Sinonasal methicillin-resistant *Staphylococcus aureus*: updates on treatment

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Purpose of review
Over the past two decades, the management of methicillin-resistant *Staphylococcus aureus* (MRSA) in chronic rhinosinusitis has posed significant challenges. This document reviews current management techniques and novel treatment modalities for sinonasal MRSA infections.

Recent findings
Topical antibiotic therapy, that is, drops (ofloxacin) and ointments (mupirocin) as off-label use for the management of MRSA chronic sinusitis, has shown beneficial results. Other more recently trialed nonantibiotic modalities such as antimicrobial photodynamic therapy and colloidal silver irrigation are also showing promise.

Summary
Sinonasal MRSA is considered to be associated with recalcitrant chronic sinusitis. Advancements in systemic and local antibiotics in its management have been slow and unsatisfactory. Attention is shifting to the use of nonantibiotic antibacterial treatments. Knowledge of these options is critical to improve the overall management of these chronic patients.

Keywords
chronic sinusitis, methicillin, methicillin-resistant *Staphylococcus aureus*, *Staphylococcus aureus*

INTRODUCTION

The current mainstay of treatment in sinus infections involves the use of culture-directed antibiotics with an appropriate duration of therapy. It has been reported that of all antibiotic prescriptions written in the US, a third are inappropriate [1]. Minimal advances have been made in the last few decades in the development of new antibiotics for the management of multidrug-resistant bacterial infections. This has led to the initiative by the Infectious Disease Society of America to support the development of 10 new antibiotics by 2020, through their 'Bad Bugs No Drugs – 10 by 20' campaign [2]. Recently, exciting advances have been made in the development of novel treatment modalities beyond the scope of antibiotic therapy.

OVERVIEW OF CHRONIC RHINOSINUSITIS METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Chronic rhinosinusitis (CRS) is diagnosed by subjective and objective findings of sinus infections lasting at least 12 weeks in duration, or occurring more than four times per year with symptoms usually lasting more than 20 days [3]. Current guidelines support maximal medical management prior to surgical therapy [4,5]. Maximal medical therapy includes long-term low-dose macrolide oral antibiotics and topical nasal steroid irrigation, among other options. Topical antibiotics provide the benefit of concentrated targeted local therapy with relatively less systemic side-effects compared with the oral or intravenous alternative. Failure of medical management may ultimately lead to surgical intervention, sometimes with large (greater than 4 mm) or mega sized openings into the sinuses. Grobler *et al.* [6] found that 3.95 mm was the minimum ostium diameter to guarantee penetration of topical therapies into the maxillary sinus. An enlarged ostium theoretically facilitates wide delivery of topical application of medication as well as

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KEY POINTS

- Sinonasal MRSA is one of the factors believed to be associated with recalcitrant disease.
- Topical management has a superior advantage to systemic treatment.
- Nonantibiotic antibacterial therapies have been developing in the past few years as a way of management.

endoscopic monitoring of the disease process. On the other hand, a large opening may negatively affect the natural physiology of the sinus cavity and instead promote the formation of biofilm [6].

A small percentage (5–10%) of postsurgical CRS patients will have recalcitrant disease, which does not respond to surgical drainage or to topical and systemic medical management. This can in part be attributed to drug-resistant bacteria and formation of biofilms within the sinus cavities. Although multiple studies have demonstrated *Staphylococcus* species in cases of acute exacerbations of CRS [7,8], MRSA does not appear to pose a significant risk of morbidity but it is concerning nonetheless [9]. A systematic review performed by McCoul *et al.* [10] demonstrated a significant variation in the prevalence of MRSA between acute rhinosinusitis (ARS) and CRS patients. They found the prevalence of MRSA in CRS patients to range from 19 to 74% which is a distinct entity to anterior nasal MRSA (4.6%).

In the following sections, we will highlight the current and novel updates on sinonasal MRSA treatments.

BIOFILMS AND SINONASAL METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Biofilms play a role in many chronic infections including cystic fibrosis, endocarditis and otitis media. It was not discovered to be a cause for CRS until 2004 [11]. Biofilm is composed of communities of microorganisms encased in a protective extracellular matrix that reside on tissue surfaces. MRSA is known to form biofilms within the sinuses thereby making it very difficult to eradicate completely. For this reason, matrix-based antibiotic delivery methods are recommended for MRSA biofilms [12].

