Nasal *Staphylococcus aureus* Carriage is not a Risk Factor for Lower Airway Infection in Young Cystic Fibrosis Patients

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**ABSTRACT**

*Staphylococcus aureus* is one of the first pathogens, which often persistently infects the airways of cystic fibrosis (CF) patients. Nasal *S. aureus* carriage is a risk factor for *S. aureus* infections in non-CF patients. Topical treatment strategies successfully eradicated nasal *S. aureus* carriage thereby decreasing *S. aureus* infection. A prospective longitudinal multicenter study was conducted to assess whether nasal carriage represents a risk factor for *S. aureus* colonization of the oropharynx in young CF patients. Cross sectional analysis revealed a significantly higher prevalence of *S. aureus* positive nasal (28/80, 35% versus 20/109; 18%; *p* < 0.01) and oropharyngeal cultures (35/80, 44% versus 20/109, 18%; *p* < 0.001) in CF children compared to a control group. The first site of *S. aureus* detection was the nose in 6 patients and the oropharynx in 14 patients, respectively. Longitudinal analysis demonstrated a significantly higher *S. aureus* prevalence (61/62; 98% versus 47/62; 76%; *p* < 0.001) and persistence (46/62, 74% versus 31/62, 50%; *p* < 0.01) in the oropharynx than in the nose. In CF patients the oropharynx and not the nose was the predominant site of *S. aureus* infection and persistence. Hence, it is unlikely that CF patients will benefit from topical treatment strategies to eradicate nasal carriage.
INTRODUCTION

Cystic fibrosis (CF) is one of the most prevalent hereditary diseases in the Caucasian population. Although quality of life and life expectancy have increased during the last decades, more than 98% of the patients still suffer from chronic airway infections, and more than 95% of deaths are related to respiratory insufficiency (16). One of the most common pathogens isolated from the airways of young CF patients is *Staphylococcus aureus*. Several longitudinal studies and data from CF registries revealed that *S. aureus* infection frequently starts in early infancy, preceding chronic *Pseudomonas aeruginosa* infection, which is characteristic for the advanced stages of the disease (5). Once *S. aureus* infects the airways of CF patients, the bacteria are difficult to eradicate despite the use of appropriate antistaphylococcal therapy (10). In many CF patients, the same *S. aureus* clone infects the airways for years and antibiotic therapy only suppresses the pathogen for a period of time giving rise to exacerbations requiring repeated courses of treatment (11,19).

The anterior nares, from which *S. aureus* can be isolated most consistently, have been shown to present an ecological niche for this microorganism (20,31) from where the bacteria can spread to other parts of the body (30). Interestingly, nasal *S. aureus* carriage has been shown to represent a risk factor for a number of *S. aureus* infections such as sternal wound infections in patients after cardiac surgery (15), peritonitis in patients on continuous ambulatory peritoneal dialysis (22) and exit-site infections in hemodialysis patients (13). Studies observing the onset of *S. aureus* bacteremia demonstrated that acquisition of the pathogen occurred mostly via the endogenous route due to the patient’s own flora rather than via external transmission (28).

Preventive strategies have been developed to eliminate nasal *S. aureus* carrier status by topical treatment with antibiotics (14). If the anterior nares were treated locally, the organism also disappeared from other sites of the body in most cases (14). Mupirocin, a
natural antibiotic derived from *P. fluorescens* (8), has been used in patients undergoing dialysis, orthopaedic or open heart surgery, revealing a significant reduction of *S. aureus* infections in patients treated topically compared to untreated patients (1,3,6,12).

If nasal carriage would be recognized as a risk factor for airway infection early in CF patients, the patients could benefit from topical antibiotic treatment. As of yet, there is no information about assessing the sequence of *S. aureus* infection in CF patients. Therefore, we conducted a prospective longitudinal multicenter study to determine whether nasal carriage represents a risk factor for *S. aureus* colonization of the oropharynx in young CF patients.
MATERIALS AND METHODS

Study design

Four specialized CF clinics (two in Muenster, one each in Duesseldorf and Essen) participated in the study. There are basically three different strategies of treatment against S. aureus: prophylactic therapy, treatment of positive cultures and treatment only in the presence of symptoms. None of the four centers used continuous prophylactic anti-staphyloccocal antibiotic therapy, but treat against S. aureus, if there are positive cultures and symptoms occur.

