSA isolates and have acquired SCC*mec* > 20 separate times, with different regulatory genes, and the associated insertion sequences, over the past 5-6 decades [39].

Selective genetic features may explain the efficient mechanism of CC5 clonal complex resistance acquisition and spread. These include the absence of bacteriocin operon and mutation in the gene encoding DprA (a molecule that promotes the efficiency of bacterial DNA transformation), as well as other genes that encode molecules and superantigens that negatively impact host immune response [38]. CC5 also contains the most diversity of SCC*mec* elements and clonal lineages that possess a high degree of inter-species/strain transmissibility. These SCC*mec* elements confer antibiotic resistance properties and virulence factors [38]. CC5 strains predominate in HA-MRSA disease among critically ill patients with high-density infections that are more likely to lead to high environmental impact; examples are patients with burns, bacteremia and critically ill patients [40-42]. These factors combined with frequent antibiotic usage in the hospital environment create a favorable selective environment for interspecies comingling and transfer of resistance genes. Despite the global pandemic spread of CC5 strains and other HA-MRSA related clonal complex, person to person transmission has not been demonstrated for VRSA.

The prolonged interval between exposure to vancomycin and VRSA development may be explained by non-genome related factors that include limited vancomycin use until the 1980s, need for an appropriate VRE Tn*1546*-containing plasmid donor and patient/health care factors that favored polymicrobial infection with VRE and *S. aureus* [30]. Whether this translates to the needed prolonged period of relative clinical quiescence before a global epidemic is unknown.

Genomic analysis of the CC5 VRSA isolates showed that Tn*1546* DNA sequences from VRSA strains segregate by region of isolation (Table 2) as opposed to the year of acquisition leading to the conclusion of the independent acquisition model of vancomycin resistance at each of these locations [30,37,43]. Kos, et al. [38] showed that transposable elements in all Michigan Tn*1546* sequences were similar or differed by few single-nucleotide polymorphisms (SNPs), as opposed to geographically distinct strains from New York, Pennsylvania, and Delaware [strains VRS2, VRS3a, and VRS11a or VRS11b {VRS11a/b}]) [38]. Explanations for the occurrence of some unrelated VRSA strains include the

possibility of initial plasmid transfer event followed by a series of other horizontal transfers over time with variability occurring at each step [38,44].

CC5 is one of the most studied *S. aureus* clonal complexes due to its association with HA-MRSA, VISA and VRSA. However, while whole genomic analysis has become the gold standard for *S. aureus* due to its comparatively larger annotated sequences, potential drawbacks may include the fact that fully assembled genomic information exists from only 2% *S. aureus* assemblies [44], the majority of which are of MRSA epidemic lineages of complexes (CC) 5 and 8.

Definitions and Testing Methods [28]

CDC definitions for classifying isolates of *S. aureus* with reduced susceptibility to vancomycin are based on the laboratory breakpoints established by the Clinical and Laboratory Standards Institute (CLSI). Last modified in 2009, CLSI breakpoints for *S. aureus* and vancomycin are MIC ≤ 2 µg/ml, MIC = 4-8 µg/ml and MIC ≥ 16 µg/ml respectively for vancomycin-susceptible, intermediate and resistant *S. aureus* [25].

Currently, methods approved for susceptibility testing in the US include automated susceptibility testing (AST), broth microdilution, agar dilution, gradient diffusion, and vancomycin screen agar plates [brain heart infusion (BHI) agar containing 6 µg/ml of vancomycin]. Disk diffusion is not currently recommended for vancomycin susceptibility in S*. aureus* due to misleading zone parameters for susceptible and indeterminate strains [43].

For US isolates, there are mandatory requirements for submission of all *S. aureus* with a vancomycin MIC of >= 8 µg/ml for confirmation of susceptibility results. If VRSA (vancomycin MIC ≥ 16 µg/ml) is suspected or confirmed, further testing is done to characterize VRSA precursor organisms. *S. aureus* strains are defined as VISA or VRSA based on the MIC for vancomycin obtained by reference broth microdilution. Additionally, CDC tests all presumptive VISA/VRSA isolates by gradient diffusion, followed by PCR if confirmed [43].

Of note is that the European Committee on Antimicrobial Susceptibility Testing (EUCAST) changed its MIC criteria in 2018. EUCAST defines glycopeptide-resistant (VRSA, TRSA) *S. aureus* isolates based on MIC values for vancomycin (VAN) and teicoplanin (TEI) of > 2.0 mg/L. Because EUCAST is more widely available and used by developing countries, the stricter criteria will likely lead to the reclassification of VISA strains to VRSA, possibly triggering earlier surveillance and investigations, collaboration and perhaps more urgent and equitable resource allocation to combat its spread. However, the CDC definition may create a less noisy background and more efficient resource allocation.

