Methicillin-Resistant *Staphylococcus aureus* in the Oral Cavity: Implications for Antibiotic Prophylaxis and Surveillance

Infectious Diseases: Research and Treatment
Volume 13: 1–8

DOI: 10.1177/1178633720976581

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ABSTRACT: The oral cavity harbors a multitude of commensal flora, which may constitute a repository of antibiotic resistance determinants. In the oral cavity, bacteria form biofilms, and this facilitates the acquisition of antibiotic resistance genes through horizontal gene transfer. Recent reports indicate high methicillin-resistant *Staphylococcus aureus* (MRSA) carriage rates in the oral cavity. Establishment of MRSA in the mouth could be enhanced by the wide usage of antibiotic prophylaxis among at-risk dental procedure candidates. These changes in MRSA epidemiology have important implications for MRSA preventive strategies, clinical practice, as well as the methodological approaches to carriage studies of the organism.

KEYWORDS: MRSA, antibiotics, prophylaxis, oral, dental

RECEIVED: October 14, 2019. **ACCEPTED:** November 3, 2020.

TYPE: IDR-9 Antimicrobial Resistance - Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Antibiotic resistance among oral microbiota is a growing concern, but has received little attention in the literature. Metagenomic studies of the oral cavity based on high-throughput sequencing have enabled us to glean insights into the resistome of the microbiome at this site. Antimicrobial resistance genes (ARGs) appear to be a natural feature of the oral microbiome, and is independent of antibiotic exposure to a large extent.[1] Consequently, the oral microbiome serves as a significant reservoir for these genes, which are transferred to pathogenic microbes by horizontal gene transfer (HGT). In the oral cavity, bacteria form biofilms, and this facilitates the acquisition of ARGs and their HGT.[2-8] Thus, it may be worthwhile investigating antibiotic resistance of microbial pathogens that inhabit the oral cavity. In this paper, the authors review antibiotic resistance in the oral flora with regard to methicillin-resistant *Staphylococcus aureus* (MRSA), and highlight the implications for antibiotic prophylaxis and surveillance.

Oral Microbial Flora

The mouth is home to an excess of 700 bacterial species, which are adapted to its inherently distinct ecological niches.[9] More than 50% of these species colonize the periodontal pocket, and the remnants are distributed across other sites of the oral cavity. In the mouth of any given person, approximately 100-200 of these 700 plus species are present, with 50 of these harbored in the periodontal pocket.[10] Some of the common oral flora belong to the genera *Enterococcus, Peptostreptococcus, Streptococcus, Staphylococcus, Actinomyces, Corynebacterium, Eubacterium, Lactobacillus, Bacteroides, Campylobacter, Leptotrichia, Prophyromonas, Treponema, Fusobacterium*, etc.[11-19] Even though the ecology of the oral flora is highly diversified, it has the hallmark of high equilibrium called microbial homeostasis.[20-22] This is of chief relevance to oral health, since it ensures that the numbers of potentially pathogenic microbes are curtailed.[20] Substantial agitations in the oral environment, including pH changes, disrupt the microbial homeostasis, and promote pathological conditions, such as dental caries and periodontitis.[20,23-25] Moreover, orthodontic appliances,[26-29] degree of dentition,[30-32] denture wearing,[32-34] periodontitis,[35] dental caries,[36] dental eruption,[37] exfoliation,[38] diet,[39-42] pregnancy,[43] and use of antibiotics[44-46] are also known to influence this homeostasis.

