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Factors Associated With Infectious Laryngitis: A Retrospective Review of 15 Cases

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Abstract

Objectives—To identify the culturable microbes associated with infectious laryngitis and outline effective treatment strategies.

Methods—This is a retrospective chart review of adult patients with persistent dysphonia plus evidence of laryngeal inflammation who underwent biopsy for culture at a tertiary care medical center. Demographic factors, symptoms as reported on validated patient assessment tools, past medical history, social history, culture results, and treatment duration and response were reviewed.

Results—Fifteen patients with infectious laryngitis were included in this study. Culture results demonstrated Methicillin-sensitive *Staphylococcus aureus* (MSSA), Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa, Serratia marcescens*, and "normal respiratory flora." In most patients, multiple courses of prolonged antibiotics were needed to treat MSSA or MRSA. Infections associated with other microbes resolved with a single course of antibiotics.

Conclusions—In this population, infectious laryngitis is defined as colonization with bacteria not found in the previously characterized laryngeal microbiome of benign vocal fold lesions. In suspected cases of infectious laryngitis, culture is recommended, by biopsy if needed. For MSSA- and MRSA-associated laryngitis, an extended course of antibiotics may be necessary for symptom improvement and resolution of laryngeal inflammation. However, the optimal treatment regimen has yet to be defined and will require larger, prospective studies.

Keywords

laryngitis; bacteria; *Staphylococcus aureus*; inflammation; chronic laryngitis; infectious laryngitis

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Introduction

Laryngitis is inflammation of the larynx caused by various etiologies and can be classified as acute or chronic based on duration of symptoms. Laryngitis is chronic if symptoms persist for 3 weeks or greater.[1] Symptoms of chronic laryngitis include dysphonia, globus sensation, odynophagia, and excessive throat clearing.[2,3] Etiologies for chronic laryngitis include laryngopharyngeal reflux (LPR), irritants (cigarette smoke or inhaled medications), rhinitis (allergic or other), mechanical irritation from voice misuse/overuse, and infectious, including bacterial laryngitis and laryngeal candidiasis.[3,4] Historically, routine use of antibiotics to treat chronic laryngitis has not been recommended,[1,5] and chronic infectious laryngitis secondary to bacterial infection remains a poorly understood disease process. Causative organisms have not been fully identified, and optimal treatment regimens are unknown. A recent study demonstrated that otolaryngologists rarely treat chronic laryngitis with antibiotics as the first-line therapy, preferring to start with a proton pump inhibitor (PPI) treating LPR as the presumed etiology.[2]

As demonstrated by studies of the human microbiome, the larynx is chronically colonized by bacteria.[6,7] Therefore, chronic laryngitis from a bacterial infection could stem from bacterial species not part of the normal laryngeal microbiome or from an overgrowth of commensal bacteria. In a recent study, biopsies were obtained from 44 benign vocal fold lesions.[6] Examination of the bacterial community by 454 pyrosequencing demonstrated 5 predominate genera, including *Streptococcus, Fusobacterium, Prevotella, Neisseria*, and *Gemella*.[6] In another study examining the microbiome of patients with laryngeal squamous cell carcinoma, the same genera were identified.[7,8] *Staphylococcus* was not identified in either of these studies.

There are limited data available on chronic bacterial laryngitis with only a few reports of Methicillin-resistant *Staphylococcus aureus* (MRSA) laryngitis in the literature.[9–11] The largest case series included 3 cases of MRSA laryngitis and 3 cases of Methicillin-sensitive *Staphylococcus aureus* (MSSA) laryngitis.[11] These patients were dysphonic (vocal roughness, fatigue, and decreased vocal endurance) and had thickened vocal folds, edema, crusting, and debris on exam.[11] All 6 patients were diagnosed via in-office cultures and were treated with multiple courses (2–4 weeks) of trimethoprim-sulfamethoxazole.[11] Additionally, there are a few case reports describing patients with prolonged dysphonia, culture proven MRSA laryngitis, and treatment with extended courses of trimethoprim-sulfamethoxazole.[9,10]

In our clinical population, we observed a cohort of patients with symptoms of chronic laryngitis and evidence of significant laryngeal inflammation on laryngoscopy for whom initial treatments were unsuccessful. Biopsy samples obtained on this group of patients were cultured. If cultures were positive for pathogenic microbes, the patient underwent treatment with sensitivity-directed antibiotics. The objectives of this retrospective chart review were to identify patients with chronic infectious laryngitis, determine the associated organisms and comorbid conditions, and review treatment regimens to develop greater understanding of this disease entity.

