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Alternative Treatment of Methicillin Resistant *Staphylococcus aureus* Infections: An Update

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Review Article

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Abstract: Vancomycin has been a predominant treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) infections for decades. Due to the resurgence of some resistant and intermediate strains to vancomycin, it is necessary to look for another alternative for continuing if not increased efforts to find novel strategies to combat MRSA infections. This review provides an overview of new conventional antibiotics registered within last three years as well as those that stayed strongly effective to MRSA despite their long usage, we also reviewed the alternative current investigational therapies in early clinical development (up to phase II clinical development) such as natural polyphenols, phage therapies, therapeutic antibodies and quorum sensing inhibitors. This developing portfolio of novel anti-staphylococcal drugs will hopefully provide us with additional and more efficient ways to combat MRSA infections in the near future and prevent us from running out of treatment options, even if new resistances arise.

Keywords: Antibiotics, phage therapy, polyphenols, quorum sensing, therapeutic antibodies.

INTRODUCTION

Resistance to antibiotics is a major threat to the effective therapy of an increasing range of infections caused by bacteria, it is a rapid serious threat to intercontinental public health that requires reaction across all research groups and society. *Staphylococcus aureus* (*S.aureus*), a gram-positive bacterium, remains one of the main causes of morbidity and mortality all-over the world due to the huge spread of antibiotic resistant strains, especially MRSA which was detected for the first time in 1961 (Britain), after approximately 20 years of penicillin efficacy , it is nowadays a "common" bacterium and spread around the world very quickly, it is highly prevalent and resistant against virtually every antibiotic deployed including antimicrobial of the host components [1].

Misuse and overuse of antibiotics has helped the microbes to become resistant, while they were primarily designed to help fight these infections (https://www.niaid.nih.gov/research/mrsa-antimicrobial-resistance-history). Actually, MRSA is completely resistant to the beta-lactams, class of antibiotics such as penicillin, amoxicillin, oxacillin, methicillin, and others. Additionally, *S. aureus* has even begun to show resistance to other antibiotics including vancomycin which had been one of a handful of antibiotics of last resort for use against *S. aureus* [2, 3]. Even if this issue appears to be scary, and possibly become a major issue in antibiotic resistance, vancomycin-resistant strains are still uncommon and rare. According to statistics, the number of resistant microbial strains as well as that of antibiotic-immune patients grows a lot faster than the number of useable antibiotics that make microbial infections the number one killer in the world [4].

The purpose of this review was to explore the updated conventional registered antibiotics for MRSA infection treatment, data related to cause resistance by both focusing on mechanisms of action of the available antibiotics, and proposing the potential and sustainable therapy; most importantly, reviewing the alternative treatments to conventional antibiotics which are being developed as another way to counteract this quick emerging issue.

Genetic basis of methicillin resistance in *Staphylococcus aureus*

The methicillin resistance in *S. aureus* is mediated through mobile genetic elements located in staphylococcal cassette chromosome *mec* (SCCmec) and its regulatory genes *mecR1* and *mecI*, and also the *ccr* gene complex, encoding site-specific recombinase responsible for the movement of the element. The acquisition of this gene encodes a new penicillin-binding protein (PBP2a) that has a lower affinity to methicillin than the endogenous PBPs [5, 6]. The

interaction of β-lactams with the PBPs takes place on the outer surface of the cytoplasmic membrane and leads to a reduction in peptidoglycan cross-linking and loss of the splitting system with the exception of ceftaroline and ceftobiprole [7]. It is important to find out the origin/reservoir of the *mecA* gene for understanding the evolution of MRSA, it may contribute to more effective control measures for MRSA. Genetic and epidemiological studies suggest that the *mec* element is acquired in *S. aureus* by horizontal transfer from methicillin-resistant coagulase-negative staphylococci. Staphylococcal genomes seem to change continuously as genetic elements move in and out, but no mechanism of transfer has been found responsible for moving SCC elements between different staphylococcal species [8]. The mode of strain-to-strain transfer has, however, not yet been elucidated. The origin of the *mec* element is still unclear. *S. sciuri* and S. *vitulinus* are considered as the highly probable origin of the *mecA* gene as they contain *mecA* gene homologues with 80% and 91% nucleotide respectively although the native *S. sciuri mecA* gene does not confer methicillin resistance [9, 10]. Methicillin resistance seems to be as complex as cell growth and separation. Apparently any factor involved in that process seems to play a role in methicillin resistance. The transposon-mediated inactivation of methicillin resistance can be exploited as a tool to identify factors involved in cell wall metabolism. The exact functions of PBP2b in resistance are still unclear; its apparently low flexibility concerning its optimal substrate is countered by the *S. aureus* versatility in making use of compensatory mutations to optimize resistance as required [5, 11]. Apart from methicillin resistant strains, since 1997 a MRSA isolate with a slight susceptibility to vancomycin was first found in Japan [12]. The isolate had only a modestly increased minimum inhibitory concentration (MIC) value for vancomycin, in the range of 3–8 μg/ml, and became known as vancomycin intermediate-resistant *S. aureus* (VISA). VISA isolates do not carry imported foreign genetic elements; rather, the increased vancomycin MIC values are related to mutations that appear in the invading pathogen during vancomycin therapy in vivo. In 2002, the first vancomycin-resistant *S. aureus* (VRSA) strain (with a vancomycin MIC value greater than 100 μg/ml) was reported in the United States [13]. Earlier in 1992, Noble *et al.*[14] demonstrated that conjugal transfer of the *vanA* gene, which mediates vancomycin resistance, from vancomycin Resistant Enterococci to MRSA on the skin surface of hairless mice could be achieved, creating VRSA. However, the mechanism of resistance in *S. aureus* is either mediated by *vanA* [15] or a change in cell physiology caused by genetic mutations and altered expression of certain genes, resulting in a characteristic thickened cell wall that prevented vancomycin from reaching its target [16]. Detailed mechanisms of vancomycin resistance in *S. aureus* has well described by Susana and Alexander [2]. Despite these complexities and controversies, vancomycin is likely to remain an option for the treatment of MRSA.