To illustrate, several lines of evidence indicate that the makeup of elements, ruggedness, and other physicochemical properties of the exteriors of orthodontic appliances are capable of putting the oral microbial adhesion, interaction, and diversity in disarray.[47-50] A study by Naranjo et al,[51] for instance, reported that the populations of *Tannerella forsythia, Fusobacterium* spp., *Prevotella nigrescens, Prevotella intermedia*, and *Porphyromonas gingivalis* increased following orthodontic appliance replacement. Another study, Ronsani et al,[52] demonstrated that Cr^{3+}, Fe^{3+}, and Ni^{2+} metal cations, which frequently leak out from orthodontic appliances, increased the biomass of *Candida albicans* biofilms. As regards the influence of diet, intake of dry-food diets has been demonstrated to have significant correlates with oral *Porphyromonas* spp.[41] A similar report has been made for vitamin C and *Fusobacterium*.[42] Diets that are rich in sugar have also been noted to be significantly associated with oral carriage of *Fusobacterium nucleatum* and *Streptococcus mutans*.[39,40] Moreover, oral administration of antibiotics—such as amoxicillin, ciprofloxacin, clindamycin,

and azithromycin—have been documented to alter microbial diversity and counts, such as a proximate reduction in the populations of throat *Actinomyces* spp.[44-46] With regard to dental caries, children with a relatively good oral health have been demonstrated to have a significantly more diverse oral microbiome than those with severe dental caries.[53]

Generally, there is very scanty information on the interaction of *S. aureus*, and therefore MRSA, with the oral microbiota. In an in vitro study, Lima et al[54] showed that *S. aureus* complexes with *Porphyromonas gingivalis* and *Fusobacterium nucleatum*. Further investigation of the *F. nucleatum-S. aureus* relationship demonstrated that the adhesin *RadD*, which is present on the outer-membrane, is somewhat involved in the configuration of the complexes, and that the *RadD*-mediated relationship induces increased staphylococcal global regulator gene, *sarA*, expression.

S. aureus and MRSA: Epidemiological and Clinical Significance

Staphylococcus aureus is considered a commensal as well as a human pathogen. As a commensal, *S. aureus* is principally isolated from the anterior nares, although it colonizes other anatomical sites, the mouth inclusive.[55] Oral *S. aureus* could have their origins in the oral cavity itself; they could also transit to the mouth from their ecological niche in the anterior nares, using the oropharynx as a conduit.[56] Prevalence of oral *S. aureus* tends to vary from one population to another—in healthy dentate adults, reports have indicated carriage prevalence that range from 24% to 84%[17,57] and 48% in denture wearers.[58] Higher carriage prevalence of *S. aureus* in patients with a predisposition to joint infections may provide a basis for considering the mouth as a seedbed for the hematogenous spread of the bacterium to compromised joint spaces.

For a period in the mid-twentieth century (early 1940s), infections of *S. aureus* were managed with the newly discovered antibiotic penicillin, which at the time, seemed a kind of panacea for the treatment of a multitude of ailments. Its relevance as a therapeutic for *S. aureus* infections nonetheless began to wane in the mid-1940s when *S. aureus* strains resistant to the antibiotic began to be discovered.[59,60] The rates at which penicillin resistance was reported in *S. aureus* has risen exponentially over the years to up to 100%.[61-64] The molecular basis of this penicillin resistance attribute is known to be the organism's production of the heterogeneously expressed enzyme, the beta lactamase, which hydrolyzes the beta lactam ring of penicillin.[60,65,66] The emergence and spread of *S. aureus* strains with this attribute necessitated the inception of methicillin usage in 1959, with the purpose of treating infections of penicillin-resistant *S. aureus*. However, in the early 1960s, S. aureus strains refractory to methicillin, identified as methicillin-resistant *Staphylococcus aureus* (MRSA), were observed in several European countries.[67-71] *S. aureus* strains that retain the attribute of methicillin susceptibility are known as methicillin-sensitive *Staphylococcus aureus* (MSSA). MRSA now has a worldwide distribution, and is prevalent in several hospitals, especially, those in Asia, Europe, and the United States.[72-74] MRSA strains harbor any of the variants of the *mec* gene, which are borne on different homologues of the Staphylococcal cassette chromosome (*SCCmec*) —these specify methicillin-resistant penicillin-binding proteins alien to *S. aureus*.[75-77] Cassette chromosome recombinases (*ccrA*/*ccrB* or *ccrC*) are also borne on the *SCCmec* homologues—these facilitate the excision and integration of the *mec* genes, and together with the *mec* genes, serve as a premise for the characterization of the *SCCmec*.[78,79] At present, more than ten *SCCmec* types have been characterized.[80] MRSA is refractory to all beta-lactam antibiotics and many commonly prescribed antibiotic groups, including aminoglycosides, fluoroquinolones, macrolides, chloramphenicol, and tetracyclines.[59,81,82] A key distressing concern is the emergence and dissemination of MRSA strains that are refractory to mainstays of MRSA therapy, such as daptomycin, linezolid and vancomycin. Even though recent reports indicate the existence of such strains, they have not spread at magnitudes that could be considered clinically significant.[83-87] Yet, such concerns are not misplaced, as several resistance determinants, including those for vancomycin and linezolid, are widespread in enterococci.[88,89] At present though, resistance to these three drugs of choice have been reported to develop during prolonged treatment.[87] Also, a significant relationship has been reported between daptomycin resistance and vancomycin resistance,[90-92] as well as daptomycin resistance and the induction of beta-lactam susceptibility.[93-95]

