

# The Microbiology Characteristics of Infected Branchial Cleft Anomalies

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## Abstract

**Objectives.** To investigate the microbiology profile of infected branchial cleft anomalies compared to deep neck infection and explore the influence of age on culture findings.

**Study Design.** A retrospective case control study.

**Setting.** A single tertiary medical center.

**Subjects and Methods.** Patients treated for branchial cleft anomalies between 2006 and 2016 were included. Demographic data, disease and treatment parameters, and microbiology profile, including bacteria classification, antibiotics resistance patterns, and number of pathogens, were analyzed.

**Results.** Of 278 cases treated for branchial cleft anomalies, we have analyzed 69 cases with infection and pathogen identification. The proportion of monobacterial infections was higher (70.6% vs 44.3%;  $P = .003$ ; odds ratio [OR], 3.02) and the proportion of *Streptococcus* species infection was lower (48.9% vs 77.2%;  $P = .001$ ; OR, 0.282) among the infected branchial cleft cases compared to deep neck infections. Anaerobic bacteria infection did not differ between groups (17.8% and 16.5%, respectively). There was a nonsignificant tendency toward more resistant bacterial strains among the infected branchial clefts (15.6% vs 6.3%;  $P = .118$ ; OR, 2.726). There was no difference between the bacterial profile of patients younger or older than 16 years.

**Conclusions.** The microbiology profile of infected branchial cleft anomalies is not age related and is different from that of deep neck infections. We demonstrate a relatively high frequency of monobacterial infections, relatively lower streptococcal infection rates, and a substantial contribution by resistant species and anaerobes. Empiric antibiotic treatment should cover *Streptococcus* species, including penicillin-resistant species, as well as clindamycin-resistant anaerobes.

## Keywords

branchial cleft anomalies, anaerobic bacteria, polymicrobial infection, antibiotics resistance, deep neck infection, streptococcal infection, microbiology profile

Impaired obliteration of the branchial apparatus and the formation of a remnant with a potential for fistula, sinus, or, most commonly, a cyst is the fundamental process for branchial arch anomalies. The clefts are lined internally by endoderm (pouches) and externally by ectoderm (clefts).<sup>1</sup>

A branchial cleft anomaly consists of respiratory epithelium with lymphoid aggregates, which secrete in response to a nonspecific upper respiratory tract infection. The representative cytological samples show epithelial cells with subepithelial lymphoid aggregations.<sup>1</sup> The swollen cyst filled with stagnant mucus is prone to infection and progression to an abscess. This process may lead to a unique bacteriology profile different from deep neck infections.

Although culture-guided antimicrobial therapy is advocated, empirical antibiotics play a critical role in the first few days. Currently, there is a paucity of data describing the microbiology profile of infected branchial cleft anomalies. In this study, we investigate the distinctive microbiological characteristics of infected branchial cleft anomalies in different age groups, compared to nonembryonal deep neck infections, by analyzing different parameters, including the role of anaerobic bacteria and incidence of antibiotic resistance, monomicrobial infection, and *Streptococcus* species.

Nonembryonic origin deep neck infections are a potentially life-threatening condition, prominently associated with odontogenic infections and a wide variety of oral cavity

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pathogens.<sup>2-4</sup> Choosing this type of infection as our comparison group highlights the unique characteristics of infected branchial cleft anomalies.

## Materials and Methods

The study was conducted after approval from the institutional review board (IRB) at the Hadassah-Hebrew University Medical Center, according to the World Medical Association Declaration of Helsinki 2008 (0614-16-HMO). Retrospective analysis and electronic chart review were performed collecting demographic data, disease and treatment parameters, and microbiology profile, including bacteria classification, antibiotic resistance patterns, and number of pathogens.

### Primary End Points

Define the microbiology profile of infected branchial cleft anomalies in different age groups and compare to nonembryonal origin deep neck infections profile. According to our institutional policy, patients younger than 16 years are considered children.

We included all patients with infected branchial cleft anomalies treated in a single referral medical center between January 1, 2006, and December 31, 2016. A patient with separate (at least 1 year apart) infections could contribute more than 1 case to the analysis.

The comparison group consisted of patients with nonembryonal origin deep neck infections (parapharyngeal and retropharyngeal abscesses) drained during the study period.