Treatment of Methicillin-Resistant *Staphylococcus aureus* infections

After methicillin failure after only two years of its usage in treatment of MRSA infections, vancomycin has since then taken over until now, even though it is expensive and must be administered intravenously [http: //apps.who.int/medicinedocs/pdf/s5406e/s5406e.pdf.]. It is a glycopeptide with activity against gram-positive pathogens through inhibition of cell wall synthesis [17]. Actually, vancomycin was discovered by Eli Lilly in the 1950s, from organism *Amycolatopsis orientalis* (previously designated *Streptomyces orientalis* and *Nocardia orientalis*) and was approved for use by the U.S. Food and Drug Administration (FDA) in 1958 [18]. It is an inhibitor of cell wall synthesis in the gram-positive organisms, it binds to the C-terminal D-Ala-D-Ala residue of the peptidoglycan precursor and forms a stable, noncovalent complex, which prevents the use of the precursor for cell wall synthesis while beta-lactam antibiotics binds to the transpeptidase active site of penicillin binding proteins [19]. It inhibits late-stage peptidoglycan biosynthesis and acts outside the cytoplasmic membrane, which results in the intracellular accumulation of UDP-linked MurNAc-pentapeptide precursors [20]. The vancomycin complex involves a number of hydrogen bonds between the peptide component of vancomycin and the D-Ala-D-Ala residue [17]. Any process that interferes with vancomycin binding to D-Ala-D-Ala residues in the cell wall will decrease the potency of the drug. The addition of "false" binding sites (e.g., a D-Ala-D-Ala-containing ligand) to a bacterial culture containing vancomycin leads to competition between binding sites and a reduction of vancomycin activity [21].

No new antimicrobial agents had demonstrated superiority over vancomycin in clinical trials, the Infectious Diseases Society of America MRSA treatment guidelines at the time of publication recommended vancomycin as first-line therapy regardless of its MIC and switching to alternative therapy if there is documented clinical or microbiologic failure [22]. For isolates with an MIC > 2 μg/mL there is no need to use vancomycin, an alternative agent should be administered. However other glycopeptides have shown their potential against MRSA infections. Teicoplanin, a glycopeptide with a similar mode of action to vancomycin has shown inferior efficacy compared with vancomycin [23]. These results can be explained by inadequate dosing of teicoplanin secondary to greater protein binding compared with vancomycin [24]. But at higher and appropriate dosing, it is not inferior to vancomycin [25] and may be associated with a lower rate of adverse events. Higher teicoplanin MICs have also been associated with poor clinical outcomes and increased mortality in

teicoplanin-treated patients with MRSA bacteremia and pneumonia [26].

For Vancomycin Intermediate *S. aureus* strains (VISA) , therapy resides on combinatorial treatment; Rifampin and fusidic acid both possess good *in vitro* activity against multiresistant MRSA infections orally [27]. Used alone, these agents develop resistant rapidly, therefore it is imperative to always be used in combination with another effective antibiotic. Typical combinations include rifampin and fusidic acid or rifampin plus an effective quinolone to MRSA [17]. Linezolid, a drug within a class of completely synthetic antimicrobial agents, oxazolidinones, antibiotics that inhibit bacterial protein synthesis by preventing the formation of the 70S initiation complex presents activity against MRSA and VISA [28]. A main challenge with linezolid, however, is toxicity. Tedizolid, an engineered oxazolidinone that has been developed to improve linezolid bioavailability and efficacy but reduce toxicity compared with linezolid, may be preferred (29). It is dosed once daily and its potency is 4 to 16 times greater than linezolid with activity against linezolid nonsusceptible *S. aureus* isolates [30]. Ceftaroline is also used where vancomycin failed. It is an advanced-generation cephalosporin that got approval back in 2010 for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP). In vitro, it has displayed activity against heterogeneous vancomycin-intermediate *S. aureus* (hVISA), vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus (31).* An *in vivo* study confirmed Ceftarolin superiority over to vancomycin in eradicating MRSA (90% versus 67%) and hVISA (60% versus 0%) [32]. Additionally, Ceftaroline has responded very well to the patients who have not been treated by vancomycin, linezolid and daptomycin for MRSA bacteremia, making it a best option for such patients [33]. Although the FDA-approved dosing regimen for ceftaroline fosamil is 600 mg every 12 hours for patients with normal renal function for the treatment of ABSSSI and CABP (https://www.allergan.com/assets/pdf/teflaro_pi), till now there is no exact dose available for MRSAB, there is some hesitation about whether more frequent doses (i.e., every 8 hours), the research is underway; an ongoing prospective clinical trial will hopefully shed light on the optimal ceftaroline dosing strategy for the treatment of MRSAB. Ceftobiprole is another antistaphylococcal cephalosporin with greater spectrum of activity than ceftaroline [34]. Similar to ceftaroline, it retains activity against more resistant *S. aureus* strains including those with elevated vancomycin MIC. Its broad-spectrum activity may allow it to be used as monotherapy in situations where a combination of antibacterials might be required.

Daptomycin, an antibacterial agent first licensed for human use in 2003 belonging to a cyclic lipopeptide class of antibiotics is also associated with a better outcome in MRSA BSIs for treatment of strains with higher vancomycin MICs [35]. Its mechanism of action consists in calcium-dependent binding to the cytoplasmic membrane resulting in rapid membrane depolarization and efflux of potassium [36]. This results in the arrest of protein synthesis and leads to rapid cell death. It is active against methicillin- and vancomycin-resistant staphylococci. Note that it cannot be used in the pneumonia treatment due to its inactivation by pulmonary surfactant (29). Some authors have recommended to use high doses to minimize the emergence of elevated MIC values, which has been associated with an increase in the vancomycin MIC and the heteroresistant phenotype (hVISA) [37]. Another powerful anti MRSA infections is Dalbavancin, a semisynthetic lipoglycopeptide with a pharmacokinetic profile that allows for once-weekly dosing, only 2 dalbavancin IV infusions, separated by 1 week, are required for the treatment of bacterial infection [38]. Dalbavancin like other semisynthetic lipoglycopeptides such as oritavancin works by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in the bacterial cell wall peptidoglycan, which prevents crosslinking. This interferes with bacterial cell wall synthesis [39].The most recent antibiotics against MRSA infections, approved by FDA are summarized in Table-1.

