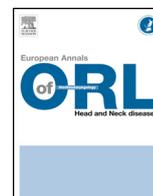




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Original article

## Intraoperative bacterial analysis in nasal polyposis: Clinical and functional impact

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### ABSTRACT

**Background:** The impact of *Staphylococcus aureus* on onset of nasal polyposis has been the focus of numerous studies, but there have been few studies of other germs found in the ethmoid of operated patients or of their impact on post-operative results.

**Material and methods:** All patients undergoing endoscopic radical ethmoidectomy for nasal polyposis in the teaching hospital of Nantes (France) between 2006 and 2016 had intraoperative ethmoid cavity bacterial sampling. Phenotypic characteristics, pre- and post-operative symptoms and endoscopic findings were analyzed. Mann–Whitney tests and Kruskal–Wallis correlation analysis were used to assess clinical/bacteriological correlations.

**Objectives:** The main objective was to describe bacterial colonization of patients undergoing surgery for nasal polyposis, and to assess correlations with phenotypic features, functional results and postoperative clinical course.

**Results:** One hundred and seven patients were included. A total of 26% were not infected, 55% mono-infected and 19% multi-infected. In 27.3%, staphylococci were isolated; in 30.5%, isolates were gram-negative bacilli. There were no significant correlations between presence or type of pathogen and symptom profile.

**Conclusion:** This study confirmed the high rate of pathogenic bacteria in nasal cavities in case of polyposis, with high frequencies of *S. aureus* but also of gram-negative bacilli, raising the question of their involvement in the inflammatory reactions underlying the nasal polyposis.

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### 1. Introduction

Nasal polyposis is a diffuse infection of the nasal fossae and sinus mucosa with bilateral ethmoid polyps. Some agents of inflammatory reaction inducing polyps are now better identified, but exact etiopathogenesis remains unknown [1].

Numerous studies have hypothesized the involvement of infection by *Staphylococcus aureus* (*S. aureus*) and its superantigens (SAG) [2]. However, *S. aureus* colonization rates seem to be identical in subjects with chronic rhinosinusitis (CRS) and healthy subjects, and a recent multicenter study found no difference in detection rates for SAGs coding for the exotoxin of *S. aureus* between CRS with and without polyps [3]. A single recent study reported no significant correlation between bacteriological findings (notably,

*S. aureus* and gram-negative bacilli) in ethmoidectomy cavities and postoperative phenotype [4].

The present study therefore aimed to perform a systematic analysis in a large cohort of bacteriological findings in intraoperative specimens from ethmoidectomy cavities in patients operated on for nasal polyposis, and to analyze correlations with clinical profile, functional impact and postoperative results.

### 2. Material and methods

A single-center retrospective study included all patients undergoing endoscopic bilateral radical total ethmoidectomy for nasal polyposis in the University Hospital, of Nantes, France, between 2006 and 2010.

Inclusion criteria comprised:

- primary nasal polyposis (isolated, associated with asthma, or part of Widal's disease) diagnosed preoperatively on presence of

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polyps in both nasal fossae on endoscopy, and bilateral anterior and posterior ethmoid opacities on CT following Lund-Mackay [5];

- failure of maximal medical treatment comprising at least daily nasal fossa saline lavage and local corticosteroids, and failure of or recurrence after at least one course of general route corticosteroids.

Exclusion criteria comprised:

- secondary nasal polyposis (cystic fibrosis, ciliary dyskinesia, systemic disease, etc.);
- antibiotic therapy during the 4 weeks before surgery;
- missing intraoperative bacteriology specimen.

The main endpoint was a significant difference in pre- to post-operative change in functional assessment according to biological findings.

Symptoms comprised: anterior or posterior rhinorrhea [APR], nasal obstruction [NO], impaired olfaction [Anosmia] and sinus pain [Pain], scored following usual clinical practice: 2 = spontaneous complaint, 1 = complaint only on directed interview, 0 = no complaint [6].

Patients were followed up at 2 weeks and 6–12 weeks.

Total functional score was calculated pre- and post-operatively (at 6–12 weeks) as the sum of the 4 scores: 0 = no symptom to 8 = maximum symptom intensity. Analysis concerned individual reduction in total score.