Disease Spectrum

Disease spectrum has been mostly complicated skin and skin structure infections in hospitalized patients with comorbidities (chronic skin ulcers, diabetes, renal diseases) on previous prolonged vancomycin therapy [26-29,43]. There have been no reports of VRSA disease in children or adults without other predisposing co-morbid factors.

Management

Primary prevention includes measures like immunization to promote individual and herd immunity against preventable infections that may predispose to alteration of human microbiota with secondary serious bacterial infections, safe food handling and preparation, hand washing, and judicious use and prescription of antibiotics in clinical and animal husbandry.

Other measures targeted at healthcare systems include adherence to recommended infection control guidelines and control of both MRSA and VRE colonization and infections.

Monitoring and surveillance in developing countries is a structured process that captures and confirms new occurrences, monitors trends and combats spread through policies and partnerships with agencies and health systems. Strategic partnerships with developing countries that create easy access to confirmatory labs and public health resources would serve to better address global spread and containment.

Antibiotic Management

The mainstay of VRSA treatment includes treating underlying co-morbidities and antimicrobial therapy combined with appropriate surgical intervention as clinically indicated.

Since VRSA disease epidemiology is still evolving with resultant high mortality rates; real-time information about the efficacy of available drugs is limited. Several agents are in research and development for highly-resistant Gram-positives including VRSA; these include modifications of various classes of glycopeptides, carbapenems, oxazolidinones, quinolones, and tetracyclines.

Since the discovery of vancom modification of glycopeptide side chains and other synthetic derivatives with varying degrees of potency have been proposed for clinical use. Examples are telavancin which binds to *S. aureus* D-ala-D-ala targets resulting in cell membrane disruption and increased permeability [18]. Table 3a, Table 3b, Table 3c, Table 3d and Table 3e summarizes currently approved antibiotics effective against VRSA.

As a general rule, alternative antibiotics or combination with at least one agent active against VISA/VRSA should be used when vancomycin MIC is > 2 µg/ml [17].

Table 3: Antibiotics for Vancomycin Resistant Staph aureus [17,34,49-51].

Table 3a: Oxazolidinones.

Drug Name	Year FDA Approved	Notes
Linezolid	2000	• Protein synthesis inhibition through P site binding of ribosomal 50S subunit interfering with peptidyl transferase and peptide bond formation. • Resistance profile is superior to other protein synthesis inhibitors. • Rare oxazolidinone resistance due to alterations of 23S rRNA has been reported but remains uncommon. • IDSA recommends usage in persistent MRSA bacteremia or vancomycin treatment failure. • Treatment failures have been noted in adults.
Tedizolid phosphate	2014	• A second-generation oxazolidinone with superior activity against resistant Gram-positive organisms compared with linezolid. • FDA approved for ABSSI

Table 3b: Streptogramins.

Quinupristin/ Dalfopristin	1999	• Combination of two semisynthetic pristinamycin derivatives. • Dalfopristin A interferes with binding of aa-tRNA and inhibits peptide bond formation while Quinupristin B binds at the beginning of the polypeptide exit tunnel where it blocks short peptidyl tRNA chains entering the tunnel at the beginning of polypeptide translation. Both act synergistically to alter rRNA conformation allowing tight binding and inhibiting cell growth. • Exerts potent *in vitro* activity against gram positives. Demonstrates activity against VISA and VRSA • Either Streptogramin A or streptogramin B molecules can be affected by horizontally transferred resistance determinants but not both. • Approved for serious infections caused by resistance Gram-positives

Table 3c: Glycopeptides, analogs and synthetic glycopeptides.

Daptomycin	2003	• A cyclic anionic peptide with a decanoyl fatty acid side chain that interacts with calcium to form Ca-Dap complex which binds to negatively charged phosphatidylglycerol groups in cell membrane causing cell death through depolarisation, permeabilization and leakage of ions [34]. • Daptomycin resistance (*DapR*) results during prolonged therapy from complex mechanisms. One well established mechanism is through the Multiple Peptide Resistance Factor protein (*MprF). MprF* confers broad-range resistance to host antimicrobial peptides, thereby promoting *S. aureus* cell virulence and pathogenicity [51]. • IDSA recommends high-dose daptomycin, if the isolate is susceptible, in combination with another agent (e.g., gentamicin, rifampin, linezolid, TMP-SMX, or a beta-lactam antibiotic). • Recommended for treatment of high bacterial density or serious infections like endocarditis. • Resistance is emerging in all of the targeted pathogens, but the resistance rates are currently low.
Telavancin	2008	• Semisynthetic lipoglycopeptides. • Inhibits peptidoglycan biosynthesis and cause cell membrane damages [33]. • Approved for ABSSI. Use is limited because of the need for IV administration. • Contraindicated in pregnancy.
Oritavancin	2014	• Oritavancin is an analog of vancomycin that has the main heptapeptide core with other unique substitutions. • Approved for ABSSI. • It shows promise for the treatment of serious infections and activity against daptomycin-nonsusceptible *S. aureus* [33].