### Main Study Exclusion Criteria

Study group cases in which needle aspiration was not performed or in which the culture medium and the gram stain did not demonstrate a bacterial pathogen were excluded. In the comparison group, we excluded superficial infections or limited intraoral abscesses in which incision and drainage were not needed. Infected surgical neck trauma or cellulitis alone, regardless of its origin, was also excluded.

Culture growths suspected of being contaminants due to their low pathogenic potential or as being part of the normal resident flora of skin (coagulase-negative staphylococci, *Corynebacterium* spp., *Lactobacillus* spp., *Propionibacterium* spp., *Rothia* spp.) were considered as negative. However, analysis was performed with and without these pathogens, investigating their potential impact.

### Microbiology

All specimens were gram stained, inoculated, and incubated at 35°C. Recovered isolates were identified during 2006 to 2012 using classic microbiologic methods and from 2012 and on mainly by matrix-assisted laser desorption/ionization time of flight mass spectrometry (VITEK MS; bioMérieux, Marcy l'Etoile, France). Susceptibility testing was performed using a disk diffusion test (Gamidor Diagnostics and E-test method; bioMérieux) in accordance with the manufacturer's instructions and performance standards for antimicrobial susceptibility testing (<http://www.facm.ucl.ac.be/>

[intranet/CLSI/CLSI-2017-M100-S27.pdf](http://www.clinical-laboratory-standards.org/CLSI-2017-M100-S27.pdf)) of the Clinical and Laboratory Standards Institute (CLSI).

### Microbiology Classification

Relevant clinical microbiology features were assessed for bacteriology profile characterization and comparison: mono- and polymicrobial infection, anaerobic pathogens, antibiotic resistance bacteria, and *Streptococcus* species incidence. *Streptococcus* species belonging to the normal oral flora (eg, *Streptococcus anginosus*, *Streptococcus milleri*, or *Streptococcus viridans*) were considered 1 group and other *Streptococcus* species (eg, group A *Streptococcus* or *Streptococcus pneumoniae*) as another group. These bacteria were evaluated both separately and all together. Anaerobic bacteria included *Bacteroides* spp., *Fingoldia* spp., *Fusobacterium* spp., *Prevotella* spp., and *Peptostreptococcus* spp. The definition of bacterial resistance correlated to the susceptibility profile and to the relevant clinical scenario considering the standard antibiotic treatment for neck infections: *Streptococcus* spp. resistant to penicillin, oxacillin-resistant *Staphylococcus aureus*, gram-negative bacteria resistant to oxyimino-cephalosporins, and clindamycin-resistant oral bacteria other than streptococci.

### Statistics

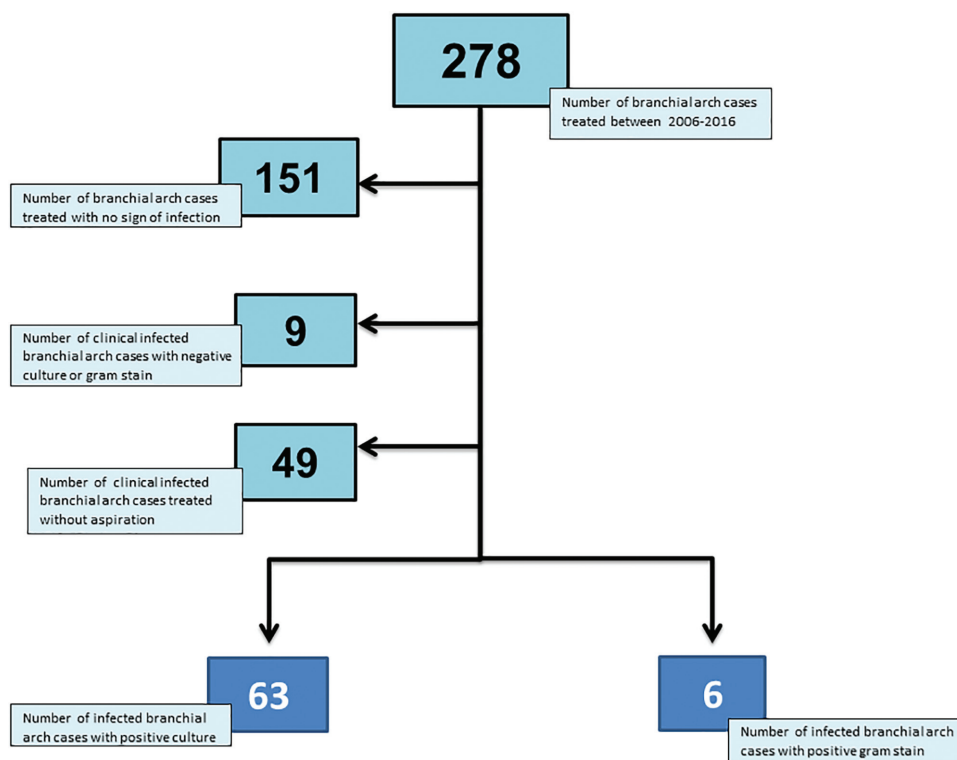
Statistical analysis was performed by a statistician using the SPSS Statistics software version 24 (SPSS, Inc, an IBM Company, Chicago, Illinois). Chi-square or Fisher exact tests were used for comparison of qualitative parameters, and the odds ratio (OR) with its 95% confidence interval (CI) was presented for each comparison. Student *t* test and Mann-Whitney test were used for quantitative parameters. A *P* value of .05 or less was considered statistically significant.