Secondary endpoints comprised:

- bacteriological analysis of isolates;
- study of bacterial resistance;
- analysis of impact of type of isolate on postoperative endoscopy score according to Lund-Kennedy for the 4 criteria assessed in the postoperative control consultation: presence of polyps, scar tissue, edema or mucopurulent secretion, each graded 0 (absent), 1 (moderate), or 2 (abundant) [7].

Polyposis was graded following Hadley: 0 (no visible polyp), 1 (a few polyps in the middle meatus), 2 (polyps filling the middle meatus), grade 3 (polyps extending beyond the middle meatus into the sphenoid recess, without total obstruction), or 4 (polyps filling the whole nasal cavity); scores on the 2 sides were summed, giving a final polyposis grade of 0 to 8.

Intraoperative specimens were systematically taken from the ethmoid, one on either side, under endoscopic control on a swab without transport medium. Specimens were immediately sent for direct bacteriological analysis with gram staining then culture on blood agar, BCP agar and chocolate agar and incubated at  $36 \pm 2^\circ\text{C}$ . After reading and identification, an antibiogram was drawn up in case of pathogenic findings.

Results were recorded as negative [NEG] if no bacterium was found on culture. When 1 or more bacteria were isolated, they were classified as *Staphylococci* [STAPH], other *Cocci* [COCCI], gram-negative bacilli [GNB], or saprophyte/opportunistic [OPPO].

The main endpoint was initially assessed in 3 groups of patients: non-infected, with negative culture; mono-infected, with a single bacterium; or multi-infected, with several. It was then reassessed in mono/multi-infected patients according to the bacteria isolated.

All data were entered anonymously on an Excel 2011 spreadsheet.

Statistical analysis used XLSTAT (Addinsoft Inc.) and R software.

Quantitative variables were reported as mean  $\pm$  standard deviation. The Mann-Whitney test was used to compare qualitative variables; non-parametric Kruskal-Wallis analysis of variance was

**Table 1**  
Patient characteristics.

Quantitative variables	Mean (standard deviation)	Median [25–75 IQR]
Mean age	50.7 (11.9)	52.0 [44.5;59.0]
Preoperative functional score	5.28 (1.27)	5.00 [4.00;6.00]
Postoperative functional score	1.84 (0.943)	2.00 [1.00;2.00]
Qualitative variables	n (%)	
<i>Gender</i>		
M	71 (66)	
F	36 (34)	
<i>Allergy</i>		
No	61 (57)	
Yes	46 (43)	
<i>Asthma</i>		
Yes	55 (51)	
No	52 (49)	
<i>Widal syndrome</i>		
No	83 (78)	
Yes	24 (22)	
<i>History of surgery</i>		
Yes	61 (57)	
No	46 (43)	
<i>Nasal polyposis grade</i>		
3	2 (1.9)	
4	6 (5.6)	
5	14 (13)	
6	34 (32)	
7	38 (36)	
8	13 (12)	
<i>Preoperative symptoms</i>		
<i>Anosmia</i>		
0	1 (0.93)	
1	7 (6.5)	
2	99 (92.5)	
<i>Pain</i>		
0	51 (48)	
1	34 (32)	
2	22 (21)	
<i>Nasal obstruction</i>		
0	5 (4.7)	
1	13 (12)	
2	89 (83)	
<i>Anterior/posterior rhinitis</i>		
0	43 (40)	
1	37 (35)	
2	27 (25)	

used to assess the main endpoint. Alpha risk of non-significance was set at 5%.

### 3. Results

#### 3.1. Clinical data

A total of 107 patients were included. Patient data are shown in Table 1.

Surgical histories comprised 28 bilateral ethmoidectomies (46%), 24 polypectomies (39%), 7 multiple polypectomies (11%) and 2 bilateral meatotomies (4%).

Table 1 shows preoperative symptoms. Patients with Widal syndrome did not significantly differ from the others, notably in terms of pain, rhinorrhea or polyposis score.

Twenty-eight patients were non-infected (26%), 59 mono-infected (55%) and 20 (19%) multi-infected (1 with 3 bacteria, the others with 2).

Table 2 shows phenotypic characteristics according to bacteriological group.

Mean age was significantly greater in mono-infection ( $P < 0.01$ ). Postoperative antibiotic therapy was significantly less frequent in non-infection ( $P < 0.01$ ).