Materials and Methods

We performed a retrospective chart review of adult patients who underwent laryngeal biopsy for chronic laryngitis with a suspected infectious etiology (January 2013–May 2016). This study was carried out under Institutional Review Board approval. Patients included in the study were referred to our tertiary care center for further workup by primary care physicians or otolaryngologists. All patients had undergone at least 1 prior treatment for laryngitis including PPI, steroids, antifungal medications, antibiotics, or speech therapy prior to evaluation in our clinic. Chronic laryngitis was defined as persistent voice changes present for 3 weeks or greater. Patients had to demonstrate significant laryngeal inflammation such as edema, erythema, crusting, exudate, and altered vibration on stroboscopic laryngoscopy to be included in the study (Figure 1). Patients completed the Voice Handicap Index (VHI-10) with scores higher than 11 considered abnormal.[12] All patients had a thorough history and a comprehensive head and neck exam including laryngoscopy with stroboscopy. Patient records including clinical notes, operative reports, culture results, pathology results, and recorded endoscopic exams were reviewed.

Initially laryngeal swabs were taken for culture; however, these were universally nondiagnostic. Instead, biopsies were obtained for culture both to increase yield and assess for intra-epithelial bacteria. Biopsies were taken either awake using an Olympus chip tip flexible laryngoscope and 1.4 mm cup forceps through the 2 mm working side channel (Hamburg, Germany) or under general anesthesia via micro-direct laryngoscopy using 1 mm cup forceps. Procedure preference was determined by the presence of concomitant laryngeal disease and the patient's ability to tolerate an awake procedure. Biopsies were taken of a representative portion of the vestibular fold when done under general anesthesia and of the anterior left vestibular fold when done awake due to the technical ease of obtaining a biopsy of this location through an Olympus channeled laryngoscope. The biopsy samples were sent for both pathologic analysis and anaerobic, aerobic, fungal, and acid-fast bacterial cultures. Viral cultures were not taken as symptom duration was longer than a typical viral course. Initial treatment was based on culture results and sensitivities, and continued treatment was based on patient response to antibiotic treatment. Patients were also referred to infectious disease for evaluation.

Results

Patient Demographics

Fifteen patients were identified via retrospective chart review (Table 1). There were 10 male and 5 female patients ages 36 to 86 years old. All patients presented with persistent hoarseness that ranged in duration from 4 weeks to 5 years. The VHI-10 scores prior to treatment were 17 to 40 (Table 1). The most frequently reported comorbid symptoms were reflux related, including heartburn, regurgitation, or belching (9 patients). Eleven patients were on a PPI at the time of evaluation. Four patients (Nos. 4, 5, 8, 14; Table 1) had diabetes mellitus, 1 (No. 5) had autoimmune disease, and 3 (Nos. 4, 6, 14) had prior treatment for head and neck cancer including radiation. There were no current smokers, but 4 had a prior history of smoking. Six patients underwent additional interventions during the microdirect laryngoscopy performed to obtain biopsies for culture. Two patients (Nos. 10, 12; Table 1)

underwent excision of papillomas, 2 (Nos. 9, 11) had treatment of subglottic stenosis, 1 (No. 4) had excision of a right vocal fold squamous cell carcinoma in situ, and 1 (No. 5) had excision of a left vestibular fold laryngocele.

