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A review on clinical management strategy and treatment modalities of resistant staphylococcal infections - Current scenario and future perspectives

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Abstract
Of all the staphylococcal species, *Staphylococcus aureus* is the most often occurring cause of infections of the skin and soft tissues as well as serious staphylococcal infections, such as *Staphylococcus aureus* bacteremia (SAB). While many medications are effective against staphylococci, antimicrobial treatment has been beset by antibiotic resistance during the past 40 years, especially resistance to beta-lactam antibiotics. The capacity of staphylococci, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), to withstand the effects of beta-lactam antibiotics is now referred to by the name "methicillin resistance," which has historical significance. The *mec*A gene, which is included in the SCC *mec* complex genetic cassette, encodes this resistance. Older antibiotics and vancomycin continue to be the mainstays of treatment for staphylococci that are resistant. The medicines that are the subject of this review, trimethoprim-sulfamethoxazole, ceftaroline, daptomycin, fosfomycin, linezolid, dalbavancin, televancin, and omadacycline, exhibit good action against resistant staphylococci. Novel modes of action for individual anti-staphylococcal drugs or in combination to enhance the activity of the primary anti-staphylococcal agent are being developed. Despite several drawbacks, including the potential for renal impairment, vancomycin therapy is still the gold standard for treating resistant staphylococcal infections. When renal impairment first appears, several medical professionals move from vancomycin as soon as possible. The near future may potentially bring about an improvement in the humoral and cellular defences against staphylococcal infection. The selection of antibiotics and the length of anti-staphylococcal therapy will depend on professional clinical judgement until more recent clinical trials demonstrate the unmistakable advantage of one anti-staphylococcal medication over another or over vancomycin.

Keywords: Staphylococcal infections, *Staphylococcus aureus*, antimicrobial resistance

Introduction

One of the numerous species of staphylococci, *Staphylococcus aureus*, typically causes skin and soft tissue infections (SSTIs) in people. Treatment for infections brought on by strains of *S. aureus* that are resistant to antibiotics has grown more challenging. *S. aureus* is one of the "ESKAPE" pathogens (“ESKAPE”-*Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enerobactger species*). The creation, promotion, and application of more recent anti-staphylococcal antibiotics have been spurred by this emerging antimicrobial resistance. Even though they can be rather serious, non-cutaneous and non-soft tissue infections are less common than SSTIs. *S. aureus* bacteremia (SAB) may be linked to both SSTIs and non-SSTIs. Because SAB tends to induce occult extra-vascular infections and metastatic abscesses, it continues to have unique reputation [1]. Clinicians must always rule out *S. aureus* endocarditis when SAB arises without a known cause. Prolonged intravenous (IV) antibiotic treatment is required in these cases. The main emphasis of clinical trials is still SSTI and (to a much lesser extent) SAB in the hopes of developing novel anti-staphylococcal antibiotics for the market. In order to demonstrate that a novel antibacterial is only non-inferior to current therapy, rather than better, research approaches have been used in clinical trials. Methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) infections are traditionally classified according to their susceptibilities to methicillin; however, the term "methicillin resistance" is archaic, having been superseded years ago by other semi-synthetic penicillins such as oxacillin, nafcillin, and cloxacillin. Antimicrobial treatment for resistant staphylococci has seen several changes in the last forty years. Several antimicrobial resistance genes were included in the complex SCC *mec* genetic cassette of the early strains of MRSA [2]. SCC *mec* has added and removed several resistance genes over time, resulting in the evolution of numerous subtypes. The sophisticated SCC *mec* seen in nosocomial clones of MRSA (USA 100 and USA 200) in the early 1970s developed ironically into a considerably less complex and resistant SCC *mec* in community-associated USA 300 clones in the 1990s. USA 300 clones are still infecting a large number of patients in hospitals as well as the general public, causing a global epidemic. Among the few bactericidal antibiotics that early MRSA strains were responsive to was vancomycin. Vancomycin is still the cornerstone of first treatment for infections caused by resistant staphylococci nowadays. But after more than 60 years of usage, broad distribution, and a "creeping" rise in minimum inhibitory concentrations (MICs), the pharmaceutical industry was forced to create new anti-staphylococcal antimicrobials. The bar for transitioning from vancomycin pre-eminence to a new era of anti-staphylococcal antimicrobial chemotherapy has been lowered by the introduction of many new anti-staphylococcal medicines onto the market [3]. In this review, we will focus on the most recent data about the effectiveness of the novel agents in lowering staphylococcal

infection-related morbidity and death, especially when compared to the proven effectiveness of vancomycin. Treatment for staphylococcal infections is a current PubMed search that produces about 15000 results. Our goal is to focus on a few "bottom line" suggestions for more modern treatments that may replace vancomycin. Furthermore, although infections caused by several species of coagulase-negative staphylococci (CNS) pose a genuine risk for human infection, we will primarily focus on the antimicrobial therapy of pathogenic coagulase-positive staphylococci, specifically *S. aureus*. The majority of our review's recommendations, though not all of them, also apply to CNS, which often show wider antibiotic resistance than their coagulase-positive counterparts.

