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Review

Review: *Staphylococcus aureus* and MRSA in cystic fibrosis☆

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Abstract

Background: Staphylococcus aureus (*S. aureus*) is one of the earliest bacteria detected in infants and children with cystic fibrosis (CF). The rise of methicillin resistant *S. aureus* (MRSA) in the last 10 years has caused a lot of attention to this organism.
Results: The aim of this review is to provide a general overview of methicillin sensitive *S. aureus* (MSSA) and MRSA, discuss special aspects of *S. aureus* in cystic fibrosis, and to review treatment concepts. Microbiology of the organism will be reviewed along with data regarding the epidemiology of both MSSA and MRSA. Antibiotic treatments both in regards to acute management and eradication of MSSA and MRSA will be reviewed. Prophylaxis of MSSA in CF remains controversial. Treatment with anti-staphylococcal agents reduces the infection rate with MSSA but may lead to a higher rate of infection with *P. aeruginosa*. In regards to MRSA, there is a paucity of clinical data regarding approaches to eradication.
Conclusions: To advance the care of CF patients, controlled clinical trials are urgently needed to find the optimal approach to treating CF patients who are infected with either MSSA or MRSA.

Keywords: Cystic fibrosis; *Staphylococcus aureus*; Methicillin-resistant S*taphylococcus aureus*; Epidemiology; Treatment

Contents

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1. Introduction

Staphylococcus aureus (*S. aureus*) is one of the earliest bacteria detected in infants and children with CF. This may in part be due to abnormal host defense to infection recently noted in the airway of a newborn CF pig model [1]. It is the most prevalent organism among US CF children with a peak prevalence between ages 11–15 years [2]. The rise of methicillin resistant *S. aureus* (MRSA) in the last 10 years has caused a lot of attention to this organism. Rates of methicillin sensitive *S. aureus* (MSSA) and MRSA are considerably lower in most European CF centers (see Table 1). Infection of the CF upper and lower airways are commonly polymicrobial, can grow in biofilms and once established rarely can be eradicated with antimicrobial therapy [3]. For instance, chronic *P. aeruginosa*, especially in the mucoid phenotype growth, can rarely be eradicated; however newly acquired *P. aeruginosa* can be eradicated successfully from the lower airway; this in turn may have profound implications for disease progression in CF. It is unclear whether such an eradication approach will have similar efficacy and safety when targeting other pathogens such as MSSA and MRSA. The aim of this review is to provide information relevant to CF on MSSA and MRSA, and to review treatment concepts for MSSA and MRSA.

2. Microbiology of *S. aureus* and MRSA

S. aureus, a gram positive coccus, is a ubiquitous bacterium and is a commensal of the human skin, especially anterior nares and skin creases in CF and non-CF. An estimated 30–50% of healthy subjects are intermittently or chronically colonized with *S. aureus*, with chronic nasal carriage being a risk factor for *S. aureus* bacteraemia [4]. *S. aureus* grows typically aerobically but also as facultative anaerobe and is capable of biofilm formation. For epidemiological purposes multiple typing systems have been developed for MSSA and MRSA. These include pulse-filed gel electrophoresis (PFGE), multilocus sequence typing (MLST), and typing of the variable tandem repeat region of staphylococcal protein A (*spa* typing). Additionally MRSA isolates are distinguished by the Staphylococcal Casette Chromosome (SCC)*mec* types, which carries the gene for methicillin resistance. To date, at least eight SCC*mec* types have been distinguished, however new types are being described [5]. Whereas *SCCmec* types I, IV, and V encode exclusively for beta-lactam resistance, the larger *SCCmec* types II and III carry non-beta-lactam antibiotic resistance genes.