Culture and Pathology Results

Figure 2 and Table 2 demonstrate the culture results obtained from the biopsies. The predominant organism isolated was MSSA (12/15 cultures). Only 1 of 15 cultures demonstrated MRSA. Other species isolated included *Serratia marcescens* (2/15 cultures) and *Pseudomonas aeruginosa* (1/15 cultures). One culture demonstrated "normal respiratory flora." There are more culture results than patients because 2 cultures grew both *Serratia marcescens* and MSSA. One culture initially grew predominantly *Serratia marcescens* with a few MSSA, but after successful treatment with a subsequent recurrence, repeat culture demonstrated only MSSA. The other patient grew MSSA and *Serratia* simultaneously. One culture was positive for fungal organisms, demonstrating moderate *Histoplasma capsulatum*. None of the biopsies that were cultured for acid-fast bacteria (AFB) were positive; however, only half of the biopsy samples were sent for AFB. Pathology results for 12 patients were consistent with inflammation, 2 were not sent for pathology, and 1 was positive for squamous cell carcinoma; however, this patient had a prior history of laryngeal squamous cell carcinoma.

Laryngoscopy With Stroboscopy Findings Consistent With Infectious Laryngitis

Figure 3 demonstrates examples of the indirect laryngoscopic findings seen in this patient population. Photos on the left are pretreatment demonstrating edema of the vocal folds, diffuse erythema, crusting, and exudate involving the endolarynx. Photos on the right are posttreatment photos obtained after multiple extended courses of antibiotics. The 4 patients represented in Figure 3 had MSSA-associated laryngitis. Initially there was an excellent response to antibiotics, but symptoms and laryngoscopy findings recurred after discontinuation of antibiotics.

Treatment

Treatment and antibiotic choice (Table 2) were governed by microbiologic sensitivities with the typical treatment course for both MRSA- and MSSA-associated laryngitis consisting of trimethoprim-sulfamethoxazole. *Pseudomonas aeruginosa* was treated with ciprofloxacin, and *Serratia marcescens* was treated with levofloxacin. Treatment duration ranged from 10 to 261 days. Three patients did not receive antibiotic treatment. Five patients at the time of this article were either currently undergoing their first course of antibiotic treatment or had complete resolution of symptoms with 1 course of antibiotics. Seven patients required multiple courses of antibiotics. These patients had an initial response to antibiotics, but symptoms and laryngeal findings of inflammation recurred after antibiotics were discontinued. In these situations, the type of antibiotic was not changed, but the duration of treatment was extended. Only patients with MSSA- or MRSA-associated laryngitis required multiple courses of antibiotics. Non-*Staphylococcus* infections were successfully treated with 1 course of antibiotics. Eleven of the 15 patients were referred to infectious disease for evaluation.

Discussion

This study describes a population of patients with chronic dysphonia plus laryngeal inflammation consisting of edema, diffuse erythema, crusting, and exudate that can be attributed to pathogenic bacteria including MSSA, MRSA, *Pseudomonas aeruginosa*, and *Serratia marcescens*. Biopsy for culture revealed pathologic bacteria that can be targeted with culture-sensitivity directed antibiotics. The majority of patients had cultures positive for MSSA (12/15). Chronic laryngitis secondary to bacterial infection may be underrecognized and should be included in the differential diagnosis of patients with prolonged dysphonia, especially if laryngeal crusting and exudate are present as these findings appear most indicative of bacterial infection.

In cases of suspected bacterial infection, a culture should be obtained. Laryngeal culture swabs can be an initial diagnostic test as they are minimally invasive and easily performed in the clinic. However, it was the experience of the primary surgeon in this study that culture swabs of the larynx were more likely to have negative results despite obvious clinical abnormality of the larynx. Culture swabs of the glottis do not demonstrate infection reliably[13] and can lead to a high false negative rate. Additionally, infectious bacteria may be intra-epithelial and therefore only apparent on tissue biopsy and not laryngeal swab. Tissue biopsy for pathology is also helpful in demonstrating an inflammatory response to bacteria rather than only colonization. Finally, the bacterial community of benign vocal fold lesions has been shown to be distinct from throat and saliva samples from healthy patients,[6] suggesting that sampling saliva or the throat is not adequate for diagnosing laryngeal infection. These samples may be contaminated with nasopharyngeal or oropharyngeal bacterial communities.