### Results

Sixty-nine cases of infected branchial anomalies were investigated. Of 278 cases treated with branchial cleft anomalies, we excluded 151 cases with no infection, 49 in which aspiration was not done, and 9 with negative cultures (**Figure 1**).

The average age of patients with infected branchial cleft anomalies was 23.3 years. Most infections were on the right side (64.1%) and among males (61.2%). Second branchial cleft infection was the most common anomaly (75.4%), followed by first cleft infections (14/69, 20%). Infected cysts (as opposed to infected sinuses and fistulas) were demonstrated in 72.5% of patients, and the average size was 37.4 mm (range, 8-70 mm).

Most demographic and clinical data of the study group and the group with nonembryonic origin deep neck infections were comparable (**Table 1**). Preadmission antibiotic treatment was significantly higher in the nonembryonal deep neck infection cases (74.7%) compared to the study group (41.2%). The patients in the study group were prone to recurrent infections, as high as 1.63 events, on average (range, 1-5 events; *P* = .05). There was no



**Figure 1.** Study scheme.

**Table 1.** Demographics, Epidemiologic Data, Disease, and Treatment Description of Branchial Arch Anomalies and Nonembryonic Origin Deep Neck Infections (Cases) between 2006 and 2016.

Characteristic	Infected Branchial Cleft Cases	Deep Neck Infection Cases	P Value	Odds Ratio (95% Confidence Interval)
Female, % (No.) [total No.]	38.8 (19) [n = 49]	50.7 (35) [n = 69]	.20	1.626 (0.77-3.42)
Right side, % (No.) [total No.]	64.1 (41) [n = 64]	51.3 (39) [n = 76]	.13	1.691 (0.856-3.340)
Mean age at event, y [total No.]	23.32 [n = 69]	25.47 [n = 79]	.51	
Mean number of repeated infection events [total No.]	1.63 [n = 49]	1.32 [n = 69]	.05 <sup>a</sup>	
Patients with preadmission antibiotic treatment, % (No.) [total No.]	41.2 (28) [n = 68]	74.7 (59) [n = 79]	<.001 <sup>a</sup>	0.237 (0.118-0.478)
Mean temperature, °C [total No.]	37.6 [n = 37]	37.5 [n = 63]	.695	
Mean number of repeated aspirations [total No.]	1.45 [n = 60]	1.12 [n = 78]	<.001 <sup>a</sup>	
Mean WBC count [total No.]	14.350 [n = 46]	14.412 [n = 70]	.962	
Mean neutrophils, % [total No.]	68.33 [n = 44]	75.12 [n = 64]	.006 <sup>a</sup>	
Mean CRP (mg/L) [total No.]	4.746 [n = 27]	10.096 [n = 34]	.008 <sup>a</sup>	
Patients having CT scan, % (No.) [total No.]	56.5 (39) [n = 69]	27.8 (22) [n = 79]	<.001 <sup>a</sup>	3.368 (1.699-6.678)
Patients having US, % (No.) [total No.]	43.5 (30) [n = 69]	5.1 (4) [n = 79]	<.001 <sup>a</sup>	14.423 (4.740-43.884)
Patients having MRI, % (No.) [total No.]	1.4 (1) [n = 69]	0 [n = 79]	.466	

Abbreviations: CRP, C-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasonography; WBC, white blood cell.