Since 1960 ~80% of all *S. aureus* isolates have been resistant to penicillin and within 2 years of introduction of methicillin in 1959, *S. aureus* strains developed resistance to methicillin through the acquisition of the *mec*A gene (MRSA). Early MRSA isolates were only associated with hospital acquisition (HA), however since approximately 1990s, community associated (CA) MRSA emerged. CA-MRSA generally differs in genetic background from HA-MRSA, is associated with SCC*mec* IV, V or VII, and tends to be resistant to fewer antibiotic classes. Given outbreaks of CA-MRSA in the hospital or HA-MRSA spreading into the community [6], the distinction between HA- versus CA-MRSA is increasingly difficult. Genetic interchange between MRSA strains also make molecular classification complicated [7]. Classification as CA- versus HA-MRSA in fact may vary depending which approach is employed: epidemiologic, SCC*mec* type, PVL status, or sensitivity to clindamycin [8]. Worldwide, CA-MRSA strains differ in their *SCCmec* type, PFGE pattern, and MLST and *spa* profiles; in the US for instance the most frequent strain is USA-300, which is increasingly being reported in European countries in CF or non CF subjects [9].

S. aureus isolates harbor a multitude of virulence factors, which overlap to a large degree in MSSA and MRSA. The leukocytolytic toxin Panton-Valentine leukocidin (PVL) is more frequently expressed in MRSA than MSSA strains. PVL has been epidemiologically associated with severe cutaneous infections and has initially been attributed as the main cause for severe, necrotizing lung infections based on clinical observations and experiments in animals using isolated PVL [10]. More recently the role of PLV as the main virulence factor for necrotizing lung infections has been questioned [11]. Expression of PVL is also associated with altered regulation (both increases and decreases) of cell wall anchored secreted proteins. Toxin expression is regulated by many factors for instance anaerobic growth and subinhibitory concentrations of antibiotics as seen in CF infections [12–14].

Special aspects of *S. aureus* associated with chronic infection as seen in CF lung disease are the appearance of small colony variants (SCV). Distinction of SCV are based on colony size on the agar plate, slower growth, non-pigmentation, reduced production of alpha-toxin, and thymidine dependence. There is evidence that exoproducts of *P. aeruginosa* enhance SCV formation and conversely SCV growth provides a survival advantage for *S. aureus* in presence of *P. aeruginosa* infection [15]. Clinically, SCV are associated with higher rates of antimicrobial resistance and more advanced lung disease in CF [16]. Chronic *S. aureus* infection in CF lung may occur as biofilms which is associated with higher in vitro antibiotic resistance. Biofilm mode of growth occurs in MSSA and MRSA regardless of genetic background [17] and mixed, likely multi-bacterial biofilms exist in chronic CF lung infection. Importantly in regards

Table 1
Prevalence of MSSA and MRSA in different countries in 2007 and 2008.

Country (Ref.)	Annual prevalence MSSA in%		Annual prevalence MRSA in%	
	2007	2008	2007	2008
USA [27,33]	50.9	51.3	22.6	23.7
France [34]	50.6	52.1	9.9	8.5
Ireland [35]	54.0	51.0	13.0	11.0
Australia [36]	44.2	44.7	2.5	3.0
Canada [37]		45.8		3.2
Belgium[38]	56.3	56.3	7.3	8.2
United Kingdom [a] [39]	17.3	15.2	3.5	2.7

[a] In the UK, MSSA that is captured is defined as chronic. All other nations capture any positive respiratory culture.

to development of resistance, *S. aureus* shows increased mutation rates (i.e. hypermutators strains) during CF lung infection compared to nasal colonization in healthy subjects [18].

S. aureus isolates, like *P. aeruginosa*, have clearly been shown to persist in CF patients over years. In a large survey of *S. aureus* in six French hospitals, 85 of 238 patients who were culture positive for *S. aureus*, had three or more consecutive isolates over at least 6 months [19]; this same group showed that 48% of the subjects harbored the identical isolate by pulse field gel electrophoresis up to 28 months [20]. Data from two large randomized controlled trials corroborated this data. One study noted persistence of *S. aureus* for a median of 37 months with most of the subjects harboring a single clone [21]. Interestingly, SCV *S. aureus* persisted no longer than normal *S. aureus*.

2.1. Molecular characteristics and antimicrobial susceptibilities in CF MRSA isolates

Some studies in the US examined MRSA isolates obtained from patients at their centers and showed that about 30% were SCC*mec* IV [22–24]. More recently acquired MRSA was more likely to be SCC*mec* IV [22]. This pattern is similar to reports from European centers, for instance a multi-center study in Italy showing 38% being CA-MRSA defined as SCC*mec* IV [25].