In addition to its extensive resistance to antibiotics, MRSA is of serious concern because of the high prevalence of its infections and association with persistent outbreaks, which have serious economic implications.[96-98] In the United States, invasive MRSA infections are estimated at an annual incidence of 94 360, with 18 650 deaths.[97] Furthermore, hospital stays for MRSA disease in the United States cost $14 000, compared with $7600 for all other stays.[97] In Europe, data from thirty-one countries reported 27 711 episodes of MRSA blood stream infections, which were associated with 5503 deaths and an estimated hospital stay cost of 44 million Euros.[98] Traditionally, MRSA is regarded as a major nosocomial pathogen in healthcare facilities, and is referred to as healthcare-associated MRSA (HA-MRSA).[98,99] Of the known clones of HA-MRSA, just a limited number is implicated in the majority of infections, and the dominance of any of these varied clones is contingent on the geographical area. To illustrate, the clone tagged as ST239-SCCmecIII is the one frequently encountered in Africa, South America, and Asia.[100-102] The clone that predominates in the United States is CC5-SCCmecII (USA100),[103,104] whereas in Europe, it is CC22-SCCmecIV (EMRSA-15).[103-109] Notably, the dominance of clones in various geographical locations have been dynamic.[110-112] Investigations centered on HA-MRSA evolution provide solid proof of a wide spectrum of antibiotic resistance mutations and transmissible genetic elements that are associated with emergence of major HA-MRSA clones in hospital epidemics.[113,114] MRSA, although

Table 1. Some points of divergence between CA-MRSA and HA-MRSA.

PARAMETER	CA-MRSA	HA-MRSA
Genetic traits	Panton-Valentine Leukocidin gene, Staphylococcal Cassette chromosome IV (most common—USA300, USA400)	Various Staphylococcal cassette chromosome (most common—USA100, USA200)
Part of body affected	Skin, Lungs	Site of implant; Surgical site; Blood stream
Resistance gene	SCC*mec* Type IV, V	SCC*mec* Types I, II, III
Panton-Valentine Leukocidin producer	Frequent (almost 100%)	Rare (5%)
Risk population	Young, otherwise healthy patients (most common); no recent hospitalizations; anyone	Immunocompromised individuals; residency in long term care facilities; recent hospitalizations; dialysis patients; recent surgery
Antibiotic used in management	Doxycylcline, Clindamycin and Cotrimoxazole often used.	First-line antibiotics used include vancomycin. Additional newer antimicrobial agents: daptomycin, linezolid and tigecycline.