**Table 2**  
Phenotypic characteristics according to bacteriology findings (negative, mono-infected, multi-infected).

Bacteriology results		Negative (n = 28)	Mono-infected (n = 59)	Multi-infected (n = 20)	n	P
Age		49.1 (±10.8)	53.4 (±10.6)	45.0 (±14.6)	107	<0.01
Allergy	no	20 (71%)	32 (54%)	9 (45%)	61	0.15
	yes	8 (29%)	27 (46%)	11 (55%)	46	–
Asthma	yes	12 (43%)	32 (54%)	11 (55%)	55	0.57
	no	16 (57%)	27 (46%)	9 (45%)	52	–
History of surgery	yes	14 (50%)	33 (56%)	14 (70%)	61	0.37
	no	14 (50%)	26 (44%)	6 (30%)	46	–
Nasal polyposis grade	3	2 (7.1%)	0 (0%)	0 (0%)	2	0.69
	4	1 (3.6%)	3 (5.1%)	2 (10%)	6	–
	5	5 (18%)	8 (14%)	1 (5%)	14	–
	6	7 (25%)	20 (34%)	7 (35%)	34	–
	7	10 (36%)	20 (34%)	8 (40%)	38	–
	8	3 (11%)	8 (14%)	2 (10%)	13	–
Gender	M	19 (68%)	35 (59%)	17 (85%)	71	0.11
	F	9 (32%)	24 (41%)	3 (15%)	36	–
Widal syndrome	no	24 (86%)	45 (76%)	14 (70%)	83	0.42
	yes	4 (14%)	14 (24%)	6 (30%)	24	–
Postoperative antibiotic therapy	no	26 (92.9%)	47 (80%)	10 (50%)	83	<0.01
	yes	2 (7.1%)	12 (20%)	10 (50%)	24	–

In the mono-infected group, bacteriology isolated:

- 25 cases of *Staphylococcus* (42%);
- 18 cases of gram-negative bacillus (31%);
- 9 cases of saprophyte (15%);
- and 7 cases of cocci (12%).

In the multi-infected group:

- 6 cases of gram-negative bacillus plus *Staphylococcus* (30%);
- cases of gram-negative bacillus plus cocci (25%);
- cases of multiple gram-negative bacilli (20%);
- cases of *Staphylococcus* plus cocci (20%);
- and 1 case of *Staphylococcus* plus opportunistic bacterium (5%).

The patient presenting 3 strains had two gram-negative bacilli plus a *coccus* bacterium.

There were no significant phenotypic difference according to isolate in the mono- and multi-infected groups.

Fig. 1 shows the distribution of bacteriology findings in the mono- and multi-infected groups.

### 3.2. Main endpoint

There was no significant difference ( $P=0.27$ ) in functional improvement between the negative and mono- and multi-infected groups.

In the mono- and multi-infected groups, was no significant difference in functional improvement according to isolate ( $P=0.78$  between isolates in mono-infection, and  $P=0.09$  in multi-infection). Mean values for functional improvement are shown in Fig. 2.

Multivariate analysis of the main endpoint screened for correlations adjusted on confounding factors: age, gender, asthma, Widal syndrome, history of surgery, and polyposis grade. There were no significant differences in functional improvement between the three infection groups ( $P=0.11$ ).

### 3.3. Microbiology

A total of 107 specimens were taken. Culture positively identified 100 bacteria and was negative in 28 cases (21.9%); in 19 cases, 2 strains were isolated, and in 1 case 3.

Table 3 shows the bacteria isolated in culture.