Apart from monotherapy used against MRSA infections, many antibacterial agents are combined to result in synergic effect. Combination therapies have a distinct advantage over monotherapies in terms of their broad spectrum, synergistic effect and prevention of the emergence of drug resistance. However, the above alternatives to vancomycin haven't indicated any inferiority to vancomycin for the treatment of MRSA infections, but none have established superiority except from VISA or VRSA. Combination therapy with Vancomycin and Ceftaroline for Refractory Methicillin-resistant *S. aureus* Bacteremia has proven its potential compared with those antibiotics used as monotherapy [40]. For cases of persistent MRSA bacteremia or VISA infections, combination antibiotic therapy may be an option. The *in vitro* studies have reported synergy between vancomycin and ceftaroline that may be greater than other β-lactam antibiotics [41].This combination possess greater bactericidal activity than ceftaroline alone, even than the combination of either vancomycin and oxacillin, or daptomycin and ceftaroline [40]. However, vancomycin plus ceftaroline showed synergistic activity against more VISA and hVISA isolates compared with the combination of vancomycin and oxacillin [42]. The mechanism for this synergy is not well elucidated [43-45]. It appears that Ceftaroline reduces cell wall thickness that is associated with hVISA and VISA, which normally would prevent vancomycin sequestration, improving vancomycin penetration into the septum of dividing. However, additional studies are warranted to further define its

dose and its role in salvage therapy of persistent MRSA bacteremia. Another interesting combination is built up with ceftaroline and daptomycin to yield an excellent clinic outcome against Daptomycin-Nonsusceptible and Vancomycin-Intermediate Staphylococcus aureus [45]. The enhanced activity observed in the model with this combination seems to be mediated through enhanced binding of the Daptomycin-calcium complex secondary to increased membrane negativity, binding of Daptomycin, and enhanced membrane depolarization in Ceftaroline-exposed cells. This proposed mechanism of therapeutic enhancement is consistent with what has been published regarding the combination of Daptomycin and beta-lactams in both staphylococci and enterococci [46, 47]. In fact, daptomycin plus antistaphylococcal β-lactams (ASBL) were used to clear refractory MRSA bacteremia. In vitro studies showed enhanced daptomycin bactericidal activity, increased membrane daptomycin binding, and decrease in positive surface charge induced by ASBLs against daptomycin nonsusceptible MRSA. The enhancement of daptomycin membrane binding and activity by ASBLs through ASBL-mediated reduction in surface charge may be linked to release of wall lipo-teichoic acid [48]. Addition of ASBLs to daptomycin may be of benefit in refractory MRSA bacteremia. Recently, *in vitro* activity with promising outcomes of daptomycin combined with dalbavancin and linezolid, and dalbavancin with linezolid against MRSA strains has been assessed by Gulseren and Sengul [49]. The rates of synergistic effects were 67% for daptomycin combined with dalbavancin and with linezolid, and 60% for dalbavancin combined with linezolid. More studies are still in need to upgrade these combinations on clinic level.

MRSA alternative treatment over to conventional antibiotics

As durable response to escape the increasingly widespread presence of *S. aureus* strains resistant to multiple antibiotics treatment, researchers are focusing on developing new antibacterial agents in new way of mechanisms of actions such as Phage Therapy, Quorum sensing inhibitors, Therapeutic antibodies and natural polyphenols.

Phage therapies

Bacteriophages, or phages, are viruses which infect bacteria. A large subset of phages infect bactericidally and, consequently, for nearly one hundred years have been employed as antibacterial agents both within and outside of medicine [50]. As the lytic action of bacteriophages is unaffected by the antibiotic resistance status of their bacterial target, it is possible that phage therapy may have considerable potential in the treatment of a wide range of topical and localized infections, even more it may be used via intravenous route for staphylococcal bacteremia. Therefore, phages have been used intravenously in 1940s for typhoid treatment [51]. Nonetheless, though the 1920s were the years of clinic use of the first human phage therapy, by the 1940s it started declining despite its early promising trend [52]. The main causes were: insufficient understanding among researchers of basic phage biology; over exuberance, which led, along with ignorance, to carelessness; and the emergence of powerful antibiotics which were easier to handle. But in some parts of world, especially in the former Soviet Republic of Georgia, phage therapy traditions and practice continue to this day. The huge antibacterial resistance emergence has helped bring about a resurgence in interest in phage therapy, but this appears not to have included the IV use of phages, which were used effectively and safely by this route over an extensive period starting almost 100 years ago against different pathogens including MRSA [51, 52]. It's up to clinic researchers, physicians and ethic committee members to reconsider this therapy. In terms of therapeutics, drug developers favor lytic phages, which replicate inside the bacterial cell and cause it to rupture, releasing the new viruses rather than Lysogenic phages, which incorporate their genetic material into the bacterial DNA because they might spread resistance or virulence factors among bacteria. If the phage does not meet its adversary, it is cleared harmlessly by the body.

However, at present, two anti-staphylococcal phage therapies are underway in clinical Phase I trials: P128 from GangaGen and CF-301 from Contrafect [53]. The first is a chimeric protein combining the lethal activity of the phage tail-associated muralytic enzyme of Phage K and the staphylococcal cell wall targeting-domain (SH3b) of lysostaphin [54]. Preclinical studies revealed that the bactericidal activity of P128 against *S. aureus* is dose dependent [7]. On the other hand, CF-301 is a bacteriophage-derived lysin with strong activity against *S. aureus* bacteremia. CF-301 is the first and only lysin to enter human clinical trials in the US and has recently completed a Phase 1 trial in healthy volunteers (https://www.contrafect.com/pipeline/cf-301). Its catalytic domain belongs to the N-terminal amidohydrolase/ peptidase family; the C-terminal domain belongs to the SH3b family of cell wall-binding proteins [55].

