

A new device to prevent contamination of nasal swabs by *Staphylococcus aureus* in acute rhinosinutitis*

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Abstract

Background: There is a risk of bacterial contamination of nasal swabs during passage of the narrow nasal vestibule in patients carrying *Staphylococcus aureus* in their nares. We aimed to test if a newly developed contamination-free bacterial swab (CFS) device for swab introduction could reduce the risk of contamination with *Staphylococcus aureus* from the nasal vestibule in patients with acute upper respiratory tract infections.

Methodology: A single-blinded non-randomized controlled trial that included 64 participants with acute upper respiratory tract infections. The left and right nasal cavities were swabbed using the present-day technique and the CFS device, respectively. Primary outcome was frequency of *Staphylococcus aureus* positive cultures; secondary outcome was growth of other bacteria.

Results: We found a significantly higher frequency of *Staphylococcus aureus* in cultures taken with the present-day technique (23%) when compared to the new device (8%, $p=0.008$). Growth of other bacteria did not differ markedly between sample techniques.

Conclusions: The newly developed device reduces contamination with *Staphylococcus aureus* significantly. It has the potential to increase diagnostic accuracy in acute upper respiratory tract infections, decrease the overall use of antibiotics and thereby counteract overuse of antibiotics and emerging antibiotic resistance.

Key words: medical devices, microbiology, *Staphylococcus aureus*, sinusitis, antibiotic resistance, diagnostic equipment, culture techniques

Introduction

Acute rhinosinusitis (ARS) is a common cause of primary care consultations and despite modest efficacy; systemic antibiotics are frequently used to treat ARS ^(1,2). ARS, defined as symptoms of rhinosinusitis lasting < 3 months, affects approximately 20 million people in the US per year and it is among the third to fifth most common diagnosis for which antibiotics are prescribed in the Nordic countries and the US ⁽³⁾. ARS accounts for

approximately 20% of the adult antibiotic prescriptions in the US ⁽⁴⁾.

The most frequently cultured pathogens in ARS are *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Moraxella catarrhalis*. It is often reported that *Staphylococcus aureus* (SA) only accounts for a small proportion of cases with reported frequencies between 0-15% depending on the method of sampling ⁽⁵⁻⁶⁾. However, a large proportion of ARS cases are due to viral infecti-

ons and studies have shown a number-needed-to-treat around 15-19 indicating that less than 10% of patients benefit from antibiotics ⁽⁷⁻⁸⁾. It follows that there is an opportunity to improve diagnostic accuracy, thereby reducing the antibiotic pressure and counteracting emerging antibiotic resistance ⁽⁹⁻¹¹⁾.

Emerging antibiotic resistance is an increasing global threat and infections with antibiotic-resistant bacteria are estimated to cause 23,000 and 33,000 annual deaths in the US and Europe, respectively ^(12,13). The total annual cost of antibiotic resistance is estimated to be around 20-50 billion dollars in the US ^(14,15). Therefore, it should be prioritized to reduce any overuse of antibiotics, not least the broad-spectrum antibiotics like amoxicillin with clavulanic acid that are often first choice in ARS ⁽¹⁶⁾.

The majority of patients with ARS are seen and treated by primary care physicians and most often empiric antibiotics are prescribed ⁽¹⁾. Bacterial cultures can be obtained by sinus puncture, a procedure not performed by primary care physicians, or more simply by a swab from the nasal cavity (middle meatus) which is well tolerated by patients ^(3,6,17,18). Nevertheless, the use of bacterial swabs from the nasal cavity has not been widely adopted and possible reasons could be that 1) it has little clinical impact as most patients get empirical antibiotics prescribed anyway or 2) because correct sampling of the middle meatus requires practice as well as proper equipment such as a headlamp and a nasal speculum.