The study consisted of 2 parts:

1. A cross-sectional part assessing the prevalence of nasal and oropharyngeal carriage in young CF children determined by analysis of the first specimens after recruitment (n=80). These data were compared to specimens of a control group from the Department of Ophthalmology comprising patients who underwent a short surgical procedure due to nasolacrimal duct obstruction (n=109).

2. A longitudinal part of the study analysing the sequence of infection in CF children, from which repeated specimens were available over a time period of at least 18 months (n=62). Nasal and oropharyngeal swabs or sputa of patients were taken during their regular (quarterly) visits to the outpatient clinics. To assess nasal carriage, the anterior 1.5 cm of the nasal vestibule of both the left and right nares was rubbed with a sterile cotton swab.

Ethical approval for the study was obtained from the institutional review boards of all participating centres, written informed parental consent was obtained in all cases.

Questionnaire

Parents were asked to answer a standardized questionnaire to determine risk factors for the acquisition of S. aureus carriage at recruitment. Information was obtained regarding
known risk factors for *S. aureus* acquisition such as the regular attending of a children care center, earlier hospitalization, use of antibiotics (orally, i.v. or inhalative), siblings (number, age, CF siblings), relatives living in the same household (close contact to the child, chronic diseases of relatives or earlier hospitalization), and pets living in the household (14,23,29). Additionally, the parents were asked if the children used stuffed animals, special favourite toys or contacted other CF patients.

**Laboratory methods**

All specimens were processed at the Institute of Medical Microbiology, Muenster. Primary cultures were performed on Columbia (Becton Dickinson, Heidelberg, Germany) sheep blood (Oxoid, Wesel, Germany) agar for Gram-positive cocci, on endo agar (Merck, Darmstadt, Germany) for Gram-negative rods for 48 h at 35ºC and on chocolate agar (Mast, Reinfeld, Germany) for *Haemophilus influenzae* for 24 – 48 h at 35ºC under 5% CO₂. Additionally, specimens were cultured in dextrose broth to enrich bacterial growth and streaked on blood and endo agar after 48 h. Special culture conditions for the isolation of SCVs were used as described (10). Briefly, primary cultures were streaked on BHI agar with 5% NaCl and on Schaedler agar, which is a rich medium agar, used to culture anaerobic bacteria, and incubated for 48h at 35ºC. Identification of *S. aureus* was confirmed by Pasteurex slide test (Biorad) and by tube coagulase testing. In case of discrepancy, PCR of the *S. aureus* specific thermonuclease was performed (2). Susceptibility testing was carried out by disk diffusion on Mueller-Hinton agar (Mast) according to the guidelines (4). Antibiotics tested were penicillin, oxacillin, ampicillin, imipenem, cefaclor, cefazolin, cefotaxime, erythromycin, clindamycin, gentamicin, levofloxacin, trimethoprim-sulfamethoxazole (SXT) and rifampin. In case of MRSA, mupirocin was tested additionally.
Persistent carriage

The longitudinal part of the study allowed determining the carriage patterns of *S. aureus* in both the nose and the oropharynx. Three different colonization patterns for nasal carriage have been described in the literature: persistent carriage, intermittent carriage and non-carriage (29). Persistent carriage/colonization/infection was defined as having *S. aureus* positive cultures for at least 6 months based on a minimum of 2 positive cultures from the respective specimens taken at regular quarterly visits.

Molecular typing

Isolates were analyzed by pulsed-field gel electrophoresis (PFGE) after *SmaI* restriction of whole chromosomal DNA (7). The gels were analyzed both visually and by the computer program Quantity One (Bio-Rad Laboratories, Hercules, Ca) and interpreted according to published guidelines (25,26). Consecutive isolates from the same patient, with identical or only minor differences in fragment patterns were assigned to the same clone or clonal lineage, if the Dice coefficient was higher than 85 % (26). Isolates with a similarity index beyond 85% were considered to belong to different clones.