Quorum sensing inhibitors

Quorum sensing (QS) is a process by which bacteria produce and detect signal molecules and thereby coordinate their behavior depending on the bacterial population density [56]. It involves small diffusible signaling molecules which activate the expression of myriad genes that control diverse array of functions such as biofilm formation, sporulation, bioluminescence, virulence, etc. Since QS is responsible for virulence in the clinically relevant bacteria, inhibition of QS appears to be a promising strategy to control these pathogenic bacteria. In fact, Quorum sensing inhibitors (QSIs) do not kill nor inhibit bacteria, they only attenuate their virulence and therefore are less

likely to yield resistant phenotype. As QS is not found in humans and is vital for the expression of bacterial virulence, QS is a highly specific antibacterial target. The QS system of Gram-positive bacteria typically consists of signaling peptides such as Accessory Gene Regulator (Agr) and RNA-III activating/inhibiting peptides (RAP/RIP) in *S. aureus*, and a two-component regulatory system made up of a membrane-bound sensor and an intracellular response regulator [57]. Agr controls expression of several cytolytic bacterial toxins and cell surface antigens. The extracellular QS signal of Agr is a post-translationally modified peptide, auto-inducing peptide (AIP). Nucleotide variation within the Agr operon generates AIPs with different amino acid sequences but a conserved thiolactone (or, rarely, lactone) ring structure. Further detailed molecular mechanism regarding Agr system has well discussed by Bhardwaj *et al.* [58]. The most important thing to highlight here is to mention that any molecular which will inhibit Agr system will result in attenuating the virulence of *S. aureus* and reducing the progression and persistence of disease caused by the pathogen. Savirin (*S. aureus* virulence inhibitor) is a such molecule that disrupted Agr-mediated quorum sensing in this pathogen, it is a *S. aureus*-specific Agr inhibitor that inhibits all Agr types and exerts its activity through direct interaction between AgrA and target DNA sequences. In vivo study in mice, *S. aureus* and savarin have been injected together resulting in severity and size reduction of dermonecrosis [59]. These findings would place savarin as one of the most promising molecules for therapeutic development targeted at Agr QS to date. Furthermore, it is suggested that antibodies may inhibit Agr system. When the isolated monoclonal antibody (mAb), AP4-24H11, was incubated with an Agr group IV strain (RN4850) a-toxin production was inhibited; also this combination were injected to the mouse resulting in significant suppression of dermonecrosis severity of skin and soft tissue infection, suggesting that AP4-24H11 interferes with the Agr QS system [60]. Despite a large number of molecules demonstrated Agr inhibitory activity against *S. aureus* in vitro, fewer *in vivo*, from different origins such as fungi, bacteria, plants and synthetics, none has stepped up to the next level of preclinical studies [7]. More studies are still remaining to upgrade these drugs at clinical level.

Therapeutic antibodies

Antibody therapies are a type of biologic. They are typically monoclonal antibodies selected to bind to a particular protein (often a cell-surface protein), and produced using recombinant DNA technology (https://www.nature.com/subjects/antibody-therapy). Generally, Antibodies are proteins made by the immune system that bind to specific markers on cells or tissues. Monoclonal antibodies are a type of antibody made in the laboratory that can be used in diagnosis or treatment of cancer, infection, or other diseases. *S. aureus* produces potent hemolysins, several superantigens, phenol soluble modulins and leukotoxins. Among the leukotoxins, some were identified to lyse neutrophils after ingestion, representing an especially powerful weapon against bacterial elimination by innate host defense [61]. Furthermore, *S. aureus* secretes many factors that inhibit the complement cascade or prevent recognition by host defenses. Antibodies can neutralize the staphylococcal toxins, staphylococcal surface proteins, staphylococcal non-protein antigens, *S. aureus* cell wall components or against AIPs. The detailed mechanisms of action of therapeutic antibodies have been recently reviewed by Vuong *et al.*, [7]. Unfortunately, at present no therapeutic antibody available to be used in clinic, most of them are still stuck on animal model level, few have stepped up and reflected to human clinical trials such as bacterial surface carbohydrate antigen, poly-N-acetylglucosamine PNAG-specific mAb, SAR279356, created by Sanofi, that was tested in a Phase II clinical trial, but after termination of this study no results were reported https://clinicaltrials.gov/show/NCT01389700). Actually, PNAG or polysaccharide intercellular adhesion , contributes to intercellular adhesion, biofilm formation, immune evasion and is an important virulence determinant [62, 63]. A deacetylated form of PNAG induces opsonic antibodies, which when administered passively protect mice against *S. aureus* induced bacteremia and lethal challenge [64].

Vaccination essays have also interested researchers with many success at level of preclinical studies [65-67]. A promising *S. aureus* 4-Antigen (SA4Ag) vaccine is being investigated in Phase II trials and the study completion is estimated to November 7, 2018 (https://clinicaltrials.gov/ct2/show/NCT02388165, http://www.mayo.edu/research/clinical-trials/cls-20151078), the purposes is to determine whether it can prevent postoperative *S. aureus* infections in patients who are undergoing elective spinal fusion surgery, and to evaluate its safety in patients who are undergoing elective spinal surgery. In clinical trial Phase I, it had increased the immune response to all patients, and antibodies demonstrated potent opsonophagocytic activities; but also this vaccine was well tolerated after one dose [68].

Natural polyphenols

In the combat against MRSA infections, natural products from higher plants were not left behind as they have traditionally been regarded as an important source of antimicrobial agents and have attracted extensive attention in fundamental and clinic applications [69]. Most of the time, screening studies combined with antibacterial studies showed that polyphenols are responsible of those activities [70]. Several *in vitro* antistaphylococcal studies against MRSA and MSSA (Methicillin Susceptible *S. aureus*) of polyphenols have revealed that there are no obvious differences in susceptibility to these MRSA and MSSA strains [71], which make us to suggest that polyphenols

mechanisms of actions are different from those for conventional antibiotics. Even if most of polyphenolic compounds exhibit anti MRSA effect, few of them are considered as strong antibacterial agents [70]; MRSA strains are resistant to most of them, but also intermediate or susceptible to some like anthraquinones and prenylated flavonoids that showed antibacterial effects with MIC values of 2–8 µg /ml [72]. In the same study, licoricidin whose low effective concentration was 4 µg /ml, in addition to its prolonged effect (24 h) which made its performance superior to that of other compounds tested together. Aloe-emodin is also classified among potent antibacterial agents with a MIC of 2 µg/ml [73]. Gossypol, a polyphenolic compound from cotton seeds has shown its power against some *S. aureus* strains; between two tested strains, susceptibility occurred at 3.12 µg/ml and 1.95 µg/ml [74].