Approximately half of the patients in this study (n = 7) had in-office biopsies for culture with the remainder done in the operating room. It is possible that this difference in procedure may have affected culture results. Currently, there are no published reports comparing the sensitivity and specificity of in-office versus operating room biopsies for culture. A recent study comparing in-office versus operating room biopsies for pathologic diagnosis found that in-office biopsies had 60% sensitivity and 87% specificity when compared to the final pathologic diagnosis obtained in the operating room.[14] There was especially poor sensitivity when diagnosing dysplasia and carcinoma in situ on in-office biopsies.[14] In these cases, pathologic diagnosis can be difficult secondary to the small biopsy size and limited depth inherent to in-office biopsies. These factors may not impact bacterial culture results from biopsied tissue. In our study, the only biopsy that was nondiagnostic (“normal respiratory flora”) was obtained in the operating room. This suggests that in-office biopsy for culture is a valid option; however, further studies comparing the 2 techniques are needed.

The cultures obtained on our 15 patients demonstrated a preponderance of MSSA and MRSA. This is the largest case series to be reported in the literature but is still a small sample size. It is possible that some cases of chronic laryngitis are due to fungal or AFB infection, and therefore, biopsies should be sent for aerobic, anaerobic, fungal, and AFB cultures. Additionally, even in patients with no suspicion for concomitant pathology, we recommend submitting a biopsy specimen for pathology. It is unclear what, if any, comorbid

conditions predispose patients to infectious laryngitis. Ruling out dysplasia, carcinoma in situ, and squamous cell carcinoma remains of utmost importance in patients with long-term voice changes. It is unknown if other laryngeal pathologies such as recurrent respiratory papillomas, subglottic stenosis, and carcinoma in situ change the host defense of the laryngeal mucosa and predispose patients to pathologic bacterial colonization of the larynx.

The medical comorbidities that predispose certain patients to develop infectious laryngitis remain unclear. None of the patients had a history of recent hospitalizations, so the bacterial infections were community acquired. We examined conditions that may cause immunosuppression and did not have a large enough patient sample to see a distinct pattern. One could hypothesize that immunosuppression from diabetes mellitus, HIV, or autoimmune disease; impaired saliva production from a history of radiation for head and neck cancer; or ciliary dysfunction from smoking could affect host defenses, resulting in chronic bacterial laryngitis. A recent study comparing the laryngeal microbiome between smokers and nonsmokers found less microbial diversity in smokers.[15] This decreased diversity may allow pathogenic bacteria to persist. The most commonly reported comorbid condition for our patients was symptoms of reflux, and a majority of patients were using a PPI at the time of study, likely a combination of their symptoms and the use of PPIs as first-line treatment for chronic laryngitis. One hypothesis is that reflux may be affecting the mucosal environment and changing the composition of the laryngeal microbiome. However, *Staphylococcus aureus* does not grow well at pH environments less than 5.5,[16] making a link between reflux and MSSA/MRSA laryngitis less likely. Additionally, comparing the laryngeal microbiome of patients with and without reflux demonstrated no change in microbial diversity or composition.[15] Understanding the underlying etiology of chronic bacterial laryngitis will be essential for prompt diagnosis, successful treatment, and prevention. Larger prospective studies will be necessary to identify contributing factors to the development of infectious laryngitis.

The cultures in this study primarily grew 1 bacterial species with the exception of 2 patients. The complete bacterial microbiome associated with chronic laryngitis is still unknown, and it is possible that there are multiple alterations to the bacterial community that allow pathogenic bacteria to persist, causing prolonged dysphonia and laryngeal inflammation. In the future, it will be important to sequence the entire microbiome and compare to healthy laryngeal tissue to fully understand the microbial shifts that take place in this disease process. This may also provide better preventive measures and treatment options.