American and European guidelines do not promote the general use of bacterial cultures in ARS as this should be reserved for research, and atypical or recurrent cases. Emphasis is instead put on antibiotic restriction in general and on the patient's infection history: duration of the infection, unilateral symptoms, and dental pain ^(3,6). Nevertheless, studies from the US and Denmark have shown that approximately 80% of patients consulting a doctor with symptoms of ARS will get antibiotics prescribed, indicating that these guidelines are difficult to implement ^(2,19). This might be due to a significant pressure from patients on clinicians to have antibiotics prescribed.

In contrast to clinical guidelines, the Centers for Disease control and Prevention (CDC) and other health authorities, generally promote culture-directed antibiotics. Furthermore, Young et al. found that clinical signs and symptoms cannot identify patients for whom antibiotics are justified ⁽⁸⁾. A diagnostic test, such as bacterial culture, could help clinicians resist the patient demand for antibiotic prescriptions and culture-directed antibiotics might be a means to lower the use of antibiotics in ARS. However, nasal cultures taken with the present-day technique might only improve the diagnostic accuracy marginally. Due to nose hairs and the small diameter of the nares it is simply dif-

icult to enter a swab without contact with the nasal vestibule, which is colonized with SA in about 30% of healthy people, thereby risking contamination ^(20,21).

We hypothesized that swabs from the nasal cavity are often contaminated with SA and consequently developed a contamination-free bacterial swab (CFS) device, which enables the introduction of a standard bacterial swab into the nasal cavity without direct or indirect contact with the nasal vestibule on its way. This device could increase diagnostic accuracy in ARS by reducing contamination with SA, and thereby make nasal cultures in acute rhinosinusitis a more viable option for clinicians. In this study we compared the frequency of SA in bacterial cultures from the nasal cavity using the present-day technique and the newly developed CFS device.

Methodology

The device

A patent application for the CFS device has been filed for several countries and has so far been granted in Europe (No. 3407798). The device consists of a plastic tube with a valve at the distal part. A standard swab can be introduced through the tube. When the tip of the CFS device has been inserted beyond the nasal vestibule, the swab is inserted through the tube into the nasal cavity and, after sampling, withdrawn into the tube again. Because of the design at the distal end, the bacterial swab has no direct or indirect contact with the nasal vestibule during passage (Figure 1).

Setting

The study was conducted between December 2016 and March 2017 in a private Ear, Nose and Throat practice. This period of the year was chosen in order to include the season with the highest occurrence of upper respiratory tract infections. The device was tested in a single-blinded controlled trial in which patients (n=64) with an acute upper respiratory tract infection functioned as their own controls. In both nostrils an E-Swab (Copan, Italy) was introduced under visual guidance using a nasal speculum and a headlamp. On the left side we used the present-day unshielded method for bacterial culture of the middle meatus and on the right side we used the CFS device. The same investigator included and examined all patients. Bacterial swabs were sent blinded to the Department of Clinical Microbiology at Hvidovre Hospital, Copenhagen, Denmark, and were analyzed according to standard procedures. The laboratory procedure did not change during the study period.

Outcome

The primary outcome was frequency of SA growth; the secondary outcome was growth of any other bacteria using the two methods.