Statistical analysis

Analysis of the *S. aureus* prevalence was carried out by standard statistical tests (median, Student’s t-test, chi-square test). The Fisher’s exact test was used to calculate the correlation of nasal and oropharyngeal carriage. To assess risk factors for *S. aureus* colonization Odds Ratios (OR) were calculated comparing cases with suitable controls. The bivariate analysis was followed by stratification and logistic regression analysis using SPSS Version 11.5.
RESULTS

Prevalence of nasal and oropharyngeal S. aureus carriage in CF and healthy children

The cross-sectional part of the study assessed the prevalence of S. aureus carriage in the anterior nares and oropharynx in 80 CF patients and 109 controls without respiratory disease. Twenty of 80 CF (25%) children were positive for S. aureus in both oropharyngeal and nasal cultures, whereas S. aureus was cultured from the nose only in 8 children (10%) and from the oropharynx only in 15 children (19%). Thus, the overall prevalence of S. aureus positive nasal and oropharyngeal cultures in CF children was 35% (28/80) and 44% (35/80), respectively (Fig. 1). Both oropharyngeal and nasal cultures were positive in 10/109 control children (9%), nasal or oropharyngeal cultures were positive for S. aureus in 10 children each, resulting in a cumulative prevalence of nasal or oropharyngeal carriage of 27% (30/109) (Fig. 1). There was a statistically significant higher prevalence of S. aureus positive nasal and oropharyngeal cultures in CF than in the control children (OR 2.4; CI 1.2 – 4.7; p < 0.01; and OR 3.4; CI 1.8 – 6.7; p < 0.001), respectively.

The probability of oropharyngeal carriage was significantly higher in nasal carriers than in non-carriers both in CF and controls (OR 6.2; CI 2.2 – 17.0; p < 0.001 for CF: OR 7.9; CI 2.6 – 23.6, p < 0.001). In contrast to the control group, who were colonized at both sites in similar frequency, the oropharynx was significantly more often colonized in CF children.

In our study population, the median acquisition age of S. aureus oropharyngeal and nasal colonization was 4.18 years and 4.45 years, respectively.

Dynamics of S. aureus infection in young CF children

Culture results from nasal and oropharyngeal specimens of 62 CF children (40 % girls) with a median age of 3.5 years, who were followed for at least 18 months, were analyzed. The median observation period was 33 months (range 18 - 65 months). Mean nasal
and oropharyngeal cultures per patient were 9.5 and 11 specimens, respectively. *S. aureus* isolates were cultured from 196/587 (33%) nasal and 305/659 (46%) oropharyngeal swabs.

In 17 (27%) children, *S. aureus* was already cultured from the nose and airways at recruitment. In 29 (47%) children *S. aureus* colonization could be observed for the first time during the observation period: In 9 (14%) children, *S. aureus* was cultured at the same time from the nose and the oropharynx, in 14 (23%) patients only from the oropharynx at first and later also from the nose and in 6 children from the nose followed later by positive cultures from the oropharynx. The only site of *S. aureus* recovery during the study period was the oropharynx and the nose in 14 patients (23%) and in one patient (2%), respectively. Only one patient never carried *S. aureus* throughout the study period. From 24 patients with nasal and oropharyngeal carriage and from 10 patients with oropharyngeal carriage only FEV₁ data were available. The lung function of the 2 groups was not different (mean 93.83 versus 95.3; P = 0.813).

In 11 patients, additional to oropharyngeal swabs 52 sputa were positive for *S. aureus*. Most clones isolated from the sputa were also recovered from the oropharynx (47/52, 90%) indicating colonization or infection of the lower airways with the same *S. aureus* clone as recovered from the oropharynx.

In summary, during the longitudinal part of the study, *S. aureus* was cultured from the upper airways and the nose in 46 children, from the oropharynx only in 14 children and from the nose only in 1 patient (Fig. 2). Thus, the most prevalent site for *S. aureus* in CF patients was the oropharynx (60/62; 97%) with a significant lower prevalence in the nose (47/62; 76%; p < 0.001).

**Persistent carriage of *S. aureus* in nose and oropharynx**

Persistent positive nasal and oropharyngeal cultures were observed in 31/62 (50%) and 46/62 (74%) children respectively with a median persistence of 23 months (mean 27; range 6
– 46 months) and 29 months (mean 27; range 6 – 50 months). While 30/31 (97%) patients with persistent nasal carriage were also persistently colonized in their oropharynx, only 30/46 (64%) with persistent oropharyngeal carriage were also persistent nasal carriers. Interestingly, the number of patients with persistent \textit{S. aureus} carriage in the oropharynx was statistically significant higher than those of the nose (p = 0.001).