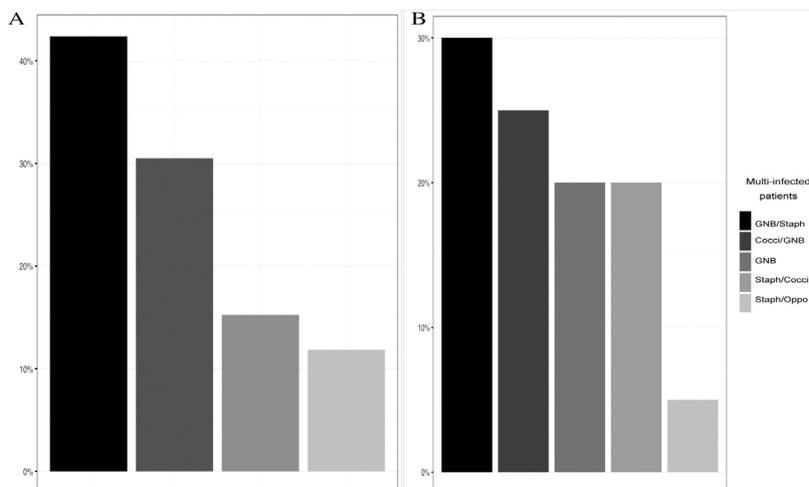
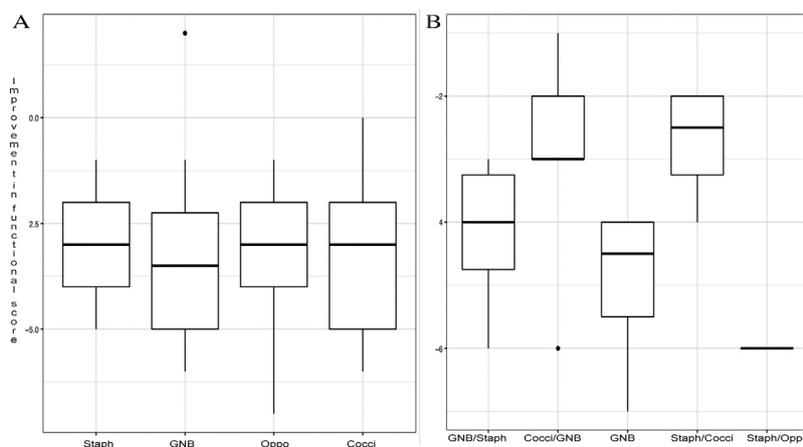


Fig. 1. Bacteriology findings. A. Mono-infected group. B. Multi-infected group.



**Fig. 2.** Box-plots of mean improvement in functional score in mono- and multi-infected patients: rectangles show data in 1st to 3rd interquartile range; horizontal lines show median; vertical lines show adjacent values and range; points outside the box are outliers (aberrant data). A. Mono-infected group. B. Multi-infected group.

**Table 3**  
Biological findings.

Type of isolate	Number of findings	Percentage
<i>Staphylococcus [STAPH]</i>	35	27.3%
<i>Staphylococcus aureus</i>		
<i>Saprophytes [OPPO]</i>	10	7.8%
<i>Coagulase-negative Staphylococcus</i>	5	
Other: <i>Corynebacterium diphtheriae</i> , <i>Staphylococcus epidermidis</i> , <i>Staphylococcus lugdunensis</i> , <i>Staphylococcus intermedius</i>	5	
<i>Other cocci [COCCI]</i>	16	12.5%
<i>Streptococcus pneumoniae</i>	9	
<i>Streptococcus agalactiae</i>	2	
<i>Streptococcus pyogenes</i>	2	
<i>Streptococcus anginosus</i>	1	
<i>Moraxella catarrhalis</i>	2	
(gram-negative cocci)		
<i>Gram-negative bacilli [GNB]</i>	39	30.5%
<i>Citrobacter koseri</i>	11	
<i>Escherichia coli</i>	5	
<i>Haemophilus influenzae</i>	5	
<i>Klebsiella oxytoca</i>	5	
<i>Pseudomonas aeruginosa</i>	2	
<i>Serratia marcescens</i>	2	
<i>Enterobacter cloacae</i>	2	
<i>Prevotella bivia</i>	2	
<i>Enterobacter aerogenes</i>	1	
<i>Morganella morganii</i>	1	
<i>Proteus mirabilis</i>	1	
<i>Shewanella algae</i>	1	
<i>Serratia liquefaciens</i>	1	
Negative	28	21.9%

Cultures positive for enterobacteria (*Enterobacter cloacae*, etc.) were not associated with any particular factor, such as gastroesophageal reflux.

Analysis by infection status (opportunistic/saprophyte, pathogen or negative culture) found no significant difference in functional improvement ( $P=0.63$ ).

### 3.4. Secondary endpoints

Concerning bacteriological resistance, out of 35 *Staphylococcus aureus* isolates:

- 2 (5.9% of the *Staphylococci*) were multi-susceptible;
- 32 (91.4%) were resistant to penicillin G but susceptible to methicillin (sensitive to oxacillin in culture, and positive cefoxitin test);

- only 1 (2.7%) was resistant to methicillin (MRSA), in a woman with Widal's syndrome and history of bilateral ethmoidectomy; it was nevertheless susceptible to gentamycin, vancomycin and rifampicin.