An ongoing six-center observational study in the US (STAR-CF, Muhlebach, PI) examines the clinical impact of different MRSA strains characterized by molecular typing [26]. Of the over 200 isolates that have been obtained from pediatric patients with chronic MRSA infection, 69.5% are *pvl* negative SCC*mec* II, consistent with HA-MRSA. The remaining isolates are SCC*mec* IV and 13% are *pvl* negative and 17% are *pvl* positive. Antimicrobial susceptibilities show that over 90% of isolates are resistant to erythromycin and show high resistance rates to quinolones (90% for HA and 35%% for CA isolates). On the other hand resistance to TMP-SMX and tetracycline was below 10% for CA or HA isolates indicating that these are good first choices for first isolation of MRSA as the overall rate of resistance is low and they both have an advantageous risk/benefit profile. In this sample of pediatric isolates resistance to linezolid was 1% and no isolate was resistant to vancomycin, thus these medications should be reserved for treatment of severe exacerbations.

3. MSSA and MRSA clinical epidemiology and impact

3.1. MSSA

Early infections in CF airways are most frequently caused by *S. aureus* and *H. influenzae* [27]. In fact, *S. aureus* is often the first organism cultured from young children with CF and is detected in bronchoalveolar lavage cultures or oropharyngeal swabs in young children with CF [28]. The overall frequency of MSSA and MRSA by country as reported by their National CF Registries is shown in Table 1. Patients with CF participating in a large phase 3 clinical trial in the US who had *P. aeruginosa* at entry, also were culture positive for *S. aureus* in 43.2% (201 patients) [29]. *S. aureus* in combination with *P. aeruginosa* may portend worse clinical outcomes as noted in a study of CF children under age 2; those who were positive for *S. aureus* and *P. aeruginosa* on throat cultures had lower Brasfield scores and by age 5 had worse obstructive lung disease than those with *S. aureus* alone [30]. Pulmonary infection with *S. aureus* and inflammation in bronchoalveolar lavage also correlated with worse nutritional status in the prospective Australian trial including mostly infants diagnosed with CF by newborn screening [31]. Early studies of immune response to *S. aureus* in CF patients noted increases in serum IgG antibodies to teichoic acid and alpha toxin but not capsular antibodies from *S. aureus* in those subjects chronically infected and found a reduction in the antibody panel with treatment of *S. aureus* [32].

There continues to be debate about the significance of *S. aureus* in the pathogenesis of lung infection in the general CF population [33] despite increased inflammatory response with *S. aureus* infection. This controversy has stemmed from findings that treatment (often prophylactic) of *S. aureus* may lead to earlier acquisition of *P. aeruginosa* as discussed below.

3.2. MRSA

Infection with MRSA, which was formerly seen only in hospitals has increased in frequency both as nosocomial infection (recent US reports suggest that 40–80% of nosocomial infections are MRSA) but also as infections in previously healthy subjects [34]. National prevalence in the US among CF patients rose from 2% in 2001 to 22.6% in 2008 [27]. Comparisons with other nations are noted in Table 1. Recent epidemiologic studies employing large multi-center longitudinal databases have evaluated the role of MRSA as contributor to clinical outcomes in CF [35,36]. In a cross-sectional study, Ren and colleagues have shown that CF patients infected with MRSA as the primary pathogen determined using standard sputum culturing techniques have lower lung function than those with MSSA as the only pathogen. Additionally MRSA positive patients had an increased rate of hospitalization and oral, inhaled and intravenous antibiotics [35]. Higher treatment intensity was also seen in a single center study where MRSA and MSSA patients were matched on *P. aeruginosa* status, age and gender. Patients did not differ in nutritional status or lung function however those with MRSA were prescribed significantly more maintenance medications [37]. An additional study using data from the Epidemiologic Study of Cystic Fibrosis (ESCF) showed that patients with MRSA had faster decline in lung function prior to MRSA acquisition noting that MRSA did not impact lung function decline [36].