The synergistic effect of polyphenols in combination with conventional antimicrobial agents against clinical multidrug-resistant microorganisms have been extensively discussed by several authors, [75-77], the purpose of that combination was to potentiate their efficacy, to lower antibiotic dose, and therefore to reduce antibiotic adverse reactions.

In study conducted by Lin *et al*., 2008, the *in vitro* activities of 10 antibiotics and 15 natural polyphenols against the MRSA isolates were evaluated [77]. All isolates were susceptible to vancomycin and resistant to rifampicin, while susceptibilities to ciprofloxacin varied. Among the natural polyphenols, kaempferol and quercetin exhibited the lowest MICs, whereas combinations of rifampicin and either kaempferol or quercetin acted synergistically against the clinical MRSA isolates. Rifampicin combined with kaempferol or quercetin displayed good β-lactamase inhibitory effects (57.8% and 75.8%, respectively) against a representative isolate. This may be explained by the fact that both quercetin and kaempferol inhibit the catalytic activity of different bacterial topoisomerases [78]. The same synergic activity was observed later with fluoroquinolones, kaempferol Glycosides purified from *Laurus nobilis*, greatly reduced the MICs of some fluoroquinolones in MRSA [79]. In other words, kaempferol greatly potentiated anti-MRSA activity of fluoroquinolones. Epigallocatechin gallate (EGCg) a main constituent of tea catechins, acts synergistically with β-lactams against MRSA [80]. Regarding to the mechanism of action, EGCg damages the bacterial cell wall by binding with peptidoglycan, hence the synergism between EGCg and β-lactams [81]. Combinations of carbapenems and EGCg also showed potent synergy against clinical isolates of MRSA [82], the MIC at which 50% of the isolates treated with Imipenem were inhibited, decreased from 128 µg/ml to 64, 32, 8, 8, and 0.25 µg/ml when in combination with 1.56, 3.125, 6.25, 12.5, and 25 µg of EGCg/ml, respectively. Despite the promising anti MRSA activity of natural polyphenols, at the moment no study went beyond the preclinical studies neither as monotherapy nor as combination with conventional antibiotics.

Table-1: New anti MRSA agents approved for treatment of acute staphylococcal skin infections

Antibiotic	Mechanism of action	Class of antibiotic/ Registration Status	Microbial resistance	Interactions	Formulations & administration
Dalbavancin[1]	Inhibits cell wall synthesis	Lipoglycopeptide/ FDA(2014)	*VanA* results in modification of the target peptide in the nascent cell wall	NE	500 mg single-use vials. 1000 mg on day one followed by 500 mg 1 week later
Oritavancin[1]	Inhibition of transglycosylation, Inhibition of transpeptidation, and cell membrane disruption	lipoglycopeptide/ FDA(2014)	NE	Synergy with linezolid gentamicin.	Three 400 mg vials as single dose
Tedizolid[1]	Inhibition of protein synthesis	oxazolidinone/ FDA(2014)	Mutations in chromosomal genes encoding 23S subunit rRNA or ribosomal proteins	NE	200 mg administered either for 6 days orally once daily or as an *i.v.* infusion over 1 h (also once daily for 6 days)
Delafloxacin[2]	Stabilize cleavable complexes by binding either gyrase or topoisomerase IV	Fluoroquinolone/ FDA(2017)	NE	Chelates metals, divalent and trivalent cations	450 mg tablet orally every 12 hours for a 5 to 14 days
Oritavancin[3]	transglycosylation and transpeptidation inhibition	Lipoglycopeptide/ FDA(2014)	NE	cholera vaccine and heparin,	Injection, 400 mg/vial

[1][30] ; [2][83] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/208610Orig1s000,208611Orig1s000ltr.pdf, [3][84].

CONCLUSION

Research on anti-staphylococcal drugs is advancing in all areas. Even though, according to statistics, the number of resistant microbial strains as well as that of antibiotic-immune patients grows a lot faster than the number of useable antibiotics [4], several alternative drugs have emerged, but the most part still in preclinical development. It's up to researchers to continue to focus on these future promising new antibiotics as the new resistant staphylococcal strains to conventional antibiotics are quickly emerging and expanding.