24 patients received postoperative antibiotic therapy:

- for 23, due to postoperative aggravation of symptoms (pain, rhinorrhea, fever);
- in the other case, there were no symptoms, but MRSA was identified in culture.

When antibiotic therapy was prescribed, the antibiogram enabled directed treatment in 87.5% of cases.

There was no significant difference in functional improvement according to postoperative antibiotic therapy ( $P=0.83$ ).

Mean clinical endoscopy score was  $1.18 \pm 1.11$ .

Phenotypic characteristics showed no associations with postoperative clinical endoscopy score, except for postoperative antibiotic therapy, which was significantly ( $P=0.048$ ) associated with higher scores ( $1.50 \pm 1.06$ ) than in patients without postoperative antibiotic therapy ( $1.08 \pm 1.11$ ).

There were no significant differences in clinical endoscopy score between the negative, mono-infected and multi-infected groups ( $P=0.81$ ), according to isolate in mono-infection ( $P=0.39$ ) or isolates in multi-infection ( $P=0.77$ ).

Mean follow-up was  $18 \pm 24$  months, ranging from 1 month to 8 years 7 months.

Six patients (5.7%) required surgical revision in the center during follow-up: 2 with Widal's syndrome; 4 with history of surgery (polypectomy in 3 cases, bilateral ethmoidectomy in 1).

In 2 cases, revision was of bilateral meato-ethmoidectomy, and in 4 cases was for nasofrontal duct re-permeabilization.

## 4. Discussion

The sinonasal cavities are heavily colonized by bacteria, in healthy subjects as well as in those with CRS. The present study confirmed this colonization of the ethmoid mucosa, with a 74% rate of positive culture associated with nasal polyposis. The implication of these bacteria in the development of nasal polyposis remains unclear.

The formation of the polyps in nasal polyposis seems largely due to an eosinophil-mediated inflammatory reaction, with a key role played by cytokines such as interleukin-5 (IL-5) and predominant activation of T-helper-2 cells (Th2). Conversely, in CRS without

polyps, the inflammatory reaction mainly activates T-helper-1 cells (Th1) [8].

In the present study, the 3 infection groups (mono-, multi-infected and negative) were comparable except for age, which was significantly greater in the mono-infection group ( $P < 0.01$ ). History of endonasal surgery did not seem to affect sinonasal cavity colonization, although 70% of multi-infected patients had such history ( $P = 0.37$ ).

The relation between *S. aureus* infection and nasal polyposis has been the focus of several studies. Bachert et al. reported significantly greater staphylococcal infection in CRS with polyps (60%) than in CRS without polyps (27%) or controls (33%) [2].

Enterotoxins released in presence of *S. aureus* act as superantigens (SAG). These proteins bind to class-II major histocompatibility complex (MHC) and T-cell receptors, stimulating a large number of T-cells and thereby inducing large cytokine release, notably of IL-5, and playing a key role in the proliferation of polyps [9,10]. The present study found an overall rate of 27.3% for *S. aureus*, close to rates usually reported in CRS, as in Cleland's cohort of 513 patients, with a rate of 35% [11]. This is close to the generally agreed 20% rate of chronic *S. aureus* carriage in nasal cavities in the general population [12].

Several recent studies, however, have questioned the implication of *S. aureus*: Heymans et al.'s 2010 multicenter genetic study using polymerase chain reaction (PCR) screened directly for genes coding for *Staphylococcus*-induced endotoxins in specimens from patients with CRS with and without polyps and in controls, and found no significant difference between the 3 groups [3].

Despite being retrospective, the present study had the strong point of systematically taking intraoperative bacteriological specimens under aseptic conditions in a surgical population with several years' follow-up. We found no other studies in the literature with such a methodology of intraoperative sampling. Notably, it provided protected specimens under endoscopic control, accounting for the low rate of saprophytes such as coagulase-negative *Staphylococcus* (3.9%). Moreover, sampling was specifically performed in the ethmoidectomy cavity, which is the site of onset of mucosal disease in nasal polyposis, whereas other studies sampled from various sites, notably the maxillary sinus, or simply from the nasal cavities.

