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Colonization of the nasal airways by *Staphylococcus aureus* on admission to a major heart surgery operating room: A real-world experience

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ABSTRACT

Introduction: Nasal swab culture is used to identify *Staphylococcus aureus* colonization, as this is a major risk factor for surgical site infection (SSI) in patients who are going to undergo major heart surgery (MHS). We determined nasal carriage of *S. aureus* in patients undergoing MHS by comparing the yield of a conventional culture with that of a rapid molecular test (Xpert® SA Nasal Complete, Cepheid).
Methods: From July 2015 to April 2017, all patients who were to undergo MHS were invited to participate in the study. We obtained two nasal cultures from each patient just before entering the operating room, independently of a previous test for the determination of nasal colonization by this microorganism performed before surgery. One swab was used for conventional culture in the microbiology laboratory, and the other was used for the rapid molecular test. We defined nasal colonization as the presence of a positive culture for *S. aureus* using either of the two techniques. All patients were followed up until hospital discharge or death.
Results: Overall, 57 out of 200 patients (28.5%) were colonized by *S. aureus* at the time of surgery. Thirty-three patients had both conventional culture- and PCR-positive results. Twenty-four patients had a negative culture and a positive PCR test. Only twenty-one percent (12/57) of colonized patients had undergone an attempt to decolonise before the surgical intervention.
Conclusion: A significant proportion of patients undergoing MHS are colonized by *S. aureus* in the nostrils on entering the operating room. New strategies to prevent SSI by this microorganism are needed. Rapid molecular tests immediately before MHS, followed by immediate decolonisation, must be evaluated.
Trial Registration Clinical Trials.gov NCT02640001.

Colonización nasal por *Staphylococcus aureus* en el ingreso quirúrgico para una cirugía cardíaca mayor: una experiencia en la práctica clínica real

Palabras clave:
Staphylococcus aureus
Colonización nasal
Cirugía cardiaca mayor
Técnicas diagnósticas de laboratorio

RESUMEN

Introducción: Los cultivos nasales se usan para identificar colonización por *Staphylococcus aureus*, ya que la colonización es un factor de riesgo para la infección de la herida quirúrgica en pacientes que van a ser sometidos a cirugía cardiaca mayor (CCM). En este trabajo, identificamos portadores de *S. aureus* en el momento quirúrgico en pacientes que van a ser sometidos a CCM, comparando el resultado del cultivo convencional con un test molecular rápido (Xpert® SA Nasal Complete, Cepheid).

Abbreviations: MHS, major heart surgery; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

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Prevención de infección de la herida quirúrgica

Métodos: Desde julio del 2015 hasta abril del 2017, a todos los pacientes que iban a ser intervenidos con CCM se les invitó a participar en el estudio. Se obtuvieron 2 cultivos nasales de cada paciente, justo antes de entrar en el quirófano, independientemente de si había un test previo de colonización nasal realizada. Una torunda fue usada en el laboratorio de microbiología para cultivo convencional y la otra para el test molecular rápido. Se definió colonización nasal como la positividad para *S. aureus* por cualquiera de las 2 técnicas. Todos los pacientes fueron seguidos hasta el alta hospitalaria o éxitus.
Resultados: Un total de 57 de 200 pacientes (28,5%), estaban colonizados *por S. aureus* en el momento de la cirugía. En total, 33 pacientes tuvieron ambas muestras positivas (convencional y PCR); 24 pacientes tuvieron cultivo negativo y PCR positiva. Solo el 21% (12/57) de los pacientes colonizados habían tenido un intento de descolonización antes de la cirugía.
Conclusión: Un porcentaje alto de pacientes están colonizados por *S. aureus* en el momento de ser sometidos a CCM. Son necesarias nuevas estrategias para prevenir la infección de la herida quirúrgica por este microorganismo. Un test molecular rápido inmediatamente antes de la CCM y descolonización posterior inmediata debe ser evaluado.
Trial Registration Clinical Trials.gov NCT02640001.