REFERENCES

1. Alipiah NM, Shamsudin MN, Yusoff FM, Arshad A. Membrane biosynthesis gene disruption in methicillin-resistant *Staphylococcus aureus* (MRSA) as potential mechanism for reducing antibiotic resistance. Indian journal of microbiology. 2015;55(1):41-9.
2. Gardete S, Tomasz A. Mechanisms of vancomycin resistance in *Staphylococcus aureus*. The Journal of clinical investigation. 2014;124(7):2836.
3. Van Hal SJ, Fowler Jr VG. Is it time to replace vancomycin in the treatment of methicillin-resistant Staphylococcus aureus infections? Clinical Infectious Diseases. 2013;56(12):1779-88.
4. Kharadze D, Memanishvili T, Mamulashvili K, Omiadze T, Kirmelashvili L, Lomtatidze Z. In Vitro Antimicrobial Activity Study of Some New Arginine-based Biodegradable Poly (Ester Urethane) s and Poly (Ester Urea) s. J Chem. 2015;9:524-32.
5. Berger-Bächi B. Genetic basis of methicillin resistance in *Staphylococcus aureus*. Cellular and Molecular Life Sciences. 1999;56(9):764-70.
6. Mustapha M, Bukar-Kolo YM, Geidam YA, Gulani IA. Review on Methicillin-resistant *Staphylococcus aureus* (MRSA) in Dogs and Cats. Int J Anim Vet Adv. 2014;6(2):61-73.
7. Vuong C, Yeh AJ, Cheung GY, Otto M. Investigational drugs to treat methicillin-resistant *Staphylococcus aureus*. Expert opinion on investigational drugs. 2016;25(1):73-93.
8. Hanssen AM, Ericson Sollid JU. SCCmec in staphylococci: genes on the move. Pathogens and Disease. 2006;46(1):8-20.
9. Tsubakishita S, Kuwahara-Arai K, Sasaki T, Hiramatsu K. Origin and molecular evolution of the determinant of methicillin resistance in staphylococci. Antimicrobial agents and chemotherapy. 2010;54(10):4352-9.
10. Calazans-Silva AC, Medeiros PT, Araujo DM, Carvalho BO, Coelho IS, Coelho SM. Genetic analysis of mecA gene and detection of homologue pbpD in *Stahylococcus sciuri* group. Brazilian Journal of Microbiology. 2014;45(2):651-5.
11. Gomez E, Chiang T, Hogan PA, Myers DE, Huang DB. Methicillin-resistant Staphylococcus aureus SCCmec type and its association with clinical presentation, severity, and length of stay among patients with complicated skin and skin structure infections. Advances in Infectious Diseases. 2014;4(2):111-5.
12. Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover F. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. The Journal of antimicrobial chemotherapy. 1997;40(1):135-6.
13. Sievert DM, Rudrik JT, Patel JB, McDonald LC, Wilkins MJ, Hageman JC. Vancomycin-resistant *Staphylococcus aureus* in the United States, 2002–2006. Clinical Infectious Diseases. 2008;46(5):668-74.
14. Noble W, Virani Z, Cree RG. Co-transfer of vancomycin and other resistance genes from Enterococcus faecalis NCTC 12201 to *Staphylococcus aureus*. FEMS microbiology letters. 1992;93(2):195-8.
15. Chang S, Sievert DM, Hageman JC, Boulton ML, Tenover FC, Downes FP. Infection with vancomycin-resistant *Staphylococcus aureus* containing the vanA resistance gene. New England Journal of Medicine. 2003;348(14):1342-7.
16. Cui L, Ma X, Sato K, Okuma K, Tenover FC, Mamizuka EM. Cell wall thickening is a common feature of vancomycin resistance in *Staphylococcus aureus*. Journal of clinical microbiology. 2003;41(1):5-14.
17. Howden BP, Davies JK, Johnson PD, Stinear TP, Grayson ML. Reduced vancomycin susceptibility in *Staphylococcus aureus*, including vancomycin-intermediate and heterogeneous vancomycin-intermediate strains: resistance mechanisms, laboratory detection, and clinical implications. Clinical microbiology reviews. 2010;23(1):99-139.
18. Levine DP. Vancomycin: a history. Clinical Infectious Diseases. 2006;42(Supplement_1):S5-S12.
19. Pootoolal J, Neu J, Wright GD. Glycopeptide antibiotic resistance. Annual review of pharmacology and toxicology. 2002;42(1):381-408.
20. Reynolds P. Studies on the mode of action of vancomycin. Biochimica et biophysica acta. 1961;52(2):403-5.
21. Allen NE, LeTourneau DL, Hobbs J. Molecular interactions of a semisynthetic glycopeptide antibiotic with D-alanyl-D-alanine and D-alanyl-D-lactate residues. Antimicrobial agents and chemotherapy. 1997;41(1):66-71.
22. Liu C. Infectious Diseases Society of America. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011;52:e18-e55.
23. Thwaites GE, Edgeworth JD, Gkrania-Klotsas E, Kirby A, Tilley R, Török ME. Clinical management of *Staphylococcus aureus* bacteraemia. The Lancet infectious diseases. 2011;11(3):208-22.

24. Bailey EM, Rybak M, Kaatz G. Comparative effect of protein binding on the killing activities of teicoplanin and vancomycin. Antimicrobial agents and chemotherapy. 1991;35(6):1089-92.
25. Yoon YK, Park DW, Sohn JW, Kim HY, Kim YS, Lee CS. Multicenter prospective observational study of the comparative efficacy and safety of vancomycin versus teicoplanin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrobial agents and chemotherapy. 2014;58(1):317-24.
26. Chen KY, Chang HJ, Hsu P-C, Yang CC, Chia JH, Wu TL. Relationship of teicoplanin MICs to treatment failure in teicoplanin-treated patients with methicillin-resistant *Staphylococcus aureus* pneumonia. Journal of Microbiology, Immunology and Infection. 2013;46(3):210-6.
27. Zinn CS, Westh H, Rosdahl VT, Group SS. An international multicenter study of antimicrobial resistance and typing of hospital *Staphylococcus aureus* isolates from 21 laboratories in 19 countries or states. Microbial drug resistance. 2004;10(2):160-8.
28. Hamdan EM, Majda AA. Linezolid versus Vancomycin for the Treatment of Methicillin-Resistant *Staphylococcus aureus* in Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia at Tertiary Care Hospital. Advances in Infectious Diseases. 2017;7(01):11.
29. Holmes NE, Tong SY, Davis JS, van Hal SJ. editors. Treatment of methicillin-resistant *Staphylococcus aureus*: vancomycin and beyond. Seminars in respiratory and critical care medicine; 2015: Thieme Medical Publishers.
30. Tatarkiewicz J, Staniszewska A, Bujalska-Zadrożny M. New agents approved for treatment of acute staphylococcal skin infections. Archives of medical science: AMS. 2016;12(6):1327.
31. Saravolatz LD, Pawlak J, Johnson LB. In vitro susceptibilities and molecular analysis of vancomycin-intermediate and vancomycin-resistant Staphylococcus aureus isolates. Clinical infectious diseases. 2012;55(4):582-6.
32. Jacqueline C, Caillon J, Le Mabecque V, Miegeville AF, Hamel A, Bugnon D. In vivo efficacy of ceftaroline (PPI-0903), a new broad-spectrum cephalosporin, compared with linezolid and vancomycin against methicillin-resistant and vancomycin-intermediate *Staphylococcus aureus* in a rabbit endocarditis model. Antimicrobial agents and chemotherapy. 2007;51(9):3397-400.
33. Pinckney White B, Barber KE, Stover KR. Ceftaroline for the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. American Journal of Health-System Pharmacy. 2017;74(4).
34. Chong YP, Park SJ, Kim HS, Kim ES, Kim MN, Kim SH. In vitro activities of ceftobiprole, dalbavancin, daptomycin, linezolid, and tigecycline against methicillin-resistant *Staphylococcus aureus* blood isolates: stratified analysis by vancomycin MIC. Diagnostic microbiology and infectious disease. 2012;73(3):264-6.
35. Moore CL, Osaki-Kiyan P, Haque NZ, Perri MB, Donabedian S, Zervos MJ. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant *Staphylococcus aureus* with a high vancomycin minimum inhibitory concentration: a case-control study. Clinical Infectious Diseases. 2011;54(1):51-8.
36. Steenbergen JN, Alder J, Thorne GM, Tally FP. Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections. Journal of antimicrobial Chemotherapy. 2005;55(3):283-8.
37. Múnera JMV, Ríos AMO, Urrego DM, Quiceno JNJ. In vitro susceptibility of methicillin-resistant *Staphylococcus aureus* isolates from skin and soft tissue infections to vancomycin, daptomycin, linezolid, and tedizolid. The Brazilian Journal of Infectious Diseases. 2017.
38. Cada DJ, Ingram K, Baker DE. Dalbavancin. Hospital pharmacy. 2014;49(9):851-61.
39. Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW. Once-weekly dalbavancin versus daily conventional therapy for skin infection. New England Journal of Medicine. 2014;370(23):2169-79.
40. Gritsenko D, Fedorenko M, Ruhe JJ, Altshuler J. Combination Therapy With Vancomycin and Ceftaroline for Refractory Methicillin-resistant *Staphylococcus aureus* Bacteremia: A Case Series. Clinical therapeutics. 2017;39(1):212-8.
41. Sakoulas G, Moise PA, Casapao AM, Nonejuie P, Olson J, Okumura CY. Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline. Clinical therapeutics. 2014;36(10):1317-33.
42. Werth B, Vidaillac C, Murray K, Newton K, Sakoulas G, Nonejuie P. Novel combinations of vancomycin plus ceftaroline or oxacillin against methicillin-resistant vancomycin-intermediate *Staphylococcus aureus* (VISA) and heterogeneous VISA. Antimicrobial agents and chemotherapy. 2013;57(5):2376-9.
43. Barber KE, Rybak MJ, Sakoulas G. Vancomycin plus ceftaroline shows potent in vitro synergy and was successfully utilized to clear persistent daptomycin-non-susceptible MRSA bacteraemia. Journal of Antimicrobial Chemotherapy. 2014;70(1):311-3.
44. Kaushik D, Rathi S, Jain A. Ceftaroline: a comprehensive update. International journal of antimicrobial agents. 2011;37(5):389-95.
45. Werth BJ, Sakoulas G, Rose WE, Pogliano J, Tewhey R, Rybak MJ. Ceftaroline increases membrane binding and enhances the activity of daptomycin against daptomycin-nonsusceptible vancomycin-intermediate *Staphylococcus aureus* in a pharmacokinetic/pharmacodynamic model.