**Dynamics of \textit{S. aureus} carriage assessed with molecular techniques**

Molecular analysis of all cultured \textit{S. aureus} isolates by PFGE allowed determining the population dynamics of \textit{S. aureus} clones. Hundred-and-seven different clones from the nose and 156 different clones from the oropharynx were isolated from 62 patients, with a mean number of 2.3 (range 1 – 8) and 2.6 clones per patient (range 1 – 11) for each site (Table 2). Eighty-five of these clones were isolated from both sites (79% of the nasal clones; 55% of the oropharyngeal clones). Fourteen clones appeared first in the nares as exemplified for one patient in Fig. 3a, 31 in the oropharynx as shown for a second patient in Fig. 3b, whereas 40 clones were isolated from both sites at the same time as demonstrated for a third patient in Fig. 3c. Overall, the number of different and persisting clones was statistically significant higher in the oropharynx than in the nose (Table 2). While nearly all clones isolated from the nose appeared either at the same time or later also in the oropharynx (82%), clones isolated from the oropharynx were less likely to be isolated from the anterior nares (57%).

**Susceptibility**

During the study, susceptibility testing was performed with 824 \textit{S. aureus} isolates cultured from the anterior nares (NA; 250 isolates), the oropharynx (OP; 436 isolates) or from sputa (64 SP from 12 patients; 138 isolates). Thirty-five (NA:13; OP:22) methicillin-resistant \textit{S. aureus} (MRSA) isolates (4%) were detected in 5 children from one centre. MRSA isolates were also resistant against clindamycin and erythromycin.
including resistance against either gentamicin (n=21) or levofloxacin (n=14). β-
lactamase expression was detected in 674/789 (85%) MSSA isolates (NA:194/237, 82%;
OP:354/424, 83%; SP:91/138, 66%). Resistance against gentamicin was observed in
10/789 MSSA strains (NA:1; OP:6; SP:3), against levofloxacin in 1 MSSA strain (SP:1),
against clindamycin and erythromycin in 70/789 (9%) MSSA isolates (N:23/237, 10%;
OP:38/424, 9%; SP:9/138, 7%), against SXT in 39/789 (5%) MSSA (NA:5, 1 SCV;
OP:10, 2 SCVs; SP:24, 21 SCVs). Neither MRSA nor MSSA isolates were rifampin
resistant. None of the MRSA isolates was mupirocin resistant. Sequential isolates of
individual patients did not increase in resistance during the study period except the
cases, in which MRSA replaced MSSA strains (3 patients) or in cases, in which SCVs
emerged (8 patients).

Risk factors for *S. aureus* carriage

Forty-three questionnaires completed by parents of 29 boys and 14 girls were included
for further analysis reflecting a response rate of 69%. The epidemiological and
microbiological data of this subgroup were representative for the whole group: The median
age of the children was 3.5 years, the median observation period 33 months. *S. aureus* was
cultured from 142/434 (33%) nasal and 220/495 (44%) throat swabs. The use of a pacifier,
oral or inhalative antibiotics, the regular attending of a children dare care center, hospital
stay or using a stuffed animal were not associated with persistent *S. aureus* carriage at either
site. However, in the logistic regression analysis having a pet at home was associated with
nasal carriage (OR 4.5; CI 1.0 – 21.1; p = 0.05).
DISCUSSION

The cross-sectional part of the study demonstrated that significantly more CF children harboured *S. aureus* in both their anterior nares and oropharynx than the control group. The carrier rate of our control group is consistent with the study by Peacock et al., in which 21% of children followed from birth were colonized at the age of 6 months (18). Our data indicate that CF by itself represents a risk factor for *S. aureus* acquisition and thus also infection. While the control group had similar carriage rates in the oropharynx and anterior nares, positive cultures of the oropharynx significantly exceeded carriage rates of the anterior nares in CF children. This finding is in contrast to many other studies as reviewed in (14), where the anterior nares were the main site for *S. aureus* colonization in humans.