Under these strict sampling conditions, no significant difference in functional improvement was found according to negative, commensal or pathogenic culture.

Concerning the implication of pathogens other than *S. aureus*, several recent studies demonstrated colonization by other bacteria, and notably gram-negative bacilli (GNB), raising the question of their involvement in the inflammatory cascade underlying CRS with polyps. In 110 bacteria isolated in culture of middle meatus specimens, Brook et al. found only 7 *S. aureus* isolates [13]; 71 (64.5%) were anaerobic or aerobic GNBs.

In the present study, the rate of anaerobic bacteria may have been underestimated due to using swabs without transport medium, preventing isolation and culture of anaerobic strains.

Busaba, in ethmoid specimens from 179 patients, found rates of 18% for *Staphylococci* and 24.6% for GNB [9]. Doyle et al. reported comparable rates, notably with 38.9% GNB [14].

The present study found generally similar rates: 27.3% *S. aureus* and 30.5% GNB, raising the question of their involvement in the onset and development of nasal polyposis.

Only 2 studies focused on the impact of sinonasal cavity bacteriology on symptom severity.

Stern et al. reported a significantly higher rate of GNB with (60%) than without polyps (42%) ( $P = 0.045$ ) [15]. This was in agreement with the study by Uhlirava et al., which found pathogenic bacteria to be associated with greater CRS severity on Lund-Mackay score [16].

The other bacteriological study of ethmoidectomy cavities in nasal polyposis is Day et al.'s, but this concerned post- rather than intra-operative specimens [4]. Culture found GNBs in 23 patients (22.5%). There was no significant correlation between clinical status and bacteriology findings.

We also, like Day, found no impact of pathogenic bacteria or of the particular isolate on postoperative clinical score assessed by nasal endoscopy. The score was, however, significantly higher (i.e., poorer) in case of postoperative antibiotic therapy, although this did not affect functional score. This might be an assessment bias, inasmuch as the endoscopic clinical score was assessed early, at 6–12 weeks, shortly after the end of antibiotic therapy.

A total of 22.4% of patients received postoperative antibiotic therapy, which was prescribed in the first postoperative month in 75% of cases, usually due to symptom recurrence. In 1 case, it followed identification of MRSA.

There are no recent guidelines on intra- or post-operative bacteriological sampling in nasal polyposis. Several studies, however, showed the interest of screening for immune deficiency and of directed antibiotic therapy when atypical bacteria (*Pseudomonas aeruginosa*, *Klebsiella*, *Serratia*, *Morganella*) are isolated [17]. Another reason for intraoperative sampling is to determine the type of colonization. Without intraoperative sampling, bacteria identified postoperatively would be defined by count as nosocomial infection, defined by the WHO as operative site infection revealed within 30 days of surgery. Identification on intraoperative specimens reduces the risk of nosocomial attribution when infection is detected postoperatively.

Other issues are raised by recent studies of the sinus microbiota. New detection techniques have been developed, such as metagenomics, screening for and quantifying micro-organisms by genetic analysis of 16S ribosomal RNA [18]. These studies notably demonstrated that there are several factors liable to disturb nasal cavity microbiome balance [19]. Endonasal polyp surgery significantly altered species predominance according to Jain et al., with an increase in *Staphylococcus* rates and other unpredictable qualitative and quantitative changes [20]. Further studies are needed to shed light on the impact of the nasal and sinus microbiome and on the concept of dysbiosis in nasal polyposis [21].

## 5. Conclusion

The present study improved the description of the microbial ecology of the ethmoid cavities in nasal polyposis. Functional score in terms of postoperative rhinorrhea, nasal obstruction, anosmia and pain did not significantly differ according to negative, mono- or multi-bacterial culture or according to the type of bacteria isolated.

Most studies in the literature focused on the relation between nasal polyposis and *S. aureus*. The present study, however, found high rates of pathogens other than the 27.3% rate of *Staphylococcus*, and notably a 30.5% rate of GNB, raising the question of their role in the onset and progression of nasal polyposis.

This question remains unclarified; studies are needed to specify the role of SAGs, the cytokines involved in the inflammatory cascade, and the role of bacteria in the phenotypic progression of nasal polyposis and implications for therapy.

## Disclosure of Interest

The authors declare that they have no competing interest.

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