Adapted from Popovich et al[118] and Bassetti et al[119]

traditionally considered a nosocomial pathogen, has surfaced in the community within the past twenty years, and accounts for several types of community-acquired infections.[99,100,115,116] These strains adapted to communities, called community-associated MRSA (CA-MRSA), are often isolated from individuals devoid of healthcare-exposure specific risk factors.[117] Epidemiologically, CA-MRSA and HA-MRSA are considered to be different from each other,[118,119] and Table 1 shows some clinical and genetic differences between them. However, this epidemiological distinction can be blurred by the fact that both genotypes are being observed in healthcare and community infections interchangeably.[120] Moreover, CA-MRSA infections could also be caused by livestock-associated MRSA (LA-MRSA).[121] LA-MRSA is initially associated with livestock (such as pigs, cattle, and chicken) and differs genotypically from HA-MRSA and CA-MRSA.[121] Globally, among the known LA-MRSA strains, CC398 is the most widely disseminated, followed by CC9.[121]

An inverse relationship between carriage of *S. aureus* and *Streptococcus pneumoniae* has been reported in children in several epidemiological studies from various geographical regions.[122-124] Selva et al[125] described an interesting mechanism through which *S. pneumoniae* produces hydrogen peroxide and kills *S. aureus*. The inverse relationship between the two organisms seems to suggest that the massive vaccination with pneumococcal conjugate vaccines that is on-going globally may cause an upward shift in *S. aureus* carriage, with the consequence of an increase in the incidence of *S. aureus* diseases, and therefore MRSA.

Occurrence of MRSA in the Oral Cavity

Recent reports indicate high *S. aureus* and MRSA carriage rates in the oral cavity.[126,127] Although it is unclear whether these reported high rates are as a consequence of increased focus on *S. aureus* and MRSA, it is noted that MRSA carriage in the mouth may constitute a reservoir for subsequent colonization of other anatomical sites or for cross-infection to other people. Evidence from several studies indicate that MRSA appears to preferentially colonize denture surfaces in the mouth. As an example, Tawara et al[58] reported a 10% MRSA carriage rate on the dentures of unselected denture wearing patients; these colonizers were refractory to standard denture cleaning agents. In another study, eradication of persistent MRSA carriage from denture wearers was successful only after heat sterilizing or remaking of the dentures that had become persistently colonized.[128] A recent study by Vanzato et al[126] reported carriage rates of 47.6% and 4.1% for *S. aureus* and MRSA respectively in the oral cavity of healthcare workers. Also, quite recently, an MRSA carriage study conducted among dental students in Italy reported a carriage rate of 1.9% (n = 3) in the mouth; the total carriage prevalence was 3.2% (n = 5), representing a composite of oral, nasal, and skin carriage.[129] Furthermore, in a retrospective study spanning a ten-year period, McCormack et al[130] reported 10% of *S. aureus* isolated from the oral cavity to be MRSA. In an earlier study involving an elderly institutionalized veteran population, it was demonstrated that 19% of them had MRSA carriage in the mouth, whereas 20% were nasal carriers.[127] Of interest, 4% of the proven MRSA oral carriers were culture negative for nasal carriage.[127] This insightful observation partly explains why decolonization exercises that target nasal carriage alone are replete with failure. Moreover, good oral care is reported to lower risks of oral and bloodstream infections.[131] Hence it is not surprising that poor oral care has been suggested as part of the risk factors for carriage of, and subsequent infection with, MRSA, that is given little attention.[132] This observation made by Small et al[132] was probably partly informed by an earlier report on the decline in ventilator-associated pneumonia risks among patients in intensive care, by virtue of decontamination of their mouths with 2% (w/v) chlorhexidine,[133] as well as the outcome of an in vitro study in which within 30 seconds, MRSA isolates from both oral and non-oral sources were killed with a 0.2% (w/v) chlorhexidine gluconate mouthwash.[134]