<sup>a</sup>P < .05.

statistically ( $P = .96$ ) or clinically (68.33% vs 75.12%) significant difference comparing the mean temperature, white blood cell count, and neutrophil differentiation, respectively. However, higher mean C-reactive protein (CRP) levels ( $P = .005$ ) were documented in the group with nonembryonic origin deep neck infections.

More patients in the study group had imaging studies, mainly sonographic and computed tomography (CT) scan investigations (43.5% and 56.5%, respectively).

Needle aspiration was performed in 78 of these 127 branchial arches infection cases. Only 9 of the 78 cases (11.5%) had no bacterial identification on either gram stain or

**Table 2.** Bacteriology Profile of Infected Branchial Cleft Anomalies.<sup>a</sup>

Organism	Number
Streptococci	25
Viridans group streptococci	20
<i>Streptococcus anginosus</i> group	10
<i>Streptococcus mitis</i>	3
<i>Streptococcus salivarius</i>	1
<i>Streptococcus sanguinis</i>	1
Other viridans group streptococci	5
Other streptococci	5
<i>Streptococcus pyogenes</i>	4
<i>Streptococcus pneumoniae</i>	1
Staphylococci	8
<i>Staphylococcus aureus</i>	6
<i>Staphylococcus lugdunensis</i>	2
Anaerobes	13
<i>Bacteroides</i> species	4
<i>Propionibacterium</i> species	6
<i>Fingoldia magna</i>	1
<i>Fusobacterium nucleatum</i>	1
<i>Actinomyces</i> species	1
Others	28
<i>Eikenella corrodens</i>	3
<i>Granulicatella adiacens</i>	1
<i>Haemophilus influenzae</i>	8
<i>Acinetobacter baumannii</i>	1
<i>Pseudomonas aeruginosa</i>	1
<i>Escherichia coli</i>	4
<i>Proteus mirabilis</i>	1
<i>Klebsiella oxytoca</i>	1
<i>Citrobacter koseri</i>	1
<i>Morganella morganii</i>	1
<i>Enterobacter cloacae</i>	1
<i>Enterococcus faecalis</i>	1
<i>Mycobacterium species avium-intracellulare</i> group	1
<i>Mycobacterium abscessus</i>	1
<i>Rothia mucilaginosa</i>	1
<i>Trueperella bernardiae</i>	1
Contaminants	19
Coagulase-negative staphylococci	14
<i>Lactobacillus</i> species	1
<i>Corynebacterium</i> species	4

<sup>a</sup>Study group consists of 63 cases, 93 organisms.

culture medium investigation (**Figure 1**). Four of those 9 cases (44.44%) had preadmission antibiotic treatment; similarly, 28 of the 69 remaining cases (41.2%) with bacterial identification had a preadmission antibiotic treatment. Six cases of the 69 had only a gram stain bacterial characterization, whereas the rest had both gram stain and culture bacterial identification of 93 organisms (**Table 2**). To minimize a selection bias, we analyzed separately the 63 cases as a whole and a subset of 50 cases, excluding the 13 cases

**Table 3.** Antibiotic Resistance in Infected Branchial Anomalies.

Resistant Bacteria <sup>a</sup>	Number of Isolates	Antibiotics
<i>Bacteroides</i> species	2	Clindamycin
<i>Staphylococcus aureus</i>	1	Oxacillin
<i>Acinetobacter baumannii</i>	1	Ceftazidime, ceftriaxone
<i>Streptococcus mitis</i>	1	Penicillin
<i>Streptococcus constellatus</i>	1	Penicillin
<i>Rothia mucilaginosa</i>	1	Clindamycin
Total	7	

<sup>a</sup>Antibiotic resistance of bacteria excluding contaminants. Resistance was defined as the presence of penicillin-resistant streptococci, oxacillin-resistant *Staphylococcus aureus*, clindamycin-resistant oral bacteria other than streptococci, and oxyimino-cephalosporin-resistant gram-negative bacteria.

defined as potential contaminants. No statistical difference was noticed when excluding the potential contaminants. Moreover, there were no contaminants in the nonembryonic origin deep neck infection cases. Therefore, results and analyses presented are of the no-contaminates cases (n = 50).