Introduction

Nasal carriage of *Staphylococcus aureus* (whether methicillin-resistant [MRSA] or methicillin-sensitive [MSSA]) before major heart surgery (MHS) is a risk factor for postoperative infection.[1–4] Carriers are usually identified by nasal cultures, but results from the microbiology laboratory are available only 24 to 72 h after sampling.[5]

Nasal decolonization of *S. aureus* carriers is standard of care in many MHS units and consists of nasal mupirocin ointments for five days before surgery.[6,7] However, carriage is not always evaluated, and patients can become recolonized after a former decolonization, performed too early. Also, cultures obtained after admission are not usually reported shortly enough to be clinically useful. Finally, given that some patients undergo emergency surgery, it is impossible to determine the real situation of nasal carriage of *S. aureus* at the time of MHS. Therefore, more rapid and readily available procedures performed immediately before surgery are necessary.

We determined nasal carriage of *S. aureus* in patients entering the operating room for MHS by comparing the yield of conventional culture with that of a rapid molecular tests in order to assess the real frequency of nasal carriage of *S. aureus* during surgery.

Material and methods

Hospital setting and patients

Our institution is a general referral hospital with 1,550 beds and approximately 50,000 admissions/year. The Department of Heart Surgery performs around 500 procedures per year. Consecutive patients admitted to undergo MHS during the study period (July 2015 to April 2016) were enrolled in the study if they consented to participate.

Prospective quasi-experimental study. All data of patients undergoing MHS were prospectively collected in an anonymous database.

Laboratory procedure

Sample processing by the microbiology laboratory

One nasal swab was taken for culture in the microbiology laboratory, and a second for the Xpert® SA Nasal Complete assay. The nasal swab was plated on a mannitol-salt agar plate and a chromogenic medium for the isolation of MRSA (chromID™ MRSA, bioMérieux, Craponne, France), and processed for a semiquantitative count. Plates were incubated for 48 h at room temperature.

Samples for PCR were processed according to the manufacturer's instructions, as detailed in previous publications.[8,9] For samples testing positive, the amplification threshold cycle for positivity (Ct) was registered.

All patients received daily bathing with clorhexidine-impregnated wipes (Clinell) during ICU stay and oral hygiene care with clorhexidine 0.12%.

Patients colonized by *S. aureus* received three-daily intranasal mupirocin for 5 days.

The study end-points were as follows:

- Primary: frequency of nasal colonization by *S. aureus* as determined by comparing isolation and PCR diagnostic methods.
- Secondary: Rate of colonization by *S. aureus* (MRSA and MSSA), at the time of surgery.
- Comparison of the Ct of the PCR assy and the semiquantitative culture results.

Definitions

Nasal colonization by *S. aureus*: a positive PCR result, or a positive culture result with *S. aureus* in nasal secretions, or both.

Patients were followed up until hospital discharge or death.

Statistical analysis

Values are expressed as the mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables, and as percentages, with a 95% confidence interval (95% CI), when applicable, for categorical variables. Categorical variables were evaluated using the chi-square test or a 2-tailed Fisher exact test. Statistical significance was set at $p < 0.05$ (2-tailed).

To determine the prediction of positive *S. aureus* cultures by the number of the Ct, we constructed a ROC curve to determine the optimal cut-off point.

For an area under the ROC curve of 80%, the sample size that gives a precision of 15% with a 95% confidence interval, is 190 patients.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, New York, USA).