The potential of chlorhexidine application in selecting for resistant strains among organisms constituting the oral microbiome has however been previously reported, hence warranting a measure of caution in its usage.[135] Nonetheless, blending nasal application of 2% mupirocin with refined oral hygiene practices—such as applying chlorhexidine oral rinses—merits consideration when designing strategies for clearing MRSA from the upper respiratory tract, especially, among persistent carriers. However, given the failure of decolonization of some persistent USA300 MRSA carriers using a similar rigorous approach during the first CA-MRSA outbreak in France,[136] it is important to have realistic expectations of decolonization approaches; regardless of the degree of decolonization efforts, decolonization should not be perceived as a fool-proof strategy. In fact, an earlier study had reported successful decolonization at a rate of 65%.[137] These reports underscore the need for further investigations on the significance of the mouth as an impediment to MRSA decolonization.

S. aureus is implicated in several infective oral pathologies, including angular cheilitis,[138] parotitis[139] and mucositis,[140] and also in dental implant failure.[141,142] Generally, very few studies have reported on MRSA clinical infections in the oral cavity, and were inconclusive as to whether the isolation of MRSA reflected disease or carriage. In the 10-year retrospective study from 1998 to 2007 at the Oral Microbiology Laboratory, Glasgow Dental Hospital (highlighted earlier), 11 312 specimens from patients with oral infections were investigated, of which *S. aureus* was isolated from 1986 (18%). Among the *S. aureus* isolates, 10% (204) were identified to be MRSA, which were of EMRSA-15 or EMRSA-16 lineage.[130] The authors indicated that detection rates of *S. aureus* and MRSA might reflect increased carriage rather than disease association. Tuzuner-Oncul et al[143] published a case report on a 35-year-old man with osteomyelitis of the mandible involving intraoral and external purulent discharges, which were culture-positive for MRSA. Although the infecting MRSA strain demonstrated in vitro susceptibility to clarithromycin, vancomycin, clindamycin, and azithromycin, the patient did not respond to the post-operative treatment involving intermaxillary fixation of the jaws, local irrigation with rifampicin, and parenteral infusion with clindamycin.

The Implications of MRSA Oral Carriage for Antibiotic Prophylaxis Among Dental Procedure Candidates

Dental procedures have long been associated with an aftermath of disseminated infections, including bacteremia,[144-147] infective endocarditis,[148] and sepsis.[149] There have been arguments that such infections could probably be of oral origin.[149-151] Hence in individuals undergoing dental procedures, particularly, those at a moderate to high risk of developing disseminated infections, it has been recommended that antibiotic prophylaxis be administered,[152-155] although consensus on the practice is in controversy.[156,157]

The antibiotic that is routinely prescribed as prophylaxis in such individuals is amoxicillin.[158] However, in light of recent reports on the high carriage rates of MRSA in the oral cavity, the issue of antibiotic prophylaxis in dental procedure candidates needs an extensive re-evaluation. Also worth considering are the several reports on *S. aureus* and MRSA resistance to amoxicillin, and its derivative, amoxicillin clavulanic acid, which had shown promise in MRSA therapy.[159] To illustrate, in the study of Groppo et al,[160] half of the isolated *S. aureus* strains were resistant to amoxicillin, and nearly a quarter (23.3%) were amoxicillin-clavulanic acid-resistant. Also, Pathak et al[161] reported a rate of 54% amoxicillin-clavulanic acid resistance among MSSA isolates from India. Moreover, Abbasi-Montazeri et al[162] reported amoxicillin-clavulanic acid resistance rates of 86% for MRSA and 56% for MSSA isolated in their study conducted in Iran. Furthermore, a more recent study reported amoxicillin-clavulanic acid resistance in nearly half of the proportion of MRSA isolated (47.9%).[163]