### Microbiology Profile

Most infected branchial cleft anomalies (70.6%) had a single bacterial pathogen identified. Almost half (49.2%) of the cases were caused by *Streptococcus* species (resident of the oral flora, 30.2%; nonresident of the oral flora, 19%) (**Table 2**).

Anaerobic bacteria were present in 17.8% of cultures. Antibiotic resistance was demonstrated in 15.6% of the cases and included 2 penicillin-resistant streptococci and 2 clindamycin-resistant anaerobes (**Table 3**).

The comparison of infected branchial anomalies (without 13 suspected contaminates cases, n = 50) to the nonembryonic deep neck infection cases (**Table 4**) revealed a significantly lower preadmission antibiotic treatment (41.2% vs 74.7%; OR, 0.237; 95% CI, 0.118-0.478;  $P < .001$ ), higher monobacterial infections (OR, 3.02; 95% CI, 1.428-6.369;  $P = .003$ ), and less streptococcal infections (OR, 0.282; 95% CI, 0.129-0.620;  $P = .001$ ) (**Figure 2**). There was a nonsignificant tendency toward a higher rate of resistant bacteria (OR, 2.726; 95% CI, 0.811-9.165;  $P = .118$ ). The anaerobic infection rate was similar in both groups (17.8% vs 16.5%; OR, 1.098; 95% CI, 0.417-2.891;  $P = .85$ ). As mentioned in the Materials and Methods section, the statistical analysis had similar results when suspected contaminants in the branchial infection group (n = 63) were not excluded.

### Infected Branchial Cleft Anomalies in Different Age Groups

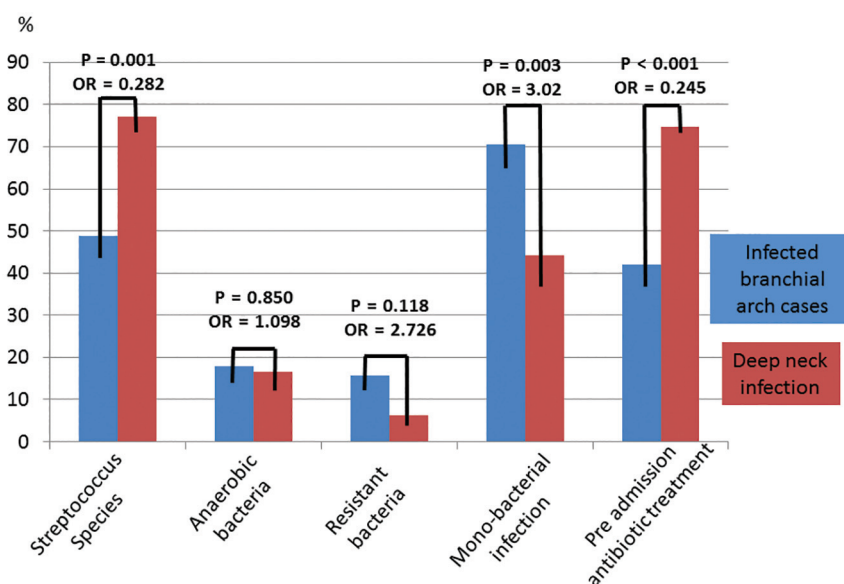
The comparison of the bacteriology profile among younger (<16 years) and older ( $\geq 16$  years) patients demonstrated no statistically significant difference comparing the infected cleft types (first vs second to fourth) (OR, 1.512; 95% CI, 0.355-6.451;  $P = .718$ ). However, fistulae and sinuses (vs cysts) were 4.118 times more common among patients