While this case series did not specifically examine the role of biofilms, there is evidence that they may play a role in chronic laryngitis. In 1 study, biopsies from 13 patients with chronic laryngitis were compared to 5 patients with benign vocal fold lesions.[17] Biopsies were analyzed with confocal scanning laser microscopy (CSLM) looking for morphological characteristics typical of biofilms. Eight of the 13 (62%) patients with chronic laryngitis demonstrated a biofilm on CSLM while only 1 patient out of 5 (20%) with benign vocal fold lesions demonstrated a biofilm. Species typically found in biofilms included *Staphylococcus aureus*, *Haemophilus influenzae*, *Candida albicans*, *Moraxella nonliquefa*, *Propionibacter acnes*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*.[17,18] Biofilms are 10 to 1000

times more resistant to antibiotics compared to planktonic bacteria, which could explain the need for extended and multiple course of antibiotics to treat MSSA and MRSA laryngitis.[19]

Most soft tissue infections in otolaryngology are treated with a 5- to 14-day course of antibiotics. This study along with previously published reports[9–11] demonstrates that a 14-day course of antibiotics may not be sufficient to treat chronic bacterial laryngitis. In our cohort, the shortest duration of antibiotics that was effective was 3 weeks for *Pseudomonas aeruginosa* laryngitis. Approximately half of the patients in this study required multiple courses of antibiotics to obtain a response. In these patients, the improvement in symptoms and appearance of the larynx on laryngoscopy was temporary. All of the patients requiring multiple courses of antibiotics secondary to recurrent symptoms had MSSA- or MRSA-associated laryngitis. This suggests that MSSA/MRSA laryngitis may behave similarly to chronic rhinosinusitis (CRS) where *Staphylococcus aureus* can persist despite multiple courses of culture-directed antibiotics.[20] Intra-epithelial bacteria may also require prolonged antibiotic treatment to clear. In CRS, intracellular *S. aureus* is associated with the need for revision sinus surgery and higher rates of early disease relapse.[21] It may be beneficial to obtain a concurrent infectious disease consult to help co-manage patients with bacterial laryngitis.

When evaluating patients with dysphonia for greater than 3 months duration, a comprehensive voice evaluation should be performed, including laryngoscopy with stroboscopy. If laryngeal edema, exudate, and crusting are observed and prior treatments have failed, a biopsy for culture could be performed. The location of the biopsy (in-office vs operating room) is dependent on patient cooperation and anxiety as well as the presence of concomitant lesions that may need further evaluation. Tissue should be sent for aerobic, anaerobic, fungal, and acid-fast bacteria cultures. Antibiotic treatment should be initiated only if culture results are positive. Cases of chronic dysphonia are heterogeneous, so clinical judgement should always be used to determine the appropriate workup, need to rule out malignancy or other underlying conditions, and treatment.

Conclusions

Patients presenting with persistent dysphonia and characteristic laryngoscopy findings of laryngeal inflammation could be biopsied for culture to assess for infectious laryngitis. Methicillin-sensitive *Staphylococcus aureus* is the most frequently isolated bacterial species in chronic bacterial laryngitis; however, further study and more in-depth sequencing strategies will be essential to understanding the microbiology and pathology of this disease process. Additionally, further study will identify comorbid conditions that may predispose patients to developing infectious laryngitis.