Alternative treatment options of Vancomycin therapy

The antimicrobials listed in Table 1 are vancomycin substitutes that are currently on the market and that we will discuss in this study. Vancomycin is still the cornerstone of anti-staphylococcal treatment despite the availability of other substitutes. In fact, vancomycin is still the primary option in community hospitals for suspected serious SSTI and invasive staphylococcal illness, even though it can cause renal toxicity and (to a lesser extent) ototoxicity. We anticipate that it will be difficult for our evaluation to discover any evidence of the superiority of the more recent anti-staphylococcal antibiotics over vancomycin in this era of designing clinical trials to demonstrate non-inferiority. Out-patient parenteral antibiotic treatment (OPAT) can significantly lower in-patient expenditures, regardless of the drug of choice—vancomycin or anything else. Oritavancin administered in OPAT was reported in one research to save per patients of $1752 - $6475 [5].

Table 1: Alternatives to semi-synthetic penicillins and cephalosporins for the treatment of resistant staphylococcal infections

1.	Ceftaroline
2.	Daptomycin
3.	Fosfomycin
4.	Linezolid
5.	Oritavancin/Dalbavancin
6.	Telavancin
7.	Omadacycline

Trimethoprim sulfamethoxazole

In order to contextualise the treatment concerns, let us first examine the most recent studies using trimethoprim/sulfamethoxazole (TMP-SMZ), one of the first anti-staphylococcal drugs. In one large experiment, after the draining of a staphylococcal abscess, TMP-SMZ or placebo was administered for seven days [6]. A cure test was conducted between 14 to 21 days. Failure was defined as a persistent fever with varying degrees of erythema or oedema on days 3 or 4, 8 to 10, or 14 to 21. The primary test resolution of the abscess occurred at 7 to 14 days. Patients who did not respond to therapy were given a placebo and could have to have further draining done. A total of 1265 patients were recruited, and 1247 of them received therapy. For placebo and treatment 607 and 606 were included in modified intention to treat. 509 and 504 of those groups, finished an extended follow-up visit. In the TMP-SMZ group, the cure rates were 80.5%, while in the placebo drainage-alone group, they were 73.6%. Clinical cure rates were 487 (92.9%) out of 524 in the treatment group and 457 (85.7%) out of 533 in the placebo group in the per-protocol group. These two groups' differences were very considerable. The two groups had comparable adverse effects. Diarrhoea linked to *Clostridium difficile* was not reported. TMP-SMZ undoubtedly continues to be a viable substitute for beta-lactam treatment in *S. aureus* strains that are sensitive to it [6]. We will talk about other, more current researches on skin and soft tissues, which this one offers a viewpoint on. Notably, three quarters of the skin abscesses in this trial did improve without the need for antibiotics, despite the fact that supplementary antibiotics were linked to marginally but statistically significantly better results. There are limitations to even huge research like this one. Not every one of these abscesses has a confirmed *S. aureus* isolation. Of each group, only around 63% had an isolated MRSA or MSSA. Therefore, in over 90% of cases, drainage combined with an antibiotic will likely result in a cure when there is a skin abscess to be cleared. Many of the studies that we will take into consideration will not use drainable SSTIs or were not designed with drainage as the primary goal. Similar to TMP-SMZ, other antibiotic drugs from the past, such as ciprofloxacin, clinidamycin, doxycycline and rifampicin are still effective against resistant staphylococci, especially those that originate from the community. It is outside the purview of this assessment to consider these veteran troops as still useful in the fight against staphylococci in therapy. Table 1 enumerates more recent antimicrobials that are currently accessible as substitutes for vancomycin or TMP-SMZ, which we will discuss below.