Dasenbrook and colleagues evaluated the longitudinal impact of MRSA acquisition on lung function in patients with CF [38]. They found that the rate of lung function decline was greater in those patients with MRSA compared to non-MRSA patients in patients age 8 to 21 years (FEV_1 decline of 2.06% predicted/year in MRSA compared to 1.44% predicted/year in those without MRSA, difference — 0.62% predicted/year, 95% CI −0.70 to −0.54; $p<0.001$). In addition, known MRSA infection has been shown to be a risk factor for failure to recover lung function after an acute pulmonary exacerbation [39]. In an

additional provocative manuscript employing data from the US CF Foundation Patient Registry, persistent MRSA infection was found to be associated with increased mortality in CF [40]. Although multiple sensitivity analyses confirmed the robustness of the primary findings, other markers of disease severity not fully addressed in the registry data (residual confounders) could still account for the results. The study may also suffer from an indication bias, notably sicker patients get treated with broad spectrum antibiotics and get hospitalized more frequently leading to higher rates of MRSA infection. All of these studies raise issues around the management of CF patients with MRSA positive cultures.

The clinical implications of CA-MRSA versus HA-MRSA in CF are not clear with very little data in the literature. A recent report noted adolescent CF patients with PLV+CA-MRSA presented with febrile respiratory illness and lung abscesses [41]. This triggered a further review of MRSA at the institution; of 226 CF children with CF followed at St. Louis Children's Hospital from 2001 to 2004, 40 were MRSA positive [41]. Six of these patients grew PLV+CA-MRSA. The patients with PVL+MRSA were more likely to be admitted for IV antibiotic therapy and have focal pulmonary infiltrates on chest radiographs. They also had a greater decline in FEV_1 at the time of MRSA detection compared to their best FEV_1 in the prior year suggesting that PLV+CA-MRSA is more virulent in CF. These findings have not yet been replicated but are concerning.

MRSA has other important implications for patients with CF. In the healthcare environment strict isolation measures have to be followed for patients infected with MRSA. These measures lead to patient isolation with negative psychological impact [42] and have been shown to be associated with worse quality of care in the inpatient setting [43] and higher costs. Lastly, chronic MRSA infection in patients with CF may be transmitted to other CF and non-CF patients. The potential for spread to and from CF patients in- or outside the healthcare setting makes this a public health concern. Increasingly spread from the hospital to the community and vice versa has been described [44,45]. In fact certain observations and models predict that community associated infections entering the hospital may become the predominant source of MRSA in hospitals, thus advocating eradication in such at risk patients [46].

4. Treatment of MSSA — prophylaxis and eradication in CF

Some of the first reports of CF lung disease were associated with *S. aureus* infection. Historically, significant improvements in patient longevity have been associated with the advent of anti-staphylococcal therapy [47,48]. No studies have specifically evaluated the treatment of acute pulmonary exacerbation in CF patients infected with MSSA. The studies to date have involved prophylaxis and eradication. An early placebo controlled clinical trial that assessed the response to cephalexin as a prophylactic treatment to prevent *S. aureus* in 17 subjects with CF [49] demonstrated clinical benefit in those with *S. aureus*. Another group looked at the clinical impact of chronic prophylactic flucloxacillin in CF children; those who were not on flucloxacillin had more frequent cough and greater numbers of *S. aureus* isolates from their sputum [50].

Despite this early evidence to support early chronic suppressive treatment of *S. aureus*, such an approach has been controversial given the evolving evidence suggesting an increase in infection with *P. aeruginosa* with treatment of MSSA. This association was reported in the early 1980s noting success in reduction of *S. aureus* with an increase in *P. aeruginosa* [51]. Ratjen and colleagues clearly demonstrated that one of the sequelae of continuous anti-staphylococcal treatment is an increased rate of *P. aeruginosa* acquisition noted in a retrospective analysis of the German CF registry [52]. The more definitive data came from a multi-center randomized placebo controlled clinical trial of cephalexin for healthy CF children under age 6; in this study antibiotic treatment for 5–7 years was associated with lower *S. aureus* rates but higher *P. aeruginosa* infection rates [53]. A systematic Cochrane review noted that anti-staphylococcal treatment if started early in infancy could reduce *S. aureus* but noted the increased prevalence of *P. aeruginosa* as a concern and in need of further research [54]. In the US CF Pulmonary Guidelines, the use of prophylactic anti-staphylococcal antibiotics was not recommended [55]. The guideline found that any potential benefit from lower *S. aureus* infection was "outweighed by the risk of earlier or more frequent *P. aeruginosa* infection" [55]. In the UK guidelines and many Australian territories however flucloxacillin prophylaxis is recommended starting in infancy.