Antimicrobial agents and chemotherapy. 2013;57(1):66-73.
46. Dhand A, Bayer AS, Pogliano J, Yang SJ, Bolaris M, Nizet V. Use of antistaphylococcal β-lactams to increase daptomycin activity in eradicating persistent bacteremia due to methicillin-resistant *Staphylococcus aureus*: role of enhanced daptomycin binding. Clinical infectious diseases. 2011;53(2):158-63.
47. Sakoulas G, Bayer AS, Pogliano J, Tsuji BT, Yang SJ, Mishra NN. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin-and vancomycin-resistant Enterococcus faecium. Antimicrobial agents and chemotherapy. 2012;56(2):838-44.
48. Al-Obeid S, Gutmann L, Williamson R. Correlation of penicillin-induced lysis of Enterococcus faecium with saturation of essential penicillin-binding proteins and release of lipoteichoic acid. Antimicrobial agents and chemotherapy. 1990;34(10):1901-7.
49. Aktas G, Derbentli S. In vitro activity of daptomycin combined with dalbavancin and linezolid, and dalbavancin with linezolid against MRSA strains. Journal of Antimicrobial Chemotherapy. 2016;72(2):441-3.
50. Abedon ST. Information Phage Therapy Research Should Report. Pharmaceuticals. 2017;10(2):43.
51. Speck P, Smithyman A. Safety and efficacy of phage therapy via the intravenous route. FEMS microbiology letters. 2015;363(3):fnv242.
52. Kutter E, De Vos D, Gvasalia G, Alavidze Z, Gogokhia L, Kuhl S. Phage therapy in clinical practice: treatment of human infections. Current pharmaceutical biotechnology. 2010;11(1):69-86.
53. Kingwell K. Bacteriophage therapies re-enter clinical trials. Nature Reviews Drug Discovery. 2015;14(8):515-6.
54. Vipra AA, Desai SN, Roy P, Patil R, Raj JM, Narasimhaswamy N. Antistaphylococcal activity of bacteriophage derived chimeric protein P128. BMC microbiology. 2012;12(1):41.
55. Schuch R, Lee HM, Schneider BC, Sauve KL, Law C, Khan BK. Combination therapy with lysin CF-301 and antibiotic is superior to antibiotic alone for treating methicillin-resistant *Staphylococcus aureus*–induced murine bacteremia. The Journal of infectious diseases. 2013;209(9):1469-78.
56. Brackman G, Coenye T. Quorum sensing inhibitors as anti-biofilm agents. Current pharmaceutical design. 2015;21(1):5-11.
57. Thoendel M, Horswill AR. Identification of *Staphylococcus aureus* AgrD residues required for autoinducing peptide biosynthesis. Journal of Biological Chemistry. 2009;284(33):21828-38.
58. K Bhardwaj A, Vinothkumar K, Rajpara N. Bacterial quorum sensing inhibitors: attractive alternatives for control of infectious pathogens showing multiple drug resistance. Recent patents on anti-infective drug discovery. 2013;8(1):68-83.
59. Sully EK, Malachowa N, Elmore BO, Alexander SM, Femling JK, Gray BM. Selective chemical inhibition of agr quorum sensing in *Staphylococcus aureus* promotes host defense with minimal impact on resistance. PLoS pathogens. 2014;10(6):e1004174.
60. Khan BA, Yeh AJ, Cheung GY, Otto M. Investigational therapies targeting quorum-sensing for the treatment of *Staphylococcus aureus* infections. Expert opinion on investigational drugs. 2015;24(5):689-704.
61. Otto M. *Staphylococcus aureus* toxins. Current opinion in microbiology. 2014;17:32-7.
62. Kropec A, Maira-Litran T, Jefferson KK, Grout M, Cramton SE, Götz F. Poly-N-acetylglucosamine production in *Staphylococcus aureus* is essential for virulence in murine models of systemic infection. Infection and immunity. 2005;73(10):6868-76.
63. Otto M. S*taphylococcus epidermidis*—the'accidental'pathogen. Nature Reviews Microbiology. 2009;7(8):555-67.
64. Maira-Litrán T, Kropec A, Goldmann DA, Pier GB. Comparative opsonic and protective activities of *Staphylococcus aureus* conjugate vaccines containing native or deacetylated staphylococcal poly-N-acetyl-β-(1-6)-glucosamine. Infection and Immunity. 2005;73(10):6752-62.
65. Bagnoli F, Fontana MR, Soldaini E, Mishra RP, Fiaschi L, Cartocci E. Vaccine composition formulated with a novel TLR7-dependent adjuvant induces high and broad protection against *Staphylococcus aureus*. Proceedings of the National Academy of Sciences. 2015;112(12):3680-5.
66. Spaulding AR, Salgado-Pabón W, Merriman JA, Stach CS, Ji Y, Gillman AN. Vaccination against *Staphylococcus aureus* pneumonia. The Journal of infectious diseases. 2013;209(12):1955-62.
67. Delfani S, Mobarez AM, Fooladi AAI, Amani J, Emaneini M. Protection of mice against *Staphylococcus aureus* infection by a recombinant protein ClfA–IsdB–Hlg as a vaccine candidate. Medical microbiology and immunology. 2016;205(1):47-55.
68. Nissen M, Marshall H, Richmond P, Shakib S, Jiang Q, Cooper D. A randomized phase I study of the safety and immunogenicity of three ascending dose levels of a 3-antigen *Staphylococcus aureus* vaccine (SA3Ag) in healthy adults. Vaccine. 2015;33(15):1846-54.
69. Zuo G, Wang G, Zhao Y, Xu G, Hao X, Han J. Screening of Chinese medicinal plants for inhibition against clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA). Journal of ethnopharmacology. 2008;120(2):287-90.
70. Daglia M. Polyphenols as antimicrobial agents. Current opinion in biotechnology. 2012;23(2):174-81.
71. Su Y, Ma L, Wen Y, Wang H, Zhang S. Studies of the in vitro antibacterial activities of several polyphenols against clinical isolates of methicillin-