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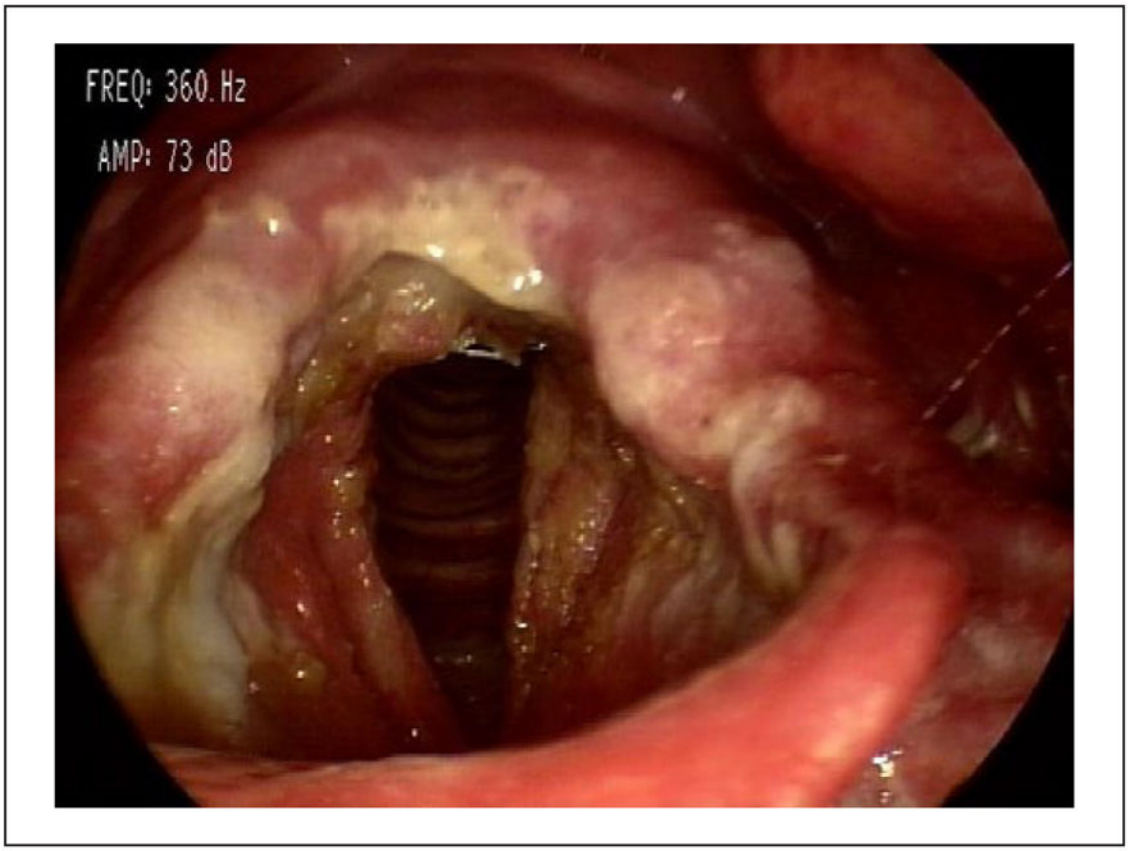

Figure 1.
Laryngoscopy image of chronic laryngitis. Laryngoscopy findings seen in chronic bacterial laryngitis include edema, erythema, crusting, and exudate. The presence of exudate is most commonly associated with bacterial etiology.