Nasal carriage has been demonstrated to be a risk factor for consecutive *S. aureus* infection (28, 29). In these studies nasal carriage of *S. aureus* preceded infection which led to the implementation of preventive strategies to eradicate nasal carriage thereby decreasing the number of *S. aureus* induced infections. To observe if such a sequence of colonization and infection also occurs in CF patients required a longitudinal study design. However, many patients already carried *S. aureus* in both oropharynx and the nose at the beginning of the study. In those patients having positive culture at only one site, the rate of *S. aureus* detection was considerably higher in oropharyngeal rather than in nasal cultures. Only in a small number of patients the anterior nares have been identified as the first site of colonization. The observed sequence of *S. aureus* colonization was confirmed by molecular techniques. While almost all clones cultured from the nose later appeared in the oropharynx, only a small fraction of the clones cultured from the oropharynx occurred in the nose. Therefore, the sequence of *S. aureus* colonization differs in CF patients from other patients and healthy persons with a higher prevalence and persistence of *S. aureus* in the oropharynx than in the nose.
The high rate of *S. aureus* detection in this study underscores the fact that *S. aureus* is acquired very early in CF patients. It is conceivable that the recruited group with a median age of 3.6 years may have already been too old to follow the sequence and the acquisition age of *S. aureus*. Interestingly, the acquisition age of *S. aureus* colonization in the oropharynx and in the nose in the investigated study population was 4.14 and 4.48 years, respectively. However, studying infants diagnosed by neonatal screening may potentially yield different results with a lower *S. aureus* acquisition age and another sequence of *S. aureus* colonization. It is also possible that the sampling interval at the quarterly clinic visits with a relatively low sampling frequency may have led to a lower detection rate of nasal carriage preceding oropharyngeal carriage. However, a very short transient period of nasal carriage would not be clinically relevant, since this could not be addressed with a topical treatment strategy.

The *S. aureus* prevalence in the nose was higher in CF patients than in the control group. However, the *S. aureus* prevalence in the nose was exceeded by the prevalence in the oropharynx in CF patients. This may be explained by additional changes present in the airways such as the impaired mucociliary clearance or changed presentation of receptors for bacterial binding present on epithelial cells (9). It may also be due to expectoration of lower airway secretions containing *S. aureus* through the oropharynx. Interestingly, a recent study in non CF patients and hospital personnel also reported a higher frequency of oropharyngeal colonization compared to the nares albeit in less bacterial numbers (17). These results are in contrast to other published studies so far, but raise the question whether differences in culture technique may affect the detection rate of *S. aureus*. Furthermore, the fact that in this study the tonsils, which have been shown to be a source for recurrent *S. aureus* carriage in some cases (27), and not the oropharynx were swabbed, may have resulted in this high *S. aureus* prevalence in the throat.
Susceptibility results did not differ in isolates cultured from the anterior nares or from the oropharynx. However, significantly less isolates recovered from sputa expressed β-lactamases compared to isolates recovered from the anterior nares or from the oropharynx indicating that different selective pressures act upon *S. aureus* depending on the source of the isolate. Importantly, susceptibility of sequential *S. aureus* isolates against antibiotics did not change during the observation period except in the cases where MRSA replaced MSSA isolates or in the cases where SCVs emerged.

Interestingly, the questionnaire which evaluated risk factors for *S. aureus* carriage revealed that having a pet at home appeared to enhance nasal carriage in CF children. While transmission of *S. aureus* between humans due to domestic animals has been shown before (24), pets have not been recognized so far as a risk factor for *S. aureus* carriage in children with CF. This result may have important implications for the regular life of CF patients.

Since most young CF children do not produce sputum, most of the specimens that we investigated were oropharyngeal swabs. It has been shown that oropharyngeal cultures represent good negative but not good positive predictive values for bacteria present in the lower airways (21). Therefore, it is difficult to draw conclusions about the number of patients with *S. aureus* infections in the lower airways. To do so, it would have been necessary to study bacterial cultures of bronchoalveolar lavage fluid, a method which would have been too unsuitable for repetitive clinical use in children. However, it was not the intention of our study to determine the rate of *S. aureus* infection in CF patients but rather to study the sequence of *S. aureus* colonization.

The results of our study have implications for treatment strategies for CF patients. Our data identified the oropharynx as the most prevalent and often the first site of *S. aureus* carriage in young CF patients. Treatment strategies to prevent infections by eradication of nasal carriage will therefore not be an option for CF patients. Our data may also be transferred to the management of MRSA eradication in CF. In non CF patients,
MRSA eradication procedures usually combine nasal eradication with the topical use of antiseptics leading in most cases to the loss of the pathogen. However, considering the high prevalence of *S. aureus* in the upper airways, it is very unlikely that MRSA in CF patients will be eradicated by standard hygiene procedures.