TOPICAL TREATMENTS IN SINONASAL METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Topical antibiotics have the theoretical advantage of providing high levels of localized concentration of drug with minimal systemic absorption, lower costs, and decreased morbidity. Various antibiotics and different methods of delivery have been studied for topical irrigation therapy for the sinuses. Topical antibiotics such as mupirocin (Pseudomonic acid A) irrigations have become the mainstay in the management of *Staphylococcus aureus* bacteria in postoperative CRS patients [13]. Solares *et al.* [14] studied the efficacy of topical mupirocin irrigations as an alternative to intravenenous antibiotics in sinonasal MRSA. They found that in acute exacerbations of CRS secondary to MRSA, patients using mupirocin in sinus irrigations showed improved symptoms and reduced MRSA load on subsequent cultures. Recently, it has been reported that twice daily nasal irrigation with 0.05% mupirocin in Ringer solution (isotonic) improved endoscopic findings in 93% of patients, with symptom improvement in 75% [15]. Changes in microbiologic culture results before and after topical mupirocin therapy in patients with CRS with medically and surgically refractory disease have been evaluated [16]. In this evaluation, evidence supporting the distinct abrogation of culturable sinus bacteria after mupirocin rinses was found, identifying a shift toward increased pathogenic bacteria, particularly gram-negative and gram-positive bacteria. For MRSA rhinosinusitis, topical antibiotic therapy with mupirocin may have a role in replacing oral and intravenous treatments in some patients; however, the potential adverse impact of this therapy on the microbiota of the sinuses should be kept in mind.

A solution of mupirocin, surfactant (baby shampoo), and normal saline irrigation rinse would in theory eradicate the bacteria locally and have less systemic effect; however, this topical combination has been found to have minimal therapeutic long-term benefits [13]. Surfactant alone appears to be effective in reducing the bacterial load of MRSA and demonstrates a synergistic antibiofilm effect in combination with mupirocin or gentamicin in sinus tissue [17].

In another study determining the effect of topical ofloxacin on bacterial biofilms for postoperative CRS patients who were nonresponsive to medical management, topical ofloxacin eye drops (0.3%) used intranasally three times a day for 12 weeks eradicated bacterial biofilm in 12 out of 12 patients. Cultures returned negative for 10 patients and were reported as normal flora for the remaining two patients. All 12 patients had electron microscopy and culture positive evidence of bacterial biofilm from their middle meatal mucosa tissue samples preoperatively. Additionally, two out of the 12 patients had MRSA positive cultures, which were cleared post-treatment [18▪▪].

A case report of anterior skull base osteomyelitis with MRSA infection that responded well to nasal irrigation containing hypochlorite super-oxidized solution mixed with topical antibiotics has shed some light on the possible use of sodium hypochlorite for MRSA. Dermacyn (Oculus, Innovative Sciences Inc., Petaluma, California, USA) which contains the active agents of 0.004% sodium hypochlorite (NaOCl) and 0.004% hypochloric acid (HOCl) may show potential benefit for MRSA-infected CRS patients [19].

Recent trials at our centre with mupirocin and doxycyline in Poloxomer-407 gel applied to recalcitrant and infected sinus cavities with MRSA biofilm have shown some very promising outcomes. Diluted iodine saline rinse is also under trial with promising outcomes in pilot studies. Further work on these interesting methods of medication delivery are being actively investigated at our centre.

MANUKA HONEY IRRIGATION

Although the precise antimicrobial action of Manuka honey is unclear, several components have been identified that contribute toward its antimicrobial activity, including high sugar content, low water activity, low pH, and the formation of hydrogen peroxide upon dilution. Methylglyoxal (MGO) has been identified as the dominant antimicrobial component of Manuka honey [20]. Manuka honey shows a promising alternative for topical use, both as a single multicomponent agent in its own right as well as in combination with antibiotics. Several studies have found synergistic interactions between Manuka honey and antibiotics *in vitro* including oxacillin [21], tetracycline, imipenem, and mupirocin against the growth of a MRSA strain, EMRSA-15 [22]. Another study also found strong synergistic activity between Manuka honey and rifampicin against multiple *S. aureus* strains, including clinical isolates and MRSA strains [23]. Manuka honey irrigation has been shown to be effective against fungal sinusitis patients [24]. There are no clinical studies on Manuka honey use in routine CRS. A 2009 study by Alandejani *et al.* [25] assessed the in-vitro efficacy of various honey preparations against 11 methicillin-susceptible *S. aureus* (MSSA), 11 MRSA, and 11 *Pseudomonas aeruginosa* isolates. Honey was effective in killing 100% of the isolates in the planktonic form. The bactericidal rates for the Sidr and Manuka honey against MSSA, MRSA, and *P. aeruginosa* biofilms were 63–82%, 73–63%, and 91–91%, respectively. These rates were significantly higher ($P < 0.001$) than those seen with single antibiotics commonly used against *S. aureus* [25]. Recent studies showed that regular topical treatment with 16.5% Manuka honey with MGO between 0.9 mg/ml and 1.8 mg/ml reduces mature *S. aureus* biofilm while demonstrating no toxic effect on the mucosa [26]. This has a potential for future development and applications in MRSA treatment.