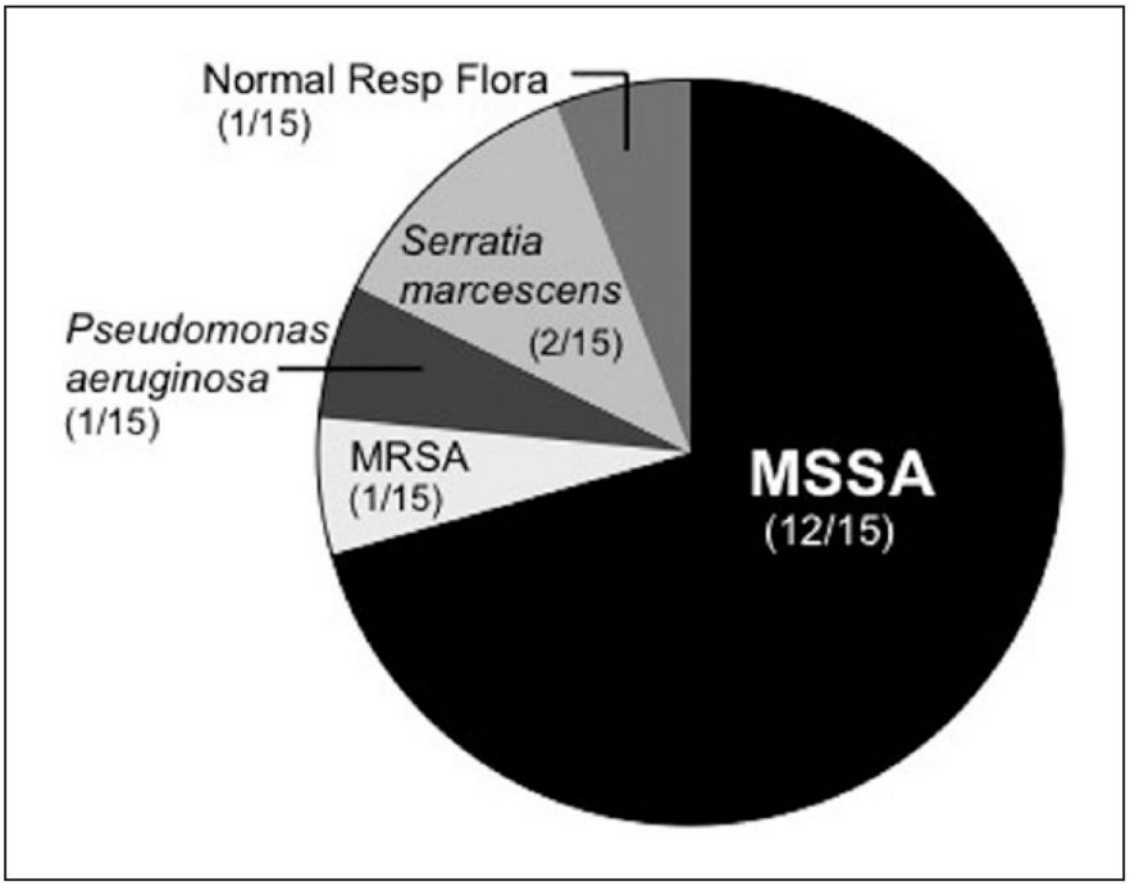

Figure 2.

Bacterial species isolated from chronic laryngitis cultures. Culture results demonstrated a predominance of Methicillin-sensitive *Staphylococcus aureus* as the causative organism for chronic laryngitis (12/15). *Serratia marcescens* was isolated from 2 cultures while *Pseudomonas aeruginosa* and Methicillin-resistant *Staphylococcus aureus* were each isolated from 1 out of 15 cultures. One culture demonstrated only “normal respiratory flora” despite the larynx having the characteristic appearance of chronic bacterial laryngitis.

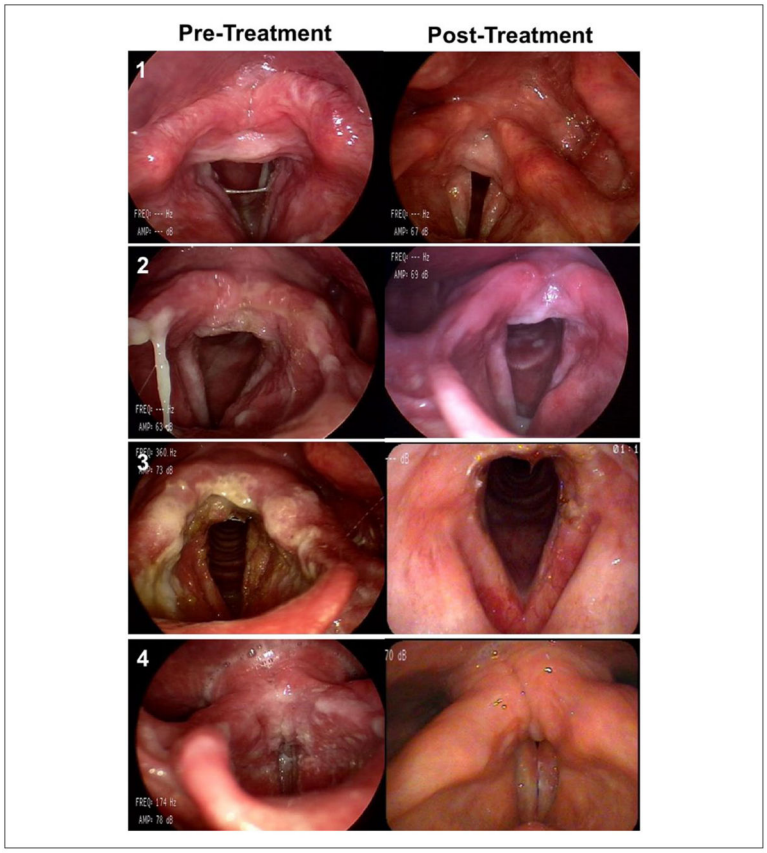

Figure 3.

Representative laryngoscopy images of chronic laryngitis pre- and posttreatment. Examples of pathologic findings seen with chronic bacterial laryngitis including edema, crusting, and exudate from 4 separate patients (Patient Nos. 1–4) are demonstrated. Panels on the left are pretreatment, and panels on the right are the corresponding posttreatment photographs.