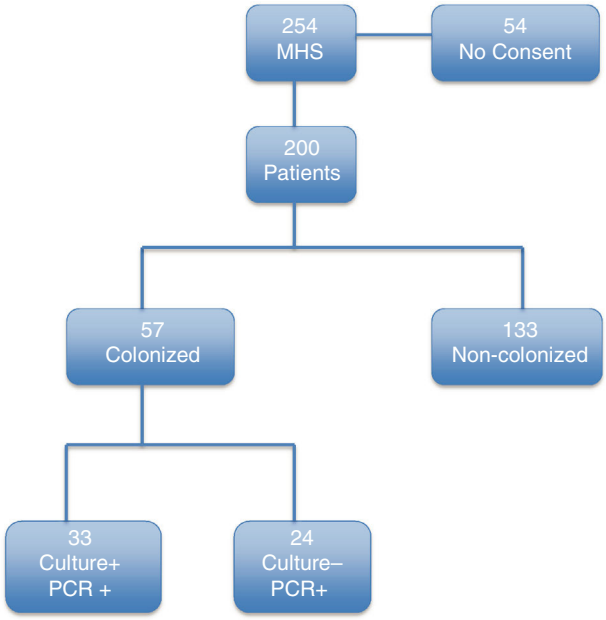

Fig. 1. Flowchart for the TREND analysis.

Results

During the study period, 254 patients underwent MHS. Of these, 200 patients fulfilled the inclusion criteria (Fig. 1). The median (IQR) age was 67 (58–75) years. The main underlying conditions were congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, and ischemic heart disease. The most frequent surgical procedure was valve replacement (Table 1). The mean (SD) EuroSCORE and median (IQR) of APACHE II score at inclusion were, respectively, 6.1 (3.3) and 8.0 (7–10) (Table 1).

Colonization rates (Table 2)

According to our definition (PCR- or culture-positive), 57 of 200 patients (28.5%) were colonized at the time of surgery. Of these, 24 cases were positive only by the molecular test and had a negative culture result. The remaining 33 patients had both culture- and PCR-positive results.

Of the 57 patients colonized with *S. aureus*, 5 were MRSA (8.8%).

Patients with concordant results

The 33 patients with positive *S. aureus* cultures at the time of surgery were distributed as follows: 25 had not been previously screened (4 because of emergency surgery), 3 had had a pre-admission nasal test that was negative a median of 13 days before surgery (range 6.0–35.09) and, consequently, were not offered decolonization. The remaining 5, had previously been decolonized a median of 11 days before surgery (range 5.0–26.5).

Patients with discordant results

A total of 24 patients were PCR-positive and culture-negative. Of these, 7 had previously been culture-positive and were decolonized (a median of 9 days before surgery range 8.0–22.0), 14 had never been screened before surgery (3 had undergone emergency surgery), and 3 had had a negative result in a nasal screening at a median of 13 days before surgery (range 11.0–32.0).

Non-colonized patients

The situation of the 143 non-colonized patients was as follows: 45 had previously had a negative nasal culture result, 4 were positive, and 94 had never been screened (20 because of emergency surgery).

Table 1
Baseline characteristics and surgical variables of patients.

	Total $N=200$	Colonized $n=57$	Non-colonized $n=143$	P value
Preoperative				
Median age in years (IQR)	67 (58–75)	65 (56–75)	68 (60–76)	0.23
Male/Female	132/68	41/16	91/52	0.26
Underlying conditions (%)				
Myocardial infarction	29 (14.5)	8 (14.0)	21 (14.7)	0.90
Congestive heart failure	112 (56.0)	32 (56.1)	80 (55.9)	0.98
Central nervous system disease	19 (9.5)	4 (7.0)	15 (10.5)	0.45
Chronic obstructive pulmonary disease	32 (16.0)	11 (19.3)	21 (14.7)	0.42
Renal dysfunction	23 (11.5)	4 (7.0)	19 (13.3)	0.21
Diabetes mellitus	59 (29.5)	23 (40.4)	36 (25.2)	0.03
Peptic ulcer disease	22 (11.0)	6 (10.5)	16 (11.2)	0.89
Peripheral vascular disease	26 (13.0)	5 (8.8)	21 (14.7)	0.42
EuroSCORE (mean; SD)	6.1 (3.3)	3.8 (0.5)	3.1 (0.2)	0.27
Apache II Score (median, IQR)	8 (7–10)	8 (7–10)	9 (7–11)	0.37
Type of surgery (%)				
Valve replacement	91 (45.5)	25 (43.9)	66 (46.2)	0.76
CABG (coronary artery bypass grafting)	50 (25.0)	15 (26.3)	35 (24.5)	0.78
Mixed (valve and CABG)	19 (9.5)	4 (7.0)	15 (10.4)	0.21
Aortic surgery	13 (6.5)	4 (7.0)	9 (6.2)	0.26
Length of hospital stay in days (median, IQR)	19.5 (13–30)	18 (12–27)	20 (13–32)	0.42
Length of ICU stay in days (median, IQR)	5 (3–8)	5 (3–8)	5 (3–8)	0.90
Respiratory infection (n, %)	16 (8.0)	4 (7.0)	12 (8.4)	0.74
Other infection (n, %)	30 (15.0)	6 (10.5)	24 (16.8)	0.26
Mortality (n, %)	19 (9.5)	5 (8.2)	14 (9.8)	0.82

