4.3.2 *Staphylococcus aureus*

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1. INTRODUCTION

- *Staphyloccocus aureus* (*S. aureus*) is a major pathogen in CF, usually the first to be found in young children.
- *S. aureus* can be divided in
  - meticillin-sensitive *Staphyloccocus aureus* (MSSA) and
  - meticillin-resistant *Staphyloccocus aureus* (MRSA)
- The prevalence of MSSA and MRSA infection in CF patients in Europe is 17-54% and 3.5-13%, respectively.
- In chronic infection with *S. aureus*, sputum culture on agar plates may show small colony variants (SCV) that are associated with an increased rate of antimicrobial resistance and lung deterioration.
- Cases of severe pulmonary infection due to strains expressing Panton-Valentine Leukocidin (PVL, a cytotoxin associated with aggressive pyogenic infections) have been described in CF patients. Research of PVL in respiratory samples is conducted with specific PCR in reference centers such as university hospital laboratories. PVL research may be recommended in case of severe infection due to MSSA or MRSA.

2. METICILLIN-SENSITIVE *STAPHYLOCCOCUS AUREUS* (MSSA)

- Adults carrying MSSA are usually chronically infected and therefore, eradication is not an issue. In children, long term prophylactic antibiotherapy to prevent *S. aureus* infection has led to higher rates of *P. aeruginosa* infection.
- There are no guidelines on the treatment of MSSA exacerbations in adult CF patients. Thus, the number of antibiotics (1 vs 2), the way of administration (oral, intravenous), and the duration of treatment are not predefined but should be guided by exacerbation and illness severity.
- The choice of antibiotics is based on in vitro sensitivity and treatment duration is usually 14 days. In non-severe cases, one antibiotic given orally should be sufficient (**Table 1**).
- Important aspects concerning MSSA treatment are presented in **Table 2**.

Table 1 : Antibiotics for MSSA in adult CF patients[1,2]

	Antibiotic	Dosage	Comments
IV	Cefazolin	1.5 g every 6h or 2 g every 8h	max. 6g/day
	Cefuroxim	1.5 g every 8h	
	Co-amoxicillin	2.2 g every 8h	
	Flucloxacillin	2 g every 6h	
Oral	Co-amoxicillin	625 – 1000 mg every 8h	
	Cefuroxime	500 mg every 12h	
	TMP/SMX	160/800 mg every 8h	may strongly select for S. aureus SCV[1]
	Flucloxacilline	1-2 g every 6h	
	Cefaclor	750 mg every 12h	max. 4g/day
	Doxycycline	200 mg on 1st day and then 100-200 mg every 24h	
	Minocyclin	100 mg every 12h	
	Clarithromycin	500 mg every 12h	
	Clindamycin	600 mg every 6h	

IV: intravenously, TMP/SMX: trimethroprim/sulfamethoxazole, SCV: small colony variants
[1]In case of SCV, treatment should be individualized according to in vitro susceptibility

Table 2: Important points concerning treatment of MSSA[1,2]

Broad spectrum cephalosporins should be avoided
Ciprofloxacin should be avoided in the exception of concomitant infection with *P. aeruginosa* or intolerance/allergy to other classes of antibiotics
In patients chronically treated with azithromycin, macrolides should be avoided because of the high risk for macrolide resistance
In exacerbations of moderate severity, administration of a anti-staphylococcal penicillin or a narrow spectrum cephalosporin given intravenously should be considered
In case of necrotizing pneumonia due to PVL-producing MSSA, the addition of an antitoxin antibiotic (clindamycin, linezolid) is recommended
In cases of a severe exacerbation or an exacerbation in a severely-ill patient, clinicians should consider the presence of other pathogens, such as *P. aeruginosa*. In this situation, a combination of intravenous penicillin (e.g. tazobactam-piperacillin) or meropenem + oral ciprofloxacin or intravenous aminoglycoside (e.g. tobramycin, amikacin) should be considered.

3. METICILLIN-RESISTANT *STAPHYLOCCOCUS AUREUS* (MRSA)

- MRSA prevalence is increasing and this may be partially due to the use of broad spectrum antibiotics.
- MRSA acquisition is associated with a faster decline of FEV_1 and reduced survival in CF.
- Chronic infection with MRSA decreases the recovery of pulmonary function following a respiratory exacerbation.
- Since MRSA is highly transmissible, CF patients infected with MRSA need to be isolated when they are in a healthcare environment.
- As for MSSA, no clear recommendations for MRSA eradication or pulmonary exacerbation treatment are available.
  - A recent Cochrane review (Cochrane MRSA) could not establish recommendations on MRSA eradication in CF patients based on published studies but results of several non-randomized trials suggest that MRSA can be eradicated.
  - Although one-third of patients may clear MRSA spontaneously, considering the increased morbidity associated with MRSA infection in CF, experts recommend to start an eradication regiment at the first positive culture.
  - In a recent retrospective study from the Royal Brompton Hospital (Hall H et al. 2015), dual regiments were superior to a single antibiotic for MRSA eradication. Particularly, the association of rifampicin 300 mg every 12h and fusidic acid 500 mg every 8h for 14 days given in newly and chronically infected patients, was associated with an immediate success rate of 82.6%. Cultures were still negative in 68% and 58.3% of patients at 6 months and 12 months respectively.