Ceftaroline

Cephalosporin that works against MRSA is ceftaroline. Clinicians have been trained for years that cephalosporins should not be used to treat MRSA. Over the past ten years, a specific cephalosporin that could bind to PBS2A and get around the block to cephalosporin effectiveness in MRSA strains has finally been available. Ceftaroline was shown to be at least as efficacious as vancomycin in treating SSTI in the CANVAS 1 and CANVAS 2 investigations [7]. Day 3 response rates for vancomycin were 66.2% (263/397) and for ceftaroline were 74.0% (296/400). Ceftaroline has been added to general formularies very slowly by community hospitals across the nation, or its usage has been limited to infectious disease consultants. Ceftaroline may end up becoming a cornerstone of anti-staphylococcal therapy for methicillin-resistant staphylococci, according to mounting evidence.

Daptomycin

Cyclic lipopeptide daptomycin has replaced vancomycin as a common antibiotic, with the exception of staphylococcal pneumonia, where the drug is more strongly linked to pulmonary surfactant. Daptomycin and vancomycin did not perform worse in SAB outcomes, according to a seminal research; nonetheless, both drugs had poor response rates [8]. However, daptomycin is currently used instead of vancomycin when issues like clinical non-response or imminent renal damage appear. A particular technical problem that has led to an increase in the usage of daptomycin is the rising minimum inhibitory concentration (MIC) of staphylococci that equals or surpasses 2 μg/mL of vancomycin. Daptomycin appeared to have better results than vancomycin in treating MRSA bloodstream infections,

according to a well-known case-control research. For SAB and severe invasive infections, some doctors recommend a daily dose of daptomycin more than 6 mg/kg. Vancomycin should be used to treat MRSA in the algorithm arm of a recent study that compared algorithm-based therapy to conventional care [4]. The algorithm arm's sole substitute for vancomycin was daptomycin. The superiority of the algorithm arm in the MRSA group was one of the study's key findings. Studies with controlled comparisons between comparators and daptomycin for the treatment of staphylococcal osteomyelitis are now underway. An early clinical issue, overt muscle toxicity owing to daptomycin, has been infrequent; yet, a consistent number of individuals show some increase of muscle enzymes.

Fosfomycin

This potent medication, which is gaining popularity in the US, is used to treat urinary tract infections temporarily. It exhibits strong antibacterial action against staphylococci as well as broad-spectrum antibacterial activity. Urine has a high concentration of it, while tissue does not. It can be used in conjunction with additional anti-staphylococcal medications [9]. It is not recommended to be used as a monotherapy at this time for severe deep tissue staphylococcal infections.

Linezolid

Originally marketed under the Zyvox brand (Pfizer Inc., New York, NY, USA); linezolid's early adoption was hindered by its expensive cost. It has been in use for about 20 years. Although it is still rwlatively expensive, it is now regarded as a valuable substitute for vancomycin in cases of moderately severe staphylococcal infection, especially in cases of MRSA and SSTI lung infections. A 5-year (2011–2015) retrospective analysis of 3031 *S. aureus* isolates' susceptibility to linezolid revealed that more than 99.9% of them still exhibited susceptibility [10]. As a standard treatment for severe non-endothelial staphylococcal infections, linezolid has replaced vancomycin. Furthermore, there have been reports that vancomycin monotherapy may be inadequate in treating MRSA in kids who also have influenza [11]. In 2014, tedisolid received approval for oral and parenteral administration at a daily dose of 200 mg. Similar to linezolid; it can cause thrombocytopenia, neuropathy, and even visual neuropathy in rare cases.

Oritavancin/Dalbavancin

A lipoglycopeptide with an incredibly extended half-life is called dalapancin. For the treatment of staphylococcal infections, it can be administered once a week. Cost is a significant factor, and many US insurance providers will not cover the cost. Dalbavancin and its relative oritavancin, however, exhibit extremely low minimum inhibitory concentrations (MICs) against staphylococci, including hetroresistant *S. aureus*. Although there aren't many endocarditis patients receiving treatment, using dalapavancin for the condition raises the possibility of a role [12]. Dalbavancin treatment failed in one patient with tricuspid valve MRSA endocarditis after four weeks [13]. Oritavancin is sold as a single-dose medication of 1200 mg, administered slowly over the course of three hours by IV infusion. It's exceptionally long half-life has also been demonstrated in clinical studies (SOLO I and SOLO II) to be non-inferior to vancomycin [5]. During IV infusion, patients should be watched for signs of hypersensitivity. The broad use of oritavancin will be hampered by its complexity of usage and potential for hepatic adverse effects.