Eradication of initial *S. aureus* infection in CF represents a different approach than outlined above (chronic suppressive treatment). One of the earliest reports of attempts to eradicate *S. aureus (*MSSA) from the CF airways was a retrospective cohort study of a Danish CF center following 191 cystic fibrosis patients treated with 2349 courses of anti-staphylococcal chemotherapy from 1965 to 79 [56]. They reported eradication of *S. aureus* in 74% of these subjects after a single course of therapy. With further treatment, only 9% of subjects were chronically infected with *S. aureus* over a 6 month period. In a follow-up study from this same group they found low levels of resistance developing in 217 patients who had received 1605 courses of anti-staphylococcal antibiotics (strains resistant to methicillin less than 0.1%, strains resistant to fusidic acid 1.2%) [57]. Based on these data, the European CF Consensus group evaluating early intervention in CF lung disease has recommended an initial 2–4 weeks of anti-staphylococcal treatment with new *S. aureus* infection [58]. If this eradication approach fails, they recommend a 1–3 month course of antibiotics. The long-term sequela of this treatment approach is not known and warrants further investigation employing existing data.

5. Eradication strategies of MRSA

To date there are no conclusive studies demonstrating that early aggressive treatment of early MRSA respiratory infection can prevent chronic infection or if this approach ultimately improves outcomes. Most of the studies are non-controlled case

series. It is important to note that there are key differences between CF and non-CF efforts regarding eradication of MRSA. Colonization sites in CF patients differ from people with MRSA in the general population [59] and in chronic care facilities or the intensive care unit. Importantly, most of the studies of eradication involved healthcare workers or in patient populations in chronic care facilities and the intensive care unit [60]. In these studies, eradication of carrier status has often been successful using intranasal mupirocin and isolation precautions only [61]. A meta-analysis and review by the CDC in 2006 included 24 non-experimental studies and these used various treatment approaches [62]. Guidelines for management of MRSA provided in non-CF patients differ between the CDC and Canadian guidelines [63,64] and attempts to eradicate MRSA colonization in non-CF hospitalized patients have had variable success.

In CF, the concern about MRSA and the success with early *P. aeruginosa* eradication has encouraged several centers to attempt eradication of MRSA. Eradication protocols have been tested in a small number of CF patients. A step-wise eradication protocol has been developed in CF centers in Belfast [65]. In a non-controlled study of 17 pediatric subjects, MRSA was successfully eradicated in 94% of the subjects using a 3 step-protocol. Eight (47%) were successfully decolonized following one five-day course of oral rifampicin and fusidic acid; this was repeated for those who did not clear MRSA. A final course of intravenous teicoplanin was used in four subjects who had still not cleared the organism. Another protocol advocated at the Royal Liverpool Children's Hospital focused on the use of aggressive screening, oral and nebulized vancomycin and attention to hygiene [66]. In 12 children treated with their protocol, 7 had MRSA negative cultures on follow-up. The longest protocol employed in CF employed a 6 month protocol of oral rifampin and oral fusidate in adults with CF living in Australia [67]. These subjects had chronic MRSA carriage (average of 31 months of MRSA isolation). Five of the 7 subjects that followed the protocol had MRSA eradicated 6 months after completing the regimen. In the US, one CF center recently reported use of a non-formalized protocol to treat first appearance of MRSA with TMP-SMX for 4 weeks and mupirocin and rifampin in the last week [68]. Over the 18 months this protocol was used MRSA was successfully eradicated in 10/17 children. These data are from uncontrolled studies and most have not evaluated rates of adverse events, however the results are encouraging in that eradication of MRSA from CF respiratory secretions is possible using systemic antibiotics with or without additional topical therapies. None of the studies evaluated if addition of a cumbersome topical decontamination is superior to oral therapy alone. A Cochran collaboration systematic review of the evidence for the treatment of MRSA colonization in non-CF subjects evaluated 6 clinical trials and concluded that there was insufficient data for efficacy with a high rate of adverse events associated with treatment (20%) [69]. Given these conflicting data and limited supportive evidence, our group along with support from the US CF Foundation has begun a clinical trial evaluating the safety and efficacy of an eradication protocol for early MRSA acquisition ($\leq$6 months). The regimen that is being studied in the US CFF clinical trial in subjects with CF ages 4–45 years involves using a two week course of oral rifampin (weight <40 kg: 15 mg/kg daily; weight $\geq$40 kg: 300 mg twice daily), TMP-SMX (weight <40 kg: 8 mg/kg trimethoprim/40 mg/kg sulfamethoxazole; weight $\geq$40 kg: 320 mg/1600 mg twice daily), nasal mupirocin, topical chlorhexidine body wash, and environmental cleaning.