3.1 MRSA eradication regimens

- Several protocols have been used in small non controlled trials.
- It is recommended to avoid long-term use of single agents such as TMP/SMX, rifampicin or fucidic acid.
- The most recent protocols are presented in **Table 3.** Drugs used for MRSA eradication and their dosages are presented in more detail in **Table 4.**
  - The choice of the protocol will depend on the clinical severity and patient drug tolerance. Different combinations of these drugs may be necessary.
  - Discussion with the local microbiologist and infectious disease specialist is recommended.

3.2 Treatment of MRSA-associated pulmonary exacerbations

- According to recent reviews, linezolid and vancomycin for 14 days are proposed as first choice drugs for MRSA-associated pulmonary exacerbations (**Table 4** for dosages). However, because of potential serious side effects of both antibiotics (fewer with vancomycin), other authors advocated that they should be reserved for severe MRSA infection requiring hospitalization.
- In case of allergy/intolerance or *in vitro* resistance, consider tigecycline or teicoplanin or a combination of oral antibiotics based on sensitivity (e.g. rifampicin + fusidic acid).

- Ceftaroline (Zinforo®), a novel cephalosporin with activity against MRSA, may be an appropriate option for treating MRSA lung infection, although CF-specific data are lacking.

Table 3: Examples of protocol for the eradication of MRSA (for dosage, see Table 4)[1-5]

Protocol 1[1] **(14 days)**	TMP/SMX (320/1600 mg) + rifampicin + standard topical treatment for nasal, throat and skin decontamination
Protocol 2[3] **(14 days)**	Rifampicin + fucidic acid + standard topical treatment for nasal, throat and skin decontamination
Protocol 3[5] **(4 or 6 weeks)**	**1st line:** doxycycline + TMP/SMX (160/800) or rifampicin or fucidic acid for 6 weeks (according to *in vitro* sensitivity) **2nd line:** if possible combination of rifampicin + fusidic acid for 6 weeks **3rd line:** vancomycin or teicoplanin IV for 2 weeks followed by oral therapy combining doxycycline + TMP/SMX or rifampicin or fusidic acid for 4 weeks, or oral linezolid for 4 weeks + standard topical treatment for nasal, throat and skin decontamination
Protocol 4[4] **(4 weeks)**	Vancomycin nebulization (250 mg) every 12h

*Standard topical treatment consists of:
nasal mupirocin (Bactroban® Nasal) for 14 days
+ topical chlorexidine body wash for 14 days

Table 4: Antibiotics used for MRSA in aduls CF patients[1-5]

	Antibiotic	Dosage	Comments
IV	Vancomycin	1 g every 12h	Risks: ototoxicity, nephrotoxicity, red man syndrome Target serum concentration : 15-20 mg/L
	Linezolid	600 mg every 12h	
	Tigecycline	100 mg at first dose *followed by* 50 mg every 12h	
	Teicoplanin	400 mg at the first dose or 400 mg every 12 h (if severe infection) at the first day *followed by* 200 mg or 400 mg (if severe infection) every 24h	TDM is recommended*[1]

(continued)

	Ceftaroline	600 mg every 12 h	
Oral	Rifampicin	300 mg every 12h	Always in combination
	TMP/SMX	160/800 mg every 8h or 320/1600 mg every 12h	May strongly select for S. aureus SCVs
	Linezolid	600 mg every 12h	
	Fusidic acid	500 mg every 8h	
	Doxycycline	100 mg every 12h	
	Minocycline	100 mg every 12h	
	Levofloxacin	Not recommended	High risk of resistance
Inhaled	Vancomycin*[1,2]	250 mg in 5 ml sterile H_2O or 0.9% NaCl every 12h	As bronchospasm may occur: - administration of bronchodilators before each dose is recommended - in case of severe bronchial obstruction, spirometry before and after administration of the first dose should be considered
Topical	Mupirocin 2%	Nasal : every 8h for 5 days	
	Chlorhexidine soap 4% or Povidone-iodine 7.5%	Skin : every day for 5 days	
	Chlorhexidine 0.1%	Throat : every 6-8h for 5 days	

IV: intravenous, TMP/SMX : trimethroprim/sulfamethoxazole, SCVs : small colony variants, TDM: therapeutic drug monitoring

***1 See also Chapter "*Medications*"**

*2 At the time of writing not licensed for inhalation

4. REFERENCES

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