Table 3d: Cephalosporins.

Ceftaroline	2010	• Fifth-generation cephalosporin with extended Gram-positive activity. • Only FDA approved cephalosporin with activity against VISA, VRSA and linezolid- and daptomycin-resistant *S. aureus* [49]. • Approved for the treatment of acute bacterial SSSIs and community-acquired pneumonia. • Demonstrates excellent affinity for prominent PBPs that are used by resistant strains [49-50]. • Synergy with carbapenems, azactams and some aminoglycosides. • Low probability of developing resistance. • Favorable safety and tolerability profile.

Table 3e: Others.

Other • Novel benzamide analogs F6. • Natural products: Chitosan (poly (1-4) 2 amino 2-deoxy β-D glucan). • Combination nontraditional agents.	Experimental	Will likely be used in combination form after extensive clinical studies/research.

These include daptomycin, linezolid, telavancin, ceftaroline, and quinupristin-dalfopristin. IDSA recommends the use of high-dose daptomycin (for susceptible isolates) in combination with another agents (e.g., gentamicin, rifampin, linezolid, TMP-SMX, or a beta-lactam antibiotic) for MRSA bacteremia with vancomycin failure [17].

Several other therapies are in the research and development phase, and some have been proposed for off label use. Selected therapies are mentioned here.

Cell-penetrating peptides which can directly deliver biomacromolecules (peptides, proteins, and nucleic acids) to their site of action have generated much attention [45] for VRSA and other Gram-positive infections. A combination of traditional medicine with conventional drugs has also generated much interest [46].

Derivatives of natural products like Chitosan (poly (1-4) 2 amino 2-deoxy β-D glucan), shows potential due to its ability to inhibit VRSA [46,47]. Chitin is one of the most abundant polysaccharides found in nature. Chitosan mechanism of action may be related to its ability to alter the cell wall permeability leading to destabilization, leakage and cell death. Additionally other poorly understood series of multiple simultaneous events may contribute to its bactericidal activity [47]. An example of its clinical application includes promising use as part of a novel nanoscale liquid film-forming system for treatment of resistant *S. aureus* wound infections [48].

Future Trends and Speculations

The prolonged interval between vancomycin use and the appearance of VRSA is reassuring. In the event of a global epidemic, especially with the threat of VRSA diseases with high mortality risk (complicated skin and skin structure diseases, pulmonary, deep organ abscesses and endovascular infections); a public health emergency of potentially epic proportions would ensue. Spread to the developing world would compound its effect; VRSA epidemic coupled with a poorly developed healthcare infrastructure and inequitable resource access would create a "triple whammy" effect, potentially leading to a global public health crisis. Due to these and other factors, VRSA is currently classified as bacteria of high priority with the potential to cause significantly devastating worldwide mortality in the absence of effective containment and therapeutic solutions. Developed countries worldwide maintain an active surveillance system to monitor and combat its spread. Whatever the case, VRSA has come to stay. The next 10-20 years will determine what happens next. Hopefully, things stay silent.

Conclusion

The global threat of a VRSA epidemic is a public health problem that is currently quiet but perhaps brewing. Unlike *S. aureus* resistance to other antibiotic classes, there has been a prolonged interval between vancomycin use and VRSA development and disease has occurred in selected patients with co-morbidities, prolonged vancomycin use and co-infection with VRE. There are limited choices of available drugs effective against VRSA; several promising therapeutic options are in research or development phases. Assessment of the actual effectiveness of these antimicrobials would need full-scale use during an epidemic, an event of global catastrophic proportions that we all hope will not occur.

Acknowledgement

The authors wish to acknowledge Patricia May and Madeline Taylor, of Library Services, at St. Joseph's Health, Paterson NJ for proofreading this paper. We also wish to acknowledge Jessica Escobar of Library services, St. Joseph Health, Paterson, NJ.

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