Table 1

Summary of the Study Population Including Demographic Data, Comorbid Conditions, VHI-10, Symptom Duration, and Workup.

			Common Comorbid Conditions					
Patient	**Age**	**Gender**	**DM**	**Reflux**	**Smoking**	**VHI-10**	**Dysphonia Duration**	**Diagnostic Procedure**
1	55	M	No	Yes	No	29	1 y	Awake FLC
2	86	M	No	Yes	No	34	2 y	Awake FLC
3	56	M	No	Yes	Prior	40	2 mo	Awake FLC
4	70	M	Yes	Yes	Prior	32	1 y	MDL
5	40	M	Yes	Yes	No	19	5 y	MDL
6	63	M	No	No	Prior	37	10 mo	Awake FLC
7	62	M	No	Yes	No	26	9 wk	Awake FLC
8	46	F	Yes	No	No	35	0	MDL
9	36	F	No	No	No	17	4 wk	MDL
10	66	M	No	No	Prior	24	1 y	MDL
11	38	F	No	Yes	No	24	4 mo	MDL
12	46	M	No	Yes	No	29	2 y	MDL
13	54	F	No	Yes	No	NA	4 mo	Awake FLC
14	69	F	Yes	No	No	38	6 mo	MDL
15	38	M	No	No	No	31	3 y	Awake FLC

Abbreviations: DM, diabetes mellitus; FLC, flexible laryngoscopy with channel; MDL, microdirect laryngoscopy; VHI-10, Voice Handicap Index 10.

Table 2

Culture Results and Treatment Regimens of the Study Population.[a]

Microbiology Results and Treatment Regimens							
			Culture Results			Treatment	
Patient	Age	Gender	Aerobic	Fungal	AFB	Antibiotic	No. of Courses/Total Duration
1	55	M	MSSA	Negative	Negative	TMP-SMX	1/180 d
2	86	M	*Pseudomonas*	Positive	NA	Ciprofloxacin	1/21 d
3	56	M	MSSA	Negative	NA	None	Patient lost to follow-up
4	70	M	MRSA	Negative	Negative	TMP-SMX	3/215 d
5	40	M	MSSA	Negative	NA	TMP-SMX	4/192 d
6	63	M	MSSA	Negative	NA	TMP-SMX	2/261 d
7	62	M	MSSA	Negative	NA	TMP-SMX	3/171 d
8	46	F	“Normal respiratory flora”	Negative	Negative	None	No treatment indicated
9	36	F	*Serratia* then MSSA	Negative	NA	Levofloxacin, TMP-SMX	1/14 d (L); 1/28 d (B)
10	66	M	MSSA	Negative	NA	TMP-SMX	1/90 d
11	38	F	MSSA	Negative	Negative	TMP-SMX	1/10 d
12	46	M	MSSA	Negative	Negative	TMP-SMX	Multiple at OSH
13	54	F	*Serratia* and MSSA	Negative	Negative	None	NA
14	69	F	MSSA	Negative	Negative	TMP-SMX	1/56 d
15	38	M	MSSA	Negative	Negative	Cephalexin	1/28 d

[a]Patient No. 3 did not follow up after his biopsy for culture, so treatment was never initiated. Patient No. 9 initially had *Serratia* and was treated with levofloxacin (L). Repeat culture demonstrated only MSSA, and treatment consisted of TMP-SMX (B). Levofloxacin appeared to be successful in treating *Serratia.* Patient No. 11 was prescribed a longer course of antibiotics but stopped TMP-SMX early secondary to a rash. Patient No. 12 had multiple courses of TMP-SMX at an outside institution, but the exact duration was not available. The culture from Patient No. 13 grew *Serratia* and MSSA simultaneously. Patient No. 13 was evaluated by infectious disease, and the decision was made not to treat the culture results. Abbreviations: AFP, acid-fast bacteria; MRSA, Methicillin-resistant *Staphylococcus aureus*; MSSA, Methicillin-sensitive *Staphylococcus aureus*; OSH, outside hospital; TMP-SMX, trimethoprim-sulfamethoxazole or Bactrim.