6. Treatment options for MRSA

There are no current recommendations or guidelines specific for MRSA in CF. There is no data regarding the treatment of CF patients infected with MRSA with an acute pulmonary exacerbation. A prophylactic MRSA protocol would be very concerning and likely enhance emergence of further resistance. A list of the currently approved antibiotics is summarized in Table 2 (those that are not licensed in US are shaded). The reader is referred to local prescriber manuals for availability, dosing information and side effect profiles.

Based on antimicrobial susceptibilities in the current US observational MRSA study and those reported in other countries the following antibiotic strategies may be advantageous. In patients in whom outpatient therapy is indicated the initial choices may include minocycline if patient is older than 8 years or TMP-SMX at all ages. Fusidic acid has been shown to be an effective regimen for eradication in combination with rifampin in CF patients with either initial or chronic colonization [65,67]. For patients failing these options but where oral therapy is preferred linezolid is a next option. In children however pharmacokinetics differs from adults, requiring TID dosing and linezolid levels have been described to be erratic in CF patients, especially children [70]. Other reasons to keep linezolid as an option of last choice are the side effect profile with potential interactions with tri-cyclic antidepressants, and irreversible neuropathy with long term use. Resistance to linezolid is increasingly being reported in CF or in situations with prolonged and frequent use [70,71]. The final decision on choice of antibiotic needs to include review of concomitant medications, side effect profile and patient tolerance. Despite the attractive option of treating MRSA and *P. aeruginosa* with a fluoroquinolone, this class should be used judiciously to avoid further resistance. Fluoroquinolone resistance occurs faster with older fluoroquinolones [72], is associated with cross-resistance to other antibiotics e.g. cephalosporines and aminoglycosides and act as selectors for methicillin resistance in *S. aureus* [73]. Reduced use of quinolones decreased the rate of MRSA [74]. Combination of rifampin with other medications has been shown to decrease emergence of resistance and increase intracellular penetration and enhance antimicrobial activity of either agent [82].

Among IV antibiotics, glycopeptides may be the most widely used choice. Resistance to vancomycin has so far not been a problem for CF; however heteroresistant vancomycin intermediate isolates (hVISA) may occur. Hetero-resistant MRSA, or hVISA in case of vancomycin, is characterized by the presence of subpopulations with poor susceptibility within a larger population of fully antimicrobial-susceptible microorganisms. Such hVISA is

Table 2
Current antibiotics used to treat MRSA.