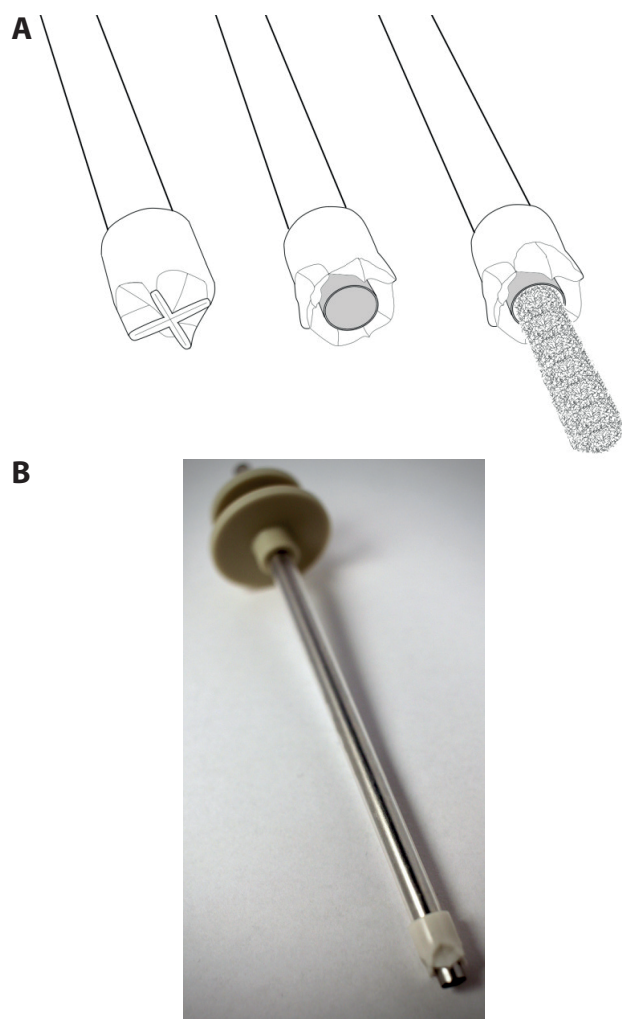


Figure 1. Graphic illustration of the CFS device. (A) Drawings of the CFS device in the closed and open configuration. (B) A picture of the prototype.

Study subjects

Inclusion criteria: patients with an upper respiratory tract infection aged 18 - 80. Pregnant and breast feeding women were also included in the study.

Exclusion criteria: severe psychiatric disorder, the need for an interpreter or allergy towards materials in the CFS (silicone, PFA [perfluoro alkoxy polymer], PP [polypropylene], stainless steel).

Statistics

The statistical package SPSS version 23.0 (IBM, Chicago, IL, USA) was used for the analysis.

The study was designed to detect a 15% difference between the groups. A power analysis was performed before initiating the study:

$$\Delta=0.15, p1=0.20, p2=0.05$$

$$F(\alpha,\beta)=F(0.05,0.20)=7.9$$

$$2\sqrt{(p^*(1-p^*))/0.15^2} \times 7.9 = 2\sqrt{(0.125(1-0.125))/0.15^2} \times 7.9 = 77 \text{ nostrils in each group.}$$

Table 1. *Staphylococcus aureus* positive cultures (present-day method vs CFS device)

		CFS device		Total
		negative	positive	
Present-day method	negative	46	1	47
	positive	10	4	14
Total		56	5	61

Only 8% (5/61) of the CFS cultures were positive for *Staphylococcus aureus* compared to 23% (14/61) of the cultures obtained by the present-day method. Fisher's exact: $p=0.008$. CFS = contamination-free bacterial swab.

Table 2. Cultures positive for other bacteria than *Staphylococcus aureus* (present-day method vs. CFS device)

		CFS device		Total
		negative	positive	
Present-day method	negative	41	5	46
	positive	9	6	15
Total		50	11	61

Growth of bacteria other than *Staphylococcus aureus* was found in 15/61 (25%) of cultures taken with the present-day method compared to 11/61 (18%) with the CFS technique. Fisher's exact: $p=0.02$. CFS = contamination-free bacterial swab.

Pearson's chi-square or Fisher's exact test was applied for contingency tables depending on expected cell counts. We considered $p<0.05$ statistically significant.

The study was terminated in early March 2017, since the season for upper respiratory disease was ending at that time, and because preliminary results after 40 patients had already shown a significant difference between the groups.

Results

We included 64 patients; data were incomplete in three: two cultures from the right side (CFS device) and one from the left side (present-day method) were missing. All results from these three patients were excluded.

The patients had a median age of 39.5 years (19-75) and 40% were men.

We found a significantly higher frequency of SA in cultures taken with the present-day method (23%) as compared to the CFS technique (8%, $p=0.008$, Table 1).