As MRSA forms part of the organisms that could cause disseminated infections in at-risk populations undergoing dental procedures, its resistance to amoxicillin undermines the administration of amoxicillin as prophylaxis in these at-risk populations. Moreover, the organism that has usually been implicated in dental procedure-associated bacteremia and endocarditis is *Streptococcus viridans*,[164] which may be more amenable to antibiotics than MRSA, owing to the propensity for extensive antimicrobial resistance of the latter.[98] Hence a shift in the predominant causative agent to MRSA, arising from selective pressure, may worsen the prognosis of at-risk populations who develop such disseminated infections. It is possible that the evolution of MRSA in the oral cavity had been influenced by the widespread usage of amoxicillin for prophylaxis; this hypothesis may require an in-depth analysis for a conclusive assertion to be made. Moreover, selecting for other antimicrobial resistance-prone organisms constituting the microbiome, other than MRSA, such as the enterococcus[88,89,165,166] could result in an invariably similar outcome.

Also worth considering is the 3% rate of untoward drug reactions accounted for by amoxicillin,[158] which reportedly doubles as a five-fold risk factor for anaphylactic shock-related deaths.[167] Besides these, the estimated cost for amoxicillin prophylaxis for patients with hip and knee prostheses alone is in excess of $50 million.[168]

Another factor that renders the administration of antibiotic prophylaxis to these at-risk populations somewhat obsolete stems from the recent reports which have demonstrated that everyday oral care practices, such as tooth-brushing, frequently result in transient bacteremia[147,169-171] that is not significantly lower than what is observed following single-tooth extraction,[171] and poses more risks for those at risk for infective endocarditis.[147] Interestingly, such bacteremia resulting from routine oral care is not pre-managed with antibiotic prophylaxis, as that is impractical. Hence it seems somewhat far-fetched to prescribe

antibiotic prophylaxis for dental procedure candidates, especially since the risks of releasing infective endocarditis-causing bacteria into circulation could be reduced by 4–8 folds when optimum routine oral care is adopted.[172] All these are fraught with the fact that infective endocarditis is rare.[173-175] That said, "to give or not to give" antibiotic prophylaxis to such individuals presents a dilemma to clinicians, as they need to reflect on the Hippocratic Oath to make a judgment call on whether to prescribe antibiotic prophylaxis to at-risk populations who may experience a rare undesired outcome, at the risk of administering the prophylaxis to tens of thousands who may not need it—and accentuate the antimicrobial resistance menace while at that. The fact is that choosing an alternative antibiotic for prophylactic purposes in this risk group is complicated by the occurrence of MRSA in the mouth. As would be expected, the antibiotic cannot be either of daptomycin, linezolid, or vancomycin, as these constitute the limited mainstays of MRSA therapy. If indeed antibiotic prophylaxis needs to be administered to this patient group, efforts in the development of new therapeutic agents of alternative sources, such as plant sources, need to be intensified.

It is important to note that the recently updated guidelines for antibiotic prophylaxis in dental procedures consider very specific categories of at-risk individuals. These include patients with prosthetic cardiac valve, previous infective endocarditis, congenital heart disease, heart transplant, and rheumatic heart disease that carry a high risk of endocarditis.[176-178] Currently, antibiotic prophylaxis is not routinely recommended for patients with prosthetic joints who are undergoing dental treatment.[176-178]

Conclusions and Future Perspectives

The increasing presence of MRSA in the oral cavity is an immense public health threat that cannot be downplayed, given its potential for enhanced MRSA transmission. Moreover, it introduces new dimensions to the already intensified debates on whether or not to administer antibiotic prophylaxis to at-risk dental procedure candidates. Probably, the choice needs to be made on a case by case basis. It follows then that newer therapeutic agents are needed more urgently than previously.

Admittedly, there is very limited data to inform on the interaction of *S. aureus*, and therefore MRSA, with the oral microbiota, and the extent to which the oral cavity mediates *S. aureus*- and MRSA-caused endocarditis as a sequel to dental procedures. Additionally, it is largely unclear whether the presence of MRSA in the oral cavity reflects disease or carriage. Subsequent studies in the area could focus on filling these identified knowledge gaps. Principally, researchers undertaking MRSA carriage studies may need to concurrently screen for oral and nasal colonization.

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