Televancin

Another lipoglycopeptide developed from vancomycin that has been licensed by the US Food and Drug Administration (FDA) over ten years ago is televancin, which is very effective against staphylococci. The clinical success rate for SSTI treatment is close to 90%, yet the only way to get televancin is by an IV infusion [14]. A black box warning for increased mortality in individuals with moderate-to-severe renal impairment has been generated by nephrotoxicity. The possibility of hypersensitive responses, longer QT intervals, and prolonged prothrombin and activated partial thromboplastin times—the latter of which is a laboratory artefact unrelated to coagulation—are among the cautions.

Tigecycline

Tigecycline still has strong intrinsic action against staphylococci despite being first prescribed as a broad-spectrum treatment for intra-abdominal abscesses. As a main monotherapy for staphylococcal infections, it still hasn't found its place. However, given its potent anti-MRSA properties and ability to permeate bone and biofilm, it may prove beneficial either alone or in conjunction with other treatments for osteomyelitis, diabetic foot infections, and infected wounds—though not pneumonias [15]. The launch of a novel once-daily parenteral and oral formulation of omadacycline (NUZYRA) has eclipsed the use of tigecycline. Omadacycline is licensed for the treatment of SSTI and community-acquired pneumonia [16]. It was created to combat tetracycline resistance.

Future perspectives

Treatment of staphylococci and other antimicrobial-resistant bacteria requires both the development of new medicines and the maintenance of existing ones. Given that it costs hundreds of millions of dollars to launch a novel antimicrobial treatment, the Infectious Diseases Society of America (IDSA) has set a lofty goal of developing ten new medicines by 2020. There are a lot of innovative drugs being developed that have antibacterial and anti-staphylococcal action through unique mechanisms. We have just touched on commercially available alternatives to older treatments in this brief assessment [17]. Some endolysins obtained from bacteriophages, when administered via innovative delivery methods, rapidly kill *S. aureus*, serving as a model for future novel agents [18]. Despite its shortcomings, vancomycin is still the gold standard for treating resistant staphylococci; nevertheless, a recent poll of doctors specialising in infectious diseases in adult patients from five sizable hospitals indicates that they may switch to vancomycin substitutes [19]. Vancomycin treatment has helped many patients—possibly millions—who had severe *S. aureus* infections to recover. Research on novel drugs that only demonstrate non-inferiority to vancomycin might not be well set up to demonstrate greater rates of cure, which would lead to a shift in preference away from vancomycin. A multicenter investigation examined why conventional medication failed to sterilise blood cultures in cases of bloodstream infections caused by MRSA [20]. Cure rates were close to 70% in 211 bacteremic patients treated with ceftaroline as salvage treatment [21]. The early selection

of therapy for staphylococcal infections might also be aided by treatment algorithms [21]. Recently, more sophisticated systematic algorithms were published to direct testing and therapy in a way that helps doctors manage staphylococcal bacteremia sequentially [3]. While the algorithm's application decreased the mean length of therapy for simple bacteremia from 6.2 to 4.4 days, it also produced a non-inferior rate of clinical success. Research on combination treatment for severe staphylococcal infections has expanded. Currently, there are a number of noteworthy studies that present positive outcomes: one that uses vancomycin plus cefazolin [23]; one that uses daptomycin plus beta-lactam combinations [24]; and one that uses daptomycin plus ceftaroline [22]. Over the next ten years, more combinations employing more recent drugs will undoubtedly be used to answer the question of whether we may get better results than monotherapy. An increasing tendency to aid in staphylococcal infection prevention or clearance is the enhancement of effective host responses. Vaccines against staphylococci have a historically poor track record. Enhancing cellular host responses has been a new emphasis in staphylococcal research since cellular immunity is essential to host resistance to staphylococci. Reduction of one CD28 receptor, inducible co-stimulator (ICOS), increases survival in murine staphylococcal pneumonia, according to a recent research on immune checkpoint treatment. This improvement is likely due to the limits of excessive cytokine expression [25]. It is probable that other disruptions to the cellular and humoral response may contribute to the mitigation and avoidance of morbidity in resistant staphylococcal infections [26].

Discussion and conclusion

Treatment for severe staphylococcal infections, particularly those that result in SAB, is still being developed. The availability of effective alternatives to vancomycin for the treatment of these infections, supported by respectable clinical studies, is encouraging. However, the drawbacks of the limited sample size and lack of funding for these clinical studies highlight the necessity of using professional clinical judgement to choose the right antibiotic and manage anti-staphylococcal medication for the appropriate amount of time [27].

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