Growth of bacteria other than SA was found in 15/61 (25%) of

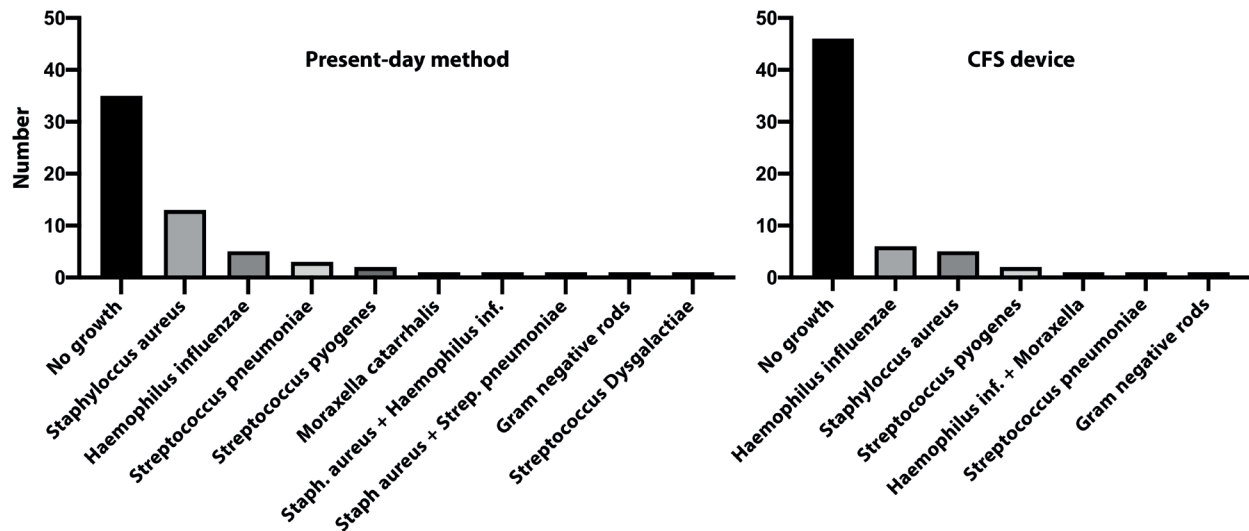


Figure 2. *Staphylococcus aureus* was the most frequently grown bacterium using the present-day technique whereas it was the 2nd most commonly grown bacterium using the CFS device. *Hemophilus influenzae*, *Moraxella catarrhalis* and *Streptococci* made up the majority of the other pathogens in cultures. CFS = contamination-free swab.

cultures taken with the present-day method compared to 11/61 (18%) with the CFS technique ($p=0.02$, Table 2).

Disagreement between cultures taken with the two sample techniques was found in 14 patients. Five patients exclusively had a positive culture using the CSF device (3 x *Hemophilus influenzae*, 1 x *Streptococcus pyogenes*, and 1 x gram negative rods); conversely, nine patients solely had a positive culture using the present-day method (1 x *Streptococcus pneumoniae*, 2 x *Hemophilus influenzae*, 1 x *Streptococcus dysgalactiae*, 1 x *Streptococcus pyogenes*, 2 x *Streptococcus pneumoniae*, 1 x *Moraxella catarrhalis* and 1 x gram negative rods).

See Figure 2 for an overview of all grown bacterial species using the two techniques. Main pathogens were *Hemophilus influenzae*, *Streptococcus pneumoniae* and to a lesser extent *Moraxella catarrhalis*. *Streptococcus pyogenes* was also grown. Notably, SA was a frequent bacterium using both techniques and the most frequently grown bacterium when using the present-day method.

Discussion

The CFS device successfully reduced the frequency of SA in cultures from the middle meatus compared to the present-day method. Thus, the device prevented contamination and could potentially increase diagnostic accuracy in ARS.