COLLOIDAL SILVER IRRIGATION

Colloidal silver irrigation is an alternative medicine that was a common topical antiseptic in the early 20th century and largely abandoned in the 1940s in favor of more effective antibiotics. It consists of silver nanoparticles suspended in water and used for irrigation of the sinus cavity. Clinical observation of patients who have shown marked improvement in sinonasal symptoms with the use of commercially available homeopathic colloidal silver sprays intranasally led to further investigation [27]. Goggin *et al.* [28] showed that colloidal silver directly attenuates in-vitro *S. aureus* biofilms. Another study assessing the safety and efficacy of topical colloidal silver solution for the treatment of *S. aureus* biofilms in a sheep model found that sheep treated with silver showed a significant decrease in the biofilm biomass and antibiofilm activity compared with saline control. There was no effect on blood counts or blood biochemical markers; however, blood silver levels in the silver-treated group were significantly higher. Histopathological analysis did not show any abnormal morphology and cilia were well preserved. These preliminary results show antibacterial and antibiofilm potential of silver nanoparticles in the management of recalcitrant *Staphylococcus* CRS and biofilms [29▪].

ANTIBACTERIAL PHOTODYNAMIC THERAPY IN SINONASAL METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Antimicrobial photodynamic therapy (aPDT) has been extensively studied in chronic periodontal disease and has demonstrated efficacy in situations where conventional antibiotic therapies can be challenged such as biofilms, gram-negative bacteria, and antimicrobial resistant organisms [30]. The mechanism of action is simple and revolves around the idea of disrupting the bacterial cell wall with oxygen-free radicals that are generated from certain wavelengths of laser light and photoactive methylene blue dye interaction. Although the clinical applicability of this nonantibiotic broad-spectrum antibacterial treatment for recalcitrant CRS is under active investigation, several studies have shown promising results in reduction of MRSA-biofilm. In a recent study, antibiotic resistant polymicrobial biofilms of *P. aeruginosa* and MRSA were grown in an

anatomically correct novel maxillary sinus model and treated with a methylene blue/ethylenediamine tetraacetic acid (EDTA) photosensitizer and 670-nm nonthermal activating light. The results demonstrated that aPDT reduced the CRS polymicrobial biofilm by >99.99% after a single treatment [31]. Bryce *et al.* [32] studied the surgical site infection with nasal photodisinfection (PDT) and chlorhexidine wipes in preoperative patients. MRSA nasal swab cultures were positive in 1.0% (54/5578) of the patients. In that cohort of patients, PDT reduced the semiquantitative colony counts successfully in 87% (47/54) of patients colonized with MRSA ($P = 0.09$) immediately after PDT. The definition of successful bioburden reduction was stated as reducing growth by one or more semiquantitative categories (heavy, medium, scant or no growth). A case series presented by Desrosiers *et al.* [33] in 2013 also showed promising results with minor side-effects. Multicenter clinical trials are currently underway. aPDT has shown efficacy in multiple clinical applications, particularly in the treatment of MRSA affecting prosthetic devices. In a study examining the use of aPDT for biofilms formation on orthopedic prosthetic materials, the reduction in biofilm and a decrease in bacterial (*S. aureus* and *P. aeruginosa*) viable cell numbers were noted [34]. In chronic periodontitis, aPDT has been shown to be effective without any damage to the healthy mucosa [35]. aPDT therapy shows a promising future in the treatment of chronic biofilm and antimicrobial resistant organisms in the realm of CRS.

SYSTEMIC TREATMENTS FOR METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Systemic antimicrobial therapy for MRSA infections has included antibiotics such as clindamycin, tetracyclines (including doxycycline), trimethoprim-sulfamethoxazole, and vancomycin. A study by Rujanavej *et al.* [36] examined the trends of MRSA incidence and antimicrobial resistance in the sinonasal cavities over a 20-year period. They found a statistically significant increasing trend ($P < 0.0001$) for MRSA sinusitis; however, over the 20-year interval studied, the patterns of antibiotic resistance among MRSA remained unaltered, especially with regard to trimethoprim-sulfamethoxazole and vancomycin. Linezolid, a member of the oxazolidinone class of antibiotics, is one of the newest systemic antimicrobial treatment for MRSA. Although no studies examining the use of linezolid specifically for patients with sinonasal MRSA currently exist, we have found excellent response in our patients. Oral linezolid has close to 100% bioavailability, thereby making it as effective as comparable intravenous antibiotics such as vancomycin [34]. This makes its high cost per tablet (approximately $100/tablet) more affordable. It is also very safe to take for short periods of time (2 weeks). Owing to the fact it is considered to be one of the last line antibiotics targeting MRSA, we currently limit the use of linezolid on patients with cystic fibrosis, and in those who suffer from severe acute lower respiratory tract infections rather than immunocompetent individuals with positive MRSA cultures from sinus biofilm infection [37].

CONCLUSION

There is an increasing prevalence of MRSA-positive cultures in CRS. Treatment options for MRSA sinonasal infections include systemic antibiotics and topical therapies. Several topical therapies including aPDT, colloidal silver, and Manuka honey irrigations show a promising future in the management of MRSA CRS and biofilm.

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Conflicts of interest

There are no conflicts of interest.

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