resistant *Staphylococcus aureus*. Molecules. 2014;19(8):12630-9.
72. Hatano T, Kusuda M, Inada K, Ogawa T-o, Shiota S, Tsuchiya T. Effects of tannins and related polyphenols on methicillin-resistant *Staphylococcus aureus*. Phytochemistry. 2005;66(17):2047-55.
73. Hatano T, Uebayashi H, Ito H, SHIOTA S, TSUCHIYA T, YOSHIDA T. Phenolic constituents of Cassia seeds and antibacterial effect of some naphthalenes and anthraquinones on methicillin-resistant *Staphylococcus aureus*. Chemical and Pharmaceutical Bulletin. 1999;47(8):1121-7.
74. Tegos G, Stermitz FR, Lomovskaya O, Lewis K. Multidrug pump inhibitors uncover remarkable activity of plant antimicrobials. Antimicrobial agents and chemotherapy. 2002;46(10):3133-41.
75. Coutinho HD, Costa JG, Lima EO, Falcão-Silva VS, Júnior JPS. Herbal therapy associated with antibiotic therapy: potentiation of the antibiotic activity against methicillin–resistant *Staphylococcus aureus* by Turnera ulmifolia L. BMC complementary and alternative medicine. 2009;9(1):13.
76. Coutinho HD, Costa JG, Lima EO, Falcão-Silva VS, Siqueira-Júnior JP. Enhancement of the antibiotic activity against a multiresistant Escherichia coli by Mentha arvensis L. and chlorpromazine. Chemotherapy. 2008;54(4):328-30.
77. Lin RD, Chin YP, Hou WC, Lee MH. The effects of antibiotics combined with natural polyphenols against clinical methicillin-resistant *Staphylococcus aureus* (MRSA). Planta medica. 2008;74(08):840-6.
78. Bernard FX, Sable S, Cameron B, Provost J, Desnottes JF, Crouzet J. Glycosylated flavones as selective inhibitors of topoisomerase IV. Antimicrobial agents and chemotherapy. 1997;41(5):992-8.
79. Liu MH, Otsuka N, Noyori K, Shiota S, Ogawa W, Kuroda T. Synergistic effect of kaempferol glycosides purified from Laurus nobilis and fluoroquinolones on methicillin-resistant *Staphylococcus aureus*. Biological and Pharmaceutical Bulletin. 2009;32(3):489-92.
80. Takahashi O, Cai Z, Toda M, Hara Y, Shimamura T. Appearance of antibacterial activity of oxacillin against methicillin resistant *Staphylococcus aureus* (MRSA) in the presence of catechin. Kansenshogaku zasshi The Journal of the Japanese Association for Infectious Diseases. 1995;69(10):1126-34.
81. Zhao WH, Hu Z-Q, Okubo S, Hara Y, Shimamura T. Mechanism of synergy between epigallocatechin gallate and β-lactams against methicillin-resistant *Staphylococcus aureus*. Antimicrobial agents and chemotherapy. 2001;45(6):1737-42.
82. Hu ZQ, Zhao W-H, Asano N, Yoda Y, Hara Y, Shimamura T. Epigallocatechin gallate synergistically enhances the activity of carbapenems against methicillin-resistant *Staphylococcus aureus*. Antimicrobial agents and chemotherapy. 2002;46(2):558-60.
83. Mccurdy S, Lawrence L, Quintas M, Woosley L, Flamm R, Tseng C. In vitro activity of delafloxacin and microbiological response against fluoroquinolone-susceptible and nonsusceptible *Staphylococcus aureus* isolates from two phase 3 studies of acute bacterial skin and skin structure infections. Antimicrobial agents and chemotherapy. 2017;61(9):e00772-17.
84. Jones RN, Moeck G, Arhin FF, Dudley MN, Rhomberg PR, Mendes RE. Results from oritavancin resistance surveillance programs (2011 to 2014): clarification for using vancomycin as a surrogate to infer oritavancin susceptibility. Antimicrobial agents and chemotherapy. 2016;60(5):3174-7.