**Table 4.** Bacteriology Comparison of Infected Branchial Cleft and Deep Neck Infection Cases.

Characteristic	Infected Branchial Cleft Cases with Positive Culture <sup>a</sup>	Deep Neck Infection Cases with Positive Culture	P Value	Odds Ratio (95% Confidence Interval)
Monomicrobial infection, % (No.) [total No.]	70.6 (36) [n = 50]	44.3 (35) [n = 79]	.003 <sup>b</sup>	3.02 <sup>b</sup> (1.428-6.369)
All <i>Streptococcus</i> species infections, % (No.) [total No.]	48.9 (22) [n = 45]	77.2 (61) [n = 79]	.001 <sup>b</sup>	0.282 <sup>b</sup> (0.129-0.620)
Anaerobic bacteria infections, % (No.) [total No.]	17.8 (8) [n = 45]	16.5 (13) [n = 79]	.85	1.098 (0.417-2.891)
Resistant bacteria infections, % (No.) [total No.]	15.6 (7) [n = 45]	6.3 (5) [n = 79]	.11	2.726 (0.811-9.165)

<sup>a</sup>Excluding suspected contaminates cases. The ratios and comparison of monomicrobial and streptococcal species, anaerobic bacteria, and resistant bacteria infections for all positive culture branchial cleft cases (n = 63), including suspected contaminates, demonstrated similar results (not shown).

<sup>b</sup>P < .05.



**Figure 2.** Bacteriology comparison of infected branchial anomalies (without suspected contaminates) and nonembryonal deep neck infections. OR, odds ratio.

younger than 16 years (OR, 4.118; 95% CI, 1-17.38;  $P = .045$ ). No difference was recorded comparing the median number of recurrent infections ( $P = .918$ ), sonographic examination performance ( $P = .467$ ), average admission time ( $P = .629$ ), median number of aspirations ( $P = .474$ ), or median number of draining procedures ( $P = .371$ ) performed among young (<16 years) and older ( $\geq 16$  years) patients. Similar laboratory inflammatory parameters were recorded in both age groups (CRP and median neutrophil percentages,  $P = .216$  and  $P = .513$ , respectively). The younger group of patients underwent less CT scans compared to the older patients (OR, 0.131; 95% CI, 0.036-0.468).

A similar percentage of patients having preadmission antibiotics treatment was documented in the older and younger patient groups (OR, 0.893; 95% CI, 0.289-2.754;  $P = .845$ ). The bacterial profile of both age groups was similar: monobacterial infection (OR, 0.667; 95% CI, 0.196-2.263;  $P = .514$ ), *Streptococcus* infection (OR, 0.928;

95% CI, 0.281-3.058;  $P = .903$ ), anaerobic infection (OR, 0.324; 95% CI, 0.066-1.582;  $P = .235$ ), and resistant strains (OR, 1.818; 95% CI, 0.312-10.638;  $P = .684$ ).

## Discussion

We defined the prevalence of monobacterial cases, anaerobic bacteria, resistant pathogens, and streptococcal strains in infected branchial arch anomalies. We demonstrated a similar bacterial profile among young and older ( $\geq 16$  years) patients. We conducted a clinically relevant comparison with nonembryonal neck infections, demonstrating more monobacterial infections, a nonsignificant tendency toward higher antibiotic resistance rates, less streptococcal infections, and a similar incidence of anaerobic bacteria in infected branchial cleft anomalies.

By the seventh week of embryonic life, the 6-paired arches join, creating a smooth contour of the neck.<sup>5</sup> Most anomalies are related to failed second branchial arch

involution, followed by first arch anomalies presenting as a parotid mass.<sup>6,7</sup>

Branchial cleft anomalies usually appear in association with a nonspecific throat infection, dental infection, or any other upper respiratory tract infection.<sup>8</sup> Serial aspirations of the abscess contents with systemic antibiotics are often sufficient. Although the preference is to avoid formal incision and drainage (which may complicate a future surgical procedure), it may be required if the skin is involved or if the infection does not resolve.

The relatively young median age (23.3 years), the predominance of second cleft defects (75.4%), and the high proportion of infected cysts, together with the other epidemiological and clinical characteristics depicted in **Table I**, are in accordance with previous publications.<sup>9</sup> To note, in view of our retrospective investigation, not all demographic and clinical data were available (as presented in **Table I**).

Most aspirations (88.5%) led to bacteriologic identification, regardless of preadmission antibiotic treatment (48.5%). A similar preadmission antibiotic treatment rate (44.44%) was recorded among the 9 patients with negative aspiration analysis. Therefore, preadmission antibiotic treatment should not be considered a reason to avoid needle aspiration for bacteriology investigation or for decreasing the bacterial load.