This study exposes a major problem of SA contamination in nasal cultures whilst at the same time suggesting a possible solution in the form of the new CFS device. To our knowledge,

the study design was unique. We chose to include patients with an upper respiratory tract infection (URT); however, not all met the criteria for ARS. This allowed for a broader inclusion of patients with conditions in the nasal vestibule similar to ARS: most importantly in the form of a runny nose. This might affect the number of SA and increase the risk of contamination during the passage of the nasal vestibule. However, had we included patients with specific ARS symptoms exclusively, the applicability of the study to the patients in focus would have increased. Furthermore, more doctors could have participated as investigators in the study to uncover any inter-observer variation. Finally, we could have applied a crossover design in which the CSF device was used on both sides during the study to eliminate any “side preference” of the examiner. In our study we did not include information about previous treatment with antibiotics or smoking status. As our patients functioned as their own control these data would not differ between groups.

We found SA in 8% of CFS samples and in 23% of traditional swabs. This is in line with previous studies of the bacteriology in ARS: using the sinus puncture technique SA was generally found in 1.4–10%, whereas studies that obtained bacteriology using a middle meatal swab found SA in up to 33% of the cultures^(22–25). Even in patients without ARS, SA has been reported in 8–13% of middle meatal swabs^(26–28).

In many of these studies special efforts were made to reduce bacterial contamination e.g. disinfecting the nasal vestibule or via sinus puncture—measures that are not routinely performed in a clinical setting.

Figure 2 shows that even with the CFS technique, SA was fre-

quently cultured in middle meatal swabs. A number of studies claim that SA only accounts for a small proportion of ARS cases and some might argue that SA in cultures can be ignored; in contrast, a meta-analysis by Payne et al. concluded that SA is a significant pathogen in ARS^(5,6,23). This study underlines the need to distinguish between 1) SA as a contaminating agent and 2) SA as an actual pathogen.

Finally, we analyzed samples for other pathogens than SA and again we found more culture positive samples using the present-day method compared to the CFS device. This difference could be due to the applied sample techniques, i.e. indicating that the problem of contamination extends to other bacteria than SA. Since differences were small, they are more likely a result of varying bacteriology between the nasal cavities, as we found no systematic trends when differences were scrutinized.

ARS is typically treated empirically with amoxicillin with/without clavulanic acid for 7–10 days. Even if a bacterial swab is obtained and cultured, antibiotic treatment is often initiated before the culture has been grown. It has generally been believed that early termination of antibiotic treatment could encourage antibiotic resistance. In contrast, it has lately been promoted that “shorter is better” and that the treatment period of antibiotics, in particular, should be shortened as much as possible, as this would markedly reduce the antibiotic pressure and the development of resistance^(29–31). After obtaining a bacterial culture, clinicians have the options to either wait-for-culture (typically 2 days) or terminate treatment early in negative cases—both strategies would reduce the antibiotic pressure. Some clinicians, however, have to wait longer than 2 days for culture results and for them it is less feasible to swab.

Conclusion

In conclusion, the new CFS device reduced *Staphylococcus aureus* contamination in bacterial swabs from the nasal cavity significantly in comparison to the present-day technique. In combination with a wait-for-culture or early-termination-of-antibiotics strategy, this new device could help reduce the overall use of antibiotics in acute rhinosinusitis.

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Authorship contribution

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

EKK and KH contributed equally as co-first authors. Both had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

Author Kåre Håkansson has submitted a patent for the CFS and owns 50% of the patent rights. Neither the investigator (Steffen Ørntoft) who performed the clinical study, nor the remaining authors have any financial disclosures in relation to the CFS.

SPT Vilecon, a company that has been involved in the design of the CFS device and owns 50% of the patent, provided prototypes for the study. They had no influence on study design; collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the regional Ethics Committee (Capital Region of Denmark, H-15014643) as well as the Danish Medicines Agency (CIV-16-04-015264). All patients gave an informed consent. The study was conducted in accordance with guidelines and monitored by the unit for Good Clinical Practice (GCP) at the University of Copenhagen. Prior to study execution, the protocol was published on www.ClinicalTrials.gov (NCT02924103).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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