In conclusion, our findings demonstrate that CF patients carried *S. aureus* mostly in their oropharynx and not in the nose which is in contrast to other patient groups and healthy individuals. Furthermore, persistent carriage rates were higher in the oropharynx than in the nose. Therefore, it is highly unlikely that CF patients will benefit from local eradication strategies of nasal carriage to prevent *S. aureus* airway infections.
ACKNOWLEDGEMENTS

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REFERENCES


Figure 1. Prevalence of *S. aureus* nasal and oropharyngeal carriage in CF and control children. There was a statistically significant higher prevalence of *S. aureus* in CF children than in healthy controls without respiratory disease in the nose (28/80 versus 20/109) and in the oropharynx (35/80 versus 20/109).

Figure 2. Cumulative frequency of *S. aureus* positive cultures in nose and/or oropharynx. During the longitudinal part of the study, *S. aureus* was cultured from the oropharynx and the nose in 47 children, only from the oropharynx in 14 children, only from the nose in 1 child, while 1 child was never colonized by *S. aureus*.

Figure 3. Sequence of *S. aureus* positive cultures on the clonal level. A. PFGE analysis of *S. aureus* isolates of a CF patient, from whom *S. aureus* was first cultured from the nose (N), later followed by culture of *S. aureus* from the oropharynx (O). B. PFGE patterns of sequential isolates of a patient, from whom *S. aureus* was first cultured from the oropharynx, later from oropharynx and nose at the same time. C. PFGE patterns from isolates of a patient, from whom 2 different *S. aureus* clones were cultured from the oropharynx and from the nose at the same time.
Prevalence of *S. aureus* nasal and oropharyngeal carriage in CF and control children.

Figure 1. Ridder-Schaphorn S et al. *S. aureus* nasal carriage in young CF patients
Cumulative frequency of *S. aureus* positive cultures in nose and/or oropharynx

Figure 2. Ridder-Schaphorn S et al. *S. aureus* nasal carriage in young CF patients
Demographic data of the CF patients and the control group

<table>
<thead>
<tr>
<th></th>
<th>CF patients</th>
<th>Control group</th>
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<tbody>
<tr>
<td>Number of patients (n)</td>
<td>80</td>
<td>109</td>
</tr>
<tr>
<td>Age (median)</td>
<td>3.6 years</td>
<td>1.6 years</td>
</tr>
<tr>
<td></td>
<td>mean 3.8</td>
<td>mean 2.2</td>
</tr>
<tr>
<td></td>
<td>range 0.4 – 9.9 years</td>
<td>range 0.1 – 8.6 years</td>
</tr>
<tr>
<td>Gender, girls (n; %)</td>
<td>36 (40)</td>
<td>41 (88)</td>
</tr>
</tbody>
</table>

Table 1. Ridder-Schaphorn S. et al. *S. aureus* nasal carriage in young CF patients
S. aureus clones isolated from the upper airways of CF patients during the study period

<table>
<thead>
<tr>
<th>site</th>
<th>Anterior nares</th>
<th>Oropharynx/upper airways</th>
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</thead>
<tbody>
<tr>
<td>Number of clones</td>
<td>107</td>
<td>155</td>
</tr>
<tr>
<td>Both sites</td>
<td>85 (79%)</td>
<td>85 (55%)</td>
</tr>
<tr>
<td>Clones/patient(^1)</td>
<td>2.3 (1-9)</td>
<td>2.6 (1-11)</td>
</tr>
<tr>
<td>Persistent clones(^2)</td>
<td>40 (37%)</td>
<td>79 (51%)*</td>
</tr>
<tr>
<td>Persistence(^3)</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Only once(^4)</td>
<td>67 (63%)</td>
<td>76 (49%)</td>
</tr>
</tbody>
</table>

\(^1\)Mean number of clones isolated from individual patients during the study period; (range)
\(^2\)Clones, which persisted \(\geq 6\) months
\(^3\)mean persistence of clones in months
\(^4\)isolated only at a single occasion

Table 2. Ridder-Schaphorn S. et al. *S. aureus* nasal carriage in young CF patients
Sequence of *S. aureus* positive cultures on the clonal level

Figure 3. Ridder-Schaphorn S et al. *S. aureus* nasal carriage in young CF patients