Table 2
Patients included in the study.

At the time of surgery	143 Non-colonized	57 Colonized		Total
		33 Culture+ PCR+	24 Culture− PCR+	
No prior screening	94 (67.7%)	25 (75.7%)	14 (58.3%)	133 (66.5%)
Prior negative screening	45 (31.5%)	3 (9%)	3 (12.5%)	51 (25.5%)
Prior positive screening	4 (21.8%)	5 (15.2%)	7 (29.2%)	16 (8%)

Column percentages are given.

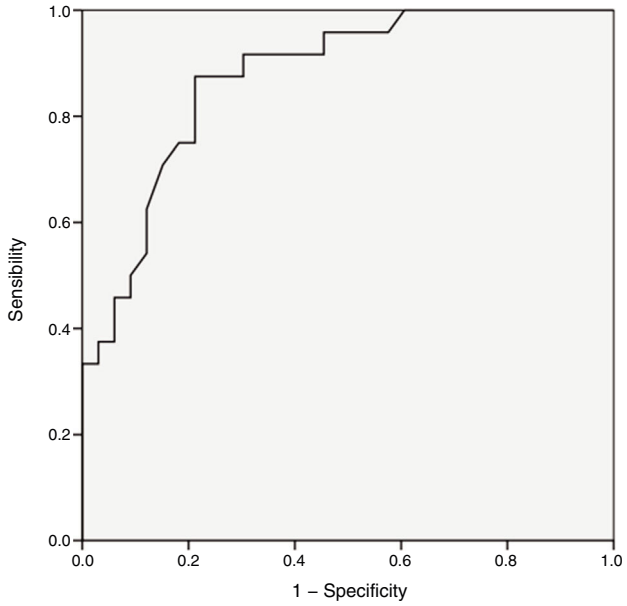

Fig. 2. ROC curve with a cut-off for amplification cycle time for the prediction of culture positivity.

Semiquantitative cultures and PCR amplification cycles

Patients with positive cultures had PCR Ct ranging from 19.9 to 32.7 (median 26.10 (23.5–28.3)), while patients with negative cultures had Ct ranging from 25.7 to 35.0 (median 30.9 (29.2–33.5); $p < 0.001$).

Analysis of the semiquantitative cultures in the 33 patients with both positive PCR and culture results revealed a range of 10^3 to 10^5 colony-forming units (CFUs) per plate.

We also recorded a correlation between Ct for positivity of cultures and CFUs (Spearman rho, 0.60; $p < 0.001$).

The ROC curve, which had a cut-off Ct of 32 for a positive result (area under the curve, 0.87; 95% CI, 0.78–0.96) showed a sensitivity of 99.7% and specificity of 64.0% for predicting positive cultures (Fig. 2).

Outcome of cases

All patients with either a positive nasal PCR result or a positive nasal culture result were decolonized with nasal mupirocin for 5 days on leaving the operating room.

There were three post-operative infections caused by *S. aureus*. In one of the three infections, the results of screening were negative before, during, and after surgery, and the patient was never decolonized. The remaining two patients were PCR-positive and culture-negative at the time of surgery and were decolonized.