Antibiotic class or name	Name/example	Tissue and lung penetration	Bacterio-static or -cidal	Place in therapy	CF specific comments
	Fusidic acid	Moderate sputum levels, no data in bronchoalveolar lavage	Concentration dependent	Early and chronic infection	Resistance very low in N America, higher in other countries [a]
Sulfon-amide Combined	TMP-SMX	Concentration in respiratory secretions parallels those in serum 2–4.5 μg [76]	bactericidal	In early and later stages [b]	Good antimicrobial susceptibilities in different MRSA strains
Tetra-cyclines	Doxycycline Minocycline	Doxy.: Approx. 16% of blood concentration. Mino.: 50–70% of serum concentration	-static	>age 8 years only Early and chronic infection	Good antimicrobial susceptibilities in different MRSA strains
Oxa-zolidinone	Linezolid	Good lung penetration	-static	Reserve for severe/resistant infection	Cross-resistance to other antibiotics unlikely
Lincosamide	Clindamycin	Good oral absorption and tissue penetration	-static	Only if MRSA is susceptible	High rate of constitutive or inducible resistance in CF [77]
Fluoro-quinolone	Levofloxacin	Lung distribution higher than plasma levels.	Compound specific -static to bactericidal	Not recommended. Cross-resistance to other antibiotics and induction of MRSA [78]	Increasing resistance of MRSA to various fluoroquinolones
Glyco-peptides	Vancomycin	Poor penetration into lung tissue	Slowly bactericidal	Exacerbations requiring IV therapy	Use additional β-lactam if co-infection MRSA/MSSA
	Teicoplanin	Poor lung penetration but better than vancomycin	bactericidal		Cross-resistance with vancomycin
Rifamycin	Rifampin	Good penetration into respiratory secretions and for nasal carriage	bactericidal in synergy	Only as combination therapy.	Resistance varies with drug concentration. Active against intracellular and biofilm bacteria
Aminoglycosides	Gentamycin				
Tobramycin	Efficacy reduced secondary to binding to mucus [79]	bactericidal	Not tested in CF. Used for synergy in blood borne infections	Clinical observations with high dose inhaled tobramycin indicate no effect on MRSA	
Glycyl-cycline	Tigecycline	Good tissue/lung penetration	-static	Only in selected cases, however in US unlabelled for MRSA pneumonia	Activity against mycobacteria and anaerobes. Some in vitro activity for biofilm MRSA [80]

Footnotes:
[a] Fusidic acid resistance include genetic mutations in bacteria leading to alterations of the drug target site and altered drug permeability but there is no cross-resistance with other antibiotics [81].
[b] Long term therapy with TMP-SMX is a risk factor for development of SCV variant *S. aureus* however it has not been evaluated if this occurs with short term or only after long term therapy.

missed by standard susceptibility testing as the isolates are present in low concentrations. Clinicians should be suspicious of hVISA in patients with recurrent use of vancomycin, poor clinical response and a MIC in the intermediately susceptible range [75]. Vancomycin is also ineffective for *S. aureus* growing in biofilms. hVISA or any glycopeptides resistance is often associated with reduced susceptibility or resistance to teicoplanin. The role of tigecycline, although approved for the treatment of some MRSA infections, is still unclear in regards to MRSA pneumonia in non-CF and should be used judiciously [76,77]. In CF tigecycline may be useful for its concomitant activity against anaerobic bacteria and atypical mycobacteria [78].

Newer medications for MRSA include quinopristin/dalfopristin which is not FDA approved for MRSA pneumonia as it was inferior to other variable treatments. This is similar to *daptomycin* which is approved for MRSA therapy for skin infections and bacteriaemia. It is not recommended for treatment of pneumonia as it binds to surfactant and eosinophilic pneumonia is one of the side effects. Fosfomycin is a phosphonic acid derivate with good activity against gram-negative organisms and available for use in urinary tract infections. A combination fosfomycin/tobramycin is being developed as an inhaled antibiotic. In vitro results show good activity of fosfomycin against MRSA but clinical experience is so far not available.

7. Conclusion

MSSA and MRSA remain important pathogens both early and late in the disease course of CF. Although there are many treatment options for treating both MSSA and MRSA, many questions remain regarding the clinical utility and tradeoffs of prophylactic therapy for MSSA and eradication and treatment for MRSA. To advance the care of CF patients, controlled clinical trials are needed to find the optimal approach to treating and managing CF patients who are infected with either MSSA or MRSA. Currently no consensus exists as to how clinicians should manage patients with CF lung disease who are infected with either MSSA or MRSA.

Conflict of interest

Neither of the authors have a conflict of interest to report.

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