The physician must be familiar with the bacteriology profile of infected branchial cleft anomalies, since patients most commonly will have empiric antibiotic treatment prior to bacterial identification. It is essential to be aware of the rates of anaerobic strains (17.8%), streptococcal infections (49.2%), antibiotic-resistant bacteria (15.6%), and prevalence of monobacterial infections (70.6%).

For the first time, we thoroughly investigated and compared the bacterial profile of infected branchial cleft anomalies and nonembryonal deep neck infections. Branchial cleft anomalies carry a triple odds of having a monobacterial infection compared to nonembryonal deep neck infections ( $P = .003$ ). Fundamental anatomical and etiological differences may explain the higher monobacterial infection rates. The respiratory epithelium and the lymphoid aggregates in branchial cleft anomalies generate a mucus-containing cavity that may develop into an abscess. Since branchial cleft cysts, with no communication to the skin or to the upper aerodigestive system, are the most common branchial anomalies, we may assume that bacteria are dispersed by the lymphatic and/or hematogenic systems<sup>10,11</sup> in contrast to a direct communication route in deep neck infections. Previous gastrointestinal system investigations have demonstrated increased barrier permeability via extracellular spread during an inflammation state.<sup>12</sup> This process has inherited pathogen selection characteristics (different from direct connection to the aerodigestive system), as only specific bacteria with particular features can migrate. This may explain potential specific bacteriology patterns in branchial cleft anomalies. Moreover, branchial cleft anomalies have expected pathways, with so-called known “corridors,”

leading to the oropharynx and hypopharynx,<sup>13</sup> in contrast to nonembryonal deep neck infections, which are mostly associated with oral cavity bacteria.<sup>2,3,14</sup> Less streptococcal infections among inflamed branchial cleft anomalies could be at least partially explained by the same differences compared to nonembryonal deep neck infections, where direct association with dental/oral cavity infections is responsible for the majority of cases.

The nonsignificant tendency (2.72 times more) for resistant bacterial strains in branchial cleft anomalies (15.6% vs 6.3%) may be related to a higher rate of recurrent infections (mean number of infection episodes, 1.63 vs 1.32,  $P = .05$ , in branchial cleft anomalies compared to nonembryonal deep neck infections). The presence of penicillin-resistant viridans group streptococci, as well as clindamycin-resistant anaerobes, mandates careful selection of an empiric antibiotic treatment.

Although most of the infected branchial cleft anomalies presented during the second and third decades of life, we investigated the bacteriology profile among younger (<16 years) and older ( $\geq 16$  years) patients. We assumed that older patients may have a different bacterial profile considering the expected higher rate of repeated infections and recurrent antibiotic treatment. However, since definitive treatment was offered regardless of age, this older subset of patients was not subject to further infections than the younger subset. This may explain the equivalent bacteriology profile.

The study’s major restraints are its retrospective nature and the limited number of patients. The meticulous clinical and laboratory data extraction and the analysis with and without potential contaminate strains may overcome its retrospective nature. Another limitation is the fact that the bacterial profile may be diverse in different populations and that local variation is conceivable, especially in the levels of resistance.

## Conclusion

Herein we present the bacterial profile of infected branchial cleft anomalies that is not age dependent. In addition, we have demonstrated a relatively high monobacterial infection rate, substantial incidence of anaerobic and antibiotic resistance infections, and a relatively low occurrence of streptococcal infections.

Our clinical recommendations for infected branchial cleft anomalies are therefore as follows:

1. Aspiration for culture is useful, even after commencement of antibiotics.
2. Empiric antibiotic treatment should cover *Streptococcus* species, including penicillin-resistant species, as well as clindamycin-resistant anaerobes. Possible empiric choices are second- or third-generation cephalosporins (eg, cefuroxime, ceftriaxone), with the addition of metronidazole against  $\beta$ -lactam-resistant anaerobes.

## Author Contributions

**Nir Hirshoren**, conception and design of the work, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Neta Fried**, acquisition of data for the work, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Jeffrey M. Weinberger**, interpretation of data for the work, revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Ron Eliashar**, interpretation of data for the work, revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **Maya Korem**, conception and design of the work, drafting the work, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Disclosures

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