Two patients had post-surgical deep wound infection (mediastinitis) and the third developed ventilator-associated pneumonia. Two of the 3 infections occurred in previously decolonized patients and occurred on days +50 and +20 after surgery.

None of the *S. aureus* isolated from nasal samples of our patients had high level resistance to mupirocin. High-level resistant to mupirocin in our institution keeps under 2%.

Discussion

Our study shows that, despite the existence of a program for *S. aureus* nasal screening and decolonization in patients undergoing MHS at our center, a high proportion of patients are colonized on entering the operating room.

Between 20% and 30% of the population carry *S. aureus* in the upper airway[10,11] and decolonization programs have been associated with a reduction in the incidence of postoperative staphylococcal infections in patients undergoing clean surgery.[6,12–15]

Decolonization is performed at different times before surgery, yet we were not able to find data showing how frequently decolonization fails owing to circumstances such as recolonization after an original negative test result or after decolonization. Furthermore, patients who are undergoing imminent MHS are not able to benefit from decolonization if they have to wait for the results of a nasal culture.

The process of decolonization often depends on the degree of adherence by physicians, patients or relatives.[16,17]

The decolonization process should last for a minimum of five days and start before surgery. However, reported data suggest that shorter interventions or interventions started immediately after surgery may be worthwhile.[12,18] We decolonized all patients based on a positive result in either culture or PCR and had only three staphylococcal severe infections in the 200 study patients, 1 of whom had never been colonized in the nares or carried *S. aureus* in the airway.

A PCR rapid screening method allows for the identification of colonized patients immediately before surgery and to start then the decolonization process. We found that the PCR amplification cycle can reasonably anticipate the presence of a positive nasal culture, as already found by other groups.[19,20]

The results of culture-based and nucleic acid amplification tests (NAATs) are sometimes discordant, and the interpretation of a PCR-positive, culture-negative result is challenging. Some explanations of "false" positive results may include the presence of non-viable organisms, as NAATs do not confirm the presence of live microorganisms. Also, low bacterial densities in the nostrils can produce a negative culture and a positive PCR, or vice versa, because this will cause both methods to provide sporadic positive or negative results under the parameters described by the statistical phenomenon known as the Poisson effect. Besides, patients with a positive PCR and a negative nasal culture can be colonized elsewhere in the body.[21]

Conventional, culture-based techniques, take 24–72 h to provide a significant result, and NAATs provide a result in less than 3 h. PCR-based techniques are also considered to be more sensitive

than culture, although the frequency of discordant results (PCR-positive and culture-negative) is estimated at between 2.4% and 13.7%, as in our study.[22,23] We were not able to find information on proper interpretation of a discordant test result in patients who had recently undergone decolonization.

One of the limitations of this study is that our results cannot be extrapolated to areas other than MHS. In addition, this study has been carried out in a single center and may not reflect the situation of other units where decontamination is done systematically.

A high proportion of patients undergoing MHS are colonized with *S. aureus* when they enter the operating room despite programs to address this problem and previous decolonization attempts. The value of a rapid PCR-based assessment of nasal colonization immediately after admission to hospital, even in the immediate preoperative period, followed by decolonization after surgery, should be evaluated to assess the clinical impact of this "delayed" complementary approach.

Conclusion

A significant proportion of patients undergoing major heart surgery are colonized by *S. aureus* in the nares on entering the operating room. New strategies to prevent surgical site infection by this microorganism, including molecular tests immediately before surgery followed by decolonization, must be evaluated.

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Authors' contributions

EB and MJPG participated in the conception and design of the study, carried out the analysis, interpreted the data, and drafted the manuscript. AB, JH, JMB and PM participated in the conception and design of the study, performed the statistical analysis, and participated in the drafting of the manuscript. TV and VDE collected the samples and data and participated in drafting the manuscript. All of the authors read and approved the final version of the manuscript.

Conflict of interests

The authors declare no conflict of interest.

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